2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
IPSEN</td><td rowspan="3">Individual Study Table
Referring to Part
of the Dossier

Volume:
Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of Finished Product:
Increlex®</td></tr>
<tr><td>Name of Active Ingredient(s):
Mecasermin</td></tr>
<tr><td colspan="3">Title of study: European Increlex® (mecasermin [rDNA origin] injection) Growth Forum Database: a European subject Registry for monitoring long-term safety and efficacy of Increlex® - EU-IGFD.
Study number: 2-79-52800-002</td></tr>
<tr><td colspan="3">Investigators: There was no coordinating Investigator for this Registry study. A steering committee was however regularly consulted.</td></tr>
<tr><td colspan="3">Study centres: 128 participating sites (112 active sites enrolled at least one subject) in 10 European countries: Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden and United Kingdom (UK).</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable.</td></tr>
<tr><td colspan="2">Studied period (years):
Date of first enrolment: 09 December 2008
Date of last completed: cut-off date for this interim report: 10 May 2017</td><td>Phase of development: 4</td></tr>
<tr><td colspan="3">Objectives:
The <u>primary objective</u> is to collect long-term safety information on the use of recombinant DNA-derived human Insulin Growth Factor-I (rhIGF-I) Increlex® replacement therapy for the treatment of children with growth failure.
The <u>secondary objectives</u> are:
• To obtain long-term effectiveness data for Increlex® replacement therapy in children with growth failure by the evaluation of changes from baseline for the following effectiveness variables: height, height velocity (HV), timing and progression of puberty, bone age development, dosing compliance, Insulin-like Growth Factor-I (IGF-I) levels;
• To model HV, predicted adult height (PAH), final adult height (FAH), timing and progression of puberty, bone age development;
• To evaluate Increlex® treatment exposure and compliance;
• To collect safety information two years and five years after the end of Increlex® therapy in subjects having being exposed for at least three years irrespective of final height.</td></tr>
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Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin		

Methodology:

The European Registry (EU-IGFD) is a descriptive, multicentre, observational, prospective, open-ended, noninterventional, post-authorisation surveillance study of Increlex® implemented since the end of 2008 in 10 European countries. Subjects with growth failures, for which Increlex® was indicated, and who were initiating or already receiving therapy with Increlex®, were enrolled into the study and followed throughout their course of treatment. Data were collected, as available, until adult height was achieved and were then retrospectively collected into the electronic case report form (eCRF). As this is a noninterventional study, the decision to prescribe Increlex®, was to be taken prior to, and independently from, the decision to enrol the subject. Prescribing of Increlex® was to be made in accordance with routine clinical practice and applicable labelling recommendations in the centres and countries concerned. In line with the European Union summary of product characteristics (SmPC), the Investigators were free to choose the dose and administration schedule, which were to be individualised for each subject.

Study visits included the enrolment visit, the baseline visit and the follow-up visits. All of the procedures performed at these visits were in accordance with routine clinical practice.

During the first visit (enrolment), the Investigator had to check the inclusion and exclusion criteria and to obtain the Informed Consent Form signed by both parents or the liable parent or the legal guardian of the subject (and the subject him/herself according to his/her capacity of understanding), before any further data collection.

After the enrolment visit was performed, Increlex® was started or continued if the subject was already treated by Increlex®.

The study follow-up visits were thereafter conducted as per routine medical practice and included the treatment administration.

After the end of treatment, study post-treatment visits were conducted and included collection of concomitant medications, related adverse events (AEs), serious AEs (SAEs), physical examination and current illnesses considered by the Investigator to be related to Increlex®.

For each subject, the treatment duration was at the discretion of the Investigator according to his/her judgment on the basis of clinical needs of the subject. Subjects could be followed throughout their course of treatment and data could be collected until FAH was achieved (even during the post-treatment period). Moreover, subjects from the Registry who were exposed to Increlex® for a minimum of three years were asked to perform a post-treatment safety visit at two years and at five years irrespective of final height (long-term safety follow-up).

Number of subjects (planned and analysed):

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin		

The EU-IGFD study aims at recruiting as many subjects as possible at the participating sites, to obtain a sample that is representative of the treated population. As the cut-off date for this report, 246 subjects were enrolled, 242 subjects had at least one follow-up visit and were included in the Registry Population and 242 subjects were included in the Safety Population. The population of eligible subjects for long-term (LT) safety follow-up included 83 subjects. Thirteen (13) subjects were included in the LT Safety Population.

