Characteristics, effectiveness and safety data from clinically relevant subgroups of patients with severe IGF-1 deficiency: results from the European Increlex® Growth Forum Database registry

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on behalf of the EU-IGFD Registry Study Group

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BACKGROUND

- Recombinant human insulin-like growth factor-1 (rhIGF-1) is approved in Europe and the US for the treatment of growth failure in children with severe primary IGF-1 deficiency (SPIGFD),[1–2] as it stimulates linear growth.[3–4]
- The European Increlex® Growth Forum Database (EU-IGFD) registry was established to monitor the safety and effectiveness of rhIGF-1 (mecasermin [rDNA origin] injection) for short stature in children with SPIGFD.
- Subgroups of interest identified from the EU-IGFD registry (patients with and without Laron syndrome [LS]; and patients considered as responders or poor responders) have previously been described, based on effectiveness and safety data.[5,6]
- Here, these subgroups are combined to describe clinically relevant effectiveness and safety data from the EU-IGFD registry.

OBJECTIVE

- To describe clinically relevant subgroups of patients likely to achieve an increase in height in response to rhIGF-1 therapy, together with safety.

METHODS

Study design

- Data were compiled from this ongoing open-label, multicentre, observational study (NCT00903110; 10 May 2017 cut-off). The study was initiated in December 2008 and children from 10 countries in Europe have been enrolled.

Patients

- Patients were divided into 5 clinically relevant subgroups.
- 3 treatment-naïve prepubertal (NPP) subgroups:
  - NPP LS (irrespective of treatment-response status).
  - Non-LS with treatment response (NPP non-LS-responder; responder = year-1 height SDS change ≥0.3).
  - Non-LS with poor treatment response (NPP non-LS-poor-responder).
- 2 subgroups of patients who were not treatment naïve or who were pubertal (non-NPP):
  - Non-NPP LS.
  - Non-NPP non LS.

Assessments at the cut-off date of 10 May 2017

- Data collected at baseline and during treatment included:
  - Baseline characteristics (demographic and growth parameters).
  - Changes in growth parameters.
- Safety data collected included:
  - Targeted adverse events (AEs), related AEs and all serious AEs, up to completion in the EU-IGFD registry.

Statistical analyses

- Height standard deviation score (SDS) was calculated:
  - In France and southern European countries using Sempé reference values.[7]
  - In the UK, Belgium, Sweden, and Poland, using UK reference values.[8]
  - In Germany and Austria using KiGGS (German Health Interview and Examination Survey for Children and Adolescents) reference values.[9]
- Annualised height velocity (HV) cm/year,[10] was calculated using height values measured at the time point of interest and at 1 year before this time point, divided by the time interval between the 2 measurements (≥6 months and ≤18 months).
- This analysis was mainly descriptive.
- Logistic regression analysis was used to identify baseline predictive factors of growth response at year-1 in the subgroup of NPP non-LS patients.

RESULTS

Patients

- Of 246 patients enrolled, 213 were included in this analysis.
  - NPP (n=109): 21 LS, 50 non-LS-responders, 38 non-LS-poor-responders.
  - non-NPP (n=104): 17 LS, 87 non-LS.
- Of 33 patients who were excluded: 29 patients had missing treatment-response status and 4 patients had missing pubertal status and/or missing previous treatment.
- Baseline characteristics (**Table 1**) indicate that:
  - There were more males than females (64.8%, 138/213 patients were male).
  - The proportion of patients with a diagnosis of SPIGFD ranged between 72.4 and 100% among subgroups.
  - In the NPP LS and NPP non-LS-responders subgroups, the mean age at first rhIGF-1 intake was lower compared with other subgroups.
  - In the NPP LS subgroup, mean height SDS at treatment start was lower compared with other subgroups.
  - Mean HV ranged between 4.19 and 5.67 cm/year among all the subgroups.

Effectiveness (year 1)

- In NPP LS and NPP non-LS-responders:
  - In addition to NPP non-LS-responders, in whom by definition a higher height SDS change was expected, there was a higher change in mean height SDS in patients with NPP LS (**Figure 1a**).
  - There was a trend toward higher year-1 HVs compared with other subgroups (**Figure 1b**).
- When comparing patients who were NPP non-LS-responders with those who were NPP non-LS-poor-responders, younger age was predictive of treatment response at year 1 (odds ratio [95% CI], responders versus poor responders: 0.75 [0.65; 0.87]).

