

Ascendis shoots higher on pivotal win



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Shares in the company surge after its weekly growth hormone treatment proves superior to daily injections, raising broader hopes for Ascendis's long-acting technology.

Ascendis has managed to surpass already high hopes for its long-acting human growth hormone, saying its once-weekly project TransCon hGH had proved itself superior to daily injections. Non-inferiority would have been enough to represent a real improvement in the treatment of human growth hormone deficiencies, and this finding could change the game for the asset.

The company is applying its technology, which can deliver unmodified parent molecules or drugs over a sustained period, to other indications. Investors are apparently already thinking big, looking to other poorly served diseases that could benefit from effective sustained-release options; Ascendis shares surged 65% in early trade, valuing the company at \$4.8bn.

The trial unveiled today was called Height, and recruited 161 children with growth hormone deficiency; two thirds were given TransCon hGH, and a third a daily hormone injection. The primary endpoint was annualised height velocity at one year, and the difference between the two cohorts was 0.86cm a year, generating a p value of $p=0.0088$.

No serious safety issues were seen, though spikes in insulin-like growth factor-1 were observed in a few patients, something that regulators could scrutinise closely. The company plans to file for approval in the first half of next year.

In the coming months a second phase III trial, Flight, will report; this is a slightly shorter study that follows patients switching from daily injections but is still important to confirm the safety and effectiveness of this therapy. Perhaps more importantly, a similarly unequivocal result will be needed to give the company a real shot at getting a superiority claim on the label, something that could make a huge difference commercially.

Previous attempts with long-acting growth hormones have broadly failed, which makes this finding even more notable. Versartis crashed out here with somavaratan in 2017, and the table below compares the two projects, with all the caveats of cross-trial comparison.

Cross-trial comparison of extended-release growth hormones

	<u>Height trial</u>		<u>Velocity trial</u>	
	TransCon hGH	Daily hGH	Somavaratan	Daily hGH
Annualised height velocity at 52 weeks	11.2cm/year	10.3cm/year	9.44cm/year	10.70cm/year

Source: company press releases.

Other once-weekly projects to watch include hGH-CTP (formerly known as Lagova), a collaboration between Pfizer and Opko Health, which could yield data towards the end of the year. Disappointing results in adults a couple of years ago make the outcome of the paediatric study hard to handicap.

Meanwhile Novo Nordisk, which markets a once-daily growth hormone, norditropin, and has had much success with long-acting insulins, is also one to keep an eye on. The company is some way behind in paediatrics, with a phase III trial of its once-weekly candidate somapacitan yet to start; mid-stage data presented earlier this year showed the agent to be non-inferior to Norditropin at two doses.

Results from Novo Nordisk's phase II Real 3 trial

	Somapacitan			Norditropin
	0.04mg/kg/wk	0.08mg/kg/wk	0.16mg/kg/wk	0.034mg/kg/day
Annualised height velocity at 26 weeks	8cm/year	10.9cm/year*	12.9cm/year*	11.4 cm/year

*Not significantly different to daily treatment. Source: company press release.

Somapacitan is a long-acting analogue of human growth hormone, modified to increase its binding to the plasma protein albumin, while hGH-CTP is a recombinant version of the hormone. Ascendis has long argued that delivering an unmodified growth hormone should produce better results, and investors sending the company's shares higher today are probably betting that the Height trial has gone some way to proving this.

The company has phase I projects looking at hypoparathyroidism and achondroplasia, although hopes for this technology must now be building beyond growth hormones, to other protein deficiencies. Ascendis has also made clear its ambitions to move into oncology. Presumably all further work would be easier with a partner, and today's data should make any talks that much easier.