Diagnosis and criteria for inclusion:

Subjects were eligible for participation in the study if they met the following criteria:

- All subjects beginning therapy with Increlex® for growth retardation or those previously treated with Increlex® prescribed by a participating qualified practitioner;
- Parents or legally authorised representatives if applicable had to give signed informed consent before any Registry-related activities were conducted. Assent from the subject should also be obtained as appropriate.

Test product, dose and mode of administration:

The decision to prescribe Increlex® 10 mg/mL was made as per local clinical practice and SmPC recommendations, prior to and independently from the decision to enrol the subject in this noninterventional study.

The drug was administered by subcutaneous injection and the injection site changed with each injection; the recommended dose and administration schedule were individualised for each subject.

The recommended starting dose is 0.04 mg per kilogram body weight twice a day. The dose should be tailored individually for each subject according to the effectiveness and tolerance. The maximum dose is 0.12 mg per kilogram twice a day.

Duration of treatment:

Treatment duration was to be individualised for each subject.

Criteria for evaluation:

<u>Effectiveness</u>:

- Height (cm and Standard Deviation Score (SDS)),
- Height velocity (cm/year),
- Weight (kg and SDS),
- Body mass index (BMI - kg/m² and SDS),
- Bone age (years),
- Tanner stage (pubic hair, genital development, testicular volume, breast

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin	Volume: Page:	

development),

- Predicted adult height (cm),
- Final adult height (cm).

Safety:

- All SAEs related or not;
- All targeted AEs defined by hypoglycaemia (suspected or documented by blood level glucose < 50 mg/dL or < 2.78 mmol/L), lipohypertrophy at injection sites, tonsillar hypertrophy, otitis media, hearing loss, sleep apnoea, intracranial hypertension, papilloedema, headache, acromegalic facial changes, oedema, myalgia, gynaecomastia, cardiomegaly and other injection site reactions (injection site reactions except lipohypertrophy);
- Nonserious AEs considered by the reporting paediatric endocrinologist to be related to Increlex®;
- Clinically significant laboratory abnormalities (related and nonrelated), as assessed by the Investigator.

Statistical methods:

The Safety Population included all subjects who received at least one Increlex® injection and with at least one follow-up visit or post-study safety data. The Safety Population was the primary population for safety analysis.

The population of eligible subjects for LT safety follow-up included subjects exposed to Increlex® for at least three years and who ended therapy.

A LT Safety Population included subjects exposed to Increlex® for at least three years, who ended therapy and with at least one visit performed over two years (± six months) after the end of treatment.

The Registry Population (effectiveness population) included all subjects who completed at least one follow-up visit and who received at least one Increlex® injection. The effectiveness parameters were also described on the subgroup of treatment-naïve prepubertal subjects, pubertal/previously treated subjects, subjects with Laron Syndrome (LS) and treatment-naïve prebubertal subjects with LS.

Primary analyses:

- Description and incidence of any SAEs including new onset and recurrence of neoplasia;
- Description and incidence of all the neoplasms reported;
- Description and incidence of all targeted AEs;
- Description and incidence of any additional drug-related AE or clinically significant

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin	Volume: Page:	

laboratory abnormalities;

- Description and incidence of AEs leading to withdrawal;
- Descriptive analyses at each timepoint and changes from baseline for biological assessments: IGF-I levels and SDS and serum Insulin-like Growth Factor Binding Protein-3 (IGFBP-3).

Secondary analyses:

- Description at each timepoint and changes from baseline for the following effectiveness variables: height (cm and SDS), HV (cm/year), weight (kg and SDS), BMI (kg/m² and SDS), bone age (years), Tanner stage;
- Description of differences between PAH and FAH;
- Multiple regression analyses on the basis of follow-up visit data only. These analyses were performed when a relevant number (50) of treatment-naïve prepubertal subjects were treated for at least one year. The objective was to identify predictive factors of change from baseline in height (SDS) at Year 1, Year 2, Year 3, HV (cm/year) at Year 1, Year 2, Year 3, FAH, timing of pubertal stage, change from baseline in bone age. The covariates entered in the model are listed hereafter: gender, parental heights, LS, height SDS at baseline, weight SDS at baseline, IGF-I at baseline (ng/mL), mean dose of Increlex® during the first year (or first two years,…), age at Increlex® intake and whether the subject was concomitantly treated with Growth Hormone (GH).
- Drug exposure and compliance.

