2 SYNOPSIS

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

EU Registry:
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
US Registry:
Title of study: Increlex® (mecasermin [rDNA origin] injection) Growth Forum Database – IGFD Registry: A Patient Registry for Monitoring Long-term Safety and Efficacy of Increlex®
Study number: W-TG-52800-010/MS305

Investigators: No co-ordinating principal investigator for these registries

Study centres:
EU Registry: 113 participating sites in nine European countries: Austria, Belgium, France, Germany, Italy, Poland, Spain, Sweden and United Kingdom; 64 active sites (at least one subject enrolled in the Registry). No subject was enrolled in The Netherlands or Greece.
US Registry: 121 participating sites; 111 active sites (at least one subject enrolled in the Registry).

Publication (references):

	EU Registry	US Registry	Phase of development: 4
Studied period (years):	3 years	5 years	
Date of first enrolment:	December 2008	May 2006	
Date of last completed: this interim report:	ongoing registries, cut-off date for 10 May 2011	12 May 2011.	

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

- 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;
- 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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US Registry:

- To obtain long-term safety data for Increlex replacement therapy in children with growth failure;
- To obtain long-term efficacy data for Increlex replacement therapy in children with growth failure.

Methodology:

Both registries are descriptive, multicenter, observational, prospective, open-ended, non interventional, post-authorisation surveillance registries utilizing electronic case report forms (e-CRF) via the Internet to collect information in European countries for one registry and in the US for the other registry. Subject enrolment occurred after the treatment regimen was prescribed and was independent of the treatment decision. Subjects who have 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 these Registries. 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 subjects (planned and analysed):

Both registries aim to recruit a maximum of Increlex treated children in each country. In Europe, the goal was to enrol at least 60% of the subjects treated with Increlex in most of the sites prescribing Increlex located in 11 European countries.

Subjects analysed: at the cut-off dates for this report, 108 subjects were enrolled in the EU Registry and 1204 subjects were enrolled in the US Registry. The safety population included 97 subjects in the EU Registry and 1093 subjects in the US Registry.

Diagnosis and criteria for inclusion in the EU and the US Registry:

- 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 in the EU Registry and the US Registry:

Efficacy:

- Weight (kg and SDS),
- Height (cm and SDS),
- Height velocity (cm/yr),
- Body mass index (BMI - kg/m²) and BMI SDS (US Registry only),
- Bone age,
- 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:
  - in the EU and the US Registries: 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;
  - in the EU Registry only: cardiomegaly;
  - in the US Registry only: urticaria and injection site reaction;
  **Note: all targeted AEs were considered related to treatment in the US Registry*
- 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.

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Statistical methods for both registries:
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 efficacy population at Year 1 includes all naïve pre-pubertal subjects with at least one efficacy data after one year of treatment
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, body mass index (BMI), bone age development, pubertal stage;
- Drug exposure and compliance;
- Biological assessments (hormone panel);
- Genetic test results (if available).

No pooled analysis of EU and US data was performed due to the heterogeneity of the enrolled population and the differences in the data collection. Therefore results are presented separately.

Summary - conclusions:

Populations:
EU Registry
At the cut-off date of 10-May 2011, 108 subjects have been enrolled in 62 active European sites, mostly in Germany, France, Italy, Spain and United Kingdom. A total of 96 subjects treated with Increlex and with at least one follow-up visit were in the Registry population. The safety population included one more subject with safety data. Five subjects had completed the treatment and were in post-treatment follow-up.
Most patients (80%) had a primary diagnosis of severe primary IGF-1 deficiency. The population of enrolled subjects included a majority of boys (63%) and most subjects (83%) were pre-pubertal. Mean age when starting Increlex was 10.6±3.9 years for boys and 9.5±3.8 years for girls. Mean height at first Increlex intake was 115±20 cm and mean height SDS was -3.8±1.5. At baseline, mean IGF-1 level was 114±135 ng/ml and median value was 68 ng/ml.
Most subjects were treatment naïve and 41% 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

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20 to 120 µg/kg BID. Median dose increased progressively up to 120 µg/kg BID after 6 months of treatment and remained around 110 µg/kg BID until month 36. Fourteen subjects (15%) ended therapy, mostly for lack of efficacy (five subjects).

