PASS Information

Title	Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)
Protocol version identifier	Registry Protocol 2-79-52800-002 Final Version of 18 September 2025 including Amendment 9 (10.0)
Date of last version of protocol	19 April 2021 (including Amendment 8)
ENCePP register number	ENCEPP/SDPP/7708
Active substance	INCRELEX® (mecasermin) Pharmacotherapeutic group: pituitary and hypothalamic hormones and analogues; somatropin and somatropin agonists ATC code: H01AC03
Medicinal product	Increlex® 10 mg/mL solution for injection
Product reference	EU/1/07/402/001
European Agency for the Evaluation of Medicinal Products (EMEA) procedure number	EMEA/H/C/000704
US registration number	15054-1040-5
Marketing authorisation holder (MAH)	Esteve Pharmaceuticals
Joint PASS	No

Purpose of registry and objectives	The main purpose of this global registry is to collect, analyse and report safety data during and up to at least 5 years after the end of treatment in children and adolescents receiving Increlex® therapy for SPIGFD according to the locally approved product information, as part of the risk management strategy for Increlex®. Primary Objective: • To collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD. Secondary Objectives: • To describe long-term safety data, for at least 5 years after the end of Increlex® therapy, in children and adolescents who have received Increlex® therapy, regardless of treatment duration and adult height; • To describe long-term safety data at 2 and 5 years after the end of Increlex® therapy, for a subset of children and adolescents who have been exposed to Increlex® therapy for at least 3 cumulative years excluding interruptions, regardless of adult height; • To describe Increlex® effectiveness throughout the study until the participant reaches adult height; • To identify predictive factors of the main effectiveness parameters by modelisation of height velocity, final adult height (FAH), height standard deviation score (SDS) change, timing and progression of puberty, bone age development; • To evaluate Increlex® therapy exposure (dose and treatment duration) and compliance; • To determine the lowest effective dose of Increlex® defined as the cut-off dose under which there is no further effect on the height velocity anymore (short-term evaluation: 1-year height velocity); • To assess quality of life (QoL) during Increlex® therapy and in the post-treatment period (using EQ-5D version EQ-5D-Y (paediatric questionnaire)); • To describe the timeframe of the occurrence of neoplasia (benign and malignant) and hypoglycaemia.
Countries of study	Countries within and outside Europe where Increlex® is registered and marketed.
Author	[redacted] ESTEVE Pharmaceuticals Passeig de la Zona France, 109, 4a Planta 08038 Barcelona Spain Tel : [redacted]

Marketing Authorisation Holder

MAH	ESTEVE Pharmaceuticals Passeig de la Zona France, 109, 4a Planta 08038 Barcelona Spain Tel : [redacted]
MAH contact person for pharmacovigilance/emergency contact	[redacted] EU QPPV ESTEVE Pharmaceuticals Passeig de la Zona France, 109, 4a Planta 08038 Barcelona Spain Tel: [redacted] Mobile: [redacted] e-mail: [redacted] For serious adverse event (SAE) reporting: Email: [redacted]

PROTOCOL SIGNATURES

Investigator Signature

I have read and agree to the post-authorisation safety study (PASS) protocol number 2-79-52800-002 entitled "Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)". I am aware of my responsibilities as an Investigator under the guidelines of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), Good Pharmacoepidemiology Practices (GPP), Good Pharmacovigilance Practices (GVP), local regulations (as applicable) and the registry protocol. I agree to conduct the registry according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: _____

TITLE: Principal Investigator SIGNATURE: _____

DATE: _____

OFFICE: _____

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the Sponsor:

NAME: [redacted]

TITLE:

[redacted] SIGNATURE: _____

DATE: _____

OFFICE: Esteve Pharmaceuticals

NAME: [redacted]

TITLE: [redacted]

[redacted] SIGNATURE: _____

DATE: _____

OFFICE: Esteve Pharmaceuticals

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2 LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALS	Acid-labile Subunit
BMI	Body Mass Index
CA	Competent Authorities
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CSR	Clinical Study Report
D3-GHR	Deletion of Exon 3 of the Growth Hormone Receptor
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC	European Commission
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
e-signature	Electronic Signature
EU	European Union
EU-IGFD	European Increlex® (Mecasermin [rDNA Origin] Injection) Growth Forum Database
FAH	Final Adult Height
FGF	Fibroblast Growth Factor
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GH	Growth Hormone
GHBP	Growth Hormone-binding Protein
GHR	Growth Hormone Receptor
GMPC	Global Medical Publications and Communications
GP	Greulich and Pyle

GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IGFBP3	Insulin-like Growth Factor-binding Protein 3
IGFD	Insulin-like Growth Factor-1 Deficiency
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NIS	Non-Interventional Studies
PAH	Predicted Adult Height
PAPPA2	Pappalysin 2
PASS	Post-authorisation Safety Study
PI	Package Insert
PIGFD	Primary IGF-1 Deficiency
PIS	Participant Information Sheet
PSC	Publications Steering Committee
PT	Preferred Term
PTPN11	Gene Encoding Non-receptor Type of Protein Tyrosine Phosphatase SHP-2
Q	Quarter
QoL	Quality of Life
rhIGF-1	Recombinant Human Insulin-like Growth Factor-1
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation

SDS	Standard Deviation Score
SHOX	Short Stature Homeobox-containing Gene
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Service Provider
SPIGFD	Severe Primary Insulin-like Growth Factor-1 Deficiency
STAT5b	Signal Transducer and Activator of Transcription 5b
TEAE	Treatment Emergent Adverse Event
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

3 PARTIES

Details of all main responsible parties, e.g. Principal Investigator, Coordinating Investigator for each participating country (if applicable) and full list of Investigators at all participating registry sites, including contact details, are included in Appendix 1 (available upon request).

4 ABSTRACT

Study Title:	Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)
Protocol Version N°:	10.0
Date of the Last Version of the Protocol:	19 April 2021 (including Amendment 8)
Author:	[redacted] [redacted] ESTEVE Pharmaceuticals Passeig de la Zona France, 109, 4a Planta 08038 Barcelona Spain Tel : [redacted]

Rationale and Background

As the current knowledge of insulin-like growth factor-1 (IGF-1) biology suggests that IGF-1 plays a role in malignancies in all organs and tissues, there is an increased risk of benign and malignant neoplasia in children and adolescents treated with Increlex®. In order to monitor the risk of neoplasms and other safety concerns such as metabolic or cardiovascular risk, and as part of the overall risk management strategy for Increlex®, the Marketing Authorisation Holder (MAH) put in place a post-authorisation safety surveillance registry in the European Union (EU), called the European Increlex® (Mecasermin [rDNA Origin] Injection) Growth Forum Database (EU-IGFD 2-79-52800-002) to monitor the safety and effectiveness of Increlex® therapy, with the Specific Obligation to investigate long-term safety until 5 years after the end of treatment for a subset of participants exposed for at least 3 years. The EU-IGFD registry was implemented at the end of 2008 in ten European countries with a Marketing Authorisation approved for Increlex® under Exceptional Circumstances.

Recently, as a result of postmarketing safety surveillance activities, occurrences of benign and malignant neoplasia were observed among children and adolescents who received treatment with Increlex®. A safety signal was submitted to the European Medicines Agency (EMA) which concluded that the benefit-risk profile of Increlex® remains positive in its approved indication only, at doses not higher than the daily recommended doses. In May 2019, a Type II variation to update the EU Summary of Product Characteristics (SmPC), Risk Management Plan (RMP) and Additional Risk Minimisation Material was submitted by the MAH which was approved by the EMA.

Considering the identified risk of malignancies, the Specific Obligation to investigate long-term safety after the end of Increlex® treatment and the possible occurrence of malignancies as well as other risks, the MAH has decided:

- To geographically expand the current EU-IGFD registry to additional countries within and outside Europe where the product is registered and marketed, and;

- To collect long-term safety data after completion of treatment for all participants who have received treatment with Increlex®, regardless of duration of therapy.

The amendment of the EU-IGFD registry into a global registry will provide the opportunity to further monitor the overall safety of Increlex® and the risks identified within the EU RMP. This expanded global registry will also aim to enhance participant enrolment and retention, to ensure that the product is used according to the locally approved product information and to measure the effectiveness of the additional risk minimisation measures. In particular, Investigators and participants and/or parents/legally authorised representatives will be made aware of the importance of the follow-up visits including as a minimum visits at years 2 and 5 after the end of treatment, to enable the registry to fulfil the EMA Specific Obligation.

Purpose of Registry and Objectives

The main purpose of this global registry is to collect, analyse and report safety data during and up to at least 5 years after the end of treatment in children and adolescents receiving Increlex® therapy for SPIGFD according to the locally approved product information, as part of the risk management strategy for Increlex®.

Primary Objective

- To collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD.

Secondary Objectives

- To describe long-term safety data, for at least 5 years after the end of Increlex® therapy, in children and adolescents who have received Increlex® therapy, regardless of treatment duration and adult height;
- To describe long-term safety data at 2 and 5 years after the end of Increlex® therapy, for a subset of children and adolescents who have been exposed to Increlex® therapy for at least 3 cumulative years excluding interruptions, regardless of adult height;
- To describe Increlex® effectiveness throughout the study until the participant reaches adult height;
- To identify predictive factors of the main effectiveness parameters by modelisation of height velocity, final adult height (FAH), height standard deviation score (SDS) change, timing and progression of puberty, bone age development;
- To evaluate Increlex® therapy exposure (dose and treatment duration) and compliance;
- To determine the lowest effective dose of Increlex® defined as the cut-off dose under which there is no further effect on the height velocity anymore (short-term evaluation: 1-year height velocity);
- To assess quality of life (QoL) during Increlex® therapy and in the post-treatment period (using EQ-5D version EQ-5D-Y (paediatric questionnaire));
- To describe the timeframe of the occurrence of neoplasia (benign and malignant) and hypoglycaemia.

Registry Design

This is a multicentre, global, prospective, non-interventional, observational, open-ended, post-authorisation safety surveillance registry designed to collect safety and effectiveness data on the use of Increlex® in children and adolescents with SPIGFD. Data on treatment exposure, compliance and QoL of participants will also be collected.

The objective is to screen all Increlex®-treated patients with SPIGFD at each participating site of the participating countries with the aim of enrolling as many patients as possible. The decision to prescribe Increlex® will be made prior to and independently of the decision to enrol the patient in the registry. Treatment with Increlex® should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders. The dose should be individualised for each participant according to the locally approved product information. The data collected for a participant will be those that exist in their medical records as part of standard medical care except for additional QoL assessments and post-treatment safety follow-up in the context of fulfilling the Specific Obligation (SO2). Data will be collected utilising an electronic Case Report Form (eCRF) via the internet. The date of the inclusion visit is not determined by the protocol. Patients who have started Increlex® treatment before the implementation of the registry in their country may also be enrolled. Data will be then retrospectively collected in the eCRF. During the first visit, the Investigator will check the patient's eligibility according to the inclusion and exclusion criteria and must obtain written informed consent before any further data collection. For each participant, Increlex® treatment duration and the frequency of follow-up visits is at the discretion of the Investigator according to his/her judgment on the basis of the clinical needs of the participant and according to the locally approved product information. All enrolled participants will be followed and monitored for safety throughout their course of treatment and for a post-treatment follow-up period of at least 5 years in addition to the treatment period for which the study Investigator is also responsible. If the participant has not reached FAH at the end of the 5-year post-treatment period, the follow-up period will be extended until FAH is achieved. Investigators and participants and/or parents/legally authorised representatives should be aware of the importance of the follow-up visits including at least visits at years 2 and 5 after the end of treatment. The primary objective of the registry is to collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD, in particular to permit the description and incidence of serious adverse events (SAEs) (including adverse event (AE) of special interest (AESI) of neoplasia), targeted AEs and all AEs. Secondary objectives include the description of long-term safety data in all participants, and in the subset exposed to Increlex® for at least 3 years, and of the effectiveness of Increlex® treatment up to adult height, evaluation of Increlex® exposure (dose and treatment duration) and compliance, description of Increlex® effectiveness according to the dose, assessments of QoL during and after treatment and description of the timeframe of occurrence of neoplasia and hypoglycaemia. An independent Data Monitoring Committee composed of external experts will be asked to conduct periodic reviews of available safety data on at least an annual basis. This expanded global registry will increase enrolment and provide the opportunity to monitor the safety of Increlex® and the risks identified within the EU RMP in a larger group of children and adolescents with SPIGFD. It will also enable the Sponsor to ensure that the product is used according to the locally approved product information and to measure the effectiveness of the additional risk minimisation measures.
Population

It is intended to collect safety data in children and adolescents receiving Increlex® therapy for SPIGFD according to the locally approved product information at sites experienced in the diagnosis and management of children and adolescents with SPIGFD.

The aim is to enrol as many Increlex®-treated patients as possible into the registry at each participating site and the results should provide valuable information on the long-term risk of malignancies and other risks in a relatively large group of children and adolescents with this rare disease.