Summary - conclusions:

Population:

At the cut-off date of 10 May 2017, 246 subjects have been enrolled in 112 active sites, in 10 European countries, mostly in Germany, France, Spain, UK and Italy. A total of 242 subjects enrolled and treated with Increlex® and with at least one follow-up visit were included in the Registry and in the Safety Population. Sixty-three (63) subjects completed the Registry: they stopped treatment and were followed-up until “near adult height” or “attained adult height”.

On the Enrolled Population, most subjects (86%) had a primary diagnosis of severe primary IGF-I Deficiency. The subjects enrolled included a majority of boys (63%) and most subjects (82%) were at pubertal stage 1 (i.e. prepubertal; no sexual development). Mean age when starting Increlex® was 10.2±4.0 years for boys and 8.9±3.9 years for girls. Mean height at first Increlex® intake was 117.8±20.2 cm for boys and 110.3±21.0 cm for girls, mean height SDS was -3.6±1.3 for boys and -4.0±1.4 for girls and mean HV was 4.6±1.7 cm/year for boys and 5.0±1.9 cm/year for girls.

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin		

Most subjects of the Enrolled Population were treatment-naïve at time of first Increlex® intake: approximately 34% had previously received a growth-related therapy, mostly growth hormone therapy (81% of the previously treated subjects).

Among subjects who ended therapy, 83 subjects were exposed to Increlex® for at least three years and were then eligible for the LT safety follow-up. Thirteen (13) subjects were included in the LT Safety Population. A visit at Year 2 was reported in 11 subjects, a visit between Year 2 and Year 5 in six subjects and a visit at Year 5 in two subjects. Only one subject completed the Year 2 and Year 5 visits. Baseline characteristics in both populations were similar.

Treatment exposure:

The median dose of Increlex® received at start of treatment was 40 µg/kg twice a day (BID), ranging from 10 to 270 µg/kg BID. The median dose increased progressively up to 120 µg/kg BID between Month 18 and Month 114.

One hundred and thirty-nine subjects (139) permanently discontinued therapy, 40% of them in the first two years of treatment. The main reasons for discontinuation remained adult height attained (37 subjects), lack of effectiveness (25 subjects) and subject/parent's decision (21 subjects).

The median treatment duration was comparable between the eligible population for the LT safety follow-up and the LT Safety Population. The median was 4.0 years, with 25% of subjects treated five years or more in the LT Safety Population (n=13) and the median dose during therapy was 97.3 µg/kg BID. No specific reasons for discontinuation of therapy appeared.

Effectiveness results:

After one year of treatment, mean HV was 6.84±2.29 cm/year and mean height SDS was -3.40±1.34 in the whole Registry Population.

In the same way after one year of treatment, mean HV was 7.17±2.04 cm/year (n=97) and mean height SDS was -3.29±1.30 (n=110) in the treatment-naïve prepubertal subjects with available data.

A linear regression analysis showed that HV at Year 1 was likely to be higher in female subjects, and that change in height SDS was likely to be higher in subjects who started Increlex® at a younger age and in female subjects.

In treatment-naïve prepubertal subjects, after two years of treatment, mean HV was 6.19±1.59 cm/year (n=77) and mean height SDS was -3.05±1.32 (n=95). Pearson test showed a correlation coefficient of 0.53 ($p<0.001$), indicating a moderate association between HV at Year 1 and HV at Year 2.

A linear regression analysis showed that HV at Year 2 was likely to be higher in subjects

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin	Volume: Page:	

with a higher HV at Year 1, and that change in height SDS was likely to be higher in subjects with lower height SDS (growth retardation more severe) at baseline.

In treatment-naïve prepubertal subjects, after three years of treatment, mean HV was 5.99±1.79 cm/year (n=67) and mean height SDS was -2.70±1.39 (n=78).

A linear regression analysis showed that HV at Year 3 was likely to be higher in subjects with a higher height SDS (growth retardation less severe) at baseline, and no significant predictive factors were evidenced for change in height SDS at Year 3.

Twenty-five (25) subjects in treatment-naïve prepubertal subgroup reported a FAH: the mean FAH was 159.8±19.2 cm in boys (-2.3±1.7 in terms of height SDS) and 150.2±5.6 cm in girls (-2.3±0.8 in terms of height SDS). Final adult height SDS was likely to be higher in subjects with high PAH at baseline and in subjects with high biological mother height.

