LB-1

A trial investigating the long-term efficacy and safety of two doses of Norditropin® (somatropin; recombinant human growth hormone) in Japanese children with short stature due to Noonan syndrome over four years of treatment

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Objective

To evaluate the growth-promoting effect and safety of Norditropin® (somatropin; recombinant human growth hormone) in Japanese children with short stature due to Noonan syndrome (NS), during a treatment period of four years.

Introduction

- NS is a genetically heterogeneous disorder caused by up-regulated RAS-MAPK signaling, typically inherited in an autosomal dominant manner, although it may also arise due to a *de novo* mutation.[1-3]
- Short stature affects up to 70% of children with NS.[4]
  - In childhood, growth is often below −2 standard deviation score (SDS) of the growth curve of normal children and puberty is often delayed.[4,5]
- Mechanisms for short stature in NS are heterogeneous and include growth hormone (GH) deficiency, neurosecretory dysfunction, and GH resistance.[2,4]
- Norditropin® (NN-220; somatropin; Novo Nordisk A/S, Denmark) is a human GH synthesized by recombinant DNA technology. It is approved in more than 100 countries for the treatment of various GH disorders in children, including short stature due to NS in Japan. The latter indication was approved based on results from the 104-week pivotal phase of the present trial, in which treatment with 0.033 mg/kg/day and 0.066 mg/kg/day GH was shown to improve height SDS (HSDS) in Japanese children with NS without safety issues.[6]
- Here, we show results of the pivotal and extension phase of the trial evaluating the efficacy and safety of 208 weeks of treatment with two doses of GH in Japanese children with short stature due to NS.

Methods

Design, patient population and endpoints

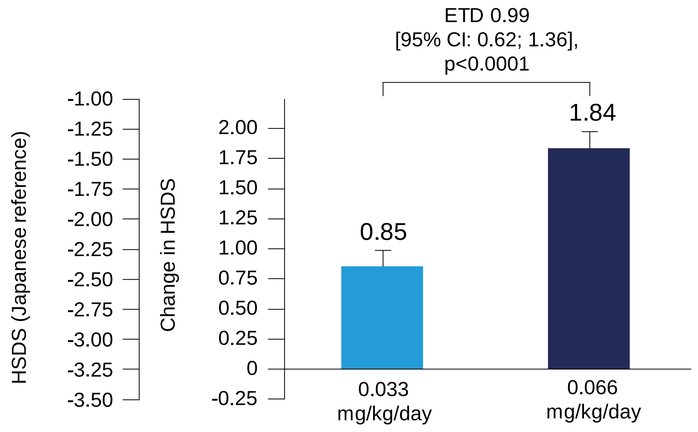
- This was a multicenter, randomized, parallel-group, double-blind trial (NCT01927861).
- Pre-pubertal children diagnosed with NS were randomized 1:1 to receive GH 0.033 mg/kg/day or 0.066 mg/kg/day as a once-daily subcutaneous injection.
- Children were treated for 104 weeks in the pivotal phase and for further 104 weeks in an extension phase, resulting in a total of 208 weeks of treatment. The extension phase could be extended to 234 weeks for subjects who agreed to continue treatment after completion of 208 weeks' treatment.
- The primary efficacy endpoint was change in HSDS from baseline to 104 weeks of treatment based on Japanese national reference data for children (Japanese reference).
- Secondary efficacy endpoints included change in HSDS from baseline to 208 weeks of treatment based on the Japanese reference as well as on reference data from Japanese patients with NS (NS reference), and height velocity SDS both from 104 to 156 weeks and 156 to 208 weeks of treatment.
- Secondary safety endpoints included the incidence of treatment-emergent adverse events (TEAEs), changes from baseline to 208 weeks of treatment in insulin-like growth factor-I (IGF-I), HbA_{1c}, clinical laboratory tests, glucose tolerance, bone age and bone age/chronological age.
- Change in HSDS was assessed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline HSDS as a covariate.

Results

Patient disposition and demographics

- From August 2013 to July 2018, 51 patients (19 girls and 32 boys) were enrolled at 26 sites in Japan.
  - 25 children were randomized to the 0.033 mg/kg/day group and 26 children to the 0.066 mg/kg/day group.
  - 48 subjects completed the pivotal and extension phase.
  - Three subjects in the 0.066 mg/kg/day group were withdrawn from the trial during the extension phase.
- Mean age [mean±SD] at baseline was 6.57±2.42 years in the 0.033 mg/kg/day group and 6.06±2.25 in the 0.066 mg/kg/day group.
- Baseline HSDS [mean±SD] was similar between groups:
  - Based on the Japanese reference 0.033 mg/kg/day: –3.24±0.76; 0.066 mg/kg/day: –3.25±0.71.
  - Based on the NS reference 0.033 mg/kg/day: –0.73±0.74; 0.066 mg/kg/day: –0.80±0.72.
- Overall, no clinically relevant differences between the two treatment groups were observed at baseline.
- The mean duration of exposure (including exposure data of patients with an extended treatment of 234 weeks) was 4.29 years in the 0.033 mg/kg/day group and 4.16 years in the 0.066 mg/kg/day group.
  - There were no differences in total exposure between the two GH treatment groups (0.033 mg/kg/day: 107.2 subject years; 0.066 mg/kg/day: 108.1 subject years).

