Evolving Strategies in Growth Hormone Treatment.

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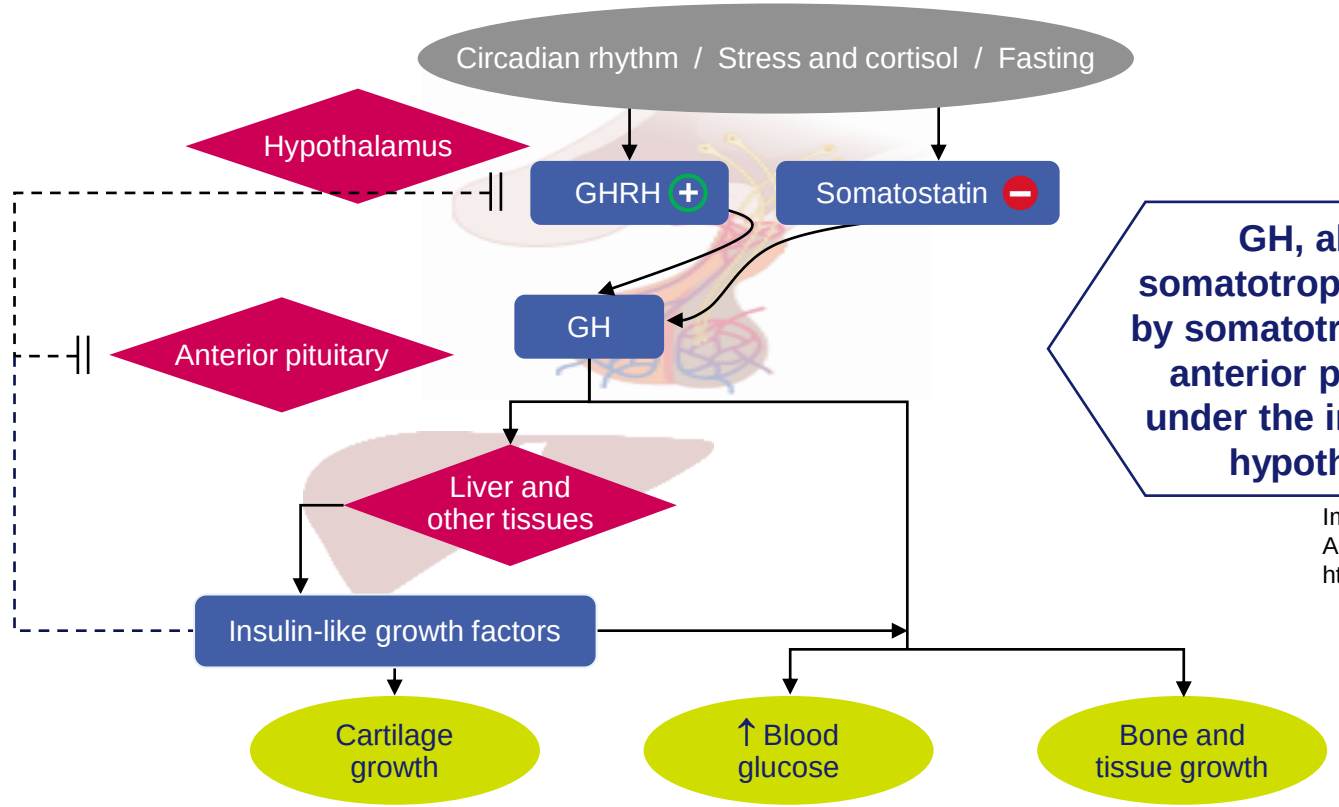
Growth Hormone Is Important for Normal Human Growth, Development, and Metabolism[1]

GH secretion is normally tightly regulated by neural, metabolic, and hormonal factors that are stimulatory (green) or inhibitory (red)[1,2]



GH, also called somatotropin, is produced by somatotroph cells in the anterior pituitary gland under the influence of the hypothalamus[1-3]

Many of the effects of GH are mediated by IGF-1, which is synthesized mainly in the liver[2,4]

Image adapted from Stepwards. Accessed August 2022 https://www.stepwards.com/?page_id=2490.[2]

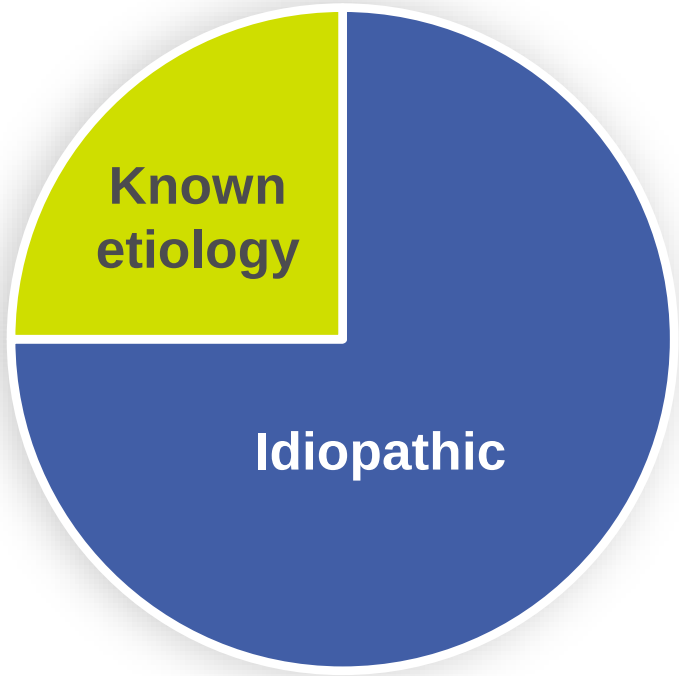
GH, growth hormone; GHRH, growth hormone releasing hormone; IGF-1, insulin-like growth factor-1.

