CME

GH Deficiency Research Highlights

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What is GH Deficiency

- Characterized by inadequate secretion of growth hormone (GH) from the anterior pituitary gland.
- Symptoms are varied and can include reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function.
- Can be congenital or acquired
- There are a number of FDA-approved human growth hormone (Somatropin) daily treatments for GH deficiency available, including Genotropin, Humatrope, Norditropin, Nutropin, and Saizen.
- Weekly formulations of human GH have also been recently approved, including Lonapegsomatropin and Somapacitan.
- Other, non-GH treatments, are also being investigated.
- Since it is a rare condition (I in 4,000 children), data presented at large medical conferences, like **ENDO 2022**, can get overlooked.

Update on Recently Presented Clinical Trials with Long-acting GH and Other Growth Promoting Hormones

Once weekly Somatrogon vs Daily Genotropin in Pediatric GH Deficiency Patients

- In 12-month phase 2 study, patients randomized to 1 of 3 somatrogon doses (0.25, 0.48, and 0.66 mg/kg/week) or genotropin (0.24 mg/kg/week). Open label extension followed trial.
- In 12-month phase 3 study, patients were randomized to somatrogon (0.66 mg/kg/week) or genotropin (0.24 mg/kg/week), followed by open label extension.

Year 1 Mean HV (Average age 7.5 yrs) **Genotropin dose: 0.22-0.31 mg/kg/week**		**Year 1 Mean HV (Average age 7.5 yrs)** **hGH dose: ~0.30 mg/kg/week**	**Mean Annual HVs During OLE period** **Somatrogon dose: 0.66 mg/kg/week**			**Mean Annual HVs During Annual Visit in Match KIGS Cohort** **Genotropin dose: 0.20-0.28 mg/kg/week**		
Mod. GH Def.	Sev. GH Def.		Yr 1	Yr 2	Yr 3	Yr 1	Yr 2	Yr 3
9.4 cm/yr	8.3 cm/yr	~10 cm/yr	9.37 cm/yr	8.97 cm/yr	9.03 cm/yr	7.09 cm/yr	6.35 cm/yr	6.08 cm/yr

- **Growth data from both studies were pooled and analyzed, then compared with growth data from matched subsets of hGH-treated patients as reported by Ranke and Lindberg and Bakker et al, and with data from a matched cohort from the Pfizer International Growth Study Database (KIGS).**
- The combined mean HV at end of 12-month main portions of the phase 2 and 3 studies was 10.37 cm/year for somatrogon-treated patients.
- **Comparisons with published literature and the KIGS database suggest children treated with somatrogon (0.66 mg/kg/week) showed good growth, compared with children treated with hGH, suggesting somatrogon-treated children are likely to achieve a satisfactory final adult height.**

Cara J et al. Growth Outcomes From the Phase 2 and Phase 3 Studies of Once Weekly Somatrogon vs Daily Genotropin in Pediatric Patients With Growth Hormone Deficiency: Comparisons With Published Literature and an International Growth Study Database. *J Endo Soc* 2022; 6 (suppl 1): A647.

1.Ranke and Lindberg. JCEM. 2010;95(3): 1229-1237.

2.Bakker, Frane, et al. JCEM. 2008;93(2): 352-357.

Safety and Efficacy of Lonapegsomatropin

Height SDS Mean		Annualized HV Mean		Average IGF-1 SDS Mean	
Baseline	Week 130	Baseline	Week 130	Baseline	Week 130
-1.56	-0.64*	--	9.32 cm/yr	0.52	1.46

*average parental height SDS mean: -0.39

- Once-weekly lonapegsomatropin is a long-acting prodrug of somatropin
- **Results are reported from Week 130 from open-label enlighten study (extension of two other trials -** heiGHt or fliGHt trials **(N=298).** 36 participants had completed the trial up to week 130 and 248 participants remain enrolled.
- **For the 36 participants, 14 had reached bone age of >14 years (girls) or >16 years (boys)**, and **24 had completed the study based on investigator judgement that treatment for growth hormone deficiency was no longer necessary.**
- The **difference between mean height SDS at last visit and average parental height SDS was -0.05 for the 36 completers, and 61.1% of these participants had met or exceeded the average parental height SDS**
- With continued lonapegsomatropin treatment, the AE profile r.emained consistent with what was observed in the parent trials, with no new safety signals.
- **Children and adolescents treated with lonapegsomatropin showed continued improvement of height SDS through their 3rd year of therapy. Lonapegsomatropin continued to demonstrate a safety profile comparable to that of daily somatropin therapy.**

Saenger P et al. Safety and Efficacy of Treatment with Lonapegsomatropin in Children with Growth Hormone Deficiency at Week 130 in the enliGHten Trial. *J Endo Soc* 2022; 6 (suppl 1): A645.

