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Safety and effectiveness of Increlex® therapy in children enrolled in the Increlex® Growth Forum Database (IGFD) in Europe: 4-year interim results

Michel Polak[1], Joachim Woelfle[2], Peter Bang[3], Aude Sicsic[4]

[1]Hôpital Necker Enfants Malades, AP-HP, Université Paris Descartes, Paris, France; [2]Children's Hospital, University of Bonn, Bonn, Germany; [3]Faculty of Health Sciences, Linköping University, Linköping, Sweden; [4]Ipsen Pharma, Boulogne Billancourt, France

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INTRODUCTION

- In the EU and USA, Increlex® (mecasermin [rDNA origin] injection, recombinant human insulin-like growth factor-1 [rhIGF-1]) is approved for the treatment of growth failure in children with severe primary IGF-1 deficiency, which is defined as
  - Height standard deviation score (SDS) ⩽–3
  - IGF-1 <2.5th percentile (in the EU) or IGF-1 SDS ⩽–3 (in the USA)
  - Normal or elevated growth hormone secretion
- The EU Increlex® Growth Forum Database (IGFD) Registry was initiated in December 2008 to monitor the safety and efficacy of Increlex® in children, and is representative of the Increlex®-treated patient population in 9 countries in Europe
- The EU IGFD Registry is ongoing and recruiting new patients

OBJECTIVES

- EU IGFD Registry objectives
  - To evaluate the long-term safety (primary objective) and effectiveness (secondary objective) of Increlex® in children with growth failure
- Objectives for this poster
  - To report baseline characteristics and 4-year interim safety data for 195 patients enrolled in the EU IGFD Registry
  - To present first-year, second-year, third-year, and fourth-year height SDS and change in height SDS for
    - Registry population comprising all children treated with Increlex® and who had completed at least one follow-up visit
    - Subgroup of prepubertal children who were naïve to growth-promoting therapy

METHODS

- Ongoing, multicentre, open-label, observational study monitoring the safety and efficacy of Increlex® in children in the clinical practice setting
- Children were eligible for enrolment if they
  - Received Increlex® for growth failure from a qualified practitioner
  - Gave informed consent, if appropriate, in addition to mandatory consent from their parents or legally authorized representative
- Data existing in the patients' medical records as part of standard medical care were collected (using an electronic Case Report Form), including
  - Baseline characteristics
  - Serum IGF-1 concentrations (by local assay providers)
  - Increlex® dose (at the start of treatment and dose escalation)
  - Treatment outcomes (e.g. height, weight, pubertal stage)
  - Concomitant medications
  - Previous growth-promoting therapy, including recombinant human growth hormone (rhGH) and rhIGF-1
  - Previous steroid therapy
  - Safety, including:
    - Targeted adverse events (TAEs) (both treatment related and non-treatment related) similar to those observed in previous Increlex® trials: hypoglycaemia (suspected and documented), headache, papilloedema, intracranial hypertension, oedema, acromegalic facial features, tonsillar hypertrophy, sleep apnoea, otitis media, hearing impairment, injection site reaction, lipohypertrophy at injection site, myalgia, gynaecomastia, and cardiomegaly
    - Serious adverse events (SAEs) irrespective of relationship to treatment*
    - All other non-serious adverse events (AEs) considered to be treatment related by the treating physician
    - All clinically significant abnormalities in laboratory data
- Linear regression analysis performed to identify predictive factors of change in height SDS between baseline and years 1 and 2 in treatment-naïve, prepubertal children, using the following covariates:
  - Sex, biological mother's and father's height (cm), height SDS at baseline, body mass index (kg/m²) at first Increlex® administration, serum IGF-1 concentration (ng/mL) at baseline, mean dose (µg/kg BID) during year 1, age (years) at treatment initiation, and whether the patient was diagnosed with Laron syndrome
  - Variables with a p-value inferior to 0.2 retained for multivariate analysis

RESULTS

Patients

- The first patients were enrolled in the EU IGFD Registry in December 2008
- 195 patients (128 male; 67 female) were enrolled as of 30 September 2013
  - 110 treatment-naïve, prepubertal children (66 male; 44 female) were treated with Increlex®
- Baseline demographic characteristics of patients enrolled in the EU IGFD Registry (enrolled population; N=195) and in the treatment-naïve, prepubertal subgroup (N=110) are summarized in **Table 1**