Table 1. Patient characteristics at baseline (enrolled population)

Characteristic	NPP						Non-NPP			
			Non LS							
	n*	LS (N=21)	n*	Responder (N=50)	n*	Poor responder (N=38)	n*	LS (N=17)	n*	Non LS (N=87)
Male, n (%)	21	12 (57.1)	50	30 (60.0)	38	27 (71.1)	17	10 (57.8)	87	59 (67.8)
Age at first injection (years), mean (SD)	21	6.07 (3.49)	50	7.00 (3.11)	38	10.28 (3.53)	17	12.78 (3.73)	87	11.43 (3.58)
Primary diagnosis: SPIGFD†, n (%)	21	21 (100)	50	43 (86.0)	38	35 (92.1)	17	17 (100)	87	63 (72.4)
Height SDS, mean (SD)	16	−5.62 (1.95)	50	−3.49 (1.15)	38	−3.44 (0.90)	15	−4.63 (1.51)	77	−3.61 (1.20)
Height velocity (cm/year), mean (SD)	7	5.67 (1.10)	35	4.99 (1.66)	18	4.19 (1.98)	12	4.43 (1.23)	52	4.70 (1.84)
IGF-1 (ng/mL), median (Q1; Q3)	9	37.00 (25.00; 38.93)	42	68.25 (31.30; 110.00)	35	91.00 (61.00; 139.00)	13	246.00 (62.00; 462.00)	78	105.50 (60.00; 171.10)

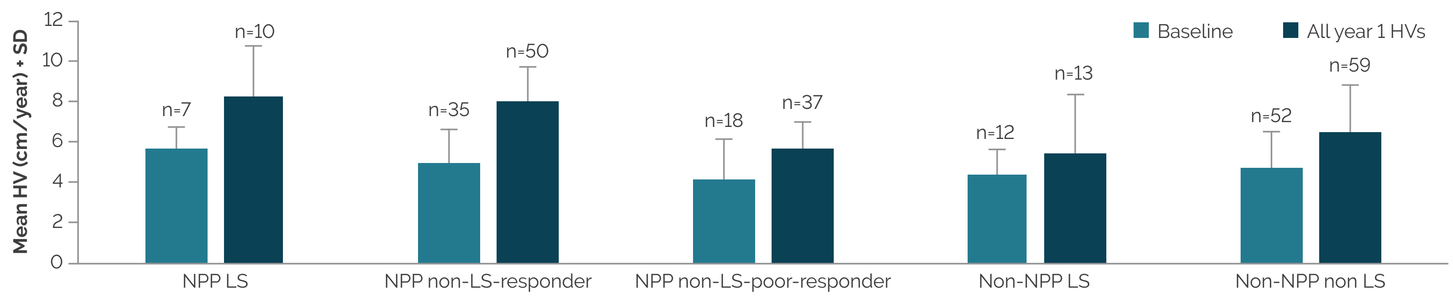
*Number of patients with available data; †including LS. Responders were defined as patients with change in height SDS in year 1 of ≥0.3; poor responders were defined as patients with change in height SDS in year 1 of <0.3. BMI, body mass index; GH, growth hormone; IGF-1; insulin-like growth factor-1; non-NPP, not treatment naïve and/or pubertal; NPP, treatment-naïve and prepubertal; LS, Laron syndrome; SD, standard deviation; SDS, standard deviation score; SPIGFD, severe primary IGF-1 deficiency.

Figure 1. Effect of rhIGF-1 therapy on A) Height SDS; and B) Height velocity (registry population)

A)

	NPP						Non-NPP			
			Non LS							
	LS (N=21)		Responder (N=50)		Poor responder (N=38)		LS (N=17)		Non LS (N=87)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	16	−5.62 (1.95)	50	−3.49 (1.15)	38	−3.44 (0.90)	15	−4.63 (1.51)	76	−3.60 (1.20)
Year 1	15	−4.68 (1.83)	50	−2.85 (1.11)	38	−3.44 (0.96)	14	−4.27 (1.60)	70	−3.40 (1.32)
Change from baseline	10	0.70 (0.56)	50	0.64 (0.26)	38	0.01 (0.21)	14	0.19 (0.50)	62	0.24 (0.47)

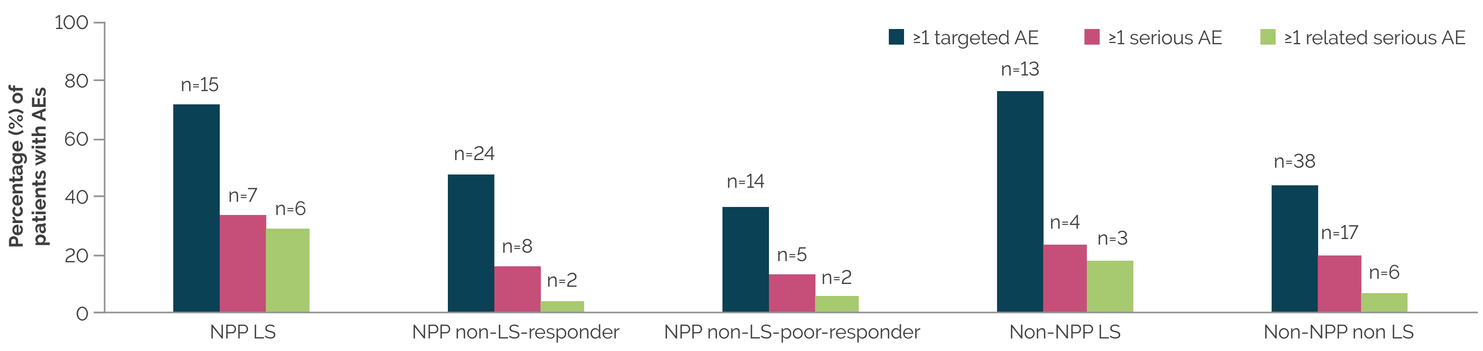
B)