1. Javorsky BR, et al. In: Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology. 10e.* McGraw Hill; 2017. **2.** Stepwards. Accessed August, 2022. https://www.stepwards.com/?page_id=2490. **3.** Olarescu NC, et al. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*. South Dartmouth, MA: MDText.com, Inc.; October 16, 2019.
4. Giustina A, et al. *Endocr Rev*. 2008;29(5):535-559.

Although Rare, Isolated Paediatric GHD Is the Most Common Pituitary Deficiency[1-3]

GHD may affect **1 in 4,000 to 1 in 10,000 children**.[3-5] Given the lack of standard diagnostic criteria, prevalence and incidence data widely vary.[3]

The **majority of paediatric GHD cases are idiopathic**, although this is likely to evolve with expanding knowledge[2,5]



GHD, growth hormone deficiency.

1. Alatzoglou KS, et al. *Endocr Rev.* 2014;35(3):376-432. **2.** Cooke DW, et al. In: Melmed S, et al. eds. *Williams Textbook of Endocrinology. 13e.* Elsevier; 2016. **3.** National Organization for Rare Disorders. Accessed August, 2022. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/. **4.** Stanley T. *Curr Opin Endocrinol Diabetes Obes.* 2012;19(1):47-52.
5. Merck Manuals. Updated July 2020. Accessed August, 2022. https://www.merckmanuals.com/professional/pediatrics/endocrine-disorders-in-children/growth-hormone-deficiency-in-children

Idiopathic Isolated GHD Is the Most Common Pituitary Hormone Deficiency in Children[1]

GHD is a rare disorder caused by inadequate secretion of growth hormone from the anterior pituitary gland[2]

GHD in children is characterized by a combination of auxologic, clinical, genetic, radiologic, metabolic, and hormonal abnormalities[3]

Short stature is a key feature of GHD in children[4]

GHD in children may be congenital, acquired, or idiopathic[2]

GHD=growth hormone deficiency.

1. Di Iorgi N, et al. *Best Pract Res Clin Endocrinol Metab*. 2016;30:705-736. **2.** National Organization for Rare Disorders (NORD). Accessed Aug 20, 2020. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/ **3.** Fideleff HL, et al. *Prog Mol Biol Transl Sci.* 2016;138:143-66. 4. Growth—disorders of growth [chapter 6]. In: Gardner DG, Shoback D, eds. Greenspan's Basic & Clinical Endocrinology. 10th ed. New York, NY: McGraw-Hill; 2017.

Clinical Diagnosis of Pediatric GHD Is Complex and Multifaceted[1]

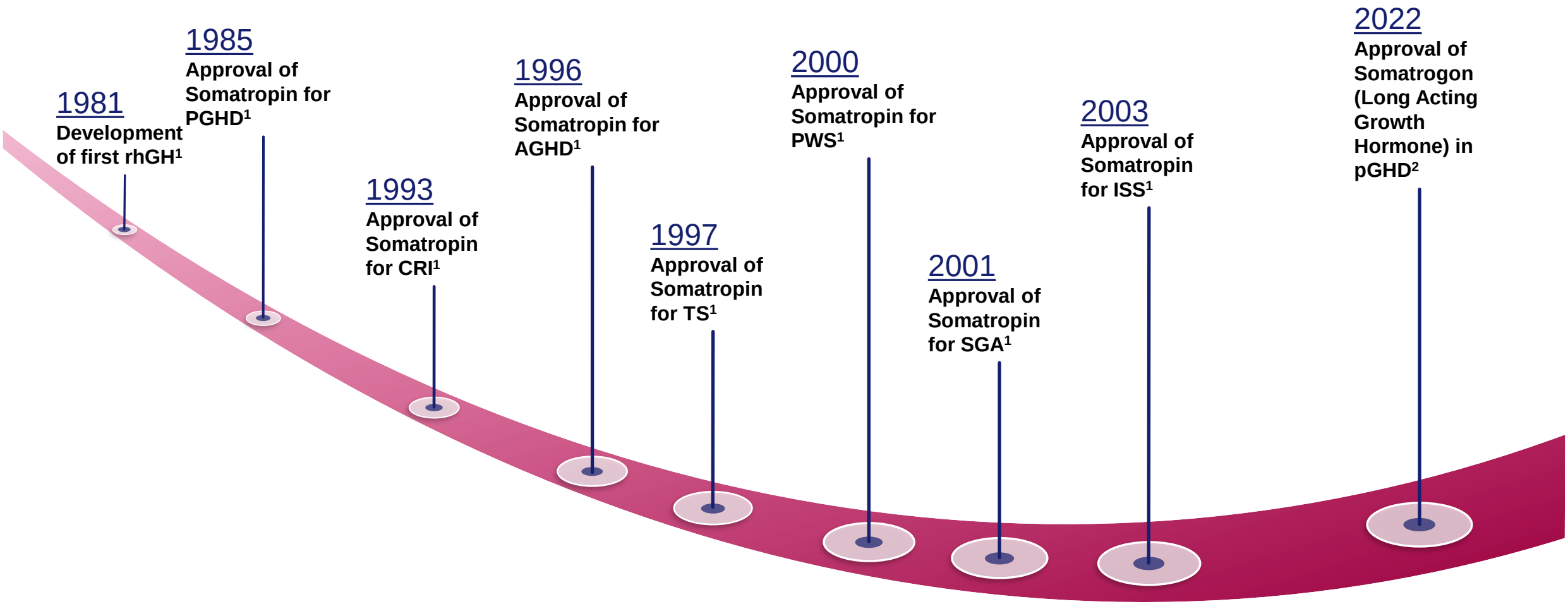
Guidelines by the Growth Hormone Research Society (2019): Evaluation of Children With Growth Failure[2]

