2 SYNOPSIS

Name of Sponsor/Company: Ipsen Pharma SAS. Name of Finished Product: Increlex®	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Active Ingredient(s): Mecasermin	Volume: Page:	
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		
Investigators: There was no coordinating Investigator for this Registry study. A steering committee is however regularly consulted.		
Study centres: 121 active sites enrolled at least one subject from 10 countries: Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden and United Kingdom (UK).		
Publications (reference): For 2015: Bang P et al, Horm Res Paediatr (2015); 83(5):345–57. For 2021: Bang et al, European Journal of Endocrinology (2021); 184,267-276.		
Studied period (years): Date of first enrolment: 09 December 2008 Date of last completed: cut-off date for this interim report: 12 May 2021	Phase of development: IV	
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, HV, timing and progression of puberty, bone age development, dosing compliance, 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;		

Name of Sponsor/Company: Ipsen Pharma SAS.	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		

- 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.

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 failure, 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 collected into the electronic case report form (eCRF) at the enrolment visit. 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 during the treatment and post-treatment periods. All of the procedures performed at these visits were in accordance with routine clinical practice.

During the enrolment visit, 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 age), before any further data collection.

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

The study follow-up visits during the treatment period were thereafter conducted as per routine medical practice, with the subject assessments performed at the enrolment visit. Data collection included effectiveness parameters, concomitant medications, all targeted AEs, serious AEs, nonserious drug related AEs and clinically significant laboratory abnormalities, physical examination and Increlex® dose and compliance information.

After the end of treatment, study post-treatment visits were conducted and included collection of effectiveness parameters, concomitant medications, all targeted AEs, serious AEs, nonserious drug related AEs and clinically significant laboratory abnormalities, physical examination and current illnesses considered by the Investigator to be related to Increlex®.

Name of Sponsor/Company: Ipsen Pharma SAS.	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		

For each subject, the treatment duration was at the discretion of the Investigator according to his/her judgement 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 have ended therapy and 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 patients (planned and analysed):

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. At the cut-off date for this report, 306 subjects were enrolled, 306 subjects had at least one follow-up visit and were included in the Registry Population and 304 subjects, for whom safety data was collected and were included in the Safety Population. The population of eligible subjects for long-term (LT) safety post-treatment follow-up included 119 subjects. Twenty-five (25) subjects were included in the LT Safety Population (subjects exposed to Increlex® for at least 3 years and with at least a 2 year post-treatment visit): 20 subjects with a post-treatment visit at Year 2, 9 subjects who attended a post-treatment visit between Year 2 and Year 5, 10 who have completed a post-treatment visit at Year 5.

Ten (10) subjects have completed the five-year follow-up period after the end of treatment, no analysis has been performed yet.

Over a 5-year timeframe, approximately 550 subjects with SPIGFD are expected to be treated in Europe.

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.

Subjects were excluded from entering the trial for the following reasons:

- Subject currently participating in an Increlex® clinical trial;
- Subject currently participating in any clinical trial for growth retardation.

Test product, dose and mode of administration:

Name of Sponsor/Company: Ipsen Pharma SAS.	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 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 had to be changed with each injection as per recommendation; 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:

Effectiveness:

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

This analysis included collection of data on scores regarding Pediatric Quality of Life Inventory (PedsQL – France only).

Safety:

- All SAEs related or not;
- Description and incidence of all the neoplasms reported;
- All targeted AEs for the treatment period 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);

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

- 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.
- The description and incidence of AEs leading to withdrawal and death.

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-treatment 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.

The 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 laboratory abnormalities;
- Description and incidence of AEs leading to withdrawal and death;
- Descriptive analyses at each timepoint and changes from baseline for biological assessments: IGF-I levels, growth hormone concentrations 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/m^2 and SDS), bone age (years), Tanner stage;

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

- Description of differences between PAH and FAH and other effectiveness parameters on subjects who reached 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 and Year 4, HV (cm/year) at Year 1, Year 2, Year 3 and Year 4, 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 12 May 2021, 306 subjects have been enrolled in 121 active sites, in 10 European countries, mostly in Germany, France, Spain, UK and Italy. A total of 301 subjects enrolled and treated with Increlex® and with at least one follow-up visit were included in the Registry Population. There were 304 subjects, for whom safety data was collected, who were included in the Safety Population (two subjects did not attend any follow-up visits and were therefore not included in the Safety Population).. Ninety-five (95) subjects completed the Registry: they stopped treatment and were followed-up until “near adult height” or “attained adult height”.

On the Enrolled Population (n=306), most subjects (84.6%) had a primary diagnosis of severe primary IGF-I deficiency. The subjects enrolled included a majority of boys (63.4%) and most subjects (83.8%) were at pubertal stage 1 (i.e. prepubertal; no sexual development). Mean age when starting Increlex® was 10.0±4.2 years for boys and 8.7±3.9 years for girls. Mean height at first Increlex® intake was 116.8±21.5 cm for boys and 109.6±20.9 cm for girls, mean height SDS was -3.7±1.3 for boys and -3.9±1.4 for girls and mean HV was 4.7±2.7 cm/year for boys and 5.0±1.8 cm/year for girls.

