1 SYNOPSIS

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		

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: No co-ordinating principal investigator for this Registry.

Study centres: 120 participating sites in 10 European countries: Austria, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Sweden and United Kingdom; 101 active sites (at least one subject enrolled in the Registry). No subject was enrolled in Greece.

Publication (reference): Not applicable

Studied period (years): 6 years Date of first enrolment: December 2008 Date of last completed: ongoing Registry, cut-off date for this interim report: 11 May 2015	Phase of development: 4

Objectives:

Primary objective: to collect long-term safety information on the use of recombinant DNA-derived human insulin growth factor-1 (rhIGF-1) Increlex® replacement therapy for the treatment of children with growth failure.

Secondary objectives:

- 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, timing and progression of puberty, bone age development, dosing compliance, IGF-I levels;
- To model height velocity, predicted adult height, final adult height, timing and progression of puberty, bone age development;
- To evaluate Increlex® treatment exposure and compliance.

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Methodology:

The European (EU) Registry (EU-IGFD) is a descriptive, multicentre, observational, prospective, open-ended, non-interventional, post-authorisation surveillance registry utilising electronic case report forms (e-CRF) via the Internet to collect information in the European countries. Subject enrolment occurred after the treatment regimen was prescribed and was independent of the treatment decision. Subjects who had started the treatment before the implementation of the Registry in their country could also be enrolled. Data was then retrospectively collected into the e-CRF. The data collected for a patient were those that exist in the patient's medical record as part of standard medical care. No additional patient procedures or activities were mandated by this Registry. Some data were mandatory for data transmission (e.g. Increlex® dose and adverse events (AEs)), while other data were optional as they may not always be available.

During the first visit, the Investigator checked the inclusion criteria and obtained signed Informed Consent before any further data collection. The treatment duration, number and frequency of the subject follow-up visits were determined by the Investigator according to his/her judgement on the basis of the clinical needs of the subject and the label recommendations. Subjects could be followed throughout their course of treatment and data could be collected until final adult height is achieved.

Number of patients (planned and analysed):

The Registry aims to recruit a maximum of Increlex® treated children in each country, and 60% of the CCI subjects treated by Increlex® in Europe CCI was firstly considered as a realistic goal. CCI [redacted]

Subjects analysed: at the cut-off date for this report, 215 subjects were enrolled, 208 subjects had at least one follow-up visit and were included in the Registry population and 209 subjects were included in the safety population.

Diagnosis and criteria for inclusion:

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

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Test product, dose and mode of administration, batch number:
Not Applicable as this is an observational Registry.

Duration of treatment:
During this non-interventional Registry, the Increlex® dose and administration schedule were determined by the subject's paediatric endocrinologist and were individualised for each subject based on weight, and tolerance.

Reference therapy, dose and mode of administration, batch number:
Not Applicable as this is an observational Registry.

Criteria for evaluation:

Effectiveness:

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

Safety:

- Serious adverse events (SAEs) including new onset and recurrence of neoplasia;
- All targeted related and non-related AE including: 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;
- Non-serious AEs considered by the reporting paediatric endocrinologist to be related to the treatment with Increlex®;
- Clinically significant laboratory abnormalities (related and non-related), as assessed by the Investigator.

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Statistical methods:

Populations:

The safety population includes all subjects who had taken the treatment at least once and with at least one follow-up visit or presence of any post study treatment safety data.

The EU Registry population (effectiveness population) includes all subjects who had completed at least one follow up visit and who had taken the treatment at least once. The effectiveness parameters were also described on the subgroup of treatment-naïve pre-pubertal subjects and the subgroup of pubertal or previously treated subjects.

Primary analyses:

- Description and incidence of any SAE;
- Incidence of all targeted AEs;
- Description and incidence of any reported drug-related AE, or clinically significant laboratory abnormalities.

Secondary analyses:

- Description at each time point and changes from baseline for the following effectiveness variables: weight (kg and SDS), height (cm and SDS), HV (cm/year), BMI (kg/m² and SDS), bone age development (years), pubertal stage;
- Drug exposure and compliance;
- Biological assessments (hormone panel);
- Genetic test results (if available).

Summary - conclusions:

Population:

At the cut-off date of 11-May 2015, 215 subjects have been enrolled in 101 active European sites, mostly in Germany, France, Italy, Spain and United Kingdom. A total of 208 subjects treated with Increlex® and with at least one follow-up visit were in the Registry population. The safety population included one more subjects with safety data. Ninety-two (92) subjects had completed the treatment and were in post-treatment follow-up. Thirty-three (33) subjects had completed the Registry (treated and followed up until final adult height is reached).

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On the enrolled population, most patients (86%) had a primary diagnosis of severe primary IGF-I deficiency. The population of enrolled subjects included a majority of boys (65%) and most subjects (82%) were pre-pubertal (ie, at Tanner stage 1). Mean age when starting Increlex® was 10.3±4.0 years for boys and 9.2±3.9 years for girls. Mean height at first Increlex® intake was 115.5±20 cm, mean height SDS was -3.7±1.3 and mean HV was 4.8±1.7 cm/year.

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).

Treatment compliance:

The median dose of Increlex® received at start of treatment was 40 µg/kg BID, ranging from 10 to 120 µg/kg BID. The median dose increased progressively up to 116-120 µg/kg BID between Month 12 and Month 78 excepted at Month 42 and at Month 54, where the median dose was 110 µg/kg BID.

