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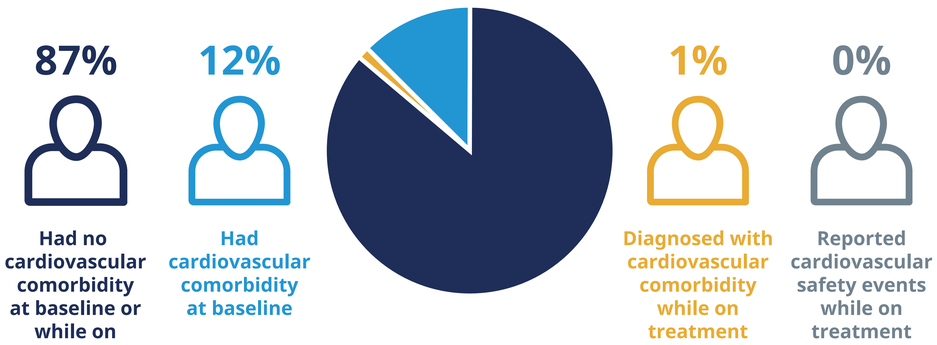
Real-world data demonstrated a favourable safety profile of growth hormone treatment in patients with Noonan syndrome



Safety of growth hormone and cardiovascular outcomes in patients with Noonan syndrome enrolled in NordiNet® International Outcome Study (IOS) and the ANSWER Program

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BACKGROUND & AIMS

- Growth hormone (GH) treatment improves height velocity and adult height in children with Noonan syndrome.[1,2]
- Noonan syndrome is commonly associated with cardiovascular (CV) anomalies, most commonly pulmonary stenosis and hypertrophic cardiomyopathy.[3]
- Concerns persist about the CV safety of GH treatment, despite data showing low rates of CV events and no change in left ventricular wall thickness.[4,5]
- This pooled analysis describes real-world evidence of the CV safety of GH treatment in patients with Noonan syndrome.

MATERIAL & METHODS

- Two non-interventional, multicentre studies (NordiNet® International Outcomes Study [IOS] and ANSWER Program) evaluating long-term effectiveness and safety of Norditropin® (Novo Nordisk A/S, Denmark) as prescribed by treating physicians in the clinical setting across 24 countries.[6]
- Safety events were reported by treating physicians and included serious adverse events, serious adverse reactions (SARs; related to GH treatment) and non-serious adverse reactions (related to GH treatment).
- CV comorbidities reported at baseline and throughout the studies were also recorded.

RESULTS

Patient population and baseline characteristics

- The safety analysis set (SAS) comprised 154 and 258 paediatric patients (naïve and non-naïve) with Noonan syndrome from the NordiNet® IOS and ANSWER Program (total n=412).
- Baseline characteristics were similar between patients in the SAS and those experiencing safety events (**Table 1**). An exception was height standard deviation score, which was lower in the latter group (p=0.322).