Most subjects of the Enrolled Population were treatment-naïve at time of first Increlex® intake (n=180): approximately 31.0% had previously received a growth-related therapy, mostly growth hormone therapy (83.2% of the previously treated subjects).

Among subjects who ended therapy, 119 subjects were exposed to Increlex® for at least three years and were then eligible for the LT safety follow-up. Twenty-five (25) subjects were included in the LT Safety Population. A visit at Year 2 was reported in 20 subjects, a visit between Year 2 and Year 5 in nine subjects and a visit at Year 5 in ten subjects. Ten

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

(10) subjects were included in the completed LT safety population (i.e. those who had five years of post-treatment safety follow-up). Baseline characteristics in both populations (eligible population for the LT safety follow-up and the LT Safety Population) 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 410 µg/kg BID (the subject who received an initial dose of 410 µg/kg BID was diagnosed with insulin resistance syndrome). The median dose increased progressively up to 120 µg/kg BID between Month 12 and Month 132, with a slight decrease (n=2) to 100 µg/kg BID at Month 138.

Two hundred and thirteen subjects (213) permanently discontinued therapy, 39.4% of them in the first two years of treatment. The main reasons for discontinuation remained adult height attained (54 subjects), lack of effectiveness (38 subjects) and subject/parent's decision (23 subjects).

The median treatment duration was comparable between the eligible population for the LT post-treatment safety follow-up and the LT Safety Population. In the LT Safety Population (n=25), the median treatment duration was 4.0 years, with 37.5% of subjects treated five years or more and the median dose during therapy was 101.3 µg/kg BID. The main reasons for discontinuation of therapy were attained adult height (28.0%) and other reasons (20.0%).

Effectiveness results on the Registry Population (n=301):

After one year of treatment, mean HV was 6.89±2.26 cm/year (n=212) (the change from baseline to Year 1 was 1.94±2.29 cm/year; n=133) and mean height SDS was -3.77±1.36 (n=273) (the change from baseline to Year 1 was 0.35±0.46; n=219) in the whole Registry Population.

In the same way after one year of treatment, mean HV was 7.18±2.09 cm/year (n=131) (the change from baseline to Year 1 was 2.57±2.58 cm/year; n=76) and mean height SDS was -3.42±1.40 (n=148) (the change from baseline to Year 1 was 0.41±0.44; n=133) in the treatment-naïve prepubertal subjects with available data.

Similarly, after one year of treatment, mean HV was 6.94±2.70 cm/year (n=30) (the change from baseline to Year 1 was 0.1±5.64 cm/year; n=19) and mean height SDS was -4.34±1.7 (n=37) (the change from baseline to Year 1 was 0.46±0.56; n=31) in subjects with Laron syndrome.

A linear regression analysis of treatment-naïve prepubertal subjects showed that HV at Year 1 was likely to be higher in female subjects, and that change from baseline in height SDS was likely to be higher in younger subjects and in female subjects.

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

In treatment-naïve prepubertal subjects, after two years of treatment, mean HV was 6.28±1.55 cm/year (n=101) and mean height SDS was -3.16±1.43 (n=124). Pearson test showed a correlation coefficient of 0.41 (p=0.001), indicating a moderate association between HV at Year 1 and HV at Year 2.

A linear regression analysis of treatment-naïve prepubertal subjects showed that HV at Year 2 was likely to be higher in subjects with a higher HV at Year 1, and that change from baseline in height SDS was likely to be higher in subjects with lower height SDS (growth retardation more severe) at baseline.

Forty-two (42) subjects (23 boys and 19 girls) in treatment-naïve prepubertal subgroup reached FAH: the mean FAH was 161.1±14.9 cm in boys (-2.1±1.5 in terms of height SDS) and 147.4±8.3 cm in girls (-2.6±1.2 in terms of height SDS). The mean height SDS gain between FAH and first Increlex® intake was 1.3 (0.8) in boys and 1.2 (0.9) in girls. Final adult height SDS was likely to be higher in subjects with high PAH and in subjects with high height SDS at baseline.

Safety results in the Safety Population (n=304):

At the cut-off date of 12 May 2021, 806 TEAEs had been reported in 207 subjects (68.1%) 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 159 subjects (52.3%).

Overall, 388 targeted TEAEs were reported in 161 subjects (53.0%) and 293 of them were considered as related to treatment by the Investigator. The most frequently reported targeted AEs were: hypoglycaemia (26.3% subjects), lipohypertrophy (13.8% subjects), headache (11.5% subjects), tonsillar hypertrophy (9.5% subjects) and otitis media (7.9% subjects). The other targeted AEs reported were acromegalic facial changes (12 subjects), hearing loss (PT: deafness) (eight [8] subjects), injection site pain (eight [8] subjects), sleep apnoea syndrome (seven [7] subjects), injection site haematoma (seven [7] subjects), myalgia (five [5] subjects), injection site erythema (four [4] subjects), gynaecomastia (four [4] subjects), injection site reaction (three [3] subjects), papilloedema (three [3] subjects) and all events of oedema, intracranial hypertension (PT: intracranial pressure increased), urticaria, injection site bruising, atrophy, extravasation, hypersensitivity, induration, inflammation, irritation, pruritus, rash or swelling (between one [1] and two [2] subjects).

