Development of a Long-Acting Growth Hormone (LAGH): Size Matters

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Background

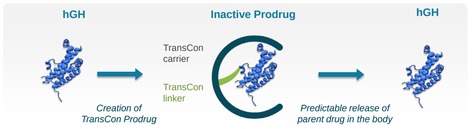
Over 500 million years of evolution, from fish to humans, growth hormone (GH) is highly conserved across species, ranging from 19.4 to 22 kDa in size.[1] GH interacts with receptors on virtually every cell.

Long-acting growth hormones (LAGHs) based on GH modification by protein enlargement leverage increased molecular size (ranging from about 47.5 kDa to over 100 kDa) to extend half-life by decreasing renal and receptor-mediated clearance.

Using various methodologies, however, molecular size has been investigated and found to compromise tissue penetration. Farnum et al have demonstrated that in a murine model, 40 kDa and larger dextrans do not enter the tibial growth plate.[2] And in a human whole-body physiologically-based pharmacokinetic model, Gill et al showed an inverse relationship between molecular size of therapeutic proteins and extravascular tissue distribution.[3]

These findings highlight the importance of GH size in maintaining natural tissue penetrance. Protein-enlarged GH analogues may have restricted access to GH receptors in some target tissues (such as growth plates and adipocytes) due to increased molecular size while still effectively stimulating normal hepatic IGF-1 production due to fenestrated (open) sinusoidal endothelium. Resulting altered tissue ratios of GH and IGF-1 may thus skew therapeutic results of GH therapy.

With these constraints in mind, a LAGH target product profile must be equivalent to daily GH in terms of safety, efficacy, and tolerability, ie, annualized height velocity (HV) on par with daily GH without metabolic complications. Ascendis Pharma A/S has developed TransCon GH, a novel LAGH prodrug in which GH is transiently linked to an inert carrier extending the half-life of the hormone. Unmodified 22 kDa GH, which is small enough to penetrate all tissues, is sustainably released via physiological pH- and temperature-induced linker autohydrolysis.



Clinical data suggested that TransCon GH was comparable to daily GH in terms of annualized HV and body mass index (BMI).[4]

Results – Annualized Height Velocity

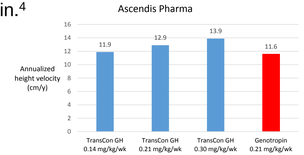
As much as 15-20% of height is estimated to be due to the direct effect of GH on growth plates.[5] Thus, to obtain efficacy on par with daily GH, novel LAGHs must ensure that both GH and IGF-1 contribute their share to growth, which is not possible if GH penetration of growth plates is compromised.

Three independent phase 2 trials evaluating LAGHs in roughly similar pediatric GHD populations have been recently conducted. Each molecule has a unique design (based on unmodified or modified GH) and therefore GH size:

	LAGH Design	GH Molecular Size (kDa)
TransCon GH	Unmodified GH	22
Somatrogon (MOD-4023)	Modified GH	47.5[a]
Somavaratan (VRS-317)	Modified GH	119

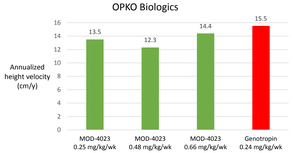
[a]Approximately (not including the O-linked glycans)[6]

Administration of TransCon GH (Ascendis Pharma A/S) led to an annualized HV of 12.9 cm/y compared to 11.6 cm/y for dose-equivalent Genotropin.[4]



Mean Age, y	8.2	8.4	7.5	7.7
Mean Bone Age, y	5.2	6.5	4.7	4.9
Mean Peak GH, µg/L	5.1	5.2	4.4	5.2
Mean Height SDS	-3.1	-2.8	-3.2	-3.3
Mean IGF-1 SDS	-2.0	-2.0	-2.2	-2.5