Figure 1 ♦ HSDS and change in HSDS at 208 weeks in the two GH treatment groups

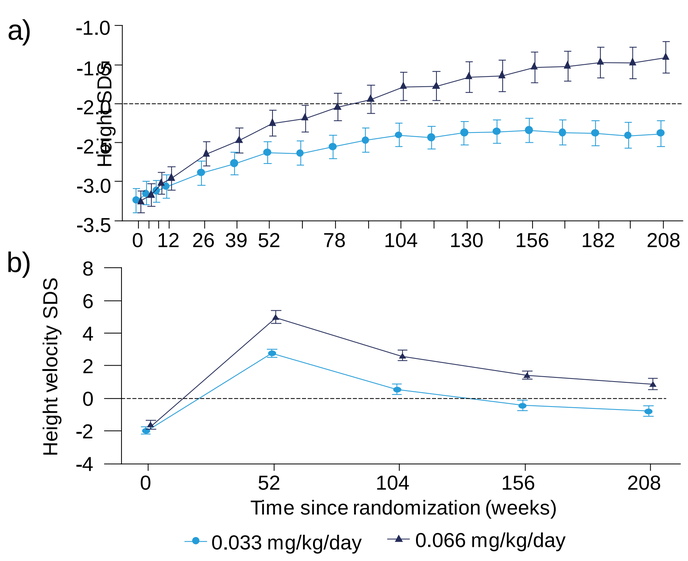


Solid line is the total average value at baseline (−3.24). Mean estimates ± standard error. CI, confidence interval; ETD, estimated treatment difference in HSDS for 0.066 mg/kg/day vs. 0.033 mg/kg/day GH; GH, growth hormone; HSDS, height standard deviation score.

Efficacy

- After 208 weeks of treatment, the estimated change in HSDS relative to the Japanese reference was 0.85 (95% CI: 0.59; 1.12) in the 0.033 mg/kg/day group and 1.84 (95% CI: 1.58; 2.10) in the 0.066 mg/kg/day group, with an estimated mean difference of 0.99 (95% CI: 0.62; 1.36), p<0.0001 (**Figure 1**).
- Mean HSDS based on the Japanese reference improved from −3.24 at baseline to −2.39 (0.033 mg/kg/day) and from −3.25 to −1.41 (0.066 mg/kg/day) after 208 weeks of treatment based on last observation carried forward imputed data (LOCF) (**Figure 2a**).
- Eight subjects (32.0%) in the 0.033 mg/kg/day group and 20 subjects (76.9%) in the 0.066 mg/kg/day group had a HSDS above −2.0 based on the Japanese reference after 208 weeks of treatment (LOCF) compared with none at baseline.
- When analyzed according to the NS reference data, the increase in HSDS was also significantly greater with 0.066 mg/kg/day compared with 0.033 mg/kg/day, with an estimated mean difference of 0.95 (95% CI: 0.65; 1.25), p<0.0001.
- Mean height velocity SDS increased from baseline values of −1.99 (0.033 mg/kg/day) and −1.70 (0.066 mg/kg/day) to 0.58 and 2.65, respectively, after two years of treatment, and remained higher than baseline after three years (−0.39 and 1.44) and four years (−0.73 and 0.92) of treatment (**Figure 2b**).

Figure 2 ♦ Height SDS (a) and height velocity SDS (b) in the two GH treatment groups



Mean ± standard error. a) Dashed line represents the lower end of the height SDS range for the Japanese national reference population (−2 SDS). b) Baseline: Height velocity SDS from 1 year prior to screening to week 0. Dashed line represents the middle of the height velocity SDS range for the Japanese national reference population. GH, growth hormone; SDS, standard deviation score.