Medical History[2]	Eliciting Symptoms[2]	Physical Examination[2]	GH Levels[2]	IGF-1 Levels[2]	MRI and Bone Age Assessment[2]
• Gestation history • Birth weight & length, head circumference • Family history	• Hypothyroidism • Precocious or delayed puberty • Poor growth due to systemic causes • Neurological symptoms	• Physical examination with special attention to dysmorphia or disproportionality • Accurate auxologic measurements	• Provocative testing; failure to respond to 2 provocative tests is essential for clinical diagnosis of GHD	• Low IGF-1 levels are suggestive of GHD	• MRI of the hypothalamus and pituitary gland to detect CNS disorders • Radiograph of the hand and wrist to evaluate short stature and skeletal dysplasia

CNS=central nervous system; GH=growth hormone; GHD=growth hormone deficiency; IGF-1=insulin-like growth factor-1; MRI=magnetic resonance imaging.

1. Growth Hormone Research Society. *J Clin Endocrinol Metab.* 2000;85:3990-3993. **2.** Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14.

Somatropin (Recombinant Human Growth Hormone) Has Been in Clinical Use for More Than 30 Years



AGHD=adult growth hormone deficiency; CRI=chronic renal insufficiency; ISS=idiopathic short stature; PGHD=pediatric growth hormone deficiency; rhGH=recombinant human growth hormone; SGA=small for gestational age; SHOX=short stature homeobox-containing gene; TS=Turner syndrome.

1. Ayyar VS. *Indian J Endocrinol Metab*. 2011;15(suppl3):S162-S165. 2. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/ngenla Accessed on 5 Spe 2023

Treatment and Monitoring Guidelines: Growth Hormone Research Society[1]

Guidelines for the Treatment of GHD in Children

Treatment of GHD in Children

- The main goal of rhGH treatment is to increase height velocity and adult height[1]

Dosage of GH

Starting dose of rhGH and dose adjustments are based on weight or body surface area and growth response[1]

- **rhGH starting doses:** Should be individualized according to GH responsiveness, aiming for the lowest effective dose at which there is an appropriate response in height velocity
- **Dose adjustments:** Appropriateness of the rhGH dose should be assessed based on height velocity and change in height SDS every 6 to 12 months
- Regulatory recommendations for rhGH dosing vary depending on the country

Monitoring GH Therapy

- The principal parameter to adjust rhGH should be the growth response[1]
- IGF-1 levels should be measured annually or more frequently, and to monitor compliance[1]
- Management of recognized side-effects and clinical monitoring, including bone age assessment and thyroid/adrenal functional testing where appropriate[2]
- Following completion of linear growth, GHD should be re-evaluated during the transition period[2]

GH=growth hormone; GHD=growth hormone deficiency; IGF-1=insulin like growth factor 1; SDS=standard deviation score; rhGH=recombinant human growth hormone.

1. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14. **2.** Allen DB, et al. *Eur J Endocrinol*. 2016;174:1–9.

Subnormal Growth Hormone Secretion Is the Key Feature of Paediatric GHD[1,2]

- Paediatric GHD is characterized by inadequate GH secretion from the anterior pituitary and by a broad range of abnormalities that can vary in presentation[1-3]

Inadequate GH secretion[1]

Auxological[3]

Radiological[3]

Hormonal[3]

Metabolic[3]

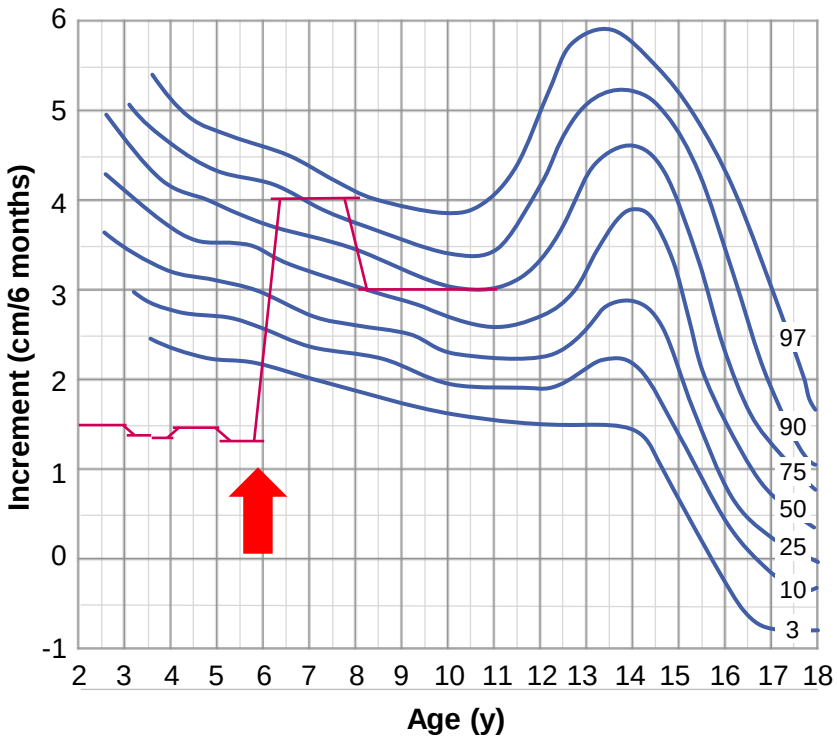
Clinical[3]

GH, growth hormone; GHD, growth hormone deficiency.