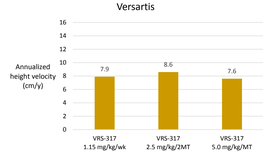
Administration of MOD-4023 (OPKO Biologics, Inc.) led to an annualized HV of 14.4 cm/y compared to 15.5 cm/y for Genotropin.[7]



Mean Age, y	6.4	5.3	6.1	5.4
Mean Bone Age, y	NA	NA	NA	NA
Mean Peak GH, µg/L	2.8	3.6	4.4	2.9
Mean Height SDS	-4.0	-3.8	-3.9	-4.8
Mean IGF-1 SDS	-2.5	-2.3	-1.8	-2.3

Abbreviation: NA, Not Available

Administration of Somavaratan (Versartis, Inc.) led to 8.6 cm/y when dosed twice monthly.[8]



Mean Age, y	7.5	8.0	8.0
Mean Bone Age, y	6.1	6.6	6.4
Mean Peak GH, µg/L	5.7	4.9	5.5
Mean Height SDS	-2.7	-2.5	-2.3
Mean IGF-1 SDS	-1.5	-2.0	-1.7

Although cross-study comparisons are challenging and no definitive conclusions can be made, these results suggest that increased size of the GH molecule may limit efficacy compared to the unmodified 22 kDa molecule. While it is possible to accelerate the effect of GH on height velocity with additional IGF-1,[9] it is undesirable to change the normal GH/IGF-1 interplay because of potentially undesirable effects of supraphysiological IGF-1.

Results – Adiposity Regulation

Similar to bone, altered fat tissue ratios of GH and IGF-1 due to protein enlargement may also alter normal adiposity regulation. GH is lipolytic whereas IGF-1 is lipogenic. If a modified GH molecule is unable to access GH receptors on fat cells, the oversupply of IGF-1 molecules may result in fat deposition, increasing BMI.

In 3 post-approval pediatric GHD registries, BMI SDS remained relatively stable during the first year(s) following daily GH treatment initiation. In a phase 2 study of GHD children, TransCon GH showed a similar stability in BMI SDS over 6 months whereas Somavaratan showed increases in BMI.

	LAGH Formulation	n	Time on GH Treatment	Δ BMI (kg/m²)	Δ BMI SDS
Daily GH Registry (ANSWER)	NA	1943	3 years		+0.23
Daily GH Registry (NCGS)	NA	1891	12 months		-0.30
Daily GH Registry (KIGS)	NA	2643	4+ years		+0.29
TransCon GH 0.14 mg GH/kg/wk[4]	Unmodified	12	6 months	-0.04	-0.13
TransCon GH 0.21 mg GH/kg/wk	Unmodified	14	6 months	+0.36	+0.15
TransCon GH 0.30 mg GH/kg/wk	Unmodified	14	6 months	-0.26	-0.26
TransCon GH (all 3 cohorts)	Unmodified	40	6 months	+0.02	-0.08
Somavaratan (VRS-317) 5.0 mg/kg monthly[8]	Modified	23	6 months	+0.96	
Somavaratan (VRS-317) 2.5 mg/kg twice monthly	Modified	20	6 months	+0.84	
Somavaratan (VRS-317) 1.15 mg/kg weekly	Modified	21	6 months	+1.02	
Somavaratan (VRS-317) 3.5 mg/kg/twice monthly[13]	Modified	45	3 years		+0.64

NA: Not applicable

Similarly, in a phase 3 study of adults with GHD, MOD-4023 missed its primary endpoint of truncal fat reduction. With a 0.4 kg weight decrease in the active arm, a statistical difference from placebo was not observed.[10]

This is in contrast to the significant truncal fat mass reduction observed in subjects treated with LB03002 (p-value <0.0002) and in subjects treated with Nutropin Depot (p-value <0.001), both LAGHs based on unmodified GH.[11,12]

Conclusions

- TransCon GH demonstrated annualized HV and BMI trends comparable to daily GH in children with GHD.
- The design of TransCon GH, in which unmodified GH with an equivalent molecular size to daily GH is sustainably released from an inert prodrug, may explain these findings.

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