Somapacitan (weekly vs. Norditropin (daily) – Safety Extension

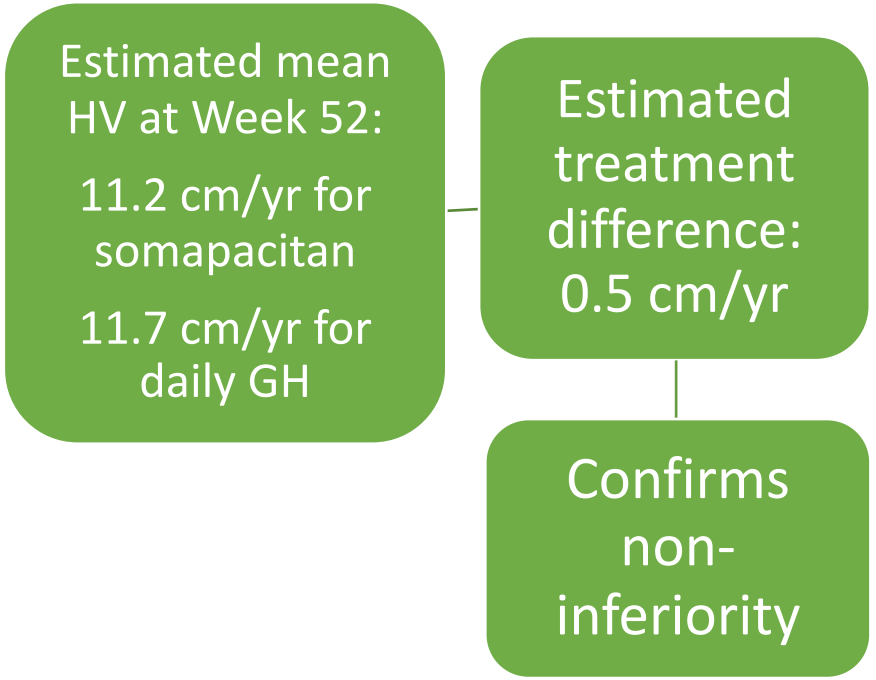
2 yr safety extension cohort	Mean HV		Mean HV SDS at Year 4	Change in Height SDS from Baseline	Mean IGF-1 SDS at Year 4
	Year 3	Year 4			
SOMA	8.3 cm/yr	7.4 cm/yr	1.55	2.85	1.29
GH	7.6 cm/yr	6.6 cm/yr	0.88	2.28	0.94

- REAL 3 is an ongoing, phase 2 trial investigating the efficacy and safety of somapacitan compared with daily GH (norditropin).
- Prepubertal children with GHD naïve to GH treatment received 0.04 (n=16), 0.08 (n=15) or 0.16 mg/kg/week (n=14) somapacitan, or daily GH 0.034 mg/kg/day (equivalent to 0.238 mg/kg/week; n=14) for 1 year.
- **The initial 52-week REAL 3 trial was followed by an ongoing 4-year long-term safety extension, patients treated with somapacitan remained on somapacitan (n=39) and all patients on daily GH switched to somapacitan 0.16 mg/kg/week (n=11).**
- During year 4, 51.3% of patients in somapacitan/somapacitan group experienced AEs, and 72.7% experienced AEs in the GH/somapacitan group. The most common AE was nasopharyngitis; all other AEs occurred in <10% of patients in either group
- These **year 4 data support the efficacy and safety results of somapacitan observed in the previous 3 years of the trial**. **Somapacitan was well tolerated, and no safety signals were identified**.

Savendahl L et al. Once-Weekly Somapacitan in Growth Hormone Deficiency: 4-Year Efficacy and Safety Results from REAL 3, a Randomised Controlled Phase 2 Trial . *J Endo Soc* 2022; 6 (suppl 1): A645–A646. .