To be eligible for enrolment in the registry, participants must comply with all of the following inclusion and exclusion criteria:

Inclusion Criteria

(1) Children and adolescents from 2 to 18 years:

- For US, patients starting or planning to start or currently receiving treatment with Increlex® therapy for severe primary IGF-1 deficiency as defined by the US Increlex® prescribing information or for growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.
- For EU, patients starting or planning to start or currently receiving treatment with Increlex® therapy according to the locally approved product information. Note: not applicable for patients enrolled in the EU-IGFD registry and entering or currently in the post-treatment period.

(2) Signed informed consent as per local regulations needs to be obtained. Parents or legally authorised representatives if applicable must give signed informed consent before any registry-related activities are conducted. Assent from the participant should also be obtained as appropriate.

Exclusion Criteria

(1) Patient currently participating in an Increlex® clinical trial.

(2) Patient currently participating in any clinical trial for growth retardation.

(3) Patient with any contraindication to Increlex® or any condition subject to special warning as per the locally approved label.

- For US patients, these include patients with hypersensitivity to the active substance or any of the excipients, patients with active or suspected neoplasia and patients with closed epiphyses.
- For EU patients: these include patients with hypersensitivity to the active substance or any of the excipients, patients with active or suspected neoplasia or any condition or medical history which increases the risk of benign or malignant neoplasia and patients with closed epiphyses. Note: not applicable for patients enrolled in the EU-IGFD registry and entering or currently in the post-treatment period.

Note: for any patients enrolled in the registry under previous inclusion/exclusion criteria (i.e. before implementation of Protocol Amendment #6), who would be ineligible according to any of the above inclusion or exclusion criteria, e.g. receiving Increlex® for an indication not covered by the locally approved product information, a letter will be sent to the Investigator to alert him/her about the off-label use of the product (specifically for the risk of neoplasias). The patient could continue to be followed up in the registry for safety data in the post-treatment period.

Variables

Demographic and Baseline Variables

The registry will collect the following data:

- Demographic data on children and adolescents receiving Increlex® treatment: sex, date of birth (month and year), birth weight and length, gestational age, previous and current height, sitting height and weight;
- Parental heights (biological relatives only);
- Baseline height, sitting height, weight, bone age and method, echocardiogram, funduscopy and pubertal (Tanner) stage;
- Pregnancy status;
- Predicted adult height (PAH);
- Diagnosis of SPIGFD (documented by height SDS; IGF-1 levels and IGF-1 SDS; growth hormone (GH) levels), date of diagnosis and associated aetiologies, and date of growth failure (short stature) diagnosis, if different from SPIGFD diagnosis date;
- IGF-1 generation test results and IGF-1/insulin-like growth factor-binding protein-3 (IGFBP3) concentrations;
- GH concentrations including basal/random and highest stimulated;
- Serum IGFBP3;
- GH-binding protein;
- Genetic test results and date of genetic testing;
- Current and previous illnesses including congenital conditions and neoplasia;
- Previous and concomitant medications;
- Personal and family history of neoplasia;
- Prior growth-promoting therapies: GH, IGF-1, steroid hormones such as sex steroids (testosterone and oestradiol);
- Baseline QoL assessment using EQ-5D version EQ-5D-Y.

Safety Variables (Primary Analyses; Treatment Period and Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data on the following safety variables will be collected from enrolment to the end of the post-treatment follow-up period:

- For all AEs, irrespective of causality, including SAEs, AESI and targeted AEs, start/end date, time to onset, nature, severity, seriousness, causality assessment, any treatment administered for the AE, action taken and outcome;
- Deaths, irrespective of causality, including date and cause of death;
- Special situations, irrespective of causality, including start/end date, category, description, whether the special situation led to an AE and outcome;
- Concomitant medications including concomitant treatment with GH, with start/end dates;
- Echocardiography and funduscopy results.

Effectiveness Variables (Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data on the following effectiveness variables will be collected at enrolment, during treatment and after the end of treatment:

- Height and sitting height;
- Weight;
- Pubertal (Tanner) stage: pubic hair, testicular volume, breast development;
- Bone age;
- IGF-1 concentrations;
- IGFBP3 (treatment period only);
- FAH.

Treatment Variables (Secondary Analyses; Treatment Period)

Data on the following treatment variables will be collected from start to end of treatment:

- Dose of Increlex® at the start of treatment (mg/kg or mcg/kg), mode of administration and date of first Increlex® intake;
- Any dose adjustments and dose interruptions (including adjusted dose and dates) throughout the study including reasons for adjustment;
- Dose of Increlex® at the end of treatment (mg/kg or mcg/kg) and date of last Increlex® intake;
- Reason for discontinuing therapy (most appropriate response): attained adult height, AE, lost to follow-up, noncompliance, participant/parent/legally authorised representative decision, financial/insurance, changed physician, lack of effectiveness, shortage of Increlex®, COVID-19 or other.

Quality of Life Variables (Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data for the following QoL assessments will be collected at baseline (start of treatment), at year one, at end of treatment and at FAH:

- Changes in QoL assessment using EQ-5D version EQ-5D-Y.

The QoL of participants will be assessed using the EQ-5D-Y paediatric questionnaire, a child-friendly standardised measure of health status developed by the EuroQol Group, denoted 'Youth' as being adequate for both children and adolescents.

The EQ-5D-Y consists of two pages, a descriptive system and a visual analogue scale (VAS). The descriptive system comprises five dimensions, using child-friendly wording: mobility; looking after myself; doing usual activities; having pain or discomfort; feeling worried, sad or unhappy. Each dimension has three levels: no problems/no pain/not worried, some problems/some pain/a bit worried, a lot of problems/a lot of pain/very worried, from which the respondent chooses the most appropriate. The EQ VAS records the respondent's self-rated health on a 0-100 vertical VAS from 'The best health you can imagine' to 'The worst health you can imagine'.

Participants aged 8+ who are able to fill in the EQ-5D-Y themselves will self-complete the questionnaire and VAS. The EQ-5D-Y proxy version, designed for a proxy (parent or legally authorised representative) to rate how he/she rates the health of the child, is recommended for younger children and can be applied to children aged from 4-7 years and to children of 8+ who

are not able to fill in the EQ-5D-Y themselves. As the minimum age recommended for the proxy version is 4 years, participants between 2 and 4 years of age will not be included in the QoL assessments. A country-specific local language version will be used for each country.
Data Sources The data collected for a participant will be those that exist in their medical records as part of standard medical care. No additional procedures or activities are required in this registry except for QoL assessments and post-treatment safety follow-up in the context of fulfilling the Specific Obligation (SO2).
Study Size The objective is to screen all Increlex®-treated patients with SPIGFD at each participating site of the participating countries with the aim of enrolling as many patients as possible.

Data Analysis

The following populations will be used for all the statistical analyses:

Screened Population: all patients included in the patient screening log (this includes both enrolled and non-enrolled patients, with the reason for non-enrolment).

Enrolled Population: all participants who are fully informed about the registry and who have given their written informed consent to participate (and/or their parents/legally authorised representatives) before implementation of any registry-related procedure.

Registry Population: all participants who have completed at least one follow-up visit and who have taken the treatment at least once.

Complete Population: all participants who have stopped treatment and who have been followed until FAH reached.

Safety Population: all participants who have taken the treatment at least once and with at least one follow-up visit or presence of any post-study treatment safety data.

Long-term Safety Population: all participants who have been exposed to Increlex® for at least 3 years and who ended therapy at least 2 years prior to the collection of long-term safety data.

Primary Analyses

The primary analyses and summary tables of safety data will be based on the Safety Population (data from the treatment period only).

An overall summary table of AEs during the treatment period (up to 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs, AEs leading to death and AEs leading to withdrawal will be presented with the number and proportion of participants and the number of events.

All treatment emergent AEs (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA primary system organ class (SOC) and preferred term (PT). The incidence of all TEAEs, SAEs, AESI, targeted AEs, AEs leading to death and AEs leading to withdrawal will be tabulated by primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

AE listings will be presented by participant, primary SOC and PT.

The relationship of frequently occurring AEs, e.g. hypoglycaemia, to prognostic variables such as age, pubertal status, and dose will be explored.

All primary safety data will also be included in the participant data listings.

Secondary Analyses

Safety Analyses

The secondary safety analyses will be based on the Safety Population. Adverse event data are from the post-treatment period only but data on special situations and concomitant medications are from the treatment and post-treatment periods.

An overall summary table of AEs occurring during the post-treatment period (over 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs and AEs leading to death will be presented with the number and proportion of participants and the number of events.

The incidence of all post-treatment AEs, SAEs, AESI, targeted AEs and AEs leading to death will be tabulated by MedDRA primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

The same analyses will be performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

Post-treatment AE listings will be presented by participant, primary SOC and PT.

An overall summary table of special situations occurring during the treatment and post-treatment periods will be presented with the number and proportion of participants and the number of events. For the post-treatment period, the same analyses will be performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

Concomitant medications during the treatment and post-treatment periods will be tabulated.

Incidence of neoplasia (benign and malignant) and hypoglycaemia will be presented according to the timeframe of occurrence (e.g. within the first 3 years after start of treatment, between 3 and 5 years and over 5 years).

All secondary safety data will also be included in the participant data listings.

Effectiveness Analyses

Effectiveness analyses will be based on the Registry Population.

The raw values of the following effectiveness parameters will be described at different timepoints (every 6 months from the start of treatment) as well as the change from baseline: height SDS, height velocity, body mass index (BMI) SDS, bone age development, pubertal stage.

For participants who reached the FAH, the estimation of the difference between the PAH and the FAH will be presented.

Main effectiveness parameters (height SDS, height velocity) will be described according to average dose received over the course of the study and according to dose ranges (e.g. 4 dose ranges (≤50,]50-80],]80-110], > 110 µg/kg BID)). This analysis will support the description of the lowest effective dose.

Multivariate linear regression analyses will be used to identify predictive factors of height SDS change, height velocity, bone age development after 1 year of treatment or more. The same method will be used to assess the predictive factors of FAH.

The Cox regression model including covariates as sex, age or height SDS at start of Increlex® will be used to estimate the time from start of treatment to reach the puberty for a subset of prepubertal patients at start of Increlex®.

Biological assessments (IGF-1, IGFBP3), raw values and change from baseline, will be described at different timepoints.

Exposure to Increlex® Therapy

The treatment duration as well as the dose of Increlex® at each timepoint (initiation, 3 months, 6 months, 1 year, and every 6 months thereafter) will be described.

Duration of post-treatment follow-up will also be summarised.

Quality of Life Analysis

The QoL will be assessed using the EQ-5D-Y paediatric questionnaire. The 5 domains and VAS will be described at each timepoint as well as the evolution from baseline.

Interim Analyses

Interim effectiveness and safety descriptive analyses are planned to be performed at least once a year.

Milestones

- Start of data collection (registry initiation date): 09 December 2008;
- Start of data collection under Protocol Amendment #8: planned Quarter (Q)2 2021;
- End of data collection: not applicable (N/A) (ongoing open-ended registry);
- Interim Clinical Study Reports (CSRs) 1 to 5: 01 December 2011, 22 November 2013, 14 December 2015, 20 December 2017 and 10 January 2020, respectively;
- Interim CSR 6: planned December 2021;
- Final report of registry results: N/A (open-ended registry).

5 AMENDMENTS AND UPDATES

The current version of the protocol was released on 18 September 2025 and includes protocol amendments 1 to 9. For all protocol amendments, amendment forms were prepared and are provided in Appendix 1.

Amendment Number	Release Date	Section of protocol (Amendment Form)	Amendment or update	Reason
1	07 October 2008	Appendix 1	Non-substantial; eCRF, local ICF, database and SAP update	Removal of the ethnic origin, requested by CNIL
2	11 February 2009	Appendix 1	Substantial; eCRF, local ICF, database and SAP update	Addition of Final Adult Height requested by the HAS. Version for ALL countries except for France.
3	18 December 2015	Appendix 1	Substantial; eCRF, local ICF, database and SAP update	To answer the commitment request of the EMA, i.e. to collect safety information 2 and 5 years after the end of Increlex® therapy in the subjects who have been exposed for at least 3 years, irrespective of final height.
4	04 August 2016	Appendix 1	Non-substantial; no update to eCRF, local ICF, database or SAP	To add references to the Good Pharmacovigilance Practice and Good Pharmacoepidemiology Practice Guidelines
5	08 January 2018	Appendix 1	Substantial; eCRF, local ICF, database and SAP update	Register 100% of patient taking Increlex® in participating centres, without recording any medical or private information without ICF signature and/or subject agreement. Remove Greece as participating country as no subjects have been included since the start of the study. Add a clarification regarding date of birth collection: • Remove day of birth date will increase subject data privacy. The recording 01 for the day of birth is a convention to facilitate data collection. • Keeping months in the birth date is mandatory for optimal SDS calculations.
6	10 July 2020	Appendix 1	Substantial; eCRF, local ICF, database and SAP update	Geographic expansion of the EU-IGFD registry to additional countries within and outside Europe where the product is registered and marketed (i.e. conversion into a global registry), with long-term follow-up for all children and adolescents treated with Increlex® to fulfil the EMA Specific Obligation (SO2) 002.1 to investigate long-term safety after the end of Increlex® treatment, regardless of treatment duration, and the possible occurrence of malignancies as well as other risks.
7	08 February 2021	Appendix 1	Substantial; SAP update	Update of secondary objectives: to include data collection of the Increlex® (or mecasermin) doses as a secondary objective of the global registry to allow for potential further descriptive analyses.