US Registry

At the cut-off date of 12 May 2011, the US Registry included 1204 subjects enrolled in 111 sites. The safety population included 1093 subjects. The US Registry enrolled even more boys (75%). Mean age at first Increlex intake was 11.1±3.6 years for boys and 9.8±3.5 years for girls. Overall 61% of the subjects were pre-pubertal and 29% had previously received growth promoting therapy.

At initiation of treatment with Increlex, mean height was 127±20 cm, mean height SDS was -2.5±1.0 and mean height velocity was 5.2±2.4 cm/year. At baseline, mean IGF-1 level was 152±153 ng/ml and median value was 108 ng/ml. The US Registry population had less severe growth failure than the EU Registry population. Primary diagnosis was mostly primary (including severe) IGF-1 deficiency (72%) and idiopathic short stature (21%).

The median dose of Increlex at initiation of treatment was higher than in the EU Registry: 60 µg/kg BID. Median dose of Increlex was 120 µg/kg BID from month 6 to month 42. Overall 34% of the subjects permanently discontinued the treatment.

Efficacy results:

After one year of treatment, mean height velocity was 7.5 ±1.8 cm/year for the sub-group of 27 naïve pre-pubertal subjects of the EU Registry.

Similar results were obtained in the US Registry, with a mean height velocity of 7.3±1.7 cm/year for 151 naïve pre-pubertal subjects.

Safety results:

EU Registry

A total of 122 AEs were reported for 48 subjects (49%), mostly of mild to moderate intensity. Out of these 122 TEAEs, 92 AEs, reported in 40 subjects, were considered related to treatment.

Overall, 77 targeted AEs were reported in 38 subjects (39%). The most frequently reported AEs were: hypoglycaemia (19%), tonsillar hypertrophy (7%), lipohypertrophy (7%) and headaches (6%).

Episodes of hypoglycaemia were generally reported once or twice but one subject had six episodes. All episodes of hypoglycaemia were resolved except two that were ongoing at the cut-off date for the report. The treatment dose was delayed or interrupted for four subjects and reduced for three subjects. For four subjects, the episodes of hypoglycaemia were considered not related to treatment.

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For four subjects, the episodes of hypoglycaemia were considered as serious. For these cases, the median dose of Increlex® at time of first occurrence was 80 µg/kg BID, ranging from 50 to 100 µg/kg BID and median duration of treatment was 78 days until occurrence of hypoglycemia. For non serious episodes of hypoglycaemia, median dose at time of first occurrence was higher (100 µg/kg BID) and median duration of treatment until occurrence was longer (195 days).
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 (17% versus 6%). They were slightly younger at the time of first Increlex intake (mean age of 9 years versus 10 years).
None of the cases of headaches (six subjects) were serious. All cases except one were considered related to treatment. In all cases except one, the treatment was not modified.
Among the seven cases of tonsillar hypertrophy only one was not considered related to treatment and only one case led to interruption of treatment.
All seven cases of lipohypertrophy were related to treatment but none led to any change in the treatment.
Injection site reactions were experienced by seven subjects (7%). For one subject, the pain at injection site was of severe intensity and led to permanent discontinuation of the treatment.
The other targeted AEs reported were acromegalic facial changes (three subjects), otitis media (two subjects), deafness, gynaecomastia and papilloedema (one subject each).
All these targeted AEs were considered related to treatment, none led to changes in the treatment except papilloedema that was considered as serious and led to interruption of the treatment for one month. Bilateral fundoscopy was normal shortly after papilloedema was reported and treatment was reinitiated with no problems referred.
Overall, 22 SAEs were reported in 10 subjects (10%), including 10 targeted AEs (five subjects). More than half of these SAEs (13) were of severe intensity. All subjects had recovered or were recovering from these SAEs.
Among all SAEs, 15 (68%) reported in eight subjects were considered related to treatment. There were mostly episodes of hypoglycaemia (four subjects) and adenoidal hypertrophy (two subjects).
Three subjects (3%) had to stop the treatment because of an AE: two subjects because of serious hypoglycaemic unconsciousness and one subject because of non-serious painful injection.
In the EU Registry, nine subjects (9%) had non-serious significant laboratory abnormalities associated to clinical symptoms as assessed by the investigator. For four subjects, these events were related to treatment: blood bilirubin increased, GH decreased, TSH increased, IGF-1 increased and thyroxine-free decreased, all of mild or moderate intensity.