Somapacitan (weekly) vs. Norditropin (daily)

- **REAL 4 is an ongoing, phase 3 trial testing efficacy and safety of weekly subcutaneous injections of somapacitan compared with daily GH (norditropin).**
- GH-treatment-naïve, prepubertal children with GHD (74.5% male, N=200) received 0.16 mg/kg/week subcutaneous somapacitan (n=132) or daily subcutaneous GH (0.034 mg/kg/day norditropin; n=68).
- The primary endpoint was annualized height velocity (HV) after 52 weeks of treatment.
- At week 52**, mean IGF-I SDS levels were similar between somapacitan (+0.28) and daily GH (+0.10) and within normal range (-2 to +2)**.
- Somapacitan was well tolerated, with no safety or local tolerability issues identified.
- In conclusion, **once-weekly somapacitan has a similar efficacy and safety profile as daily GH with similar mean IGF-I levels in treatment-naïve children with GH deficiency**.



Miller B et al. Once-weekly Somapacitan Is Effective And Well Tolerated In Children With GH Deficiency: A Randomized Phase 3 Trial . *J Endo Soc* 2022; 6 (suppl 1): A640–A641.

Effect of rhGH on Measures of Strength, Endurance, and FFM

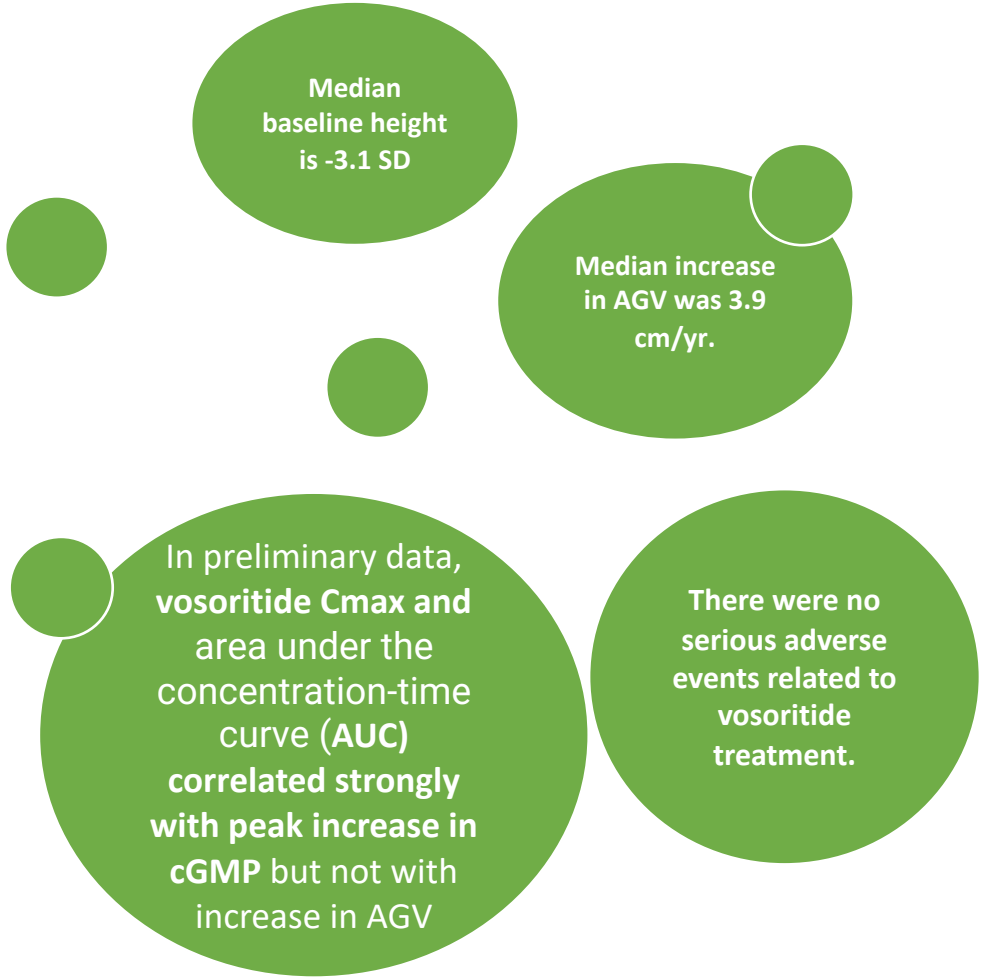
- Objective was to **investigate impact of rhGH on measures of skeletal muscle strength, power, endurance, agility, and lean body mass accrual** in prepubertal boys with significant short stature compared to age-matched healthy controls growing normally.
- 40 prepubertal boys recruited, 25 with significant short stature - either isolated GH deficiency or idiopathic (mean age: 8.9 yrs; HT SDS: -2.3) and 15 normally growing healthy controls (age: 8.8 yrs; HT SDS: -0.3).
- There are significant differences in fat free mass (FFM) and skeletal muscle strength and endurance in prepubertal boys with severe short stature compared to healthy age-matched controls.
- **FFM accrual and isokinetic measures of muscle strength, endurance, agility and power improve after 12 months of rhGH**, **changes approaching measures of those of healthy controls**.