Amendment Number	Release Date	Section of protocol (Amendment Form)	Amendment or update	Reason
8	19 April 2021	Appendix 1	Non-substantial, SAP update	Modification of secondary objective related to the determination of lowest effective dose Precisions on participating countries Update of the off-label patients follow-up
9	18 September 2025	Appendix 1	Substantial	Change of sponsor

CNIL = *Commission nationale de l'informatique et des libertés*; eCRF = electronic Case Report Form; EMA = European Medicines Agency; EU-IGFD = European Increlex® (Mecasermin [rDNA Origin] Injection) Growth Forum Database; HAS = *Haute Autorité de Santé*; ICF = informed consent form; SAP = Statistical Analysis Plan; SDS = standard deviation score.

6 MILESTONES

Milestone	Date
Start of data collection (registry initiation date)	09 December 2008
Start of data collection under Protocol Amendment #8	Planned Q2 2021
End of data collection	N/A (ongoing open-ended registry)
Registration in the ENCePP register	17 October 2014
Interim CSR 1	01 December 2011
Interim CSR 2	22 November 2013
Interim CSR 3	14 December 2015
Interim CSR 4	20 December 2017
Interim CSR 5	10 January 2020
Interim CSR 6	Planned December 2021
Final report of registry results	N/A (ongoing open-ended registry)

CSR = Clinical Study Report; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; N/A = not applicable; Q = quarter.

7 RATIONALE AND BACKGROUND

7.1 Disease Review

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are the two key hormones that regulate statural growth in children and its metabolic processes. Activity of the GH:IGF-1 system is coordinated via the brain and is responsive to changes in many biological processes throughout the body. Under normal circumstances, GH binds to its receptor in the liver and other tissues and stimulates the synthesis/secretion of IGF-1. In target tissues, the IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signalling which stimulates multiple processes leading to statural growth. The metabolic actions of IGF-1 are, in part, directed at stimulating the uptake of glucose, fatty acids and amino acids so that metabolism supports growing tissues [1, 2].

Defects at all levels of the GH:IGF-1 system have been described in humans; many children with these defects will have growth failure either because of a deficiency in GH or IGF-1, or an inability to respond to GH or IGF-1.

Growth hormone replacement therapy is required to restore normal growth in children with GH deficiency. For some children with IGF-1 deficiency, short stature is associated with very low serum IGF-1 concentrations despite normal levels of GH. In these cases, IGF-1 therapy is the appropriate treatment.

Primary insulin-like growth factor-1 deficiency (PIGFD) is the inability to produce normal levels of physiologically active IGF-1 when exposed to normal levels of GH and without secondary aetiologies of IGF-1 deficiency (IGFD) such as malnutrition, chronic disease, hypopituitarism and hypothyroidism [3]. The underlying cause of PIGFD may be genetic mutations involving the GH receptor (GHR) [3], postreceptor defects in GH action [4, 5, 6, 7], or abnormalities in the IGF-1 gene [8, 9]. Children with these defects have normal or elevated endogenous GH secretion due to negative feedback resulting from low blood IGF-1 concentrations at the hypothalamus and pituitary gland [3, 10, 11, 12] and they exhibit the diagnostic triad of: i) short stature, a height standard deviation score (SDS) $\leq$-2; ii) a basal serum IGF-1 SDS $\leq$-2; and iii) normal or elevated serum GH concentrations.

Some patients present a particularly severe form of PIGFD. The most severely affected individuals described to date are those with Laron Syndrome, which was first identified in 1966 [13] and later documented to be caused by genetic mutations involving the GHR [14, 15]. Other molecular defects of the GHR, GH signalling cascade, or IGF-1 gene expression resulting in PIGFD have since been identified [7, 16]. The common feature in all children with these defects is extreme short stature. Epidemiological data show that severe primary insulin-like growth factor-1 deficiency (SPIGFD) is a rare condition with an estimated prevalence of less than 1 in 100,000 worldwide [17].

SPIGFD is defined in the European Union (EU) by:

- height SDS $\leq$-3.0 and
- basal IGF-1 levels below the 2.5th percentile for age and gender and
- GH sufficiency.
- Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

The EU definition of SPIGFD includes patients with mutations in the GHR, post-GHR signalling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they

cannot be expected to respond adequately to exogenous GH treatment. In some cases, when deemed necessary, the physician may decide to assist in the diagnosis by performing an IGF-1 generation test.

SPIGFD is defined in the United States of America (USA) by:

- height SDS ≤-3.0 and
- basal IGF-1 SDS ≤-3.0 and
- normal or elevated GH
- Exclusion of secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.

In summary, growth failure in children with SPIGFD is a serious and chronically debilitating condition which, if untreated, can result in final adult height (FAH) 4 to 10 standard deviations (SDs) below average and a range of health conditions such as obesity, hyperlipidaemia, insulin resistance, muscle weakness and osteoporosis as well as short stature with thin bones and undeveloped muscles [18, 19].

7.2 Rationale for Treatment with Increlex®

Children with SPIGFD have low blood IGF-1 levels and normal or elevated endogenous GH so they cannot be expected to respond to exogenous GH but can be expected to respond to IGF-1 therapy. The objective of therapy with recombinant human insulin-like growth factor-1 (rhIGF-1) is to raise blood levels of IGF-I towards the normal ranges and provide the necessary stimulus to improve growth [20].

The mechanism of action of rhIGF-1 is well characterised. The actions of IGF-1 as a "somatomedin" are obligate for GH to be able to stimulate bone and body growth. Therefore, a deficiency in IGF-1 leads to reduced body size in animals and humans. In addition to mediating many of the activities of GH including its skeletal growth promoting effects, IGF-1 also has "insulin-like" metabolic activities, including hypoglycaemic activity. The hormonal, cellular and molecular mechanisms mediating the actions of rhIGF-1 on growth and metabolism are well characterised. In cell membranes of target tissues, the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by the binding of rhIGF-1 leading to intracellular signalling which stimulates multiple processes leading to statural growth [20].

Mecasermin, the active ingredient of Increlex®, is a rhIGF-1 identical in structure to endogenous human IGF-1 and children with SPIGFD have been shown to respond to therapy with Increlex® [21].

In the long-term pivotal study of Increlex® (Study 1419), height velocity observed at Year 1 improved substantially from 2.6±1.7 cm/year pretreatment to 8.0±2.3 cm/year and a statistically significant increase in height velocity versus pretreatment was observed for 8 years [21]. For 21 treatment-naïve subjects with near-adult height, the mean (±SD) of the difference between observed increase in height versus that expected from Laron was approximately 13 cm (±8 cm) after an average of 11 years of treatment [22, 23].

The first Marketing Authorisation (MA) for Increlex® (10 mg/mL solution for injection) was granted in the USA in August 2005. It is indicated for the treatment of growth failure in paediatric patients 2 years of age and older with SPIGFD or GH gene deletion who have developed neutralising antibodies to GH.

Increlex® received MA in the EU and the European Economic Area (including Iceland, Liechtenstein and Norway) under Exceptional Circumstances in August 2007 and is indicated for the long-term treatment of growth failure in children and adolescents from 2 to 18 years with confirmed SPIGFD. There is an ongoing Specific Obligation to complete certain post-authorisation measures, discussed in Section 7.3.

Although the prevalence of SPIGFD is low (less than 1 in 100,000 worldwide [17]), at present there is no licensed treatment available for this indication other than Increlex® (Somazon® in Japan), and Increlex® treatment offers the potential for life-long benefits in these patients. The safety profile of Increlex® is well known as the drug has been approved for more than 12 years in the EU and USA, and the benefit/risk ratio of Increlex® in this indication is considered to be favourable in respect of the approved label and the recommended dose. Nevertheless, the benefit-risk of the product is reviewed by the European Medicines Agency (EMA) on a yearly basis through the submission of yearly Periodic Safety Update Reports and annual reassessments of the licence.

Increlex® may increase the risk of benign and malignant neoplasias, particularly in case of off-label use and doses over the maximum dose tolerated. Increlex® is contraindicated in children and adolescents with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia. Therapy should be discontinued if evidence of neoplasia develops.

7.3 Rationale for the Registry

As the current knowledge of IGF-1 biology suggests that IGF-1 plays a role in malignancies in all organs and tissues, there is an increased risk of benign and malignant neoplasia in children and adolescents treated with Increlex®. In order to monitor the risk of neoplasms and other safety concerns such as metabolic or cardiovascular risk, and as part of the overall risk management strategy for Increlex®, the Marketing Authorisation Holder (MAH) put in place a post-authorisation safety surveillance registry in the EU, called the European Increlex® (Mecasermin [rDNA Origin] Injection) Growth Forum Database (EU-IGFD 2-79-52800-002) to monitor the safety and effectiveness of Increlex® therapy, with the Specific Obligation to investigate long-term safety until 5 years after the end of treatment for a subset of participants exposed for at least 3 years. The EU-IGFD registry was implemented at the end of 2008 in ten European countries with a MA approved for Increlex® under Exceptional Circumstances.

Recently, as a result of postmarketing safety surveillance activities, occurrences of benign and malignant neoplasia were observed among children and adolescents who received treatment with Increlex®. A safety signal was submitted to the EMA which concluded that the benefit-risk profile of Increlex® remains positive in its approved indication only, at doses not higher than the daily recommended doses. In May 2019, a Type II variation to update the EU Summary of Product Characteristics (SmPC), Risk Management Plan (RMP) and Additional Risk Minimisation Material was distributed in the EU and relevant global markets between December 2019 and July 2020.

Considering the identified risk of malignancies, the Specific Obligation to investigate long-term safety after the end of Increlex® treatment and the possible occurrence of malignancies as well as other risks, the MAH has decided:

- To geographically expand the current EU-IGFD registry to additional countries within and outside Europe where the product is registered and marketed, and;
- To collect long-term safety data after completion of treatment for all participants who have received treatment with Increlex®, regardless of duration of therapy.

The amendment of the EU-IGFD registry into a global registry will provide the opportunity to further monitor the overall safety of Increlex® and the risks identified within the EU RMP. This expanded global registry will also aim to enhance participant enrolment and retention, to ensure that the product is used according to the locally approved product information and to measure the effectiveness of the additional risk minimisation measures. In particular, Investigators and participants and/or parents/legally authorised representatives will be made aware of the importance of the follow-up visits including as a minimum visits at years 2 and 5 after the end of treatment, to enable the registry to fulfil the EMA Specific Obligation.

8 PURPOSE OF REGISTRY AND OBJECTIVES

8.1 Purpose of Registry

The main purpose of this global registry is to collect, analyse and report safety data during and up to at least 5 years after the end of treatment in children and adolescents receiving Increlex® therapy for SPIGFD according to the locally approved product information, as part of the risk management strategy for Increlex®.

8.2 Objectives

8.2.1 Primary Objective

- To collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD.

8.2.2 Secondary Objectives

- To describe long-term safety data, for at least 5 years after the end of Increlex® therapy, in children and adolescents who have received Increlex® therapy, regardless of treatment duration and adult height;
- To describe long-term safety data at 2 and 5 years after the end of Increlex® therapy, for a subset of children and adolescents who have been exposed to Increlex® therapy for at least 3 cumulative years excluding interruptions, regardless of adult height;
- To describe Increlex® effectiveness throughout the study until the participant reaches adult height;
- To identify predictive factors of the main effectiveness parameters by modelisation of height velocity, FAH, height SDS change, timing and progression of puberty, bone age development;
- To evaluate Increlex® therapy exposure (dose and treatment duration) and compliance;
- To determine the lowest effective dose of Increlex® defined as the cut-off dose under which there is no further effect on the height velocity anymore (short-term evaluation: 1-year height velocity);
- To assess QoL during Increlex® therapy and in the post-treatment period (using EQ-5D version EQ-5D-Y (paediatric questionnaire));
- To describe the timeframe of the occurrence of neoplasia (benign and malignant) and hypoglycaemia.

9 RESEARCH METHODS

9.1 Registry Design

This is a multicentre, global, prospective, non-interventional, observational, open-ended, post-authorisation safety surveillance registry designed to collect safety and effectiveness data on the use of Increlex® in children and adolescents with SPIGFD. Data on treatment exposure, compliance and QoL of participants will also be collected.

The objective is to screen all Increlex®-treated patients with SPIGFD at each participating site of the participating countries with the aim of enrolling as many patients as possible.

The decision to prescribe Increlex® will be made prior to and independently of the decision to enrol the patient in the registry. Treatment with Increlex® should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders. The dose should be individualised for each participant according to the locally approved product information. The data collected for a participant will be those that exist in their medical records as part of standard medical care except for additional QoL assessments and post-treatment safety follow-up in the context of fulfilling the Specific Obligation (SO2). Data will be collected utilising an electronic Case Report Form (eCRF) via the internet.

The date of the inclusion visit is not determined by the protocol. Patients who have started Increlex® treatment before the implementation of the registry in their country may also be enrolled. Data will be then retrospectively collected in the eCRF.