Responders were defined as patients with change in height SDS in year 1 of ≥0.3. Poor responders were defined as patients with change in height SDS in year 1 of <0.3. HV, height velocity; LS, Laron syndrome; non-NPP, not treatment naïve and/or pubertal; n, number of patients with available data at each time point; NPP, treatment-naïve and prepubertal; rhIGF-1, recombinant human insulin-like growth factor-1 SD, standard deviation; SDS, standard deviation score.

Figure 2. Safety profile of rhIGF-1 therapy: A) Summary of AEs and B) Most common targeted AEs (safety population)

A)



B)

Most common targeted AEs	NPP						Non-NPP			
			Non LS							
	LS (N=21)		Responder (N=50)		Poor responder (N=38)		LS (N=17)		Non LS (N=87)	
	NAE	n, (%)	NAE	n, (%)	NAE	n, (%)	NAE	n, (%)	NAE	n, (%)
Hypoglycaemia	21	11 (52.4)	21	12 (24.0)	7	5 (13.2)	8	7 (41.2)	33	15 (17.4)
Tonsillar hypertrophy	7	5 (23.8)	6	6 (12.0)	2	2 (5.3)	2	2 (11.8)	4	3 (3.5)
Lipohypertrophy	5	4 (19.0)	10	7 (14.0)	2	2 (5.3)	3	3 (17.6)	8	7 (8.1)
Injection site reaction	2	2 (9.5)	8	5 (13.2)	4	3 (6.0)	–	–	13	11 (12.8)
Headache	3	2 (9.5)	9	5 (10.0)	6	6 (15.8)	3	2 (11.8)	16	10 (11.6)
Sleep apnoea syndrome	2	2 (9.5)	–	–	–	–	–	–	2	2 (2.3)
Otitis media	5	1 (4.8)	9	8 (16.0)	–	–	4	4 (23.5)	4	3 (3.5)
Acromegaly*	1	1 (4.8)	–	–	–	–	3	3 (17.6)	7	6 (7.0)
Deafness	–	–	5	4 (8.0)	–	–	1	1 (5.9)	–	–
Gynaecomastia	–	–	–	–	–	–	2	2 (2.3)	1	1 (5.9)

*Acromegalic facial changes, not acromegaly (coding constraint). Most common targeted AEs are those reported by ≥5% patients. Responders were defined as patients with change in height SDS in year 1 of ≥0.3. Poor responders were defined as patients with change in height SDS in year 1 of <0.3. AE, adverse event; LS, Laron syndrome; n, number of patients; non-NPP, not treatment naïve and/or pubertal; NPP, treatment-naïve and prepubertal; NAE, number of adverse events; SD, standard deviation; SDS, standard deviation score.

Safety

- Safety is summarised in **Figure 2**.
- In the non-NPP LS, and the NPP LS subgroups, targeted AEs were highest (76.5 and 71.4% respectively).
- The targeted AE reported in the greatest proportion of patients was hypoglycaemia, except in patients who were NPP non-LS-poor-responders (headache).

CONCLUSIONS

- Patients who were NPP responded better to rhIGF-1 treatment than those who were non-NPP, in terms of height SDS and HV improvements at year 1.
- Patients who were NPP with LS were younger and shorter than those who were NPP non-LS at first rhIGF-1 intake, and showed a slightly better response at year 1.
- Compared with other subgroups, patients in the NPP with LS and NPP non-LS-responders subgroups had:
  - Lower mean age at first rhIGF-1 intake.
  - Higher mean height SDS changes from baseline at year 1.
  - Trends toward higher year-1 HVs.
- Safety is consistent with the known profile of rhIGF-1 in all 5 subgroups.

References

1. FDA. Increlex - Package insert 2016
2. EMA. Increlex - Summary of Product Characteristics 2017
3. Ranke M. *Horm Res* 1995
4. Chernausek S. *J Clin Endocrinol Metab* 2007
5. Bang P. *Horm Res Paediatr* 2015
6. Bang P. *Horm Res Paediatr* 2016
7. Sempé M. Théraplix, Paris 1979
8. Cole TJ. *Eur J Clin Nutr* 1999
9. www.rki.de/DE/Content/Gesundheitmonitoring/Gesundheitberichterstattung/GBEDownloadsB/referenzperzentile/einzelkapitel_tab.html
10. Bang P. *Horm Res Paediatr* 2015

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