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US Registry

In the US Registry, 282 subjects (26%) reported at least one AE for a total of 837 AEs. Targeted AEs were reported for 197 subjects (18%). The most frequent were hypoglycaemia (9%) and headache (6%). The other most frequent AEs (more than 1% of the subjects) were injection site reactions (1.7%), lipohypertrophy (1.3%), tonsillar hypertrophy (1.2%), gynaecomastia (1.1%). Intracranial hypertension was reported for eight subjects (0.7%) and papilloedema for three subjects (0.3%).

A total of 23 subjects (2%) presented with at least one SAE for a total of 43 SAEs. For two subjects, these SAEs occurred after the end of treatment. Most SAEs were of moderate intensity and resolved. Seven SAEs were ongoing at time of report.

Among all SAEs, 31 (70%) reported in 17 subjects were considered related to treatment. There were mostly intracranial hypertension (benign intracranial hypertension: five subjects, increased intracranial pressure: two subjects), headaches (three subjects), hypoglycaemia, eye swelling, swelling face (two subjects each).

For eight subjects (0.7%), SAEs led to treatment withdrawal: major depression, benign intracranial hypertension (three subjects), intracranial pressure increased (two subjects), dyspnea, eye and face swelling (for the same subject) and haematuria, IgA nephropathy and adenotonsillectomy (for the same subject). The dose had to be interrupted for six subjects mostly because of benign intracranial hypertension (three subjects).

In the US Registry, 43 subjects (4%) had clinically significant abnormal laboratory results as assessed by the investigator. The most frequently reported were IGF increased (12 subjects, 1.1%), IGF decreased (seven subjects, 0.6%), blood creatinine decreased and thyroxine decreased (three subjects each). All other abnormalities were reported for no more than two subjects.

Conclusion:

EU Registry

From December 2008 to May 2011, targeted AEs were reported for 39% of the subjects in the Eu-IGFD Registry, the most frequent being hypoglycaemia (19%), headaches (6%), tonsillar hypertrophy (7%) and lipohypertrophy (7%). Papilloedema was reported for one subject. Increlex was generally well tolerated and only three subjects (3%) had to stop the treatment because of an AE.

Results of efficacy after one year of treatment were available for only a small number of naïve pre-pubertal subjects (27 subjects). Mean first year height velocity was 7.5±1.8 cm/year.

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.

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US Registry

From May 2006 to May 2011, targeted AEs were reported in 18% of the subjects in the US registry, which included a population of children with less severe growth failure than the EU registry. The most frequent targeted AEs were hypoglycemia (9%) and headache (6%). Tonsillar hypertrophy and lipohypertrophy were reported for less than 2% of the subjects. Intracranial hypertension was reported for 8 subjects (0.7%). Increlex was generally well tolerated and only eight subjects (0.7%) in the US Registry had to stop the treatment because of an AE.

Results of efficacy after one year of treatment were available for only 151 naïve pre-pubertal subjects. Mean first year height velocity was 7.3±1.7 cm/year.

Therefore the data obtained in the US-IGFD Registry do not change the benefit/risk profile of the use of Increlex, within this patient population.

Date of report: 29 November 2011