During the first visit, the Investigator will check the patient's eligibility according to the inclusion and exclusion criteria and must obtain written informed consent before any further data collection.

For each participant, Increlex® treatment duration and the frequency of follow-up visits is at the discretion of the Investigator according to his/her judgment on the basis of the clinical needs of the participant and according to the locally approved product information. All enrolled participants will be followed and monitored for safety throughout their course of treatment and for a post-treatment follow-up period of at least 5 years in addition to the treatment period for which the study Investigator is also responsible. If the participant has not reached FAH at the end of the 5-year post-treatment period, the follow-up period will be extended until FAH is achieved. Investigators and participants and/or parents/legally authorised representatives should be aware of the importance of the follow-up visits including at least visits at years 2 and 5 after the end of treatment.

The primary objective of the registry is to collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD, in particular to permit the description and incidence of serious adverse events (SAEs) (including adverse event (AE) of special interest (AESI) of neoplasia), targeted AEs and all AEs.

Secondary objectives include the description of long-term safety data in all participants, and in the subset exposed to Increlex® for at least 3 years, and of the effectiveness of Increlex® treatment up to adult height, evaluation of Increlex® exposure (dose and duration) and compliance, assessments of QoL during and after treatment and description of the timeframe of occurrence of neoplasia and hypoglycaemia.

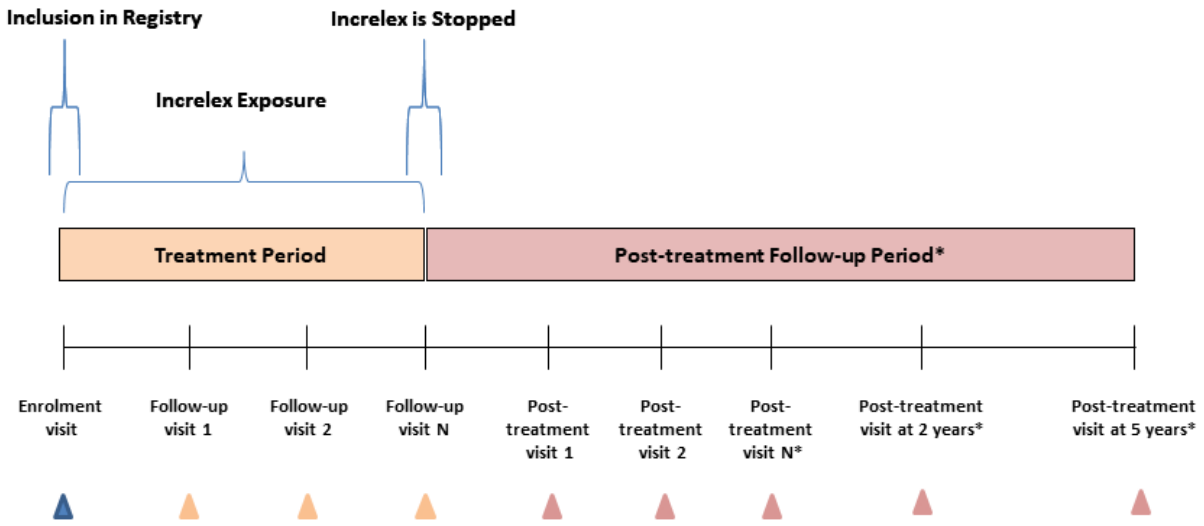
An independent Data Monitoring Committee (DMC) composed of external experts will be asked to conduct periodic reviews of available safety data on at least an annual basis.

This expanded global registry will increase enrolment and provide the opportunity to monitor the safety of Increlex® and the risks identified within the EU RMP in a larger group of children

and adolescents with SPIGFD. It will also enable the Sponsor to ensure that the product is used according to the locally approved product information and to measure the effectiveness of the additional risk minimisation measures.

The design of the registry is shown diagrammatically in Figure 1.

Figure 1 Registry Periods



FAH = final adult height.

*Participants will be followed for a post-treatment follow-up period of at least 5 years after the end of treatment. If the participant has not reached FAH at the end of the 5-year post-treatment period, the follow-up period will be extended until FAH is achieved. Investigators and participants and/or parents/legally authorised representatives should be aware of the importance of the follow-up visits including at least visits at 2 and 5 years after the end of treatment.

9.2 Setting

The registry setting is countries within and outside Europe where Increlex® is registered and marketed.

It is intended to collect safety data in children and adolescents receiving Increlex® therapy for SPIGFD according to the locally approved product information at sites experienced in the diagnosis and management of children and adolescents with SPIGFD in participating countries.

The aim is to enrol as many Increlex®-treated patients as possible into the registry at each participating site and the results should provide valuable information on the long-term risk of malignancies and other risks in a relatively large group of children and adolescents with this rare disease.

To be eligible for enrolment in the registry, participants must comply with all of the following inclusion and exclusion criteria:

9.2.1 Inclusion Criteria

(2) Children and adolescents from 2 to 18 years:

- For US, patients starting or planning to start or currently receiving treatment with Increlex® therapy for severe primary IGF-1 deficiency as defined by the US Increlex® prescribing information or for growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.
- For EU, patients starting or planning to start or currently receiving treatment with Increlex® therapy according to the locally approved product information. Note:

not applicable for patients enrolled in the EU-IGFD registry and entering or currently in the post-treatment period.

(2) Signed informed consent as per local regulations needs to be obtained. Parents or legally authorised representatives if applicable must give signed informed consent before any registry-related activities are conducted. Assent from the participant should also be obtained as appropriate.

9.2.2 Exclusion Criteria

(1) Patient currently participating in an Increlex® clinical trial.

(2) Patient currently participating in any clinical trial for growth retardation.

(3) Patient with any contraindication to Increlex® or any condition subject to special warning as per the locally approved label.

- For US patients, these include patients with hypersensitivity to the active substance or any of the excipients, patients with active or suspected neoplasia and patients with closed epiphyses.
- For EU patients: these include patients with hypersensitivity to the active substance or any of the excipients, patients with active or suspected neoplasia or any condition or medical history which increases the risk of benign or malignant neoplasia and patients with closed epiphyses. Note: not applicable for patients enrolled in the EU-IGFD registry and entering or currently in the post-treatment period.

Note: for any patients enrolled in the registry under previous inclusion/exclusion criteria (i.e. before implementation of Protocol Amendment #6), who would be ineligible according to any of the above inclusion or exclusion criteria, e.g. receiving Increlex® for an indication not covered by the locally approved product information, a letter will be sent to the Investigator to alert him/her about the off-label use of the product (specifically for the risk of neoplasias). The patient could continue to be followed up in the registry for safety data in the post-treatment period.

9.2.3 Registry Population

9.2.3.1 Physician Profile

Eligible Investigators for the global registry will be:

- Physicians who are experienced in the diagnosis and management of children and adolescents with SPIGFD;
- Physicians located in a country where Increlex® is approved and marketed and where the study is implemented;
- Physicians who have prescribed/plan to prescribe Increlex® according to the locally approved product information.

9.2.3.2 Participant Population

Eligible participants will be children and adolescents from 2 to 18 years starting or planning to start or currently receiving treatment with Increlex® therapy for SPIGFD according to the locally approved product information in participating countries. In order to be enrolled, participants must comply with all the inclusion criteria (Section 9.2.1) and exclusion criteria (Section 9.2.2).

9.2.3.3 Patient Screening and Number of Participants

The current global Increlex® registry should be proposed to all eligible Increlex®-treated patients at the site.

During screening, Investigators must explain the purpose of the registry as well as the identified risk of neoplasia and the need to be followed up until at least 5 years after the end of treatment. Investigators must give the Participant Information Sheet (PIS) to the participant (and/or the participant's parents or legally authorised representative) which summarises all information related to the study given by Investigators:

- If participation in the registry is confirmed (the participant/parents or legally authorised representative agree to participation), the informed consent will be discussed and signed (before any related data collection) and the enrolment visit will be recorded.
- If the patient is not participating in the registry, registration date and reason for non-participation should be recorded in the eCRF in order to assess the proportion of non-included patients, only if the patient has no objection to this data collection.

A unique number will be attributed to each participant enrolled, to be used throughout the registry.

9.2.4 Registry Duration

9.2.4.1 Recruitment Period

This is an ongoing open-ended registry. Enrolment in the EU-IGFD registry started in December 2008.

For each new participating site/country, enrolment will start following local site initiation with all necessary regulatory and ethics local approvals.

9.2.4.2 Treatment Duration

For each participant, Increlex® treatment duration is at the discretion of the treating physician according to his/her clinical judgment and according to the locally approved product information.

9.2.4.3 Follow-up Duration

The registry will cover a post-treatment follow-up period of at least 5 years in addition to the treatment period for all enrolled participants regardless of treatment duration, for which the study Investigator is also responsible.

If the participant has not reached the FAH at the end of 5-year post-treatment period, the follow-up period will be extended up to the achievement of the FAH.

9.2.5 Registry Place

Countries within and outside Europe where Increlex® is registered and marketed.

9.2.5.1 Site Selection

In each participating country, sites who are experienced in the diagnosis and management of patients with SPIGFD will be contacted to perform a site feasibility assessment. Sites will be selected to participate in the study if they meet the study requirements. Site selection may be conducted by a Service Provider (SP) directed by the Sponsor. All procedures will be completed in accordance with the Sponsor and the contracted SP's Standard Operating Procedures (SOPs).

Considering that the objective of this registry is to enrol the maximum possible number of Increlex® treated patients in each participating country, the number of sites will not be limited to a maximum per country.

Investigators must be informed about the importance of the follow-up visits including at least visits at years 2 and 5 after the end of treatment, and it should be emphasised that they need to inform potential patients and/or parents/legally authorised representatives of the importance of attending these visits.

9.2.6 Registry Schedule

The schedule of observations and assessments during the registry are summarised in Table 1.

Table 1 Schedule of Assessments

	Enrolment Visit	Follow-up Visits (in Treatment Period)	Post-treatment Visits
Informed consent[a]	X		
Visit date	X	X	X
Eligibility criteria[a]	X		
Pregnancy test[b]	X		
Demographics	X		
Birth weight and length	X		
Gestational age	X		
Prior heights and sitting heights	X		
Prior weights	X		
Medical history	X		
Personal and family history of neoplasia	X		
Concomitant medications	X	X	X
Parental heights[c]	X		
Predicted adult height	X		
Diagnosis of SPIGFD and associated aetiologies	X		
Genetic tests	X		
All AEs, SAEs, AESI, targeted AEs and special situations		X	X[d]
Physical examination	X[e]	X	X
Height and sitting height	X	X	X
Weight	X	X	X
Pubertal (Tanner) stage	X	X	X
Previous treatments (e.g. GH)	X		
GH concentration[f] and stimulation test[g]	X		
IGF-1 generation test (if locally applicable)[g]	X		
IGF-1 concentration[f] [g]	X	X	X
IGFBP3[f] [g]	X	X	
GHBP[g]	X		
Bone age, echocardiogram and funduscopy	X	X	X[h]
QoL[i]	X	X	X
Dose of Increlex® with corresponding dates and compliance	X	X	
Therapy discontinuation		X	
Final Adult Height		X	X

AE = adverse event; AESI = adverse event of special interest; GH = growth hormone; GHBP = growth hormone-binding protein; IGF-1 = insulin-like growth factor-1; IGFBP3 = insulin-like growth factor-binding protein 3; QoL = quality of life; SAE = serious adverse event; SPIGFD = severe primary insulin-like growth factor-1 deficiency.

a For participants already enrolled in the registry, eligibility must be reconfirmed and a new written informed consent must be obtained for any substantial protocol amendments before implementing them. For any participants enrolled in the registry under previous inclusion/exclusion criteria (i.e. before implementation of Protocol Amendment #6), who would be ineligible according to any of the current inclusion or exclusion criteria, e.g. receiving Increlex® for an indication not covered by the locally approved product information, a letter will be sent to the Investigator to alert him/her about the off-label use of the product (specifically for the risk of neoplasias). The participant could continue to be followed up in the registry for safety data in the post-treatment period

b A negative pregnancy test must be obtained and documented for all female patients of childbearing potential prior to enrolment/treatment with Increlex®. It is also recommended that all female participants of childbearing potential use adequate contraception during treatment

c Biological relatives only

d List of targeted AEs during the post-treatment period is adjusted (see Section 11.1.5)

e Including dysmorphic features

f GH, IGF-1 and IGFBP3 levels will be performed by local laboratory (assay has to be documented)

g Prior to treatment with Increlex®

h In case of adult height not reached

i QoL assessments at baseline (start of treatment), at year one, at end of treatment and at Final Adult Height

9.2.7 Registry Visits

9.2.7.1 Enrolment Visit

Investigators at participating sites will identify patients who fulfil the inclusion and exclusion criteria. Written informed consent should be obtained prior to enrolment according to local regulations, and when inclusion and exclusion criteria have been checked.

All reported measures will be performed by the paediatric endocrinologist.

The following participant history and clinical data will be recorded.

