A New Era in Relieving the Burden and Improving Health Outcomes of Children with Growth Hormone Deficiency

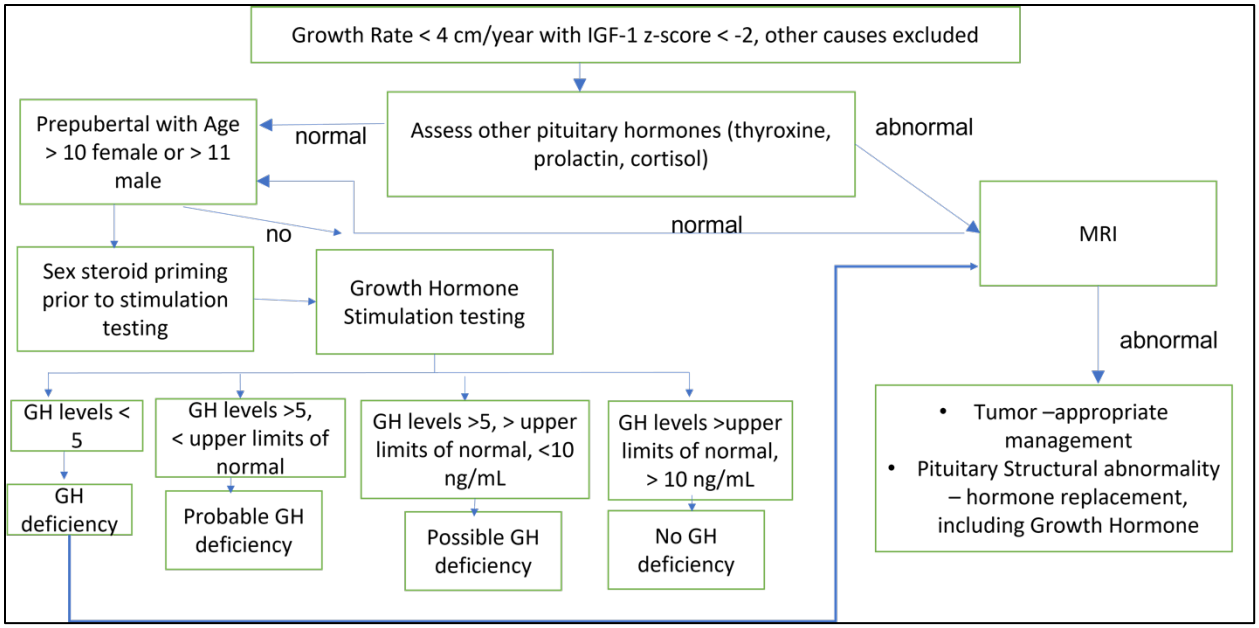
Epidemiology, Burden, Unmet Needs in Children and Adolescents

- Growth hormone deficiency (GHD) is underrecognized and underdiagnosed, affecting about 1 in 4,000 to 1 in 10,000 people in the general population.
- The majority of GHD in children is idiopathic, with about 20% attributed to organic causes.
- Although the burden of short stature on quality of life in children remains unclear, there is evidence demonstrating the benefits of 1 year of treatment with growth hormone on improving quality of life.
- However, growth hormone therapy with a somatropin product can itself be burdensome, including daily (possibly weekly) injections, frequent medical visits and blood draws, long-term therapy, and variable growth and health outcomes among patients.

Diagnosis

- Pediatric Endocrine Society Guidelines state that a diagnosis of GHD can be made without GH provocative testing if the patient meets all 3 of the following criteria:
  - Auxological criteria
  - Hypothalamic-pituitary defect
  - Deficiency of at least 1 additional pituitary hormone
- There are numerous endocrine and nonendocrine disorders that should be considered in the differential diagnosis of GHD **(Figure 1)**