Table 1 ♦ Overview of ADRs by SOC and preferred term.*

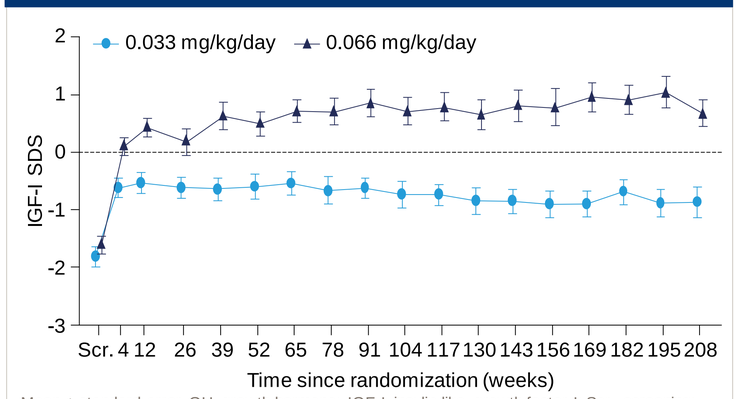
	0.033 mg/kg/day GH N = 25				*0.066 mg/kg/day GH N = 26*			
	N	*%*	*E*	*Rate*	*N*	*%*	*E*	*Rate*
ADR	8	32.0	14	13	11	42.3	12	11
Metabolism and nutrition disorders	0	-	-	-	4	15.4	4	4
Hyperinsulinemia	0	-	-	-	2	7.7	2	2
Glucose tolerance impaired	0	-	-	-	1	3.8	1	1
Insulin resistance	0	-	-	-	1	3.8	1	1
Musculoskeletal and connective tissue disorders	1	4.0	1	1	3	11.5	3	3
Arthralgia	0	-	-	-	1	3.8	1	1
Polymyositis	0	-	-	-	1	3.8	1	1
Scoliosis	0	-	-	-	1	3.8	1	1
Sever's disease	1	4.0	1	1	0	-	-	-
Respiratory, thoracic and mediastinal disorders	3	12	3	3	1	3.8	1	1
Asthma	0	-	-	-	1	3.8	1	1
Nasal polyps	1	4.0	1	1	0	-	-	-
Rhinorrhea	1	4.0	1	1	0	-	-	-
Tonsillar hypertrophy	1	4.0	1	1	0	-	-	-

*≥10% of patients in SOC; ADR, adverse drug reaction; E, number of events; GH, growth hormone; N, number of patients; Rate, event rate per 100 exposure years; %, percentage of patients; SOC, system organ class.

Safety

- Rates and patterns of TEAEs and the frequency of serious TEAEs during 208 and 234 weeks of treatment were similar between groups.
- An overview of adverse drug reactions (ADRs) showing ADRs occurring in ≥10% of patients in a given system organ class (SOC) is shown in **Table 1**.
- Three patients receiving 0.066 mg/kg/day GH were withdrawn; two due to 'polymyositis' and 'scoliosis' TEAEs at days 1041 and 1289, respectively, one because he reached average height.
- There was no evidence of a negative effect of GH on cardiac function.
  - All nine cardiac events reported occurred in four subjects with existing congenital heart disorders.
- An initial steep increase in mean IGF-I SDS was observed in the first four weeks of treatment, after which it remained stable (**Figure 3**).
- Estimated mean IGF-I SDS increased from –1.71 at baseline to –0.75 (0.033 mg/kg/day) and to 0.57 (0.066 mg/kg/day) after 208 weeks of treatment.

Figure 3 ♦ Mean IGF-I SDS in the two GH treatment groups over time



Mean ± standard error. GH, growth hormone; IGF-I, insulin-like growth factor-I; Scr., screening; SDS, standard deviation score.

- Bone age/chronological age ratios approached 1.0 after 208 weeks (0.033 mg/kg/day: 0.88; 0.066 mg/kg/day: 0.96).
- In both groups, there were only minor HbA_{1c} changes, similar oral glucose tolerance test (OGTT) insulin response increases and no clinically relevant changes in OGTT blood glucose, vital signs, electrocardiogram or transthoracic echocardiography.

Conclusions

- Japanese children with short stature due to NS, treated with 0.033 or 0.066 mg/kg/day GH for 208 weeks, showed an improved HSDS compared to baseline.
- The increase in HSDS was significantly greater with 0.066 mg/kg/day GH vs. 0.033 mg/kg/day.
- Treatment with GH was well-tolerated with no new safety concerns.

Conflict of interest disclosures

YM and SY have nothing to declare. TE, KN and YO are employees of Novo Nordisk Pharma Ltd. RH, TO and KO have received lecture fees and research grants from Novo Nordisk Pharma Ltd. KO has further received lecture fees from Kyowa-Kirin and Alexion and research grants from Ribomic. TO and KO have received scholarship donations from Novo Nordisk Pharma Ltd.

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