1. National Organization for Rare Disorders. Accessed August, 2022. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/. **2.** Cooke DW, et al. In: Melmed S, Polonsky KS, Kronenberg HM, eds. *Williams Textbook of Endocrinology*. *13e*. Elsevier; 2016:964-1073. **3.** Fideleff HL, et al. *Prog Mol Biol Transl Sci.* 2016;138:143-166.

The Major Clinical Features of GHD in Children Are Short Stature and Poor Growth Velocity[1]

Growth Velocity Curves of a 6-Year-Old Patient Treated With rhGH[2]



- Most children with GHD are normal size at birth, with normal features and proportions[3]
- Children with GHD show reduced height velocity from birth[4]
- The figure on the left shows the growth velocity of a patient with GHD who was treated with rhGH at age 6 (denoted by arrow). Initial catch-up growth is noted for 2 years, with a lower (but normal) velocity of growth in subsequent years[2]

Republished with permission of McGraw-Hill, from Greenspan's Basic & Clinical Endocrinology. Gardner DG, Shoback D, eds. 10th ed. 2018. Permission conveyed through Copyright Clearance Center, Inc.

GHD=growth hormone deficiency; rhGH=recombinant human growth hormone.

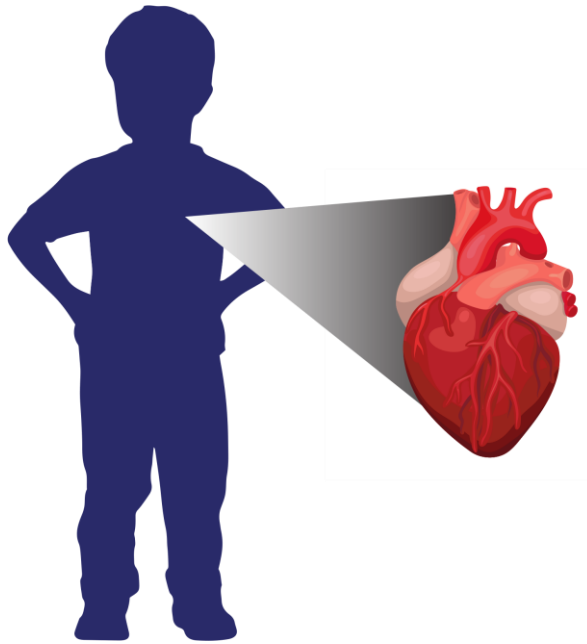
1. Calabria A. Accessed August, 2022. https://www.merckmanuals.com/professional/pediatrics/endocrine-disorders-in-children/growth-hormone-deficiency-in-children. **2.** Styne D. In: Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology. 10e.* McGraw-Hill; 2018;137-170. **3.** National Organization for Rare Disorders. Accessed August, 2022. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/. **4.** Murray PG, Clayton PE. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; November 16, 2016.

Paediatric GHD Is Associated With Physical Consequences in Addition to Growth Defects[1-3]

Signs and Symptoms seen in Paediatric GHD[1,2]

Signs
- Short stature
- Immature facial appearance
- High-pitched voice
- Chubby appearance, increased subcutaneous fat
- Small genitalia (males)
- Poor growth velocity
- Delayed bone maturation

Symptoms*
- Poor sleep
- Reduced strength, poor muscle development
- Poor appetite
- Poor energy
- Reduced endurance
- Poor focus or concentration



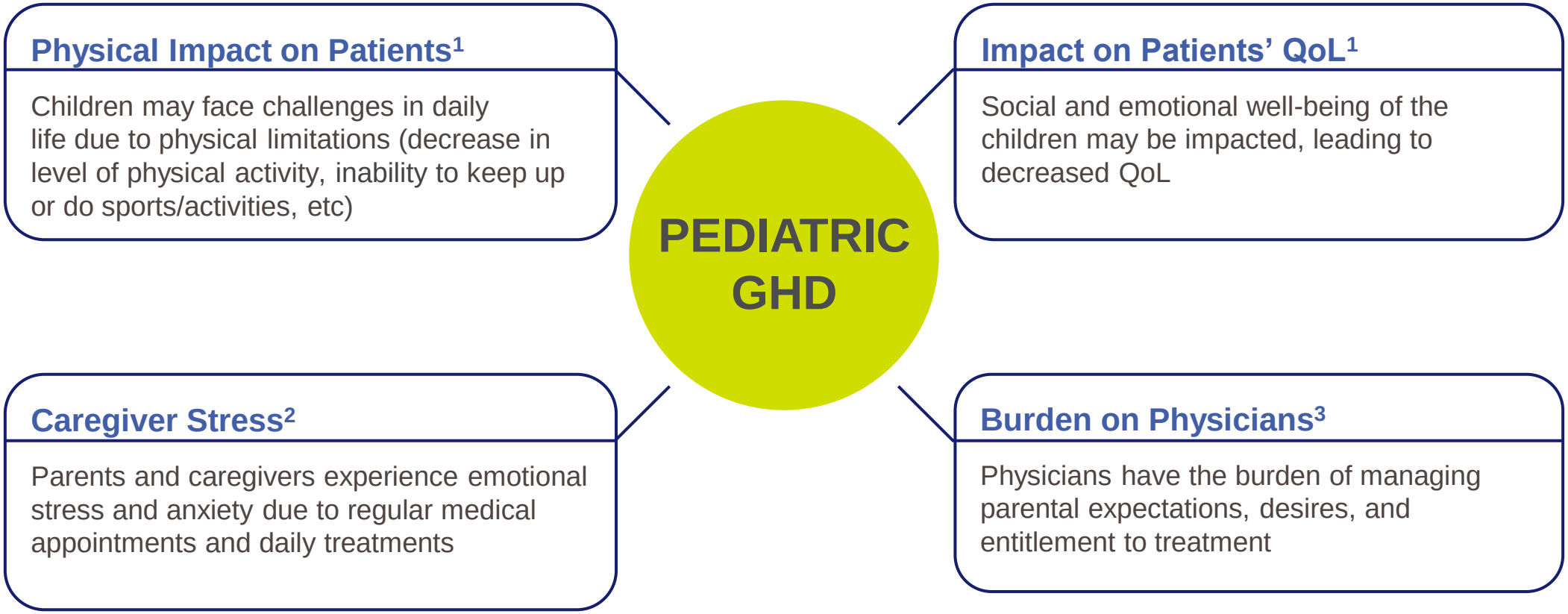
Additional Consequences in Children Diagnosed With GHD[3]