Increlex® dose

- Within the enrolled population (N=195):
  - Mean (±SD) Increlex® starting dose was 43.4 (±23.4) µg/kg/dose administered twice daily (BID), and the mean Increlex® dose (±SD) at Months 12, 24, 36, and 48 was 97.7 (±32.7), 103.6 (±31.6), 104.9 (±28.1), and 105.4 (±35.2) µg/kg BID, respectively
  - Mean treatment duration (±SD) was 831.9 (±491.2) days, equivalent to 433.0 patient-years
- Within the treatment-naïve, prepubertal population (N=110):
  - Mean (±SD) Increlex® starting dose was 37.9 (±16.8) µg/kg BID, and the mean Increlex® dose (±SD) at Months 12, 24, 36, and 48 was 97.2 (±32.4), 104.9 (±28.7), 105.5 (±23.0), and 103.9 (±34.0) µg/kg BID, respectively
  - Mean treatment duration (±SD) was 835.1 (±457.2) days, equivalent to 249.4 patient-years

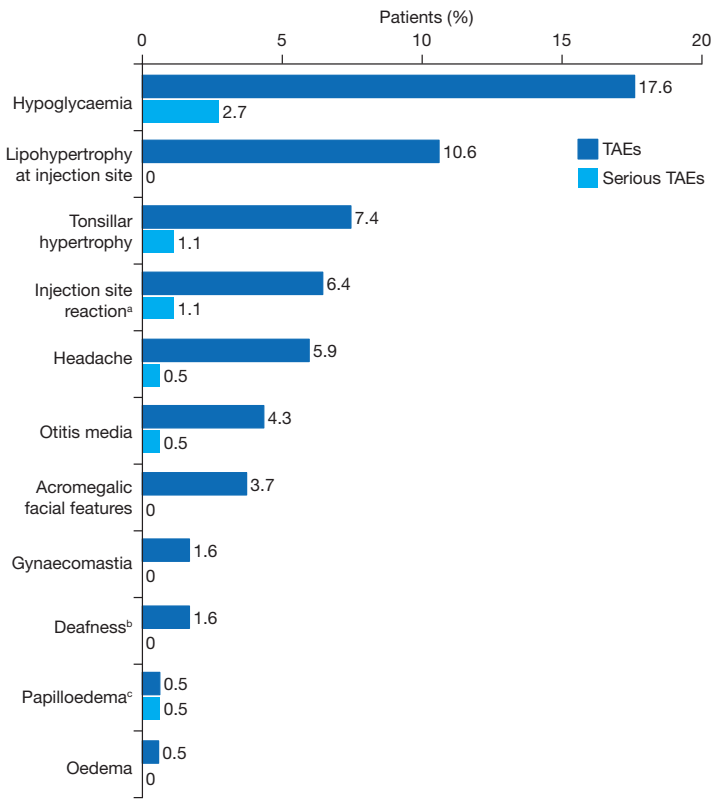
SAFETY PROFILE OF INCRELEX®

- The safety population comprised 188 patients for whom safety follow-up data were available
- 349 treatment-emergent AEs were reported in 99 patients (53%)
- Most AEs (60%) were considered to be related to treatment

Targeted adverse events

- One or more TAE was reported in 74 patients (39%)
- Most (86%) of the 155 TAEs were considered to be related to treatment
- The treatment-emergent TAEs, together with those considered serious, are shown in **Figure 1**
- The most frequent TAE was hypoglycaemia (59 events in 33 patients [18%]):
  - This included suspected hypoglycaemia based on patient symptoms (25 events) and events verified by blood glucose measurements (<2.78 mmol/L; 26 events)
  - 4 patients (of the 33 who experienced hypoglycaemia) had a previous history of hypoglycaemia
  - 8 hypoglycaemic events were considered SAEs in 5 patients
- There were no reported occurrences of the following TAEs: intracranial hypertension, myalgia, sleep apnoea, or cardiomegaly

Figure 1. Treatment-emergent targeted adverse events (total TAEs and serious TAEs)



[a]Comprising: erythema, haematoma, hypersensitivity, induration, inflammation, pain, pruritus, rash, reaction, and swelling
[b]Hearing impairment was coded as deafness; 1/3 patients had medical history of deafness; deafness resolved in 1 patient and ongoing in 2 patients
[c]Intracranial hypertension was not reported.