- Demographics:
  - Sex
  - Date of birth (month and year)
  - Birth weight and length
  - Gestational age
  - Previous and current height, sitting height and weight measurements
- Parental heights (biological relatives only)
- Medical history including:
  - Anorexia nervosa, asthma, attention deficit disorder, carpal tunnel syndrome, cystic fibrosis, diabetes, oedema, enlarged tonsils or adenoids, headache, hearing loss, hypoglycaemia (documented or suspected - documented means blood level glucose < 50 mg/dL or 2.78 mmol/L), hypothyroidism, neoplasia, organomegaly, otitis media, retinopathy, scoliosis, seizures, sleep apnoea, slipped capital femoral epiphysis, snoring, tonsillectomy and/or adenoidectomy, cardiomegaly and any other significant medical history
- Personal and family history of neoplasia
- Chronic concomitant medications including:
  - Antibiotics, medication for attention deficit disorder, anti-depression medication, aromatase inhibitors, gonadotrophin releasing hormone agonists, thyroid

hormone, GH, androgens, oestrogens, glucocorticoids, bronchodilators, other psychiatric medications and other chronic medications

- Most recent IGF-1 concentrations including:
  - Unit of measure, level and IGF-1 SD score, date acquired, name of assay, normal ranges
- IGF-1 generation test (if locally applicable) including test date, dose of GH used, total number of doses, baseline IGF-1, stimulated IGF-1 and IGF-1 laboratory kit
- GH concentrations including:
  - Basal/random GH
  - Highest stimulated GH
- Serum insulin-like growth factor-binding protein 3 (IGFBP3; serum level in ng/ml and name of assay)
- GH-binding protein (GHBP; level in pmol/L and name of assay)
- Genetic tests performed (Yes/No) and date and results of any tests performed including:
  - GH gene deletion/mutation, IGF-1 gene deletion/mutation, fibroblast growth factor (FGF) deletion/mutation, gene encoding non-receptor type of protein tyrosine phosphatase SHP-2 (PTPN11) deletion/mutation, GHR gene deletion/mutation, deletion of exon 3 of the GHR (D3-GHR), signal transducer and activator of transcription 5b (STAT5b) deletion/mutation, acid-labile subunit (ALS) deletion/mutation, short stature homeobox-containing gene (SHOX) deletion/mutation, pappalysin 2 (PAPPA2) gene deletion/mutation, karyotype, any other genetic tests performed (e.g. whole exon sequencing)
- Bone age and method (e.g. Greulich and Pyle (GP) method) and date of X-ray, echocardiogram and funduscopy
- Most recent physical examination including:
  - Pubertal (Tanner) stage: pubic hair, testicular volume, breast development
  - Dysmorphic features
- Pregnancy test for female patients of childbearing potential. Any pregnant patients should be excluded from the registry.
- Predicted adult height (PAH)
- Date of growth failure (short stature) diagnosis
- Diagnosis of SPIGFD (according to the local approved definition of SPIGFD) and date of diagnosis with corresponding levels of IGF-1 and GH, and IGF-1 SDS and height SDS
- Associated aetiologies, all that apply should be ticked in the list below: GH gene deletion with anti-GH antibodies, small for gestational age, idiopathic short stature, Noonan syndrome, Prader-Willi syndrome, chondrodysplasia, bone dysplasia, insulin resistance syndrome (e.g. leprechaunism, Rabson-Mendehall syndrome), diabetes mellitus, Russell Silver, or other
- Previous therapy:
  - GH: duration (months), maximum dose (mg/kg/day), start of maximum dose date and height, end of maximum dose date and height
  - Steroids type (specify, e.g. GH, IGF-1, steroid hormones such as sex steroids (testosterone and oestradiol))

- IGF-1, name of preparation (rhIGF-1, rhIGF-1/IGF-1/IGFBP3, other), in a clinical trial (Yes/No) or compassionate use (Yes/No)

- Increlex® therapy
  - Starting Increlex® dose (mg/kg or mcg/kg)
  - Starting Increlex® dose date
  - Planned posology of Increlex® injections (per day) at start date
  - Dose escalation planned (Yes/No)
- QoL assessment using EQ-5D version EQ-5D-Y on participants aged 4 and over (see Section 9.3.2.5).

9.2.7.2 Follow-up Visits (in Treatment Period)

The following data will be recorded:

- Visit date
- Chronic concomitant medications including:
  - Antibiotics, medication for attention deficit disorder, anti-depression medication, aromatase inhibitors, gonadotrophin releasing hormone agonists, thyroid hormone, GH, androgens, oestrogens, glucocorticoids, bronchodilators, other psychiatric medications and other chronic medications
- IGF-1 concentrations (unit of measure, level, date acquired, name of assay) including both absolute value and SD or percentile of assay-specific reference, if references available
- Serum IGFBP3 (serum level in ng/ml and name of assay)
- Bone age and method (e.g. GP method) and date of X-ray, echocardiogram and funduscopy
- Physical examination including:
  - Current height, sitting height and weight measurements and FAH (if available)
  - Pubertal (Tanner) stage: pubic hair, testicular volume, breast development
- Increlex® therapy: all doses changes (including interruptions) with posology, dates and reasons for change will be collected. For drug compliance, number of missing doses will also be collected
- All AEs, including SAEs, AESI and targeted AEs (see Section 11.1.5), and special situations. Onset and recurrence of benign and malignant neoplasias will be considered as AESI and should also be reported as SAE
  - For hypoglycaemia (documented or suspected), time from last Increlex® dose to time of event, blood glucose level (if available) and event resolution without intervention other than feeding (Yes/No) should also be collected
- Discontinuation of therapy
  - Date of last dose
  - Reason for discontinuing therapy, the most appropriate response should be selected: attained adult height, AE, lost to follow-up, noncompliance, participant/parent/legally authorised representative decision, financial/insurance, changed physician, lack of effectiveness, shortage of Increlex®, physician decision, COVID-19 or other (if other the reason should be specified)

- QoL assessment using EQ-5D version EQ-5D-Y on participants aged 4 and over at year one, at end of treatment and at FAH (see Section 9.3.2.5).

9.2.7.3 Post-treatment Visits

The importance of the follow-up visits, including at least visits at years 2 and 5 after the end of treatment, should be noted. The following data will be recorded:

- Visit date
- Concomitant medications including:
  - Antibiotics, medication for attention deficit disorder, anti-depression medication, aromatase inhibitors, gonadotrophin releasing hormone agonists, thyroid hormone, GH, androgens, oestrogens, glucocorticoids, bronchodilators, medication for diabetes, medication for high blood pressure, medication for malignancy, medication for hyperlipidaemia, medication for immune system disorders, medication for coagulation disorders, other psychiatric medications and other chronic medications
- IGF-1 concentrations (unit of measure, level, date acquired, name of assay)
- Bone age and method (e.g. GP method) and date of X-ray (in case adult height not reached), echocardiogram and funduscopy
- Physical examination including:
  - Current height, sitting height and weight measurements and FAH (if available)
  - Pubertal (Tanner) stage: pubic hair, testicular volume, breast development
- All AEs, including SAEs, AESI and targeted AEs (see Section 11.1.5), and special situations. Onset and recurrence of benign and malignant neoplasias will be considered as AESI and should also be reported as SAE
  - For hypoglycaemia (documented or suspected), time from last Increlex® dose to time of event, blood glucose level (if available) and event resolution without intervention other than feeding (Yes/No) should also be collected
- QoL assessment using EQ-5D version EQ-5D-Y at FAH (see Section 9.3.2.5).

9.2.8 Registry Discontinuation/Withdrawal

The participant will be withdrawn from the registry:

- If informed consent is withdrawn (participant/parent or legally authorised representative decision; the participant must be informed that they may decide to withdraw from the registry at any time without any effect on their treatment and the normal follow-up of the disease);
- At the end of the post-treatment follow-up (5 years after stopping treatment or at adult height if later);
- If the participant is lost to follow-up;
- If the participant is included in a clinical trial for growth retardation.

If a participant is withdrawn from the registry, the date and primary reason for withdrawal should be recorded in the eCRF as well as if the participant stopped Increlex® therapy or not.

Investigators may decide to stop their participation in the registry at any time without consequences on the normal participant follow-up. If this occurs, every effort should be made to transfer care of the participant to a new physician to enable the participant to continue in the registry.

9.2.9 Treatment Discontinuation

If benign or malignant neoplasia develops, Increlex® treatment should be discontinued definitely and appropriate expert medical care sought. If a US patient develops benign neoplasm, Increlex® treatment can continue.

Increlex® treatment may be discontinued in the event of any SAEs, AEs or special situations deemed by the Investigator to warrant treatment discontinuation.

Discontinuation of treatment due to AEs should be distinguished from discontinuation/withdrawal from the registry due to participant/parent decision or end of post-treatment follow up. In all cases due to AEs, the Investigator must ensure that the participant receives appropriate medical follow up and this should be properly documented in the participant's medical records.

All participants discontinuing Increlex® treatment will be followed up in the registry in the post-treatment period (unless consent is withdrawn).

9.3 Endpoints and Variables

9.3.1 Endpoints

9.3.1.1 Primary Endpoints

- Incidence of SAEs (including AESI of neoplasia), targeted AEs, all AEs, deaths and withdrawals due to AEs during Increlex® treatment.

9.3.1.2 Secondary Endpoints

- Incidence of SAEs (including AESI of neoplasia), targeted AEs, all AEs, deaths, withdrawals due to AEs, special situations and concomitant medications within the 5-year post-treatment period, overall and in the subset of children and adolescents exposed to Increlex® for at least 3 cumulative years excluding interruptions;
- Incidence of special situations and concomitant medications during Increlex® treatment;
- Changes from baseline for the following effectiveness variables: height SDS, height velocity, body mass index (BMI) SDS, bone age development, pubertal (Tanner) stage;
- Estimation of differences between PAH and FAH;
- Modelisation to identify predictive factors of height SDS change, height velocity, FAH, pubertal (Tanner) stage, bone age development;
- Description of Increlex® therapy exposure (dose and duration) and compliance;
- Description of effectiveness parameters (height SDS, height velocity) according to average dose received and according to dose ranges (e.g. 4 dose ranges (≤50,]50-80],]80-110], > 110 µg/kg BID)). This analysis will support the description of the lowest effective dose;
- Biological assessments (IGF-1 levels, GH concentrations, serum IGFBP3);
- Genetic test results;
- Description and evolution of QoL in participants aged 4 and over using EQ-5D version EQ-5D-Y including changes from baseline at year one, at end of treatment and at FAH;
- Description of neoplasia (benign and malignant) and hypoglycaemia according to the timeframe of occurrence (e.g. within the first 3 years after start of treatment, between 3 and 5 years and over 5 years).

9.3.2 Variables

9.3.2.1 Demographic and Baseline Variables

The registry will collect the following data:

- Demographic data on children and adolescents receiving Increlex® treatment: sex, date of birth (month and year), birth weight and length, gestational age, previous and current height, sitting height and weight;
- Parental heights (biological relatives only);
- Baseline height, sitting height, weight, bone age and method, echocardiogram, funduscopy and pubertal (Tanner) stage;
- Pregnancy status;
- PAH;
- Diagnosis of SPIGFD (documented by height SDS; IGF-1 levels and IGF-1 SDS; GH levels), date of diagnosis and associated aetiologies, and date of growth failure (short stature) diagnosis, if different from SPIGFD diagnosis date;
- IGF-1 generation test results and IGF-1/IGFBP3 concentrations;
- GH concentrations including basal/random and highest stimulated;
- Serum IGFBP3;
- GHBP;
- Genetic test results and date of genetic testing;
- Current and previous illnesses including congenital conditions and neoplasia;
- Previous and concomitant medications;
- Personal and family history of neoplasia;
- Prior growth-promoting therapies: GH, IGF-1, steroid hormones such as sex steroids (testosterone and oestradiol);
- Baseline QoL assessment using EQ-5D version EQ-5D-Y.

9.3.2.2 Safety Variables (Primary Analyses; Treatment Period and Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data on the following safety variables will be collected from enrolment to the end of the post-treatment follow-up period:

- For all AEs, irrespective of causality, including SAEs, AESI and targeted AEs, start/end date, time to onset, nature, severity, seriousness, causality assessment, any treatment administered for the AE, action taken and outcome;
- Deaths, irrespective of causality, including date and cause of death;
- Special situations, irrespective of causality, including start/end date, category, description, whether the special situation led to an AE and outcome;
- Concomitant medications including concomitant treatment with GH, with start/end dates;
- Echocardiography and funduscopy results.

9.3.2.3 Effectiveness Variables (Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data on the following effectiveness variables will be collected at enrolment, during treatment and after the end of treatment:

- Height and sitting height;
- Weight;
- Pubertal (Tanner) stage: pubic hair, testicular volume, breast development;
- Bone age;
- IGF-1 concentrations;
- IGFBP3 (treatment period only);
- FAH.

9.3.2.4 Treatment Variables (Secondary Analyses; Treatment Period)

Data on the following treatment variables will be collected from start to end of treatment:

- Dose of Increlex® at the start of treatment (mg/kg or mcg/kg), mode of administration and date of first Increlex® intake;
- Any dose adjustments and dose interruptions (including adjusted dose and dates) throughout the study including reasons for adjustment;
- Dose of Increlex® at the end of treatment (mg/kg or mcg/kg) and date of last Increlex® intake;
- Reason for discontinuing therapy (most appropriate response): attained adult height, AE, lost to follow-up, noncompliance, participant/parent/legally authorised representative decision, financial/insurance, changed physician, lack of effectiveness, shortage of Increlex®, COVID-19 or other.