- Increased risk of developing CVD at an early age
- Altered metabolic profile
- Increased inflammatory and oxidative stress markers
- Altered body composition
- Altered bone mineral density
- Abnormalities in cardiac morphology and function

CVD, cardiovascular disease; GHD, growth hormone deficiency.
*Symptoms reported by patients/caregivers were noted at higher frequency for children 4 to less than 8 years of age. There were little to no differences in the narrative descriptions of signs and symptoms between boys and girls with GHD.[2]

1. Styne D. Growth. In: Gardner DG, Shoback D. eds. *Greenspan's Basic & Clinical Endocrinology, 10e*. McGraw Hill; 2017. **2.** Brod M, et al. *Qual Life Res.* 2017;26(7):1673-1686.
3. De Leonibus C, et al. *Horm Res Paediatr.* 2016;85(6):363-371.

The Burden of Pediatric GHD Is Multifaceted[1-3]



GHD, growth hormone deficiency; QOL, quality of life.

1. Brod M, et al. *Qual Life Res.* 2017;26(7):1673-1686. **2.** Silva N, et al. *Clin Psychol Psychother.* 2018;25(1):e107-e118. **3.** Allen DB. *Horm Res Paediatr.* 2017;87(3):145-152.

Living With Pediatric GHD Presents Psychosocial Challenges

Paediatric GHD is characterized by a range of impacts including psychosocial challenges that can lead to impaired quality of life

Social Concerns and Impacts (n=73)*

56% Being mistaken for younger than actual age

48% Teasing or bullying

27% Being treated differently by adults and other children

26% Not fitting in, social unease

25% Choosing not to participate

Emotional Impacts (n=73) *

63% Bothered by height or size

38% Concerns about being different

33% Having poor self-confidence

21% Worry about growing

21% Sad or hurt feelings

18% Being embarrassed

GHD, growth hormone deficiency.
*Percentage indicates total narrative descriptions provided by children (n=39) and parents (n=34).
Brod M, et al. *Qual Life Res.* 2017;26(7):1673-1686.

Accurate and Repeated Auxologic Measurements Are Key for Diagnosis of Growth Disorders[1]

Children with any of the following characteristics should be considered for further evaluation[1]*

- Short stature with a height SDS below -2
- Height that deviates from familial background
- Significant decrease in height SDS†

In congenital GHD, children may present with slightly decreased birth length and a decrease in growth rate soon after birth[2]

Patients with mild forms present with few abnormal characteristics apart from short stature, decreased growth rate, and delayed bone age[2]

Children of the same age

GHD, growth hormone deficiency; SDS, standard deviation score.
*Diagnosis of GHD does not require a height cut-off, particularly in very young children with hypoglycemia and/or midline defects/pathologies or recently developed GHD.[1]
†Defined as a deflection of least 0.3 SDS/year unexplained by the normal channeling in infancy to adjust linear growth to target height trajectory, by the prepubertal growth dip, or by pubertal delay.[1]
1. Collett-Solberg PF, et al. *Horm Res Paediatr*. 2019;92:1-14. **2.** Styne D. In: Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology. 10e.* McGraw-Hill; 2018;137-170.

- Short stature is defined as height below the third percentile of the general population[a]
- Etiology: congenital, acquired, idiopathic[b]
- In addition to GHD, growth is affected by race; lifestyle; nutritional, cultural, and socioeconomic factors; and underlying conditions[a]

GHD, growth hormone deficiency;.

a. Yadav S, et al. Indian J Pediatr. 2015;82:462-470; b. Boguszewski MCS. Rev Endocr Metab Disord. 2021;22:101-108.