Ninety-two subjects (43%) had ended therapy, half of them in the first 2 years of therapy. The main reason for discontinuation of therapy remained lack of effectiveness (21 subjects), adult height attained (20 subjects), and subject/parent decision (20 subjects).

Effectiveness results:

After 1 year of treatment, mean HV was 7.22±2.02cm/year for the sub-group of 90 treatment-naïve pre-pubertal subjects.

A linear regression analysis showed that HV at Year 1 was likely to be higher in subjects with LS and 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.

After 2 years of treatment, data were available for 68 subjects, and mean HV was 6.23±1.54 cm/year. Pearson test showed a correlation coefficient of 0.52 (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 with a higher velocity at Year 1, and that change in height SDS was likely to be higher in subjects with low height SDS at baseline.

After 3 years of treatment, data were available for 52 subjects, and mean HV was 5.80±1.73.

No significant predictive factors were evidenced for HV and for change in height SDS at Year 3.

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Safety results:

At the cut-off date of 11 May 2015, 410 AEs had been reported for 115 subjects (55%) since the start of the EU Registry in December 2008. These AEs were mostly of mild to moderate intensity and were considered related to treatment by the Investigator in 94 subjects (45%).

Overall, 191 targeted AEs were reported in 91 subjects (43.5%) and only 37 of these AEs were considered non-related to treatment by the Investigator (the relationship was not indicated for 10 targeted AEs). The most frequently reported targeted AEs were: hypoglycaemia (17%), lipohypertrophy (10.5%), headaches (10%), injection site reactions (8%) and tonsillar hypertrophy (7%). The other targeted AEs reported were otitis media (12 subjects, 6%), acromegalic facial changes (nine subjects, 4%), deafness and gynaecomastia (respectively five and three subjects) and papilloedema (one subject).

Overall, 67 SAEs were reported in 35 subjects (17%), including 17 targeted AEs (11 subjects). Most SAEs had resolved or were resolving at the time of the report, three cases were ongoing and one SAE was fatal: myelodysplastic syndrome, non-related to treatment according to the Investigator but related to treatment according to the company.

Among all SAEs, 36 (54%) reported in 23 subjects were considered related to treatment by the Investigator. The SAEs most frequently reported were hypoglycaemia (five subjects) and adenoidal hypertrophy (three subjects). Injection site reaction, headache and tonsillar hypertrophy were each reported in two subjects; serious papilloedema was also reported in one subject. All other SAEs were reported in one subject each.

Serious cases of hypoglycaemia tended to appear earlier after the start of treatment than non-serious cases (respectively, 98 days versus 297 days after treatment initiation). Furthermore, subjects who experienced episodes of hypoglycaemia during the treatment had more frequently a past history of hypoglycaemia (14% versus 4%), were slightly younger at the time of first Increlex® intake (median age of 9 years versus 11 years) and were more often presenting with LS (34% versus 10%).

A multivariate analysis showed that statistically significant predictive factor for hypoglycaemia was the presence of LS.

Ten subjects (5%) had to stop the treatment due to AE; 11 AEs leading to Increlex® withdrawal in eight subjects (4%), were considered as treatment-related based on the Investigator's judgement: hypersplenism, splenic infarction and splenomegaly for one subject, injection-site reaction and lipohypertrophy for one subject, injection-site pain, hypoglycaemia, angioedema, thyroid neoplasm, IGF increased or hypertrophy, each in one subject.

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Non-serious laboratory abnormalities, assessed as clinically significant by the Investigator, were reported for 38 subjects (18%). These events were considered related to treatment by the Investigator for 9 subjects (4%).

Conclusion:

At the cut-off date of 11 May 2015, the safety results, observed on a larger number of subjects, confirmed those reported at the cut-off date of 13 May 2013. From December 2008 to May 2015, targeted AEs were reported for 43.5% of the subjects, the most frequent being hypoglycaemia (17%), lipohypertrophy (10.5%), Headaches (10%), injection site reaction (8%) and tonsillar hypertrophy (7%). Papilloedema was reported for one subject. Increlex® was generally well tolerated and only ten subjects (5%) had to stop the treatment because of an AE.

Results of effectiveness after 1 year of treatment were now available for 90 treatment-naïve pre-pubertal subjects and confirmed those reported in 2013 on 62 subjects. Mean first year HV was 7.22±2.02cm /year and decreased thereafter to 3.99±1.57 at Year 5. Height velocity at Year 1 was likely to be higher in subjects with LS and in female subjects.

After 2 years of treatment, data were available for 68 subjects, and mean HV was 6.23±1.54 cm/year, results slightly higher than those reported in 2013 on 36 subjects. Height velocity at Year 2 was likely to be higher in subjects with a higher velocity at Year 1.

After 3 years of treatment, data were available for 52 subjects, and mean HV was 5.80±1.73 cm/year. No significant predictive factors were evidenced.

In terms of height SDS, at Year 1, change was likely to be higher in subjects who started Increlex® at a younger age and in female subjects. Change in height SDS at Year 2 was likely to be higher in subjects with low height SDS at baseline and no significant predictive factor was evidenced for change in height SDS at Year 3.

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:14 December 2015