9.3.2.5 Quality of Life Variables (Secondary Analyses; Treatment and Post-treatment Follow-up Periods)

Data for the following QoL assessments will be collected at baseline (start of treatment), at year one, at end of treatment and at FAH:

- Changes in QoL assessment using EQ-5D version EQ-5D-Y.

The QoL of participants will be assessed using the EQ-5D-Y paediatric questionnaire, a child-friendly standardised measure of health status developed by the EuroQol Group, denoted ‘Youth’ as being adequate for both children and adolescents [24].

The EQ-5D-Y consists of two pages, a descriptive system and a visual analogue scale (VAS). The descriptive system comprises five dimensions, using child-friendly wording: mobility; looking after myself; doing usual activities; having pain or discomfort; feeling worried, sad or unhappy. Each dimension has three levels: no problems/no pain/not worried, some problems/some pain/a bit worried, a lot of problems/a lot of pain/very worried, from which the respondent chooses the most appropriate. The EQ VAS records the respondent’s self-rated health on a 0-100 vertical VAS from ‘The best health you can imagine’ to ‘The worst health you can imagine’.

Participants aged 8+ who are able to fill in the EQ-5D-Y themselves will self-complete the questionnaire and VAS. The EQ-5D-Y proxy version, designed for a proxy (parent or legally authorised representative) to rate how he/she rates the health of the child, is recommended for younger children and can be applied to children aged from 4-7 years and to children of 8+ who

are not able to fill in the EQ-5D-Y themselves. As the minimum age recommended for the proxy version is 4 years, participants between 2 and 4 years of age will not be included in the QoL assessments.

The version used for each participant should be clearly documented and a copy of the questionnaire retained in their medical records.

A country-specific local language version will be used for each country.

9.4 Data Sources

The data collected for a participant will be those that exist in their medical records as part of standard medical care. No additional procedures or activities are required in this registry except for QoL assessments and post-treatment safety follow-up in the context of fulfilling the Specific Obligation (SO2).

Definitions of source data and source documents are provided in Section 9.8.3.

9.5 Study Size

The objective is to screen all Increlex®-treated patients with SPIGFD at each site of the participating countries with the aim of enrolling as many patients as possible.

9.6 Data Management

Data management will be conducted by a SP directed by the Sponsor's Clinical Data Group Leader. All data management procedures will be completed in accordance with the SOPs of the Sponsor and the contracted SP.

9.6.1 Data Collection

The specific data to be collected at each visit are summarised in the Schedule of Assessments (Table 1).

Data will be collected in an eCRF via the internet utilising a secured website. The Sponsor and the SP will ensure that the eCRF developed is appropriate to capture the data required by the protocol. The Sponsor will ensure that the entrusted SP uses adequate technology to ensure data security transfer and backup.

Each site is required to have a computer and internet connection available for site entry of clinical data. Data entry in the eCRF will be performed by the Investigator or by the designated person from his/her team and in order to ensure confidentiality and security of the data, all entries into the eCRF will be made under the electronic signature (e-signature) of the person performing the action (username and password). Only Sponsor-authorised users will be given access to the eCRF as appropriate for their study responsibilities. All users must have successfully undergone software application training prior to entering data into the eCRF.

Once written informed consent has been obtained, the eCRF will provide a numeric participant identifier to pseudonymise the data from each participant. Data for each participant must be entered into the eCRF within 5 days of the participant's enrolment. The data in the eCRF will be transmitted to the Sponsor for analysis. Data transmitted will be pseudonymised and will be identified only by the participant number. Only investigating sites will be able to link the numeric identifier to each participant's identity.

In compliance with GPP, the participant's medical records should be clearly marked and permit easy identification of their participation in this study.

Medical history and AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by the contracted SP and reviewed by the Sponsor.

Queries will be edited in English and addressed to the investigational site using the eCRF.

Investigators or authorised registry staff members will answer the queries directly into the eCRF.

The eCRF will be signed electronically to certify that all the data recorded in it are consistent with the source documents and reflect the status of the participant during the corresponding part of the registry.

9.6.2 Data Archiving and Retention

During the initiation visits, the monitor must ensure that the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Registry documents should be retained for at least 15 years after registry completion. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of registry documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

9.7 Data Analysis

9.7.1 Analyses Population Definitions

At the site level:

Screened: site which has been contacted for participation in the registry and confirmed that they are currently following patients who may be eligible for the registry (this includes both participating and non-participating sites).

Participating: site which has agreed to participate in the registry and has completed a patient screening log (as minimum data requested for participation).

At the patient/participant level:

Screened Population: all patients included in the patient screening log (this includes both enrolled and non-enrolled patients, with the reason for non-enrolment).

Enrolled Population: all participants who are fully informed about the registry and who have given their written informed consent to participate (and/or their parents/legally authorised representatives) before implementation of any registry-related procedure.

Registry Population: all participants who have completed at least one follow-up visit and who have taken the treatment at least once.

Complete Population: all participants who have stopped treatment and who have been followed until FAH reached.

Safety Population: all participants who have taken the treatment at least once and with at least one follow-up visit or presence of any post-study treatment safety data.

Long-term Safety Population: all participants who have been exposed to Increlex® for at least 3 years and who ended therapy at least 2 years prior to the collection of long-term safety data.

The primary analysis based on the primary endpoint will be performed on the Safety Population.

9.7.2 Statistical and Analytical Methods

9.7.2.1 Statistical Analyses

The statistical analyses will be performed by an external SP managed by the Sponsor.

A Statistical Analysis Plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9 or higher).

As this is a non-interventional study, no formal statistical testing will be performed and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, 2-sided 95% confidence intervals (CIs) will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive statistics will include number of available data, number of missing data and the following:

- Mean, SD, 95% CIs for means when appropriate, median, quartile, minimum and maximum for continuous variables;
- Frequency count, percentages and 95% CIs when appropriate for categorical nominal variables;
- Both the above for categorical ordinal variables.

Missing data will not be replaced but they will be displayed in all relevant tables.

9.7.2.2 Participant Inclusion

Based on the screened population, the proportion of non-included patients will be assessed as well as the reasons for non-inclusion.

9.7.2.3 Demographic and Other Baseline Characteristics

Descriptive statistics of demographic and baseline data will be presented for the Registry Population.

Previous/concomitant medications will be summarised by drug categories.

Data on medical history, coded using MedDRA, and previous growth therapy will be summarised.

Information on SPIGFD diagnosis, personal or familial risk factors for neoplasia and genetic test results (deletion/mutation of GH gene, IGF-1 gene, FGF, PTPN11, GHR, D3-GHR, STAT5b, ALS, SHOX, PAPPA2 and any other genetic tests performed, e.g. whole exon sequencing) will be described.

9.7.2.4 Participant Disposition and Withdrawals

The numbers and percentages of participants included in the analysis populations will be tabulated overall and by country and site. The reasons for participant exclusions from each of the populations will also be tabulated.

In addition, the number of participants who ended the treatment, withdrew or completed the registry will the presented with the primary reasons for discontinuation.

9.7.2.5 Primary Analyses

The primary analyses and summary tables of safety data will be based on the Safety Population (data from the treatment period only).

An overall summary table of AEs during the treatment period (up to 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs, AEs leading to death and AEs leading to withdrawal will be presented with the number and proportion of participants and the number of events.

All treatment emergent AEs (TEAEs) will be coded according to MedDRA and will be classified by MedDRA primary system organ class (SOC) and preferred term (PT). The incidence of all TEAEs, SAEs, AESI, targeted AEs, AEs leading to death and AEs leading to withdrawal will be tabulated by primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

AE listings will be presented by participant, primary SOC and PT.

The relationship of frequently occurring AEs, e.g. hypoglycaemia, to prognostic variables such as age, pubertal status, and dose will be explored.

All primary safety data will also be included in the participant data listings.

9.7.2.6 Secondary Analyses

Safety Analyses

The secondary safety analyses will be based on the Safety Population. Adverse event data are from the post-treatment period only but data on special situations and concomitant medications are from the treatment and post-treatment periods.

An overall summary table of AEs occurring during the post-treatment period (over 30 days after the last dose) including SAEs, AESI, targeted AEs, all AEs and AEs leading to death will be presented with the number and proportion of participants and the number of events.

The incidence of all post-treatment AEs, SAEs, AESI, targeted AEs and AEs leading to death will be tabulated by MedDRA primary SOC and PT. In addition, summary tables by maximum intensity and drug relationship will be presented.

The same analyses will be performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

Post-treatment AE listings will be presented by participant, primary SOC and PT.

An overall summary table of special situations occurring during the treatment and post-treatment periods will be presented with the number and proportion of participants and the number of events. For the post-treatment period, the same analyses will be performed in a subset of children and adolescents exposed to Increlex® for at least 3 years.

Concomitant medications during the treatment and post-treatment periods will be tabulated.

Incidence of neoplasia (benign and malignant) and hypoglycaemia will be presented according to the timeframe of occurrence (e.g. within the first 3 years after start of treatment, between 3 and 5 years and over 5 years).

All secondary safety data will also be included in the participant data listings.

Effectiveness Analyses

Effectiveness analyses will be based on the Registry Population.

The raw values of the following effectiveness parameters will be described at different timepoints (every 6 months from the start of treatment) as well as the change from baseline: height SDS, height velocity, BMI SDS, bone age development, pubertal stage.

For participants who reached the FAH, the estimation of the difference between the PAH and the FAH will be presented.

Main effectiveness parameters (height SDS, height velocity) will be described according to average dose received over the course of the study and according to dose ranges (e.g. 4 dose ranges (≤50,]50-80],]80-110], > 110 µg/kg BID)). This analysis will support the description of the lowest effective dose.

Multivariate linear regression analyses will be used to identify predictive factors of height SDS change, height velocity, bone age development after 1 year of treatment or more. The same method will be used to assess the predictive factors of FAH.

The Cox regression model including covariates as sex, age or height SDS at start of Increlex® will be used to estimate the time from start of treatment to reach the puberty for a subset of prepubertal patients at start of Increlex®.

Biological assessments (IGF-1, IGFBP3), raw values and change from baseline, will be described at different timepoints.

Exposure to Increlex® Therapy

The treatment duration as well as the dose of Increlex® at each timepoint (initiation, 3 months, 6 months, 1 year, and every 6 months thereafter) will be described.

Duration of post-treatment follow-up will also be summarised.

Quality of Life Analysis

The QoL of participants aged 4 and over will be assessed using the EQ-5D-Y paediatric questionnaire (see Section 9.3.2.5 for details).

The 5 dimensions/domains (mobility; looking after myself; doing usual activities; having pain or discomfort; feeling worried, sad or unhappy) will be described at each timepoint as well as the evolution from baseline. The VAS will be described as a quantitative parameter at each timepoint as well as the change from baseline.

9.7.3 Subgroup Analyses

Descriptive statistics on SAEs including neoplasia, other AEs, and concomitant medications within the 5-year post-treatment period in the subset of children and adolescents exposed to Increlex® for at least 3 years will be provided.

Additional subgroup analyses, e.g. by previous treatment, Laron syndrome, pubertal status or sex, may be planned in the SAP according to clinical interest.

9.7.4 Interim Analyses

Safety data analyses will be performed every 6 months. There will be regular updates in the Periodic Safety Update Reports.

Interim effectiveness and safety descriptive analyses are planned to be performed at least once a year and an interim Clinical Study Report (CSR) will be prepared every two years.

The Sponsor will review safety data on an ongoing basis. In addition, an independent DMC composed of external experts will be asked to conduct periodic reviews of available safety data on at least an annual basis. All collected AEs will be summarised for inclusion as part of any interim safety analysis.

9.8 Quality Control

9.8.1 Routine Monitoring and Monitoring Procedures

The monitoring procedures of the study may be conducted by an external SP directed by the Sponsor. All monitoring activities will be completed in accordance with the Sponsor and the

SP's SOPs and as per the monitoring plan. The monitoring of the study should ensure that the rights and wellbeing of the participants are protected, that the registry data are accurate (complete and verifiable to source data) and that the registry is conducted in compliance with the protocol, GPP [25] and regulatory requirements.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiogram, funduscopy and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs. The Investigator must also keep the original informed consent form (ICF) signed by the participant or their parent/legally authorised representative and a signed copy is given to them.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry.

The Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, AESI, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

The frequency of the monitoring may be adapted according to participant recruitment rate or any other suitable reason. The Investigator will allow direct access to all relevant files (for all participants) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site Investigator or authorised registry staff members must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the registry monitor.

Whenever a participant's name is revealed on a document required by the Sponsor (e.g. laboratory print-outs) the name must be blacked out permanently by the site personnel, leaving only the initials visible, and annotated with the participant number as identification.