Safety results:

At the cut-off date of 10 May 2017, 614 Treatment-Emergent AEs (TEAEs) had been reported in 158 subjects (65.3%) since the start of the EU Registry in December 2008. These TEAEs were mostly of mild to moderate intensity and were considered possibly related to treatment by the Investigator in 123 subjects (50.8%).

Overall, 289 targeted TEAEs were reported in 119 subjects (49.2%) and 210 of them were considered as related to treatment by the Investigator. The most frequently reported targeted AEs were: hypoglycaemia (21.5%), lipohypertrophy (12.0%), headaches (11.6%), tonsillar hypertrophy (8.7%) and otitis media (7.9%). The other targeted AEs reported were acromegalic facial changes (ten subjects), hearing loss (PT: deafness) (six subjects), injection site pain (six subjects), sleep apnoea syndrome (five subjects), injection site haematoma (five subjects), myalgia (four subjects), injection site erythema (four subjects), injection site reaction (three subjects), gynaecomastia (three subjects), papilloedema (two subjects), oedema (one subject), intracranial hypertension (PT: intracranial pressure increased) (one subject), urticaria (one subject) and all events of injection site bruising, extravasation, hypersensitivity, induration, inflammation, irritation, pruritus, rash or swelling (between one and two subjects).

Forty-two (42) serious TEAEs were reported related to Increlex® in 26 subjects (10.7%). These serious TEAEs were mostly hypoglycaemia (six subjects), adenoidal hypertrophy (four subjects) and tonsillar hypertrophy (four subjects). Angioedema was reported in two subjects. All other serious related TEAEs were reported in one subject each.

Overall, 103 serious TEAEs were reported in 49 subjects (20.2%). The most frequent serious TEAEs reported were hypoglycaemia, adenoidal hypertrophy or tonsillar hypertrophy. Most serious TEAEs had resolved or were resolving at the time of the report. Two cases were ongoing and two serious events were fatal: myelodysplastic syndrome and

Name of Sponsor/Company: IPSEN	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Increlex®		
Name of Active Ingredient(s): Mecasermin	Volume: Page:	

severe complications of bone marrow transplant, both assessed as not related to treatment.

Subjects who experienced episodes of hypoglycaemia during the treatment had more frequently a past history of hypoglycaemia (17.3% versus 4.2%) and were more often presenting with LS (34.6% versus 11.1%).

A multivariate analysis showed that statistically significant predictive factors for hypoglycaemia were presence of LS and history of hypoglycaemia at treatment initiation.

Thirteen subjects (5.4%) had to stop the treatment due to TEAE. Fifteen (15) TEAEs leading to Increlex® withdrawal in 11 subjects (4.5%) were considered as treatment-related based on the Investigator's judgement: hypersplenism, splenic infarction and splenomegaly in one subject, headache in two subjects, aortic valve incompetence, thyroid mass, injection site pain, hypertrophy (soft tissue of the nose), IGF increased, hypoglycaemia, pain in extremity, hypoglycaemic unconsciousness, ovarian enlargement and lipohypertrophy, each in one subject.

Nonserious laboratory abnormalities, assessed as clinically significant by the Investigator, were reported in 53 subjects (21.9%). These events (mainly IGF-I increased) were considered related to Increlex® in 15 subjects (6.2%).

During the LT safety follow-up, 4/13 subjects (30.8%) experienced five AEs: one SAE (tonsillitis) recovered after three days and four nonserious events including hearing loss (PT: deafness) and tonsillar hypertrophy (both recovered) and two clinically significant laboratory abnormalities (thyroxine free decreased and Vitamin D decreased), one ongoing and one with unknown outcome. No events were reported as related to treatment by the Investigator.

Conclusion:

In conclusion, at the cut-off date of 10 May 2017, 31 additional subjects have been enrolled and treated since the previous interim report (at the cut-off date of 11 May 2015). The overall safety results are consistent with the previous interim report (December 2015) and with the known safety profile of Increlex®.

Increlex® continues to demonstrate clinical and meaningful effectiveness while there has been no significant change in the safety profile. Long-term treatment, albeit in a small sample of subjects, is consistent with the known safety profile over short/medium term and no additional risks have been identified. Therefore the data obtained in the EU–IGFD Registry do not change the benefit/risk profile of the use of Increlex®, within this subject population.

Date of report: 20 December 2017