Characteristics of responders and poor responders to Increlex® therapy – data from children enrolled in the European Increlex® Growth Forum Database (EU-IGFD)

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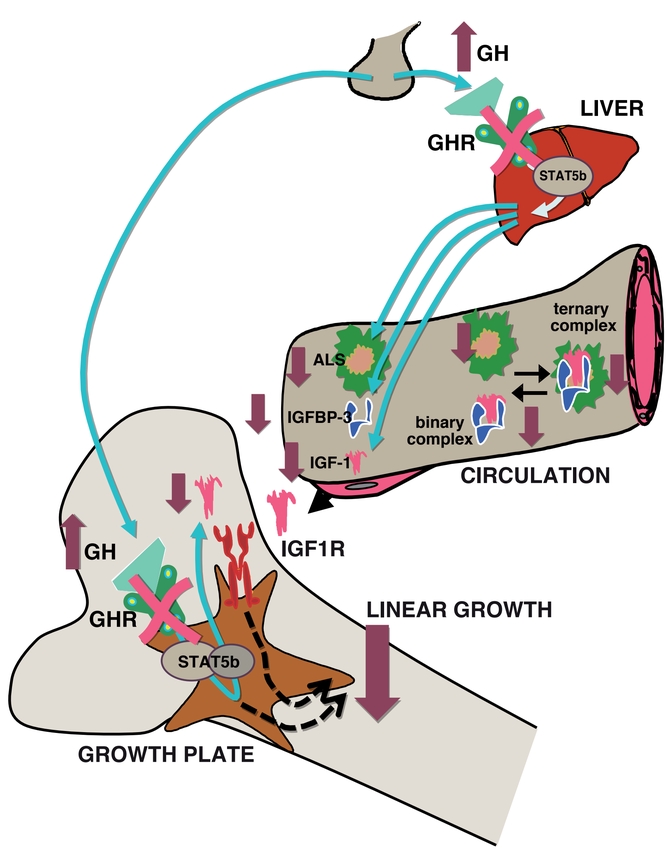
Introduction

- The growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis is crucial for affecting post-natal growth and is defective in severe primary IGF-1 deficiency (SPIGFD) (**Figure 1**).
- Increlex® (mecasermin [rDNA origin] injection) is recombinant human IGF-1 (rhIGF-1) approved for the treatment of SPIGFD.
- European Medicines Agency (EMA) criteria for rhIGF-1 therapy in SPIGFD are:
  - Height standard deviation score (SDS) ≤-3
  - IGF-1 serum concentration <2.5th percentile
  - GH sufficiency
  - Exclusion of acquired forms of IGF-1 deficiency, such as malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Figure 1. The growth hormone/insulin-like growth factor 1 axis in SPIGFD caused by a GH receptor defect



ALS, acid-labile subunit; GH, growth hormone; GHR, growth hormone receptor; IGF-1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; IGFBP-3, insulin-like growth factor-binding protein 3; STAT5B, signal transducer and activator of transcription 5B

EU Increlex® Growth Forum Database registry

- As part of the Risk Management Plan, patients starting rhIGF-1 therapy should be registered on the European Increlex® Growth Forum Database (EU-IGFD) registry.
- Multicentre, open-label, observational study.
- Initiated in December 2008 to monitor long-term safety (primary objective) and effectiveness (secondary objective) of Increlex® (rhIGF-1) in children with growth failure in 10 countries in Europe.
- Ongoing and recruiting new patients, using electronic case report form (eCRF) data collection.

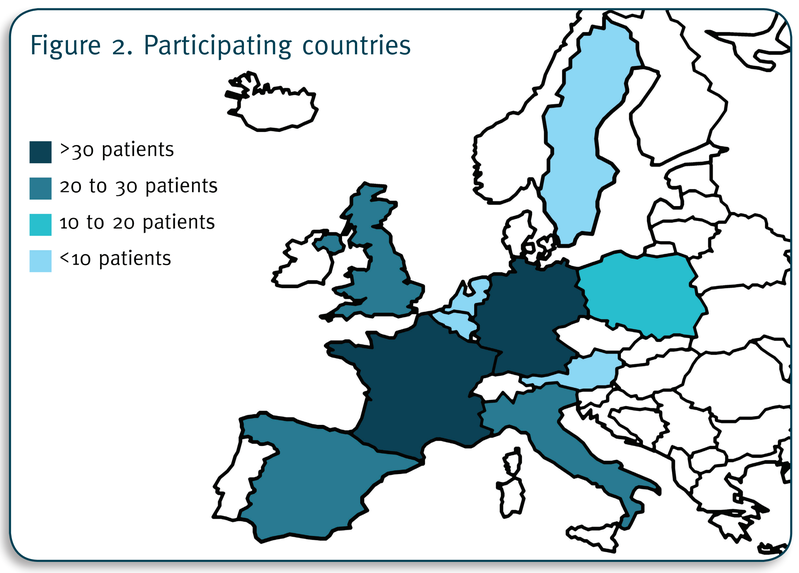
Objectives

- To better understand the determinants which are influencing the response to Increlex® therapy in treatment-naive prepubertal patients (NPP):
  - Describe baseline characteristics of patients according to the level of response to Increlex® therapy
  - Describe effectiveness and safety according to the level of response to Increlex® therapy.