Measures	Short-Stature (n=25)	Control (n=15)
FFM		
At baseline	15.9	20.4
At 12 months	Improved by 27.3%	Improved by 10.7%
Agility (Baseline to 12 months)		
At baseline	--	--
At 12 months	Improved by 5.5%	Improved by 2.7%
Power (Baseline to 12 months)		
At baseline	--	--
At 12 months	Improved by 9.1%	Improved by 3.8%
Elbow Flexion		
At baseline	79.7 Newtons	97.6 Newtons
At 12 months	Improved by 25.7%	Improved by 12.5%
Knee Flexion		
At baseline	82.6 Newtons	95.7 Newtons
At 12 months	Improved by 24.1%	Improved by 28.0%
Endurance		
At baseline	17.5 reps	24.9 reps
At 12 months	Improved by 63%	Improved by 43%

Welch L et al. Impact of recombinant human growth hormone (rhGH) on skeletal muscle strength, power, endurance and agility in prepubertal boys with significant short stature: preliminary results. *J Endo Soc* 2022; 6 (suppl 1): A634 .

First Study of Vosoritide in Short Stature Caused by Various Genetic Mutations

- Vosoritide is a C-type natriuretic peptide analog which binds its receptor on chondrocytes, leading to increased chondrocyte proliferation and differentiation via its inhibition of the **Ras-dependent extracellular signal-regulated kinase (ERK)1/2 mitogen-activated protein (ERK1/2-MAPK) pathway.**
- Approved for children with achondroplasia.
- Current phase 2 study assessing safety and efficacy of vosoritide in children with genetic mutations in 6 categories: hypochondroplasia, Rasopathies (including Noonan syndrome), aggrecan deficiency, carriers of heterozygous *NPR2* mutations, CNP deficiency, and SHOX deficiency.
- The primary outcome will be change in annualized growth velocity (AGV) from baseline in patients receiving subcutaneous vosoritide (15 mcg/kg/day) for 12 months. Preliminary data in 10 patients who have completed 6 months of therapy shows promise.
- Conclusion: This is the first clinical trial of vosoritide for children with genetic short stature who do not have achondroplasia. **Vosoritide treatment may work as a precision therapy to improve growth in multiple genetic conditions which interact with the ERK1/2-MAPK pathway**.



Boucher K et al. A Prospective Clinical Trial of Vosoritide in Selected Genetic Causes of Short Stature. *J Endo Soc* 2022; 6 (suppl 1): A618–A619.

Real World Studies & Registries

Economic Burden of GH Deficiency

Comorbidities

- GH deficiency patients were disproportionately affected by endocrine conditions (>68% in GH deficiency cases vs. ≤10% in controls),
- GH deficiency patients disproportionately affected by metabolic conditions (>93% in GH deficiency cases vs. ≤39% in controls),
- GH deficiency patients disproportionately affected by hepatic and renal function conditions (18-23% in GH deficiency cases vs. <10% in controls)
- GH deficiency patients disproportionately affected by cardiovascular disease (41-53% in GH deficiency cases vs. <29% in controls)
- GH deficiency patients disproportionately treated with concomitant medications.