Serious adverse events

- 61 SAEs were reported in 31 patients (16.5%); 39 of these events occurring in 21 patients have been previously reported[1–3]
- The remaining 22 SAEs, occurring in 15 patients since the previous interim analysis of January 2013 (cut off 3 October 2012), included 11 SAEs (in 7 patients) that were considered to be related to treatment:
  - Angioedema (1 event), adenoidal and tonsillar hypertrophy (1 event each in 1 patient), hydrocele (2 events in 1 patient), arthralgia (1 event), headache (1 event), ovarian enlargement (1 event), volvulus (2 events in 1 patient), hypoglycaemia (1 event)

INCRELEX® EFFECTIVENESS

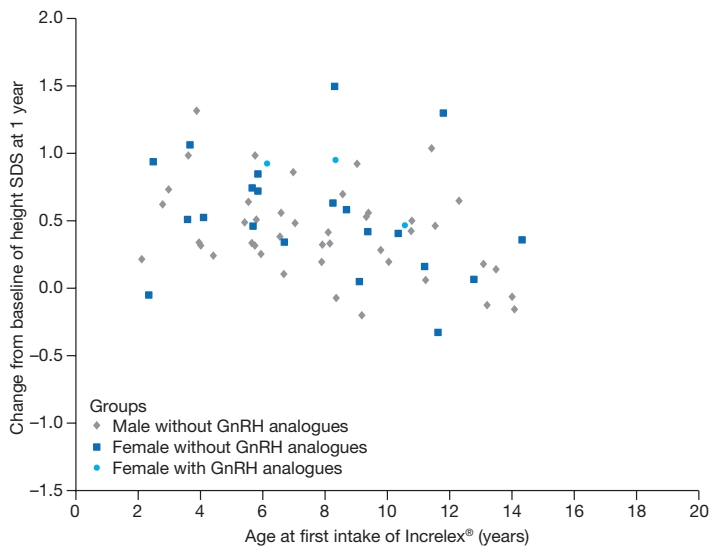
- Mean (±SD) change in height SDS from baseline was 0.9 (±0.8) after 4 years of treatment in the Registry population, and 0.9 (±0.8) after 3 years of treatment in the subgroup of treatment-naïve, prepubertal patients (**Table 2**)
- In the treatment-naïve, prepubertal population:
  - Predictors for the first-year change in height SDS were
    - Age at Increlex® initiation (estimate [95% CI], by 1 unit increment: –0.04 [–0.06; –0.02] p<0.001)
    - Sex (male as reference: 0.18 [0.02; 0.33] p=0.026)
    - Height SDS at baseline (by 1 unit increment: –0.06 [–0.12; –0.00]; p=0.041)
  - **Figure 2** shows change in height SDS at year 1 according to age at initiation of Increlex®
  - Height SDS at baseline remained a predictor of change in height SDS between baseline and year 2:
    - –0.11 [–0.22; –0.01]; p=0.031

Table 2. Mean (±SD) of height SDS and change in height SDS in the Registry population and in a subgroup of treatment-naïve, prepubertal patients

		Height SDS		Change in height SDS
Registry population	n[a]		n[a]	
Baseline	176	–3.50 (1.34)	–	–
Year 1	151	–3.18 (1.37)	144	0.34 (0.42)
Year 2	104	–3.14 (1.58)	98	0.59 (0.64)
Year 3	66	–2.76 (1.78)	62	0.73 (0.74)
Year 4	25	–2.87 (1.75)	23	0.92 (0.80)
Treatment-naïve, prepubertal patients				
Baseline	102	–3.35 (1.34)	–	–
Year 1	71	–2.92 (1.33)	67	0.47 (0.38)
Year 2	41	–3.06 (1.59)	39	0.78 (0.64)
Year 3	22	–2.70 (2.00)	21	0.90 (0.79)

[a]Number of patients for whom data are available at each time point.
SD, standard deviation; SDS, standard deviation score.

Figure 2. Change from baseline in height SDS at year 1 according to age at treatment initiation (treatment-naïve, prepubertal patients)



GnRH, gonadotropin-releasing hormone.
Pearson Correlation Coefficient = –0.33 (p=0.006)

CONCLUSIONS

- These 4-year interim data from the EU IGFD Registry did not demonstrate any new safety concerns for Increlex®, with the safety profile remaining consistent with the product labelling.
  - Hypoglycaemia incidence was similar to that reported in previous interim analyses[1–3]
- An increase in height SDS observed in a previous analysis[3] was confirmed in this larger cohort, with greater growth response observed in treatment-naïve, prepubertal patients than in the total Registry population.
- Positive predictors of first-year change in height SDS were identified as female sex, younger age at start of Increlex® therapy, and lower baseline height SDS.
- These effectiveness findings suggest that a better growth response can be achieved by starting Increlex® therapy early, many years before the start of puberty, and in patients with a severe growth phenotype.

