As much as 15-20% of height is estimated to be due to the direct effect of GH on growth plates. 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 populations have been recently conducted. Each molecule has a unique design (based on unmodified or modified GH) and therefore GH size:

- TransCon GH
- Somavan H (MOD-4023)
- Genotropin

These findings highlight the importance of GH size in maintaining natural tissue penetrance. Protein-enlarged GH analogues may have natural tissue penetrance. Protein-enlarged GH analogues may have

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, it is undesirable to change the normal GH/IGF-1 interplay because of potentially undesirable effects of supraphysiological IGF-1.

### 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 substantially released from an inert prodrug, may explain these findings.

### References