Economic Burden

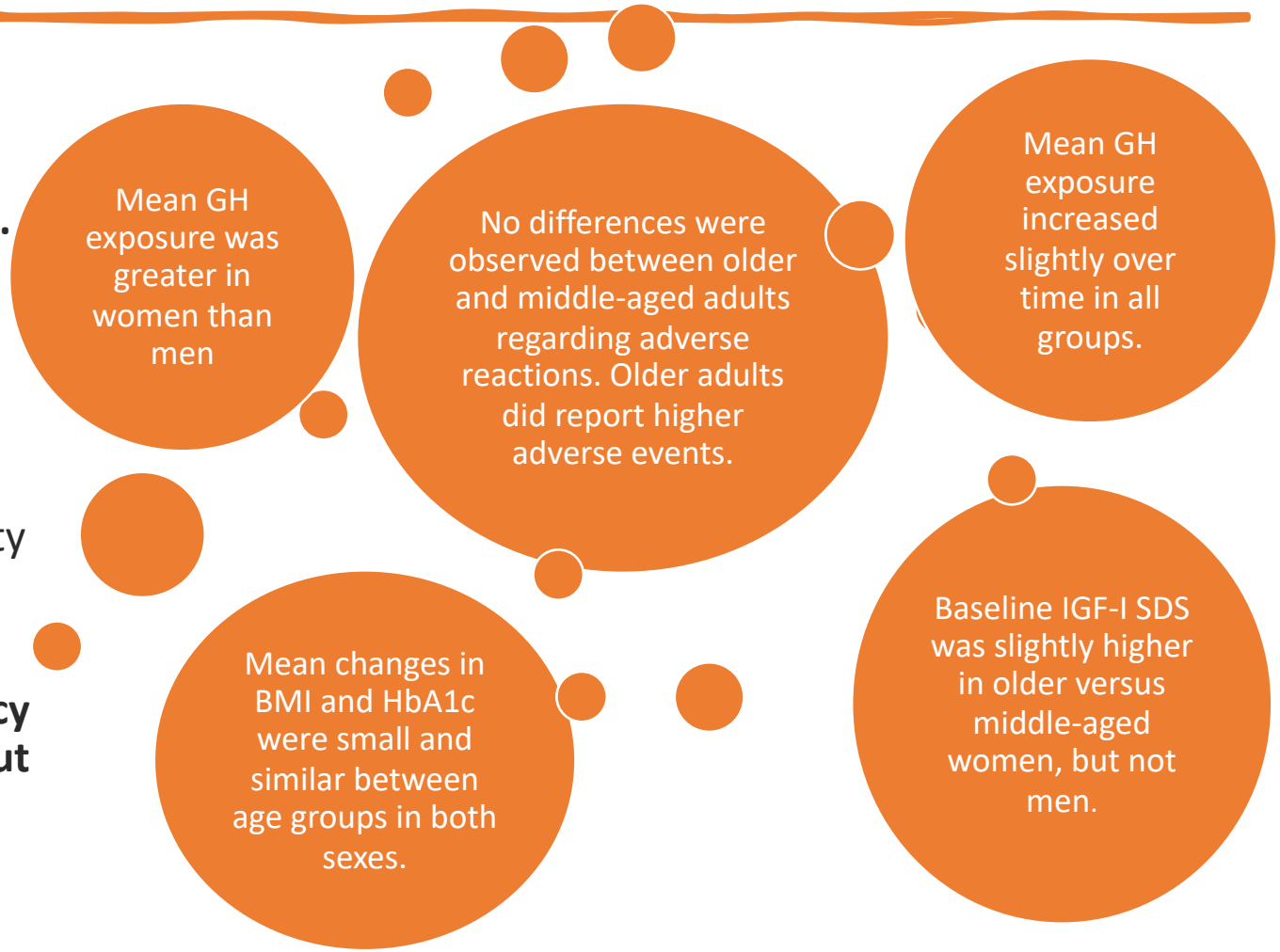
- Mean annual all-cause healthcare costs 4.6x greater ($42,309 vs. $9,146) for Medicaid GH deficiency patients than controls.
- Mean annual all-cause healthcare costs 4.1x greater ($30,111 vs. $7,376) for commercial GH deficiency patients than controls.
- For Medicaid GH deficiency patients, inpatient costs were a primary driver ($22,385 vs. $3,494 for controls), while outpatient costs made up the largest proportion for commercial patients ($13,083 vs. $4,057 for controls).
- Few patients were treated with somatropin therapy in both Medicaid (5.8%) and commercial (9.5%) GH deficiency cohorts.

- This study **analyzed healthcare costs and daily somatropin use among adults with GH deficiency** who had Medicaid or commercial health insurance in the US.
- Adult patients with a GH deficiency diagnosis between January 1, 2008, and December 31, 2017 were identified and matched (1:3) to controls without GH deficiency on age, gender, plan type, region, and race (Medicaid only).
- Baseline comorbidities and medications were measured during the 12 months pre-index. All-cause and GH deficiency-related healthcare costs and somatropin use were measured during the variable follow-up period.
- **Adult patients with GH deficiency experience a substantial comorbidity and economic burden compared to non-GH deficiency controls**.
- **Adult GH deficiency remains primarily untreated and presents a significant healthcare burden.**

Smith A et al. Economic Burden of Growth Hormone Deficiency in a US Adult Population. *J Endo Soc* 2022; 6 (suppl 1): A559–A560.