Table 1. Baseline characteristics of all enrolled patients and of a subgroup of treatment-naïve, prepubertal children

	All enrolled patients (N=195)			Treatment-naïve, prepubertal patients (N=110)		
Characteristic	n[a]	Mean (SD) [95% CI]	Median (25th, 75th percentile)	n[a]	Mean (SD) [95% CI]	Median (25th, 75th percentile)
Age at first injection, years	195	10.1 (4.0) [9.5; 10.7]	10.6 (6.8, 13.2)	110	8.5 (3.5) [7.8; 9.2]	8.3 (5.8, 11.2)
Height SDS	183	–3.5 (1.3) [–3.7; –3.3]	–3.2 (–4.4, –2.6)	105	–3.4 (1.3) [–3.6; –3.1]	–3.0 (–3.9, –2.5)
Weight SDS	182	–3.1 (1.4) [–3.3; –2.9]	–3.0 (–3.8, –2.1)	104	–3.1 (1.2) [–3.4; –2.9]	–3.1 (–3.7, –2.4)
BMI SDS	167	–0.7 (1.5) [–1.0; –0.5]	–0.8 (–1.6, 0.0)	95	–0.8 (1.3) [–1.1; –0.5]	–0.8 (–1.7, –0.1)
Bone age, years	38	8.5 (3.5) [7.4; 9.6]	8.5 (5.5, 11.5)	22	7.4 (3.0) [6.1; 8.7]	8.0 (5.0, 10.0)
Mother's height, cm	178	157.2 (8.2) [156.0; 158.4]	158.0 (151.9, 163.0)	101	157.7 (7.3) [156.3; 159.2]	158.0 (153.6, 162.0)
Father's height, cm	176	172.1 (7.9) [170.9; 173.2]	172.0 (167.9, 178.0)	100	172.6 (8.1) [171.0; 174.2]	173.0 (168.0, 178.0)
IGF-1, ng/mL	167	120.7 (121.6) [102.1; 139.3]	85.0 (44.0, 142.0)	90	91.8 (71.0) [76.9; 106.6]	73.5 (38.9, 123.0)
GH test: stimulated GH_{max}, ng/mL	133	27.8 (38.7) [21.1; 34.4]	16.8 (11.3, 29.0)	78	24.4 (25.0) [18.7; 30.0]	15.6 (11.0, 26.1)
Height velocity, cm/year	109	4.8 (1.7) [4.5; 5.1]	4.7 (3.9, 5.6)	57	5.0 (1.9) [4.5; 5.5]	5.1 (4.0, 6.2)
Primary diagnosis: severe primary IGF-1 deficiency[b]	195	165 (84.6%) [78.9%; 89.0%]	N/A	110	99 (90.0%) [83.0%; 94.3%]	N/A
History of hypoglycaemia	195	11 (5.6%)	N/A	110	4 (3.6%)	N/A
Prior growth-promoting therapy	195	65 (33.3%) [27.1%; 40.2%][c]	N/A		N/A	N/A

[a]Number of patients for whom data are available; [b]including Laron syndrome; [c]rhGH in 52 (80.0%) and rhIGF-1 in 21 (32.3%).
BMI, body mass index; CI, confidence interval; GH, growth hormone; GH_{max}, maximal growth hormone concentration; IGF-1, insulin-like growth factor-1; N/A, not applicable; rhGH, recombinant human growth hormone; rhIGF-1, recombinant human insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score.

*Relationship of SAEs to treatment was determined by the treating physician and also reviewed by an expert board.

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REFERENCES

1. Bang P et al. Poster presented at 50th Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), 25–28 September 2011, Glasgow, UK.
2. Polak M et al. Poster presented at 51st Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), 20–23 September 2012, Leipzig, Germany.
3. Woelfle J et al. Poster presented at the 9th Joint Meeting of Paediatric Endocrinology, 19–22 September 2013, Milan, Italy.

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