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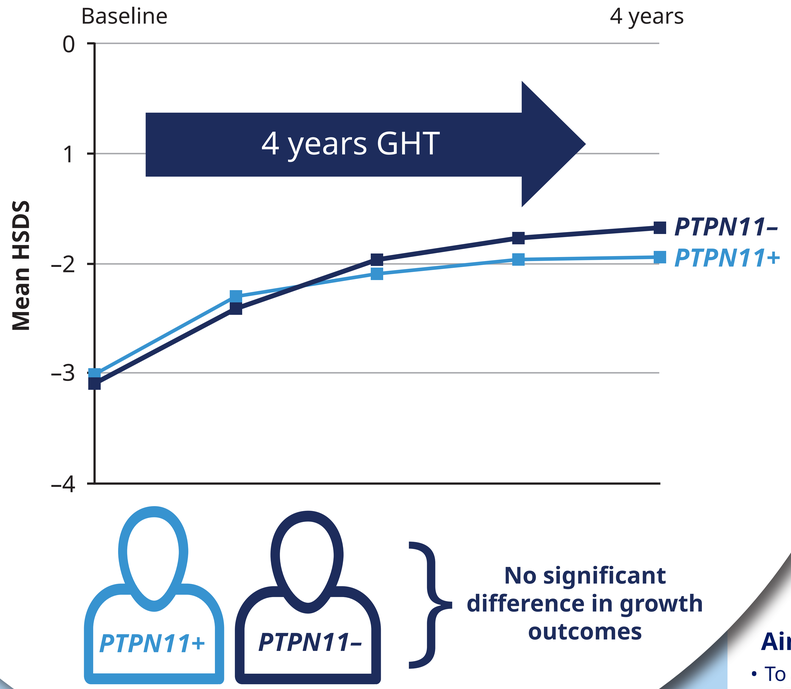

Following 4 years of growth hormone treatment, growth outcomes were similar in pre-pubertal *PTPN11*-positive and *PTPN11*-negative Noonan syndrome patients.

Outcomes in growth hormone-treated Noonan syndrome children: impact of *PTPN11* mutation status

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BACKGROUND & AIMS

- A higher prevalence of short stature is reported among Noonan syndrome (NS) patients with a *PTPN11* mutation compared with NS patients with other mutations.[1]
- Norditropin® (somatropin; Novo Nordisk A/S) is approved for the treatment of short stature in children with NS.
- The effectiveness of growth hormone therapy (GHT) in treating short stature due to NS has been previously demonstrated, although data on the effect of *PTPN11* mutation status on long-term GHT outcomes are discordant.[2,3]

Aim

- To assess the impact of *PTPN11* mutation status on long-term effectiveness and safety outcomes in pre-pubertal NS patients receiving GHT.

MATERIAL & METHODS

- Pooled data from two studies were analysed:
  - The observational, multicentre American Norditropin Studies: Web-Enabled Research (ANSWER) Program® conducted in the US between 2002 and 2016[4]
  - The 3-year randomised, double-blind, phase 3 Norditropin® trial, GHLIQUID-4020, carried out in Japan.[5]
- Paediatric patients with clinically diagnosed NS and confirmed *PTPN11* mutation status were eligible for inclusion in this analysis.
- The safety analysis set (SAS) included all patients with confirmed *PTPN11* mutation status. The effectiveness analysis set (EAS) was a subset of the SAS and included pre-pubertal and GHT-naïve patients.
- Safety and effectiveness, as measured by height standard deviation score (HSDS) and change in HSDS (ΔHSDS) were assessed over 4 years of GHT.

CONCLUSIONS

- After 4 years of GHT, growth outcomes were improved in GHT-naïve, pre-pubertal NS patients, irrespective of *PTPN11* mutation status.
- Long-term safety data are reassuring regarding the safety of GHT in this population and are consistent with previous reports.[6,7]

RESULTS

- In total, 69 NS patients were included in the EAS: 49 patients (71%) were *PTPN11* positive and 20 (29%) were *PTPN11* negative.
- Baseline characteristics are shown in Table 1 and were similar between groups.

Table 1 Baseline characteristics (EAS, n=69)

	PTPN11+		*PTPN11–*	
	n		n	
Female, n (%)	49	16 (32.7)	20	6 (30.0)
Mean (SD) age at GH start (years)	49	6.4 (3.3)	20	6.4 (2.5)
Mean (SD) baseline GH dose (mg/kg/day)	48	0.047 (0.015)	20	0.054 (0.016)
Mean (SD) HSDS (national reference)[a]	49	–3.0 (0.8)	20	–3.1 (0.8)
Mean (SD) HSDS (NS population)[b]	48	–0.5 (0.8)	20	–0.6 (0.8)
Mean (SD) BMI SDS	47	–0.6 (1.3)	20	0.0 (1.1)

[a]Based on national reference growth charts; [b]Based on NS-specific growth charts.
Abbreviations: ΔHSDS, change in height standard deviation score; BMI, body mass index; GH, growth hormone; HSDS, height standard deviation score; NS, Noonan syndrome; SD, standard deviation; SDS, standard deviation score.

Figure 1a HSDS by year from baseline

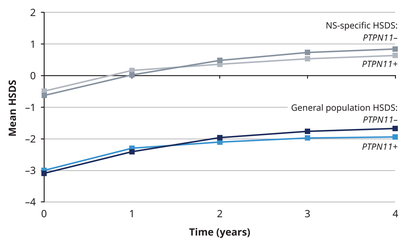
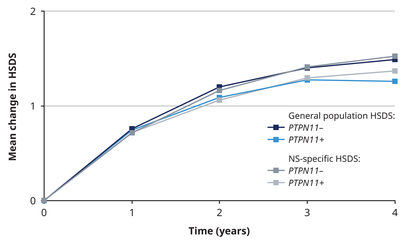


Figure 1b ΔHSDS by year from baseline



Growth outcomes

- No statistically significant differences in HSDS and ΔHSDS over 4 years of GHT were observed between *PTPN11+* and *PTPN11–* patients (Figures 1a and 1b).
- The mean (standard deviation [SD]) ΔHSDS from baseline at 4 years was +1.3 (0.8) for *PTPN11+* and +1.5 (0.7) for *PTPN11–* patients, based on general population reference data.
- There were no significant differences between *PTPN11+* and *PTPN11–* patients in the change in body mass index SD score from baseline (–0.02 vs –0.04, respectively).

Safety

- Of the SAS (n=113), 38 patients (33.6%) reported an adverse drug reaction or serious adverse event (SAE).
- The most frequently reported events were headache (n=5 events reported in five patients) and arthralgia (n=3 events reported in three patients).
- One SAE of atrial fibrillation was reported in a patient with a history of hypertrophic cardiomyopathy, although this was deemed unlikely related to GHT.

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Growth and syndromes (to include Turner syndrome)
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