Before study initiation, at a site initiation visit or remote site initiation visit, a Sponsor/delegated SP representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, the Sponsor (or designee) employs several methods of ensuring protocol, GCP and GVP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralised Sponsor/delegated SP/Clinical Research Organisation. In addition to on-site monitoring visits, the sites will receive regular monitoring phone calls from monitors, in order to:

- Allow for early identification and direct solving of any issue with the site;
- Follow the enrolment of the participants listed in the patient screening log, and in particular, to remind the sites to propose the registry to all eligible patients presenting for a consultation, and to identify any issue related to recruitment (e.g. to identify a site with specific difficulties in collecting informed consents, etc.);
- Follow the included participants and avoid/limit the drop out of participants;

- Answer any questions related to the completion of the eCRF.

9.8.2 Inspections and Auditing Procedures

Authorised personnel from external Competent Authorities (CA) and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to registry documents and site facilities, and to any other locations used for the purpose of the registry in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

9.8.3 Source Data Verification

According to the study monitoring plan, during monitoring visits, the monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF. However, this verification will only address key data of the eCRF and only be based on available Investigator's participant notes.

The source documents must, as a minimum, contain the following; a statement that the participant is included in a registry, the date on which informed consent was obtained prior to participation in the registry, the identity of the registry, diagnosis and eligibility criteria, visit dates, and any AEs and associated concomitant medication.

Definitions for source data and source documents are given below:

- **Source data**: all original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the registry. Source data are contained in source documents (original records or certified copies).
- **Source documents**: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the registry).

The participant (if adult) or their parent/legally authorised representative (if participant is non-adult) must have consented to their medical records being viewed by Sponsor authorised personnel, and by local, and possibly foreign, CAs. This information is included in the ICF.

9.8.4 Data Quality

The Investigator is responsible for the validity of all data collected and must provide an e-signature, consisting of an individual and confidential username and password combination, to each eCRF to attest to the accuracy and completeness of all the data. This e-signature is declared to be the legally binding equivalent of the handwritten signature.

The eCRF is a validated system with restricted access to study staff only with a personal username and password. The eCRF data transferred from the investigational site to the assigned Data Management group will be reviewed for completeness, consistency and protocol compliance. Inadequate data can be queried for clarification and any queries generated during

the data management process will be tracked by the contracted data management SP according to the Data Handling Manual.

Data consistency and accuracy will be ensured by running real-time checks at the time of data entry in the eCRF. All corrections to the eCRF data are recorded in the system audit trail which automatically tracks the data changes, the user, the time and the reason. The audit trail function will also allow the changes and clarifications made to be viewed.

9.9 Limitations of the Research Methods

Following the EU approval of Increlex®, a commitment was made to conduct an EU Subject Registry for Long-term Safety and Efficacy Monitoring of Increlex® for subjects with Growth Failure (to build up a safety and effectiveness database related to the use of Increlex® in paediatric populations) including a commitment to evaluate long-term safety for 100 subjects enrolled in the registry who have been treated with Increlex® for, at least 3 years, with post-treatment safety visits at 2 and 5 years.

As a result of slow recruitment in this long-term safety follow up and considering the Specific Obligation to investigate long-term safety after the end of Increlex® treatment and the possible occurrence of malignancies as well as other risks, the MAH has decided to expand the EU-IGFD registry into a global registry by involving additional countries where the product is registered and marketed, and to collect long-term safety data post-treatment for all participants regardless of duration of therapy.

Since this is a non-interventional observational registry, the decision to start treatment with Increlex®, and which tests and assessments to perform, will have been taken prior to the participant's inclusion in the study and therefore a limitation of the registry is that some key data may be missing. The assessments performed and data provided from different study sites may vary depending on each local site's routine clinical practice.

In particular, it is likely that some pre-treatment measures required to assess treatment effectiveness outcomes (height, height velocity, height SDS, weight, pubertal stage) may be missing and therefore the effectiveness assessments may not be possible for all participants.

The determination of the lowest effective dose has been included as a secondary objective of this registry. The design of the registry being non randomized and without fixed dose, we have no certainty to be able to determine the lowest effective dose.

Despite these limitations, the registry is considered valuable by enhancing enrolment of children and adolescents with the rare disease SPIGFD and ensuring that Increlex® is used according to the locally approved product information. This expanded global registry should enable the Sponsor to measure the effectiveness of the additional risk minimisation measures put in place, particularly with regard to neoplasias, and should improve the generalisability of the registry to routine clinical practice in this disease area.

9.10 Contractual and Financial Details

The Investigator (and/or the hospital administrative representative, as appropriate) and the Sponsor and/or the SP will sign a contract prior to their involvement in the registry, outlining the respective overall responsibilities of the Sponsor and/or the SP and the Investigator in relation to the registry. The financial remuneration will cover the cost per included participant and the specified terms of payment will be described in the contract.

9.11 Regulatory and Ethics Approval

The SP will ensure that all legal and regulatory aspects are covered, including submitting the protocol to the national CAs in accordance with local regulatory requirements and obtaining any necessary approvals from the appropriate regulatory authorities prior to registry initiation.

Before initiating the registry, the Investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the registry protocol/amendment(s), ICF, any ICF updates, participant recruitment procedures (e.g. advertisements), any written information to be provided to participants such as the PIS and a statement from the IEC/IRB that they comply with local requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

Any changes to the protocol after IEC/IRB approval will require a formal protocol amendment. Changes that do not affect participant safety or data integrity are classified as administrative changes and generally do not require ethics approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethics approval of administrative changes will be obtained if required by local/site IEC/IRB.

Any protocol amendments will be submitted to CAs according to local regulatory requirements.

The MA of Increlex® in the EU has been granted under Exceptional Circumstances based on Specific Obligations that the MAH has to fulfil as agreed with the EMA. The long-term safety study is one of the Specific Obligations for which any substantial change in the approved protocol of the Registry must be assessed and approved by the EMA.

9.12 Compliance with Good Pharmacoepidemiology Practice and Ethical Considerations

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki, 1964, and all subsequent amendments) [26], ICH-GCP guidelines and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences (CIOMS) [27].

This study is non-interventional and falls outside the scope of European Commission (EC) EU Directive 2001/20/EC [28] and EU Directive 2005/28/EC [29].

This study complies with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data [30].

This study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (GEP) [31], the International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP [25], the EMA Guideline on GVP [32, 33] (unless safety data collection and reporting is dictated by relevant local legislation in which case that must be followed instead) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [34]. The completed ENCePP Checklist for Study Protocols is provided in Appendix 2.

This study will also be conducted in compliance with the ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies [35] Sponsor’s Code of Conduct and any other applicable local regulations.

9.13 Informed Consent

Prior to registry entry, the Investigator (or a person designated by the Investigator) will explain the nature, purpose, benefits and risks of participation in the registry to each participant, the participant's parents or the participant's legally authorised representative. Participants (if adult) or parents/legally authorised representatives (if non-adult) will be provided with a PIS containing information in readily understood language on the benefits and risks associated with participating in the registry and will be given sufficient time to discuss any concerns and to consider their decision to participate. The Investigator should inform patients and/or parents/legally authorised representatives about the importance of the follow-up visits including at least visits at years 2 and 5 after the end of treatment. Signed written informed consent must be obtained prior to the participant's entering the registry.

The Sponsor will provide a template of the ICF. In addition to the ICF to be signed by the parents or the legally authorised representative, there will be two specific ICF versions for the child (in case the child is old enough to use it): under or over 12 years old.

The ICF and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The final versions of the forms must be approved by the Sponsor and the IEC/IRB and must contain all the elements included in the template form, in language readily understood by the participant. Each participant's original ICF, personally signed and dated by the participant, the participant's parents or by the participant's legally authorised representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled participants with a copy of their signed ICF.

The ICF may need to be revised during the course of the registry if new information becomes available that may be relevant to the safety of the participant or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all participants subsequently entered into the registry, as well as those currently in the registry, sign the amended form. This is documented as previously described. Parents of participants (or participants' legally authorised representatives) and participants having completed the registry should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the participant, the participant's parents or the participant's legally authorised representative, inform the participant's primary General Practitioner about their participation in the registry.

For participants already enrolled in the registry, eligibility must be reconfirmed and a new written informed consent must be obtained as per local regulations for any substantial protocol amendments before implementing them. For any participants enrolled in the registry under previous inclusion/exclusion criteria (i.e. before implementation of Protocol Amendment #6), who would be ineligible according to any of the current inclusion or exclusion criteria, e.g. receiving Increlex® for an indication not covered by the locally approved product information, a letter will be sent to the Investigator to alert him/her about the off-label use of the product (specifically for the risk of neoplasias). The participant could continue to be followed up in the registry for safety data in the post-treatment period.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Data Collection, Privacy and Confidentiality

After recruitment, each site will be assigned a unique identification number. At enrolment, each participant will be assigned a unique identification number by the Sponsor to enable site and paediatric endocrinologist specific reports to be generated and shared with participating paediatric endocrinologists.

The participant identifier will include the participant and site identification numbers. These numbers will be provided automatically by the eCRF. The data will be entered into this system via the internet in a secured website.

Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal registry-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by the Sponsor's auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Clinical staff from each participating site will be trained in appropriate data entry techniques by Sponsor representatives, or this may be delegated to the SP in charge of monitoring. Specific user's manuals of the registry eCRF will be downloaded on the website of the registry.

Each user will have a personal and confidential login and password to connect to the eCRF. All data will be treated as confidential and the collection, transmission, and storage will be in compliance with the United States Code of Federal Regulations (21 CFR, Part 11).

In case of public data presentation or publication, personal identifiers of participants will not be used.

10.2 Data Protection

As the data controller (study Sponsor) is located in Spain, this study will be conducted in compliance with EU data protection requirements and in particular the EU General Data Protection Regulation 2016/679 [30].

10.3 Insurance

Insurance may be contracted according to local regulatory requirements.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS

11.1 Definition

11.1.1 Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient/participant, administered a medicinal product [Increlex® in this registry] and which does not necessarily have a causal relationship with this treatment. NOTE: An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events Meeting the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Any instances of overdoses irrespective of whether they are associated with AEs or not must be provided to the MAH with the overdose, duration of overdose and outcome. In addition, all cases of off-label use should also be reported as AEs. The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of effectiveness” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.1.2 Special Situations

A special situation is any incidence of drug exposure during pregnancy or breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic effectiveness whilst using the medicinal product. A "special situation" should be collected by the Investigator and reported to the Sponsor whether or not these "special situations" are associated with an AE.

11.1.2.1 Pregnancy and Breastfeeding

Women of childbearing potential/Contraception in males and females

A negative pregnancy test is recommended for all women of childbearing potential prior to treatment with mecasermin. It is also recommended that all women of childbearing potential use adequate contraception during treatment.

Pregnancy

There are no or limited amount of data for the use of mecasermin in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3 of Increlex® SmPC [22]). The potential risk for humans is unknown.

This medicinal product should not be used during pregnancy unless clearly necessary.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the medicinal product has interfered with a contraceptive method. If pregnancy occurs whilst using the medicinal product, the outcome of the pregnancy will then need to be collected. This applies irrespective of whether the pregnancy is considered to be related to interference by the medicinal product with a contraceptive method or not.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the ICF and until the end of registry participation and/or one month after delivery.

The Investigator is to report to the Sponsor if they become aware of a pregnancy occurring in the partner of a registry participant. If the female partner gives her consent, the pregnancy outcome should be followed up and reported.

Information regarding any pregnancies must be collected on the AE eCRF **and** the Sponsor Adverse Drug Reaction Form [redacted]

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs. If there is an abnormal pregnancy outcome or an AE is reported in the foetus/neonate/child following exposure to a marketed Sponsor's product, attempt to follow-up until the end of registry participation and/or one month after delivery.

The Investigator must instruct all female participants to inform them immediately should they become pregnant whilst using the study medication.

Reports of pregnancy must be reported to the Sponsor within 24 hours of the Investigator's knowledge.

Breastfeeding

Breastfeeding while taking Increlex® is not recommended, because there is insufficient information on the excretion of mecasermin in human milk.

Any use of an Sponsor product during lactation/ breastfeeding must be collected on the AE eCRF and the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.2 Overdose

Acute overdose could lead to hypoglycaemia. Treatment of acute overdose of mecasermin should be directed at alleviating any hypoglycaemic effects. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous glucose or parenteral glucagon may be required to reverse the hypoglycaemic effects.

Long-term overdose may result in signs and symptoms of acromegaly or gigantism. Overdosing may lead to supraphysiological IGF-1 levels and may increase the risk of benign and malignant neoplasm.

In case of an acute or a chronic overdose, Increlex® must be discontinued immediately. If Increlex® is restarted, the dose should not exceed the recommended daily dosage.

An overdose is defined as any dose higher than the maximum recommended dose in the local label/SmPC, or in the protocol. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labelling text will be assessed as 'overdose'. Overdoses are not considered as AEs however should be reported in the AE eCRF page whether or not they were associated with a clinical event. All overdoses should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.3 Off-label Use

Off-label use relates to situations where the medicinal product is used for a medical purpose not in accordance with the terms of the Marketing Authorisation. Off-label use should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All off-label use should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.4 Medication Error

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported as AEs in the AE eCRF whether or not they were associated with a clinical event. All medication error should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.5 Occupational Exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported as AEs in the AE eCRF. All occupational exposure should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.6 Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All abuse should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.2.7 Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the Marketing Authorisation.

Misuse should be reported as AEs in the AE eCRF page whether or not they were associated with a clinical event. All misuse should be reported to the Sponsor within 7 calendar days using the Sponsor Adverse Drug Reaction Form [redacted]

11.1.3 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other Important Medical Event

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse. **A suspected or confirmed coronavirus COVID-19** (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).
Is a suspected transmission of any infectious agent via an authorised medicinal product

Regardless of the above criteria, any additional AEs that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor. Any onset or recurrence of neoplasia must also be reported as an SAE.

11.1.4 Deaths

All AEs resulting in death must be reported as an SAE within 24 hours of the Investigator's knowledge of the event. All fatal outcomes should be considered as AEs, even if this fatal outcome is not considered to be related to the medicinal product. The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction); *death is not an event term*.
- Outcome: fatal.

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be 'Death' or 'Sudden death'.

11.1.5 Targeted Adverse Events

The targeted AEs for this registry are:

(1) **During the treatment period:** hypersensitivity; scoliosis; immunogenicity (presence of antibodies if available); slipped capital femoral epiphysis, headache, otitis media, papilloedema, hypoglycaemia (suspected or documented – documented means blood level glucose < 50 mg/dL or 2.78 mmol/L), acromegalic facial changes, gynaecomastia, hearing loss, intracranial hypertension, lipohypertrophy at injection sites, sleep apnoea, tonsillar hypertrophy, cardiomegaly, oedema and myalgia.

(2) **During the post-treatment period:** All targeted AEs mentioned in the treatment period except lipohypertrophy at injection sites.

11.1.6 Adverse Event of Special Interest

All neoplasias (benign and malignant) are categorised as AESI and should be collected and reported following the same process as the one for SAE reporting, i.e. within 24 hours of awareness by the investigator.

11.2 Collection and Reporting of AEs, SAEs and Special Situations

11.2.1 Collection of the AEs/SAEs/Special Situations in the eCRF

The collection and reporting of AEs will follow regulations related to non-interventional studies.

All AEs, whether they are serious/nonserious, related/unrelated, and all special situations should be collected in the eCRF during the course of the study. Adverse events will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

All AEs will be collected in the eCRF from the signing of the ICF until the end of the long-term post-treatment follow-up.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/related AE reports are provided below.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

11.2.2 Reporting of SAEs, Nonserious Adverse Drug Reactions and Special Situations to Sponsor Pharmacovigilance

Investigators must report to the Sponsor's Pharmacovigilance contact all the following events using the Adverse Drug Reaction Form [redacted]

- All SAEs/AESI/targeted AEs – related and non-related;
- All related nonserious AEs (Adverse Drug Reactions (ADRs));
- Any special situations (see definitions in Section 11.1.2).

Primary Data Collection Noninterventional Studies (NIS)		
Safety Event	**Collected on the eCRF**	**Reported on the « AE NIS Form » to Sponsor's Pharmacovigilance contact**
Nonserious AE	All AEs related or not	Only the related AEs - within 7 calendar days of awareness

SAE/AESI/targeted AE	All SAEs/AESI/targeted AEs related or not	All - within 24 hours of awareness
Pregnancy	All pregnancies	All - within 24 hours of awareness
Special situations	All special situations related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) - within 7 calendar days of awareness

All SAEs, AESI, targeted AEs and pregnancies will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The Investigator will submit any updated SAE/AESI/targeted AE and pregnancy data to the Sponsor within 24 hours of it being available [32].

All nonserious related AEs and special situations other than pregnancy will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

AE (related), SAE, AESI, Targeted AE and Special Situation Reporting to Sponsor's Pharmacovigilance contact via specific NIS AE Form
To report initial or any follow-up information to the Sponsor, a completed ***Adverse Drug Reaction Form*** [redacted] should be filled on the eCRF within 24 hours of awareness of the event for a SAE/AESI/targeted AE and pregnancy and within 7 calendar days for a nonserious related AE and special situation other than pregnancy and stored on a platform. The Sponsor's Pharmacovigilance contact receive by email the link to access to the platform to download the form. If it is not possible to fulfil the form on the eCRF, it should be sent by fax. In rare circumstances where neither email nor fax notification is possible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Note: All AE and special situation data must also be entered into the eCRF.

All AEs will be processed by the Sponsor according to their relevant SOPs. This includes the follow up of AE reports with the Investigator, as required.

If an AE occurs with a "non-Sponsor product", the Investigator should consider informing the CA in the Member State where the event occurred or to the MAH of the suspected medicinal product, but not to both (to avoid duplicate reporting).

11.2.3 Mandatory Information for Reporting an Adverse Event

The following information is the minimum that must be provided to the Sponsor's Pharmacovigilance contact within 24 hours for a SAE and within 7 days for a nonserious related AE of awareness for each AE:

- Participant identifier;
- Product name;
- AE description including assessment of causal relationship and seriousness;
- Investigator name and contact details.

The additional information included in the AE report form must be provided to the Sponsor as soon as it is available.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. The Investigator should also provide the batch number and expiry date of the concerned product wherever possible.

11.2.4 Follow-up of AEs including SAEs, AESI and Targeted AEs

After the initial AE/SAE/AESI/targeted AE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs including SAEs, AESI and targeted AEs (as defined in Section 11.1) will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up. Specific Adverse Reaction Follow-up Questionnaires for Hypersensitivity and Neoplasia are in place and should be used to follow-up these two events Further information on follow-up procedures is provided below.

Follow-up of AEs including SAEs, AESI and Targeted AEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the registry or during a recognised follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE/AESI/targeted AE data to the Sponsor within 24 hours of receipt of the information.

11.3 Safety Classifications

11.3.1 Relationship of Events to the Medicinal Product

The Investigator is obligated to assess the relationship between the approved medicinal product and each occurrence of each AE/SAE.

The relationship of an AE to the registry treatment will be classified as follows:

Related: reports including good reasons and sufficient information (e.g. plausible time sequence) to assume a causal relationship with the treatment studied in the sense that it is plausible, conceivable or likely.

Not related: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the treatment studied.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the approved medicinal product administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

11.3.2 Intensity of Events

The Investigator will make an assessment of intensity for each AE/SAE reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

11.3.3 Expectedness of Events

The expectedness of an AE shall be determined by the Sponsor according to the SmPC or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the MA. If the product has MAs in several countries with different SmPCs or PIs, one will be selected by the study team as the reference document for assessing expectedness and agreed by the Sponsor's pharmacovigilance representative.

The reference document for assessing expectedness of AEs/events in this study will be the current approved EU SmPC for Increlex®.

11.4 Regulatory Reporting Requirements for SAEs, AESI, Targeted AEs and Related AEs

- Prompt notification by the Investigator to the Sponsor of a SAE/AESI/targeted AE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will

review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

11.5 Safety Review

The Sponsor will review safety data on an ongoing basis. In addition, an independent DMC composed of external experts will be asked to conduct periodic reviews of available safety data on at least an annual basis or earlier if required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Registry Reports

Interim CSRs will be prepared every two years including safety and effectiveness results. These reports will be in compliance with any applicable regulatory requirements and national laws in force and will be in English.

12.2 Publication Policy

12.2.1 Ethical Obligation to Publish

The Sponsor is committed to disclosing information about the studies it sponsors. Results may be communicated at scientific meetings and all reasonable efforts must be made to seek publication of key data in a peer-reviewed scientific journal.

As a minimum, summary results of the final data should be posted in an associated publicly available database.

12.2.2 Publications Steering Committee

As data for this registry will be collected by multiple centres, a Publications Steering Committee (PSC) should discuss and agree the publication plan and appropriate authors to be invited for planned publications in advance. Where possible, all contributing investigators should be acknowledged, together with any others who may have contributed, but not sufficiently to qualify for authorship.

A dedicated PSC, involving interested members of the registry's Investigators as well as other personnel from the Sponsor (e.g. Medical Director, Biometry lead), will be established to plan publications and review data sharing requests.

12.2.3 Company-sponsored Publications

Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the Sponsor, reviewed by the Publications Strategy Group, and incorporated in the relevant publication plan before initiation.

All company-sponsored publications arising from this registry will be reviewed by relevant functions at the Sponsor. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of the registry findings will be conducted along principles of honest scientific debate and mediated by the lead author. Review comments must be answered before a final version for submission can be approved by the authors. All company-sponsored manuscripts should be published as immediate open access.

12.2.4 Non-company-sponsored Publications

For registry publications not sponsored by the Sponsor, the sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or manuscript before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements (different time periods are allowed according to the types of publication), including registry agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments should be carefully considered

by the author(s), provided they do not alter the scientific value of the material. Where possible, non-company-sponsored manuscripts should be published as immediate open access.

12.2.5 Authorship

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html]. Those named as authors, whether employed by the Sponsor or a Sponsor's affiliate, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'. Time spent on authorship activities should not be reimbursed.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Every author must agree to their inclusion in the list of authors. Professional medical writing support may be used.

12.2.6 Intellectual Property

If patentability would be adversely affected by data publication, publication will be delayed until (i) a patent application has been filed for the content of the publication in accordance with applicable provisions of the registry agreement concerned, (ii) the Sponsor consents to the publication, or (iii) after such a time as may be agreed in the contractual arrangements, including registry agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of these provisos (i), (ii) or (iii) is satisfied first.

The author(s) undertake(s) to reasonably consider the Sponsor's request for delay to the proposed publication should the sponsor reasonably deem it premature to publish the results obtained at the stage of the registry concerned.

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LIST OF APPENDICES

Appendix 1 LIST OF STANDALONE DOCUMENTS

Number	Date	Title
1	07 October 2008	EU-IGFD Registry 2-79-52800-002 Protocol Amendment #1 Summary & Outcome of Changes and WAS IS form (available on request)
2	11 February 2009	EU-IGFD Registry 2-79-52800-002 Protocol Amendment #2 Summary & Outcome of Changes and WAS IS form (available on request)
3	18 December 2015	EU-IGFD Registry 2-79-52800-002 Protocol Amendment #3 Summary & Outcome of Changes and WAS IS form (available on request)
4	04 August 2016	EU-IGFD Registry 2-79-52800-002 Protocol Amendment #4 Summary & Outcome of Changes and WAS IS form (available on request)
5	08 January 2018	EU-IGFD Registry 2-79-52800-002 Protocol Amendment #5 Summary & Outcome of Changes and WAS IS form (available on request)
6	10 July 2020	Global Patient Registry 2-79-52800-002 Protocol Amendment #6 Summary of Changes Table (available on request)
7	10 July 2020	Details of all main responsible parties and full list of Investigators at all participating registry sites (available on request)
8	08 February 2021	Global Patient Registry 2-79-52800-002 Protocol Amendment #7 Summary of Changes Table (available on request)

Number	Date	Title
9	19 April 2021	Global Patient Registry 2-79-52800-002 Protocol Amendment #8 Summary of Changes Table (available on request)
10	18 September 2025	Global Patient Registry 2-79-52800-002 Protocol Amendment #9 Summary of Changes Table (available on request)

Appendix 2 EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE (ENCEPP) CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

Study reference number

2-79-52800-002

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 Study progress report(s)	☒	☐	☐	12.1
1.1.4 Interim progress report(s)	☒	☐	☐	9.7.4, 12.1
1.1.5 Registration in the ENCePP register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6, 12.1
Comments: Interim reports are planned every two years.				

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	7.2 and 8.1
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
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?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	N/A
Comments: This is a descriptive study with no a priori hypothesis.				

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	N/A
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	N/A
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: This is a descriptive study therefore no formal statistical testing will be performed and the analyses will be primarily descriptive.				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.3
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.4
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☐	☒	☐	9.2.5
4.2.4 Disease/indication?	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4
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
Comments: The study will be conducted in countries within and outside Europe where Increlex® is registered and marketed.				

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)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	N/A
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A
Comments: This study will report the use of Increlex® in a real world setting with descriptive results only.				

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, 9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3, 9.7
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	N/A
Comments: N/A				

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	N/A
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	N/A
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	N/A
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	N/A
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	N/A
Comments: Confounding and covariates do not apply to this study.				

Section 8: Effect 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)	☐	☐	☒	N/A
Comments: Effect modifiers are not applicable to this study.				

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, etc.)	☒	☐	☐	9.4, 9.8.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, subject interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4, 9.8.3
9.1.3 Covariates?	☐	☐	☒	N/A
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, 9.8.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.8.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle, etc.)	☐	☐	☒	N/A
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates?	☐	☐	☒	N/A
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6
Comments: Covariates do not apply to this study.				

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☐	☒	N/A
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	N/A
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5
Comments: This study will report descriptive results only.				

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, 10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.7.4, 11.5
Comments: An independent Data Monitoring Committee composed of external experts (paediatric endocrinologists) will be asked to conduct periodic reviews of available safety data on at least an annual basis.				

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)	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, subject recruitment)	☒	☐	☐	9.5
Comments: Confounding does not apply to this study.				

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.11, 11.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.2
Comments:				

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5
Comments:				

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:				

Name of the main author of the protocol:

Date: / /

Signature: _____