Endocrine causes

GH-related causes

• Growth hormone (GH) deficiency: isolated or combined with other pituitary hormone Deficiencies

• GH insensitivity

Hypothyroidism

Glucocorticoid excess

• Cushing syndrome

• Poorly managed congenital adrenal hyperplasia

• Exogenous corticosteroid administration

Pseudohypoparathyroidism

Causes: others

- **Non-pathogenic**

– Constitutional Delay of Growth and Puberty
– Familial short stature

- **Skeletal dysplasias**

- **Intra-Uterine Growth Restriction & Genetic disorders**

– Syndromic e.g Silver-Russell syndrome
– Non-syndromic

- **Systemic disorders and medications related**

– Cardiovascular disease e.g. congenital heart disease
– Renal e.g. chronic renal failure, RTA
– Respiratory e.g. cystic fibrosis, asthma
– Gastrointestinal disease e.g. IBD
– Neurological e.g. brain tumour
– Psychosocial e.g. anorexia nervosa, child abuse

Safety With Daily rhGH Therapy

- More than 500,000 patient-years of exposure data[a]
- Rare side effects: pseudotumor cerebri, slipped capitofemoral epiphysis (SCFE), pancreatitis, worsening of scoliosis[b]
- No increased risk of malignancy while on therapy[c]
- Unknown if there are long-term implications of receiving rhGH during childhood

Rosenfeld RG, et al. J Clin Endocrinol Metab. 2012;97:68-72; b. Miller BS, et al. Adv Pediatr. 2011;58:207-241; Savendahl L, et al. Lancet Diabetes Endocrinol. 2020;8:683-692.

Long-Term Safety Databases

SAGhE[a]

- European database of 24,232 patients treated with rhGH during childhood (> 400,000 patient-years of follow-up)
- Raised concerns about long-term cardiovascular disease; remains unclear if this is related to underlying condition or rhGH exposure

KIMS[b]

- 15,809 GH-treated adolescents and adults were analyzed (mean follow-up 5.3 years)
- De novo cancer incidence was comparable to that in the general population (standard incidence ratio 0.92; 95% CI, 0.83, 1.01)
- Neither adult-onset nor childhood-onset GHD was associated with increased de novo cancer risks

GH, growth hormone.

a. Savendahl L, et al. Lancet Diabetes Endocrinol. 2020;8:683-692; b. Johannsson G, et al. J Clin Endocrinol Metab. 2022;107:1906-1919.

Safety of GH Replacement in Survivors of Cancer

Growth Hormone Research Society Consensus Statement

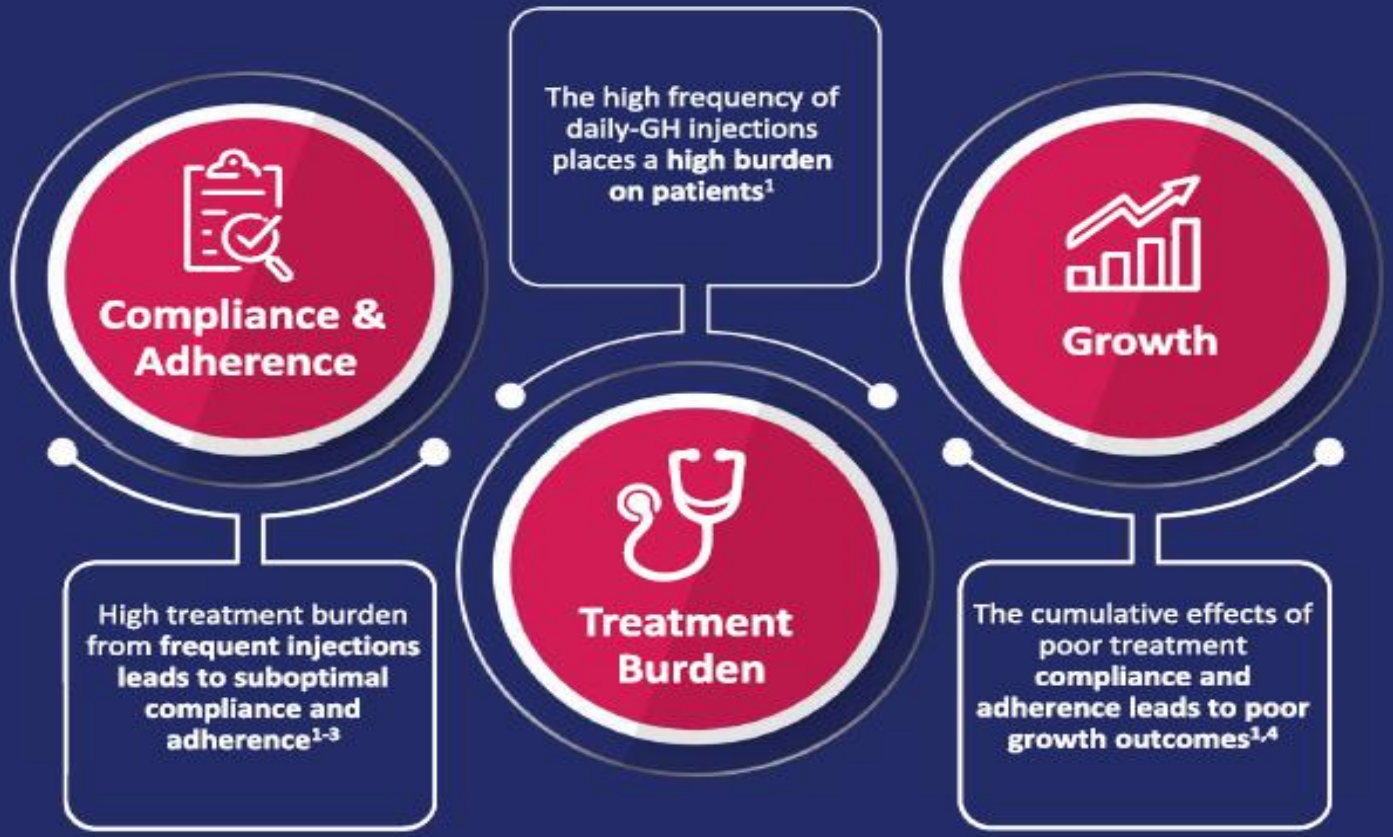
There is no evidence for an association between GH replacement and increased mortality from cancer amongst GH-deficient childhood cancer survivors

- Patients with pituitary tumor or craniopharyngioma remnants receiving GH replacement do not need to be treated or monitored differently than those not receiving GH
- GH replacement might be considered in GH-deficient adult cancer survivors in remission after careful individual risk/benefit analysis.
- In children with cancer predisposition syndromes, GH treatment is usually *contraindicated* but it may be cautiously considered in particular cases with proven GHD

Boguszewski MCS, et al. Eur J Endocrinol. 2022;198:P35-P52.