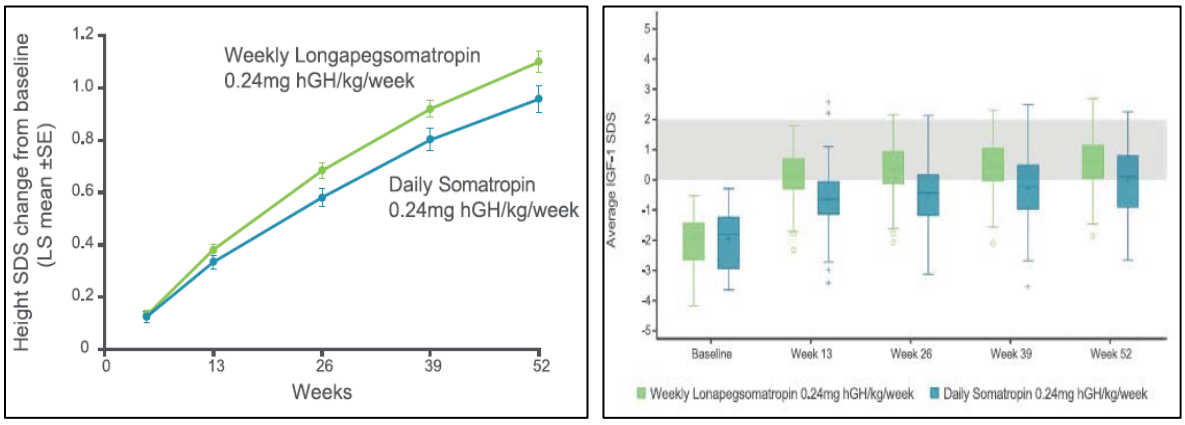
Figure 1.: GH deficiency diagnosis



Pediatric Treatment Recommendations

- Six daily and 1 weekly somatropin products are approved by the US Food and Drug Administration for GHD.
- Daily somatropin injections are associated with an increase in height for appropriate candidates. In addition, somatropin therapy can improve bone mass accretion, muscle mass accretion, and cardiovascular health.
- Benefits of GH treatment must be balanced with the burden of injections (daily or weekly) and the small risk of potential safety concerns (intracranial hypertension, slipped capital femoral epiphysis, progression of scoliosis, and increased risk of diabetes in patients with pre-existing insulin resistance).
- Clinicians should employ a shared decision-making process to discuss GHD treatment with children and their parents.
- Each daily and weekly product has unique indications and starting doses; subsequent dosing is recommended to titrate IGF-1 levels in the upper half of normal range for age. Patients should be monitored every 3 to 6 months for efficacy and safety/tolerability, including IGF-1 level, height, weight, side effects, and diabetes in patients at risk.
- Challenges with daily somatropin injections include inconvenience and pain, which can interfere with optimal adherence.
- Lonapegsomatropin is the first weekly somatropin preparation approved in the US, involving weekly treatments for children at least 1 year of age.
    - Data from the phase 3 heiGHt trial in CGHD demonstrate greater effectiveness in height SDS change from baseline vs daily somatropin **(Figure 2)**.

Figure 2.: Phase 3 heiGHT trial in CGHD



Near-Term Long-Acting Growth Hormone Treatments

- Numerous approaches are being explored to extend the dosing interval of somatropin injections, including depot injections, pegylation, GH fusion proteins, noncovalent albumin binding, and use of prodrugs.
- Somapacitan is a long-acting product approved by the FDA in August 2020 for weekly dosing in adult patients with GHD based upon the results of the REAL 3 study **(Figure 3);** it has not yet been made available for distribution in the US.

Figure 3.: Somapacitan vs Norditropin: REAL 3 study

	Somapacitan 0.04 mg/kg/wk	Somapacitan 0.08 mg/kg/wk	Somapacitan 0.16 mg/kg/wk	Daily GH 0.034 mg/kg/d)
26 weeks: mean (SD) annualized HV	8.0 (2.0) cm/yr	10.9 (1.9) cm/yr	12.9 (3.5) cm/yr	11.4 (3.3) cm/yr
52 weeks: mean annualized HV	7.8 cm/yr	9.7 cm/yr	11.50 cm/yr	10.0 cm/yr
Mean (SD) IGF-1 SDS	-1.62 (0.86)	-1.09 (0.78)	0.31 (1.06)	-0.40 (1.50)

- Somatrogon is another long-acting agent in development; it was shown to be noninferior to daily Genotropin and was well tolerated over 12 months.
- All LAGH preparations (approved and emerging) have different characteristics and, as with daily injections, cannot be used interchangeably.
- LAGH preparations have the promise of improving adherence and long-term outcomes but lack data from large, prospective clinical trials.