RESULTS

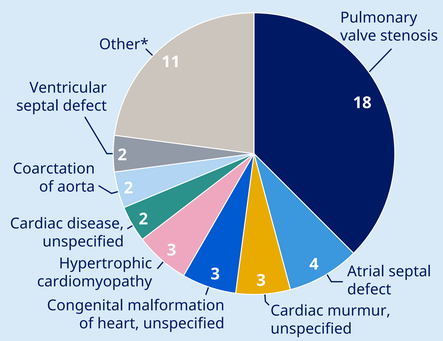
Table 1 Baseline characteristics

	SAS (n=412)		Patients with safety events (n=22)	
	n	Mean (SD)[†]	n	Mean (SD)[†]
Female/male, %	120/292	29.1/70.9	9/13	40.9/59.1
Age, years, mean (SD)	412	9.3 (3.9)	22	9.7 (4.1)
Height SDS,* mean (SD)	371	–2.65 (0.95)	17	–3.13 (0.79)
Weight SDS,* mean (SD)	308	–2.03 (1.31)	13	–2.57 (1.54)
Bone age/chronological age, mean (SD)	163	0.83 (0.19)	8	0.87 (0.10)
IGF-I SDS,[7] mean (SD)	162	–1.13 (1.62)	7	–1.22 (1.98)
GH dose at baseline (mg/kg/day), mean (SD)	404	0.044 (0.014)	21	0.040 (0.019)
GH-naïve at baseline, %	282	68.5	12	54.6
GH treatment duration (years), mean (SD)	412	3.1 (2.6)	22	3.3 (2.5)
Mean GH dose during study (mg/kg/day), mean (SD)	412	0.047 (0.014)	22	0.047 (0.016)

*Height and weight SDS were calculated using age- and gender-specific national references. [†]Unless otherwise specified.
GH, growth hormone; IGF-I, insulin-like growth factor-I; SAS, safety analysis set; SD, standard deviation; SDS, standard deviation score.

- Genotype data were available for 61 patients in ANSWER. *PTPN11* gene variants were most commonly observed (n=56), followed by *RAF1* (n=5), *KRAS* and *SOS1* (n=2 each) and *SHOC2* (n=1).
- Cardiac comorbidities at baseline were reported in 48 (11.7%) patients (**Figure 1**).
- Common concomitant medications included central nervous system stimulants (n=51), antihistamines (n=27) and thyroxine replacement therapy (n=21).

Figure 1 CV comorbidities at baseline



*Other includes one case of each: aortic valve disorder (unspecified), atrioventricular septal defect, benign and innocent cardiac murmurs, cardiac arrest with successful resuscitation, cardiomegaly, CV disease (unspecified), CV disorder originating perinatally (unspecified), mitral valve disease (unspecified), other pulmonary valve disorders, stenosis of pulmonary artery and tetralogy of Fallot. Patients could have >1 diagnosis in a given period.
CV, cardiovascular.

Safety events and comorbidities after GH treatment initiation

- In total, 22 patients experienced 34 safety events (**Table 2**).
- No CV safety events were reported in patients with Noonan syndrome.
- The most common safety events were headache (n=8) and arthralgia (n=5). Two SARs occurred in a single patient after 2.5 years of treatment.
- Five patients (1.2%) were diagnosed with CV comorbidities after initiation of GH treatment: unspecified CV disease (n=3), pulmonary valve stenosis (n=1) and ruptured abdominal aortic aneurysm (n=1).

Table 2 Summary of safety events

Preferred term	No. of safety events (n of patients)			Total n of safety events (total n of patients)
	NSAR	SAR	SAE not related to GH	
Headache	8 (7)			8 (7)
Arthralgia	5 (3)			5 (3)
Scoliosis	2 (2)		1 (1)	3 (3)
Myalgia	2 (2)			2 (2)
Condition aggravated	1 (1)		1 (1)	2 (2)
Brain neoplasm		1 (1)	1 (1)	2 (2)
Metastases to spine		1 (1)		1 (1)
Giant cell epulis			1 (1)	1 (1)
Epilepsy			1 (1)	1 (1)
Glioneuronal tumour			1 (1)	1 (1)
Spinal fusion surgery			1 (1)	1 (1)
Moyamoya disease			1 (1)	1 (1)
Other*	6 (5)			6 (5)
Total	**24 (17)**	**2 (1)**	**8 (5)**	**34 (22)**

*Other NSARs were oedema, injection-site erythema, growing pains, muscle spasms, off-label use and injection-site extravasation. A patient may have experienced >1 event.
GH, growth hormone; NSAR, non-serious adverse reaction; SAE, serious adverse event; SAR, serious adverse reaction.

CONCLUSIONS

- GH treatment was well tolerated in patients with Noonan syndrome, including those with existing CV comorbidities and those receiving concomitant medications.
- All CV complications were reported as comorbidities and may have been pre-existing at baseline.
- Further studies are warranted to assess the CV safety of GH treatment in patients with Noonan syndrome.

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