UNMET NEED
IN DAILY GROWTH HORMONE

There is an unmet need to reduce treatment burden in order to improve adherence and compliance in pGHD, which will impact the patient's clinical outcomes, and health-related quality of life.[1-4]



1. Mcnamara et al. 2020, Factors Driving Patient Preferences for Growth Hormone Deficiency (GHD) Injection Regimen and Injection Device Features: A Discrete Choice Experiment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7198440/.
2. Loftus et al. 2021 Systematic review of patient experience with a less frequent injection schedule for growth hormone deficiency, Presented at the Annual Academy of Managed Care Pharmacy (AMCP 2021) Virtual Congress April 12-16, 2021.
3. Marcus SF, Ledger WL (2001) Efficacy and safety of long-acting GnRH agonists in in vitro fertilization and embryo transfer. *Hum Fertil* 4: 85–93.
4. Bozzola et al 2011, https://pubmed.ncbi.nlm.nih.gov/21294891/.

GROWTH HORMONE DEFICIENCY TREATMENTS CURRENT CHALLENGES[1-3]

Treatment of GH deficiency involves **DAILY INJECTIONS** of recombinant human growth hormone (GH).[1]

Maintaining maximal treatment adherence to the **daily recombinant human growth hormone (rhGH) injections** is **CHALLENGING,** not only for children but also for caregivers and adults with growth hormone deficiency (GHD).[2]

Up to 71%

of GH-deficient pediatric patients were found to be **non-adherent** to their treatment.[3]

21

Study design: A systematic review was conducted and reported in accordance with the method outlined in the Cochrane Handbook for Systematic Reviews. A search of 11 electronic databases was undertaken to identify relevant articles, published between 1985 and 2018. Twenty-one full-text articles were assessed for eligibility, of which 6 articles met the inclusion criteria.[3]

GH: Growth hormone; rhGH: Recombinant human growth hormone; GHD: Growth hormone deficiency

1. Pollock, R., Kappelgaard, A. and Seitz, L. (2015). An analysis of product wastage arising from dosing increment granularity in four modern growth hormone administration devices. *Expert Opinion on Drug Delivery*, 12(3), pp.353-360. 2. Yuen, K., Miller, B., Boguszewski, C. and Hoffman, A. (2021). Usefulness and Potential Pitfalls of Long-Acting Growth Hormone Analogs. *Frontiers in Endocrinology*, 12, pp.1-10. 3. Graham, S., Weinman, J. and Auyeung, V. (2018). Identifying Potentially Modifiable Factors Associated with Treatment Non-Adherence in Paediatric Growth Hormone Deficiency: A Systematic Review. *Hormone Research in Paediatrics*, 90(4), pp.221-227.

OPTIMIZING ADHERENCE TO r-hGH INJECTIONS IS NECESSARY[1]

Non-adherence may lead to[1]

Additional diagnostic tests or hospitalization[1]

Increased health care costs[1]

Unnecessary changes in the drug dose or treatment course[1]

Suboptimal responses to r-hGH, and the resulting mean final height attained is **below** that of the general population.[1]

rhGH: Recombinant human growth hormone.

1. Fisher, B. and Acerini, C. (2013). Understanding the Growth Hormone Therapy Adherence Paradigm: A Systematic Review. *Hormone Research in Paediatrics*, 79(4), pp.189-196.