Study population

- Cut-off date for the database: 6th October 2015.
- 221 patients enrolled from 10 countries (**Figure 2**).
- 93 NPP were eligible for this analysis.
  - Responders defined as: Year 1 change in height SDS ≥0.3; n=55 (59%).
  - Poor responders defined as: Year 1 change in height SDS <0.3; n=38 (41%).
- We have previously suggested to define a responder to rhGH therapy as anyone with a Year 1 change in height SDS of ≥0.5. This difference should reflect the fact that patients with Laron syndrome (SPIGFD caused by a GH receptor defect) gain less height with rh1GF-1 treatment than do patients with severe GH deficiency receiving rhGH.

Figure 2. Participating countries



Baseline characteristics

	Responders (n=55)	Poor responders (n=38)
Boys, n (%)	32 (58)	25 (66)
Laron syndrome, n (%)	7 (13)	3 (8)
Age at first dose, mean (SD) years	7.2 (3.0)	10.1 (3.9)*
Weight SDS at first dose, mean (SD)	-3.2 (1.1)	-3.3 (0.9)
Height SDS at first dose, mean (SD)	-3.7 (1.4)	-3.5 (1.1)
Mid parental adult height, mean (SD) cm	165.7 (8.7)	168.2 (9.3)
IGF-1 concentration, mean (SD) ng/ml	84.7 (69.1) (n=44)	108.8 (78.9) (n=34)

IGF-1, insulin-like growth factor 1; SD, standard deviation; SDS, standard deviation score
*Effect of age in group assignment: odds ratio [95% confidence intervals] = 0.78 [0.69; 0.90]; p<0.001; responders are significantly younger

Treatment characteristics

	Responders (n=55)	Poor responders (n=38)
Treatment duration, median (95% confidence intervals) days	1381 (1167–1829)	1221 (891–1422)
Dose at initiation, median (Q1; Q3) µg/kg BID	40 (20; 40)	40 (20; 40)
Dose at Year 1, median (Q1; Q3) µg/kg BID	120 (80; 120)	107 (100; 120)
Dose at Year 2, median (Q1; Q3) µg/kg BID	120 (90; 120)	120 (100; 120)

*BID, twice daily

Effectiveness

	n*	Height (SDS)	Δheight (SDS)	n*	HtV (cm/year)	n*	Δheight (cm/year)
Responders							
Baseline	55	-3.7 (1.4)	–	36	5.2 (1.6)	–	–
Year 1	55	-3.0 (1.3)	0.7 (0.3)	55	8.3 (1.7)	36	3.0 (2.1)
Year 2	43	-2.7 (1.3)	1.0 (0.6)	38	6.4 (1.4)	25	1.7 (1.7)
Poor responders							
Baseline	38	-3.5 (1.1)	–	17	4.3 (2.0)	–	–
Year 1	38	-3.5 (1.1)	0.0 (0.2)	36	5.7 (1.4)	15	1.1 (2.8)
Year 2	30	-3.5 (1.2)	0.2 (0.4)	30	6.0 (1.8)	13	2.0 (3.2)

HtV was annualised. Mean (SD) values are presented.
*Number of available data
HtV, height velocity; SDS, standard deviation score

Safety

	Responders (n=55) n (%)	Poor responders (n=38) n (%)
Patients with ≥1 TEAE	30 (55)	18 (47)
Patients with ≥1 serious TEAE	5 (9)	5 (13)
Patients with ≥1 serious targeted TEAE	1 (2)	1 (3)
Patients with ≥1 non-serious targeted TEAE	24 (44)	14 (37)
Most common targeted adverse events		
Hypoglycemia	11 (20)	6 (16)
Headache	6 (11)	5 (13)
Tonsillar hypertrophy	5 (9)	4 (11)
Lipohypertrophy	8 (15)	1 (3)
Otitis media	5 (9)	1 (3)

TEAE, treatment-emergent adverse event

Conclusions

- Response to treatment with Increlex® in NPP is positively related to a younger age at treatment initiation, poor responders being older.
  - No other predictor of response to Increlex® in NPP has been identified
- The safety profile is consistent with previous reports, independent of the level of response to Increlex®
- On a group level, poor responders do not show any significant catch-up growth over the second year of treatment
  - The first-year response to Increlex® should be evaluated and a decision whether to continue treatment taken.

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