## 2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:<br>IPSEN</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier<br><br>Volume:<br>Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of Finished Product:<br>Increlex®</td></tr>
<tr><td>Name of Active Ingredient(s):<br>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.<br>Study number: 2-79-52800-002</td></tr>
<tr><td colspan="3">Investigators: No co-ordinating principal investigator for this Registry.</td></tr>
<tr><td colspan="3">Study centres: 124 participating sites in 10 European countries: Austria, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Sweden and United Kingdom; 90 active sites (at least one subject enrolled in the Registry). No subject was enrolled in Greece.</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td colspan="2">Studied period (years): 5 years<br>Date of first enrolment: December 2008<br>Date of last completed: ongoing Registry, cut-off date for this interim report: 13May 2013</td><td>Phase of development: 4</td></tr>
<tr><td colspan="3">Objectives:<br>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.<br>Secondary objectives:<br>• To obtain long-term efficacy data for Increlex replacement therapy in children with growth failure by the evaluation of changes from baseline for the following efficacy variables: height, height velocity, timing and progression of puberty, bone age development, dosing compliance, IGF-I levels;<br>• To model height velocity, predicted adult height, final adult height, timing and progression of puberty, bone age development;<br>• To evaluate Increlex treatment exposure and compliance.</td></tr>
<tr><td colspan="3">Methodology:<br>The EU Registry is a descriptive, multicenter, observational, prospective, open-ended, non interventional, post-authorisation surveillance registry utilizing electronic case report forms (e-CRF) via the Internet to collect information in 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</td></tr>
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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) 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. However, 60% of the subjects treated by Increlex in Europe is considered as a realistic goal.
Subjects analysed: at the cut-off date for this report, 181 subjects were enrolled, 172 subjects had at least one follow-up visit and were included in the Registry population and 174 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.

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:

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Efficacy:

- Weight (kg and SDS),
- Height (cm and SDS),
- Height velocity (cm/year),
- Body mass index (BMI - kg/m² and SDS),
- Bone age (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 (SAE) including new onset and recurrence of neoplasia;
- All targeted related and non-related adverse events (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 adverse events 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.

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 Registry population (efficacy population) includes all subjects who had completed at least one follow up visit and who had taken the treatment at least once.

Primary analyses:

- Description and incidence of any serious adverse events;
- Incidence of all targeted adverse events;
- Description and incidence of any reported drug related adverse events or clinically significant laboratory abnormalities.

Secondary analyses:

- Description at each time point and changes from baseline for the following efficacy variables: weight (kg and SDS), height (cm and SDS), height velocity (cm/year), body mass index (BMI - kg/m² and SDS), bone age

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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 13-May 2013, 181 subjects have been enrolled in 90 active European sites, mostly in Germany, France, Italy, Spain and United Kingdom. A total of 172 subjects treated with Increlex and with at least one follow-up visit were in the Registry population. The safety population included two more subjects with safety data. Fifty-five (55) subjects had completed the treatment and were in post-treatment follow-up. Eleven subjects had completed the Registry (treated and followed up until final adult height is reached).

Most patients (83%) had a primary diagnosis of severe primary IGF-I deficiency. The population of enrolled subjects included a majority of boys (66%) and most subjects (81%) were pre-pubertal. Mean age when starting Increlex was 10.4±4.1 years for boys and 9.5±3.8 years for girls. Mean height at first Increlex intake was 116±20 cm and mean height SDS was -3.6±1.4.

Most subjects were treatment naïve and 32% had already received growth promoting therapy, mostly growth hormone therapy.

The median dose of Increlex received at start of treatment was 40 µg/kg BID, ranging from 18 to 120 µg/kg BID. Median dose increased progressively up to 120 µg/kg BID after 12 months of treatment and until month 36. Fifty-five subjects (30%) had ended therapy, half of them in the first year of therapy. The main reason for discontinuation of therapy remained lack of efficacy (14 subjects).