Overall, 139 serious TEAEs were reported in 68 subjects (22.4%). The most frequent serious TEAEs reported were hypoglycaemia (8 subjects), tonsillar hypertrophy (7 subjects) or adenoidal hypertrophy (4 subjects). Most serious TEAEs had resolved (119) or were resolving (4) at the time of the report. Five (5) cases were ongoing and two serious events

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

were fatal: myelodysplastic syndrome and severe complications of bone marrow transplant, both assessed as not related to treatment.

Fifty-one (51) serious TEAEs were reported as related to Increlex® in 32 subjects (10.5%). These serious TEAEs were mostly hypoglycaemia (eight (8) subjects), tonsillar hypertrophy (seven (7) subjects) and adenoidal hypertrophy (four (4) subjects). Angioedema was reported in two subjects. All other serious related TEAEs were reported in one subject each.

There were eight benign and malignant neoplasms reported from the registry: Cartilage neoplasm, Dysplastic naevus, Haemangioma of skin, Melanocytic naevus (three events), Myelodysplastic syndrome and Papillary thyroid cancer. Five of these events were considered related to Increlex® treatment (three events of Melanocytic naevus, the event of Dysplastic naevus and the event of Haemangioma of skin); three of the neoplasms (Cartilage neoplasm, Myelodysplastic syndrome and Papillary thyroid cancer) were considered serious, none of which were considered related to Increlex® treatment.

Subjects who experienced episodes of hypoglycaemia during the treatment had more frequently a past history of hypoglycaemia (18.8% versus 4.5%) and were more often presenting with LS (27.5% versus 10.3%).

A multivariate analysis identified presence of LS and history of hypoglycaemia at treatment initiation as statistically significant predictive factors for hypoglycaemia.

Sixteen (16) subjects (5.3%) had to stop the treatment due to TEAE. Twenty (20) TEAEs leading to Increlex® withdrawal in 14 subjects (4.6%) were considered as treatment-related based on the Investigator's judgement: hypersplenism, splenic infarction and splenomegaly in one subject, headache and ovarian enlargement in one subject, pain in extremity and headache in one subject, lipohypertrophy, hypoglycaemic unconsciousness, injection site pain, hypoglycaemia in three subjects, hypertrophy, aortic valve incompetence, thyroid mass, IGF increased in two subjects, drug ineffective and drug intolerance.

Nonserious laboratory abnormalities, assessed as clinically significant by the Investigator, were reported in 67 subjects (22.0%). These events (mainly IGF-I increased) were considered related to Increlex® in 21 subjects (6.9%).

Among the 213 subjects who ended therapy, 119 subjects were exposed to Increlex® for at least three years and were then eligible for the LT safety post-treatment follow-up. Twenty-five (25) subjects were included in the LT Safety Population since they ended therapy after three years of exposure to Increlex® and since they reported a follow-up visit at least two years after the end of treatment. Ten (10) subjects were included in the completed LT Safety Population as they had five years of post-treatment safety follow-up. During the LT safety period, eight (8) subjects (32.0%) out of 25 subjects included in the LT safety population experienced nine (9) AEs: four (4) SAEs (pertussis resolved after an unknown number of days, tonsillitis resolved after three days, cyclic vomiting syndrome not resolved

Name of Sponsor/Company: Ipsen Pharma SAS.	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:	

at the end of registry and chronic kidney disease) and five (5) nonserious events (three AEs hearing loss [PT: deafness], tonsillar hypertrophy [both resolved], gynaecomastia considered ongoing and two clinically significant laboratory abnormalities [thyroxine free decreased and Vitamin D decreased], one ongoing and one with unknown outcome). All events, except for gynaecomastia, were reported as not related to treatment by the Investigator. Ten (10) subjects have completed the five-year follow-up period after the end of treatment, no analysis has been performed yet for this population.

Since the previous interim CSR (cut-off: 13 May 2019; submitted: 14 January 2020), there was no new safety findings which require further investigation.

Conclusion:

In conclusion, at the cut-off date of 12 May 2021, 25 additional subjects have been enrolled and treated and 8 additional subjects have entered into the long-term safety follow-up since the previous interim report (at the cut-off date of 13 May 2019). The overall safety results are consistent with the previous interim report and with the known safety profile of Increlex®.

Increlex® continues to demonstrate clinical and meaningful effectiveness while there has been no new 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 new safety risks have been identified. Therefore, the data reported from in the EU-IGFD Registry does not change the positive benefit/risk profile of the use of Increlex®. The MAH plans to undertake further validation and evaluations measures exposed in the 14th Annual Reassessment which received positive EMA opinion on 16 December 2021.

Date of report: 07 January 2022