L

Potential Benefits of LAGH

Potential to Maximize Efficacy

Potential to Improve Adherence to Therapy

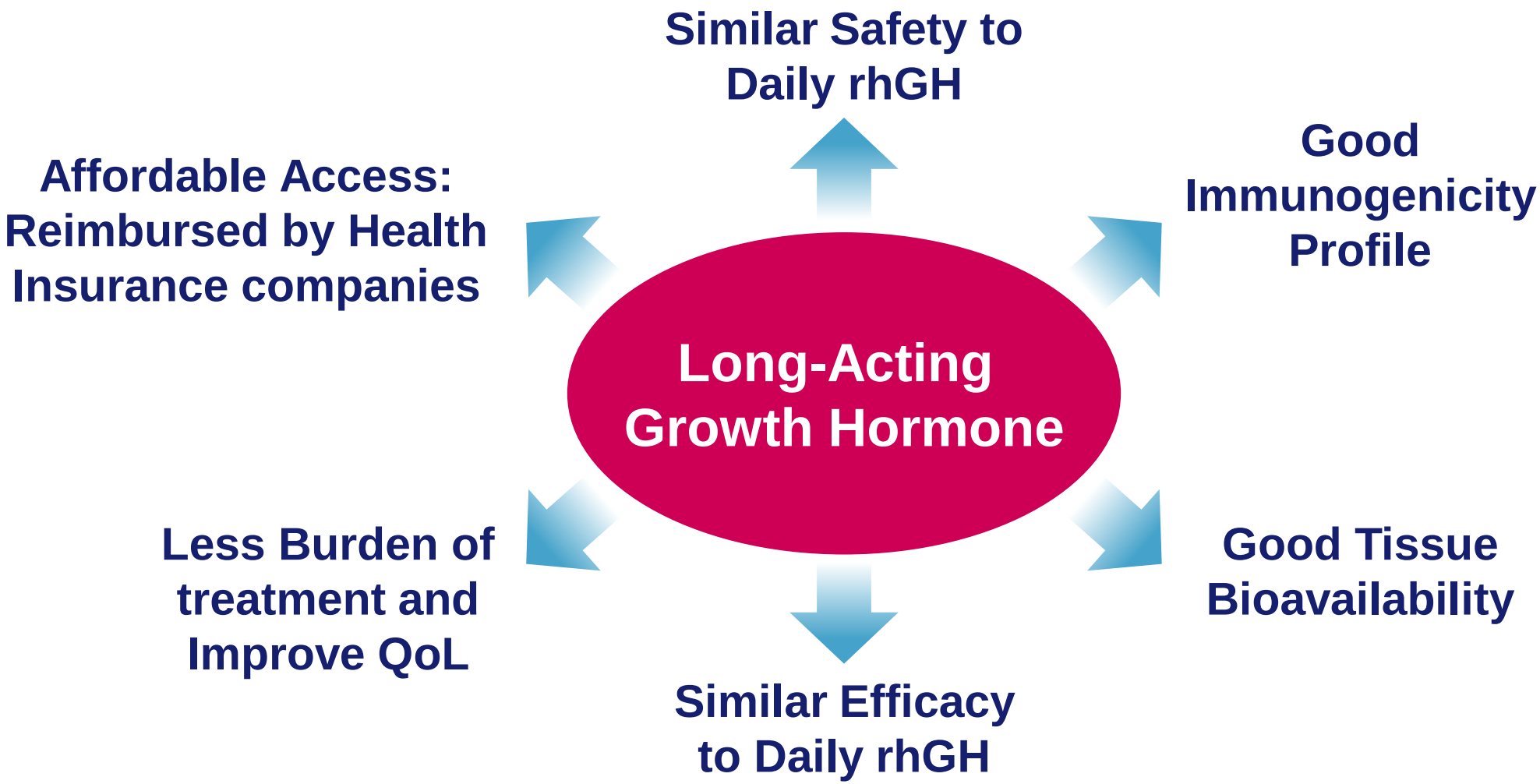
Decrease Injection Frequency

Increased Patient Flexibility

Potential to Decrease Disease and Treatment Burden with Similar Safety and Efficacy

Christiansen JS, et al. *Eur J Endocrinol*. 2016;174(6):C1-C8.

Which Should be the Ideal Features of LAGH?



Once-Weekly Somatrogon Is Supported by 5 Years of Efficacy and Safety Data in Pediatric GH Deficiency[1,2]

COMPLETED

CP-4-004[3-5]	2	Safety and dose-finding study of different somatrogon dose levels compared to daily Somatropin® therapy in pre-pubertal growth hormone–deficient children	53
CP-4-006[1,6]	**3**	**A phase 3, open-label, randomized, multicenter, 12-month, efficacy and safety study of weekly somatrogon compared to daily Somatropin therapy in pre-pubertal children with growth hormone deficiency**	**224**
CP-4-009[7,8]	3	A phase 3, open-label, randomized, multicenter, 12-month, efficacy and safety study of weekly somatrogon compared to daily Somatropin therapy in Japanese pre-pubertal children with growth hormone deficiency	44
O&E Study[1,9,10]	3	A phase 3, randomized, multicenter, open-label, crossover study assessing subject perception of treatment burden with use of weekly growth hormone (somatrogon) versus daily growth hormone (Somatropin) injections in children with growth hormone deficiency	87
CP-4-004-E[2,11]	**2**	**CP-4-004 open-label extension (in the 5th year of treatment)**	**48**

ONGOING

Study ID	Phase	Title	Enrollment
CP-4-006-E[6,12]	3	CP-4-006 open-label extension	212

GH, growth hormone; GHD, growth hormone deficiency; O&E, outcomes and evidence.

1. Somatrogon injection [summary of product characteristics]. LPDGEN092022 . **2.** Zadik Z, et al. Poster presented at: Annual Meeting of the Endocrine Society [virtual]; March 20-23, 2021. Poster 6887. **3.** Zelinska N, et al. *J Clin Endocrinol Metab.*2017;102(5):1578-1587. **4.** Clinicaltrials.gov. Accessed April 6, 2022. https://clinicaltrials.gov/ct2/show/NCT01592500. **5.** Data on file. REFSMT1185, PFIZER LTD: Somatrogon® (somatrogon) CP-4-004-ISRs. **6.** Data on file. REFSMT1181**,** PFIZER LTD: Somatrogon® (somatrogon) CP-4-006 Bone Maturation. **7.** Horikawa R, et al. Poster presented at ENDO 2021; March 20-23, 2021. Poster 6600. **8.** Data on file. REFSMT1190, PFIZER LTD: Somatrogon® (somatrogon) CP-4-009 Treatment Group Characteristics. **9.** Maniatis AK, et al. Poster presented at ENDO 2021; March 20-23, 2021. Poster 6895. **10.** Data on file. REFSMT1176, PFIZER LTD: Somatrogon® (somatrogon) C0311002 O and E – Missed Injections. **11.** Data on file. REFSMT1183, PFIZER LTD: Somatrogon® (somatrogon) CP-4-004 Open Label Extension – Disposition of Subjects.
12. Wajnrajch M, et al. Poster presented at ENDO Online 2021; March 20-23, 2021. Poster 7129.

THANKS