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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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.1,2

• Short stature affects up to 70% of children with NS.3–6 In children, growth is often below –2 standard deviation score (SDS) of the growth curve of normal children and growth is often delayed.4,5

• Mechanisms for short stature in NS are heterogeneous and include growth hormone (GH) deficiency, neurosecretory dysfunction, and GH resistance.6,7

• 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.10

• The indication was approved based on results from the 104-week pivotal phase of the present trial, in which treatment with 0.33 mg/kg/day and 0.666 mg/kg/day was shown to improve height SDS (HSDS) in Japanese children with NS without safety issues.6

• Here, we report the results of the 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 0.33 mg/kg/day or 0.666 mg/kg/day as a once-daily subcutaneous injection.

• Children were treated for 104 weeks in the pivotal phase and for another 104 weeks in an extension phase, resulting in a total of 208 weeks of treatment. The extension phase could be extended to 254 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).6

• Secondary efficacy endpoints included change in HSDS from baseline to 208 weeks of treatment based on the Japanese reference as well as reference data from Japanese patients with NS (JSI 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 (IGF), HbA1c, clinical laboratory tests, glucose tolerance, bone age and bone age/chronological age.8

• 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 treated 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.46 subjects completed the pivotal and extension phases.

• 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±4.22 years in the 0.033 mg/kg/day group and 6.06±2.25 in the 0.066 mg/kg/day group.

• Baseline HSDS (means/SD) was similar between groups:

  • Based on the Japanese reference 0.033 mg/kg/day: 0.50±0.40
  • Based on the JSI reference 0.033 mg/kg/day: 0.66±0.66
  • Baseline HSDS (means/SD) was similar between groups:

  • Based on the Japanese reference 0.033 mg/kg/day: 0.50±0.40
  • Based on the JSI reference 0.033 mg/kg/day: 0.66±0.66

– 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 (mean: 0.066 mg/kg/day; 108.1 subject years).

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).

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 ≥10% of patients in a given system organ class (SOC) are 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 2089, respectively, 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.

• 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.

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

References

Table 1 Overview of ADRs by SOC and preferred term.

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Poster presented at: