Supplementary materials

Non-treatment-naïve and/or pubertal patient subgroup analysis

More than half of both non-treatment-naïve/prepubertal subgroups were prepubertal. Although 81% of the non-treatment-naïve/prepubertal Laron syndrome subgroup received rhIGF-1 therapy prior to enrolment in the Eu-IGFD Registry (Table S1), patients had a significantly shorter stature, significantly higher BMI SDS and peak stimulated GH level, and were significantly more likely to have history of hypoglycaemia than the non-treatment-naïve/prepubertal patients without Laron syndrome at baseline (Table S2). The non-treatment-naïve/prepubertal Laron syndrome subgroup was treated with rhIGF-1 therapy for longer (*P*=0.004) and had a higher starting dose compared with the non-treatment-naïve/prepubertal patients without Laron syndrome (median [Q1; Q3]: 90 [40; 100] versus 40 [40; 40] µg/kg BID; *P*=0.001), however, no significant difference in doses were observed from years 1-5 (median: 112-120 µg/kg BID). Changes in height, height velocity (Table S3 and S4), BMI and weight (Table S5 and S6) for the non-treatment-naïve/prepubertal subgroups should be interpreted with caution, due to the heterogeneity of the subgroups (Table S1).

Discussion of the non-treatment-naïve and/or pubertal patient subgroup data

As expected, the non-treatment-naïve/prepubertal Laron syndrome subgroup had higher GH levels than the non-treatment-naïve/prepubertal patients without Laron syndrome at baseline, while the higher mean serum IGF-1 in the non-treatment-naïve/prepubertal Laron syndrome subgroup at baseline was not expected given that levels of IGF-binding protein-3 and ALS are GH-dependent. However, a high percentage of the non-treatment-naïve/prepubertal Laron syndrome subgroup had been previously treated with rhIGF-1 therapy, which may have elevated the baseline IGF-1 levels, depending on how soon treatment occurred prior to sample collection [1].

The heterogeneity of the non- treatment-naïve/prepubertal subgroups does not allow for meaningful reporting, therefore we refrain from interpreting the effectiveness of rhIGF-1 therapy in these patients. The majority of patients in the non-treatment-naïve/prepubertal Laron syndrome subgroup were likely to have had their catch-up growth prior to entering the Eu-IGFD Registry, and therefore were not expected to gain much additional height during pubertal years. This has been observed in patients with GH deficiency receiving GH for many prepubertal years [2] and is also in accordance with the dynamics of catch-up growth in response to rhIGF-1 therapy in patients with Laron syndrome/SPIGFD reported here. Again, these data should be interpreted with caution until adult height data analyses are available.

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References

1. Ekstrom K, Carlsson-Skwirut C, Ritzen EM & Bang P. Insulin-like growth factor-I and insulin-like growth factor binding protein-3 cotreatment versus insulin-like growth factor-I alone in two brothers with growth hormone insensitivity syndrome: effects on insulin sensitivity, body composition and linear growth. *Horm Res Paediatr* 2011 **76** 355-366.
2. Polak M, Blair J, Kotnik P, Pournara E, Pedersen BT & Rohrer TR. Early growth hormone treatment start in childhood growth hormone deficiency improves near adult height: analysis from NordiNet(R) International Outcome Study. *Eur J Endocrinol* 2017 **177** 421-429.