Efficacy results:

After one year of treatment, mean height velocity was 7.2±2.0 cm/year for the sub-group of 62 naïve pre-pubertal subjects. A linear regression analysis showed that height velocity at year 1 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 36 subjects, and mean height velocity was 5.8±2.1 cm/year. Pearson test showed a correlation coefficient of 0.34 (p=0.053), indicating a low association between height velocity at year 1 and height velocity at year 2.

Safety results:

At the cut-off date of 13 May 2013, 302 AEs had been reported for 90 subjects (52%) since the start of the EU Registry in December 2008. These AEs were mostly of mild to moderate intensity and 60% of them, reported for 79 subjects (45%), were considered related to treatment by the Investigator.

Overall, 140 targeted AEs were reported in 66 subjects (38%) and only 17 of these AEs

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were not considered related to treatment by the Investigator (the relationship was not indicated for three targeted AEs). The most frequently reported targeted AEs were: hypoglycaemia (17%), lipohypertrophy (10%), tonsillar hypertrophy (8%) and headaches (6%). The other targeted AEs reported were acromegalic facial changes (seven subjects, 4%), otitis media (seven subjects), deafness and gynaecomastia (three subjects each) and papilloedema (one subject). Injection site reactions were experienced by 10 subjects (6%). Targeted AEs led to treatment modifications (dose interrupted, reduced or delayed) for 16 subjects, essentially hypoglycaemia (nine subjects) and injection site reactions (three subjects).

Overall, 54 SAEs were reported in 27 subjects (16%), including 15 targeted AEs (14 subjects). Most SAEs were resolved or resolving at the time of the report, four cases were ongoing and one SAE was fatal: myelodysplastic syndrome, non-related to treatment according to the Investigator but the experts considered that if the cause of the disease is clearly not related to Increlex, the relation of Increlex in speeding the malignancy process cannot be excluded.

Among all SAEs, 34 (63%) reported in 21 subjects were considered related to treatment by the Investigator. There were mostly episodes of hypoglycaemia (four subjects) and adenoidal hypertrophy (three subjects). Papilloedema was also considered as serious and led to interruption of the treatment for one month. Treatment was reinitiated with no problems referred.

Serious cases of hypoglycaemia tended to appear earlier after the start of treatment than non-serious cases. Furthermore, subjects who experienced episodes of hypoglycaemia during treatment had more frequently a past history of hypoglycaemia than the subjects who did not experience hypoglycaemia during treatment (13% versus 5%). A multivariate analysis showed that statistically significant predictive factors for hypoglycemia were the presence of Laron syndrome and a younger age at treatment initiation.

Seven subjects (4%) had to stop the treatment because of an AE, treatment-related for five subjects: hypersplenism, splenic infarction and splenomegaly for one subject, injection-site reaction and lipohypertrophy for one subject, injection-site pain, angioedema and hypertrophy for one subject each.

Non-serious laboratory abnormalities, assessed as clinically significant by the Investigator, were reported for 26 subjects (15%). These events were considered related to treatment by the Investigator for 12 subjects (7%)

Conclusion:

The safety results reported at the cut-off date of 13 May 2013 confirmed on a larger number of subjects those reported at the cut-off date of 10 May 2011. From December 2008 to May 2013, targeted AEs were reported for 38% of the subjects, the most frequent being hypoglycaemia (17%), lipohypertrophy (10%), tonsillar hypertrophy (8%) and headaches (6%). Papilloedema was reported for one subject. Increlex was generally well

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| tolerated and only seven subjects (4%) had to stop the treatment because of an AE.<br>Results of efficacy after one year of treatment were now available for 62 naïve pre-pubertal subjects and confirmed those reported in 2011 on 27 subjects. Mean first year height velocity was 7.2±2.0 cm/year. After 2 years of treatment, data were available for 36 subjects, and mean height velocity was 5.8±2.1 cm/year.<br>Therefore the data obtained in the EU–IGFD Registry do not change the benefit/risk profile of the use of Increlex, within this patient population.<br><br>Date of report:22 November 2013 | | |