Treatment Efficacy in Older GH Deficiency Patients

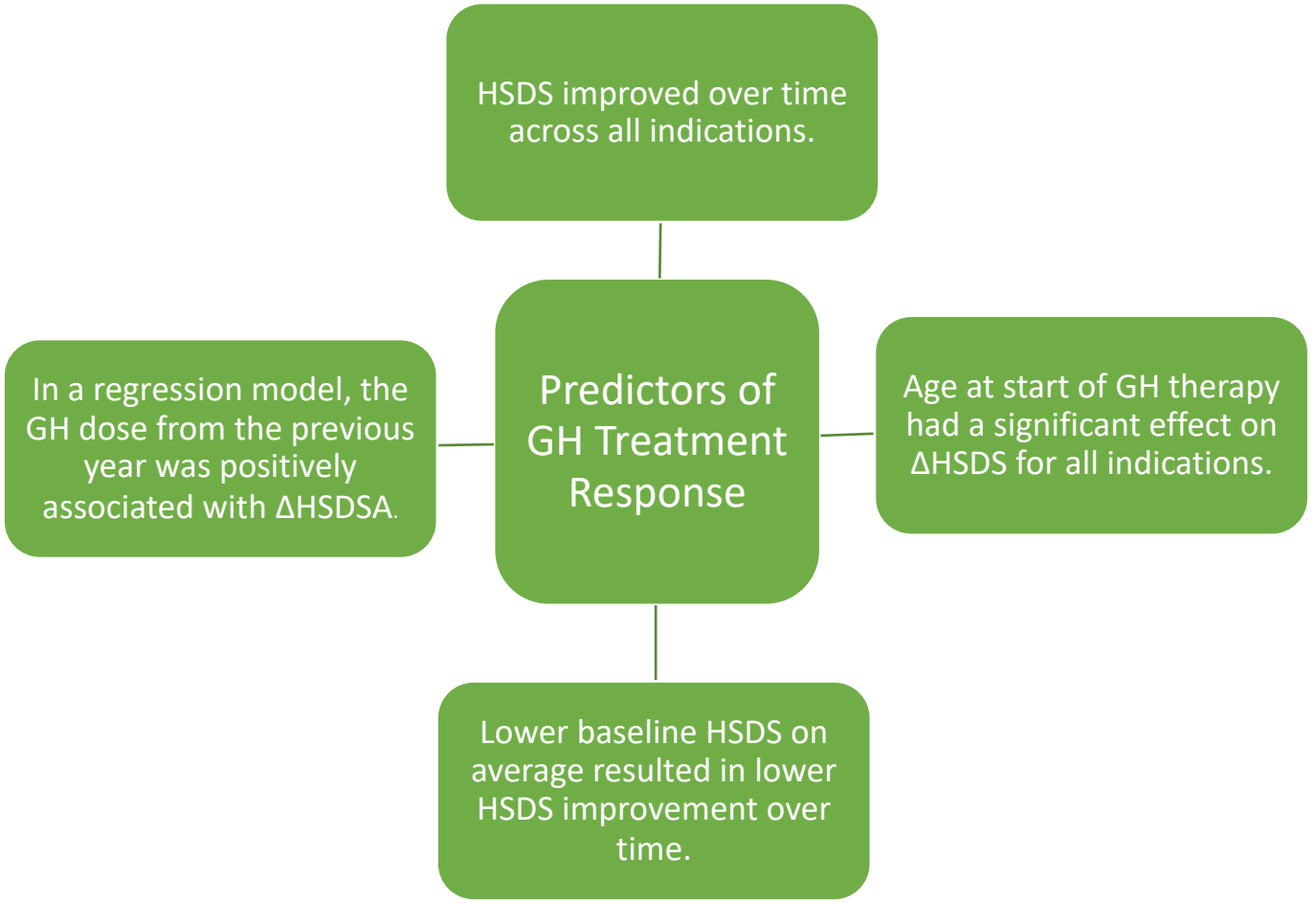
- Aim of this investigation is to **compare real-world growth hormone replacement therapy (GHRT) outcomes in older (aged ≥60 years) vs. middle-aged (35–<60 years) adults.**
- NordiNet IOS and ANSWER were non-interventional studies investigating long-term effectiveness and safety of GHRT with Norditropin (somatropin). Data were collected in the US and Europe from 2006 to 2016. Safety and efficacy was assessed.
- These data suggest **similar clinical outcomes with GHRT in patients with adult GH deficiency aged ≥60 compared with 35–<60 years without additional risk of adverse drug reactions in older patients**.



Biller B et al. Growth Hormone (GH) Replacement Therapy (GHRT) in Patients with Adult GH Deficiency (AGHD) Aged ≥60 Years: Data from NordiNet® IOS and the ANSWER Program. *J Endo Soc* 2022; 6 (suppl 1): A558.

Predictors of GH Treatment Response in Pediatric Patients

- Objective of this investigation was to **determine predictors of response to daily GH for height outcomes using longitudinal analysis across 5 years of real-world data from pediatric patients with GH deficiency, Turner syndrome, Noonan syndrome, and Prader-Willi syndrome**.
- Data were combined for ANSWER and NordiNet IOS studies for GH-treatment-naïve pediatric patients on daily somatropin.
- Overall, 14,295 patients were included: **3766 females and 8917 males with GHD,** 1307 patients with TS, 55 females and 148 males with NS, and 52 females and 50 males with PWS.
- On average, **GH treatment resulted in HSDS improvements over baseline across all indications; patients with GH deficiency had the highest improvement**, while patients with Turner syndrome had the lowest improvement. **Earlier treatment with GH led to better outcomes in HSDS. Increasing the dose of GH also led to better outcomes in HSDS.**



Ross JL et al. Predictors Of Response To Growth Hormone Treatment In Pediatric Growth Disorders: Analysis From The Answer Program And Nordinet® IOS. *J Endo Soc* 2022; 6 (suppl 1): A592.

Long-term effect of GHRT on Glucose Tolerance in Adults with GH Deficiency

- The goal of this investigation was to **evaluate the long-term effect of growth hormone replacement therapy (GHRT) on glucose tolerance in adults with GH deficiency**.
- Retrospective single-center study at Kobe University Hospital. 53 patients met inclusion criteria.
- Data collected at baseline, 3, 6, 12 months after treatment, and at each patient's last visit. The influence of GHRT on glucose metabolism and its associated factors were analyzed.
- Fifty-three patients were analyzed.
- Overall, **GHRT was safely used in regard with impaired glucose tolerance in adults with GH deficiency.**

Clinical Outcomes	Baseline (median)	Last visit (median)
IGF-1	56	119
IGF-1 SDS	-3.4	-0.2
Waist circumference	85	78.5
BMI	23.1 kg/m^2	22.9 kg/m^2
HvA1c	5.7%	5.7%

Bando H et al. ODP329 Long-term Effect of Daily Growth Hormone Replacement Therapy on Glucose Tolerance in Adult growth Hormone Deficiency. *J Endo Soc* 2022; 6 (suppl 1): A499-A500.

Clinical Pearls

- GH deficiency is a rare endocrine disorder characterized by inadequate secretion of GH from the anterior pituitary gland.
- Children treated with once-weekly somatrogon showed good growth, compared with children treated with hGH
- Children and adolescents treated with lonapegsomatropin showed continued improvement of height SDS through 3rd year of therapy.
- Lonapegsomatropin continued to demonstrate a safety profile comparable to that of daily somatropin therapy.
- Once-weekly somapacitan has a similar efficacy and safety profile as daily GH with similar mean IGF-I levels in treatment-naïve children with GH deficiency; safety profile confirmed in extension trial.

Clinical Pearls cont.

- Adult patients with GH deficiency experience a substantial comorbidity and economic burden compared to non-GH deficiency controls. Adult GH deficiency remains primarily untreated and presents a significant healthcare burden.
- Older adults with GH deficiency had similar clinical outcomes with GHRT compared with middle-aged patients
- GH treatment resulted in HSDS improvements over baseline across a number of indications; patients with GH deficiency had the highest improvement. Earlier treatment with GH led to better outcomes in HSDS. Increasing the dose of GH also led to better outcomes in HSDS.
- GHRT was safely used in regard with impaired glucose tolerance in adults with GH deficiency.