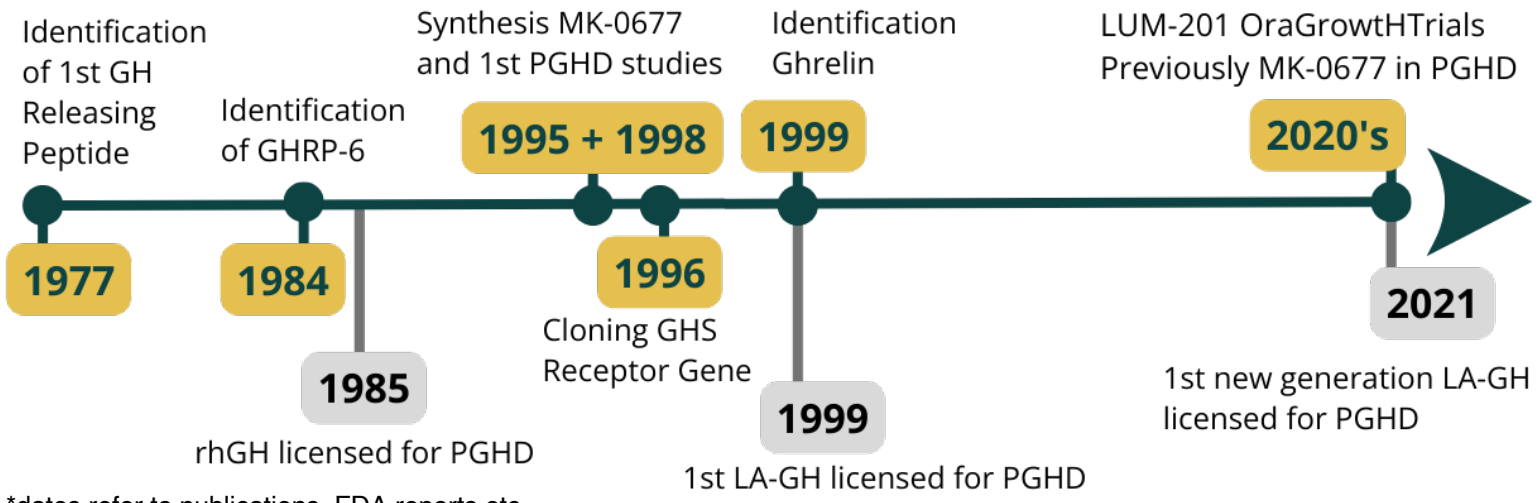
# Approaching the Reality of Restoring GH Secretion and Growth with the Investigative Oral Growth Hormone Secretagogue (GHS) LUM-201 in Moderate Paediatric Growth Hormone Deficiency (PGHD)

***Timeline* for key events in the development of GH Secretagogues and rhGH in PGHD***




*dates refer to publications, FDA reports,etc

*Is restoring physiological GH secretion a better approach to treating moderate paediatric GHD than using exogenous rhGH?*

OraGrowtH TRIALS
*oral therapy to increase natural GH secretion*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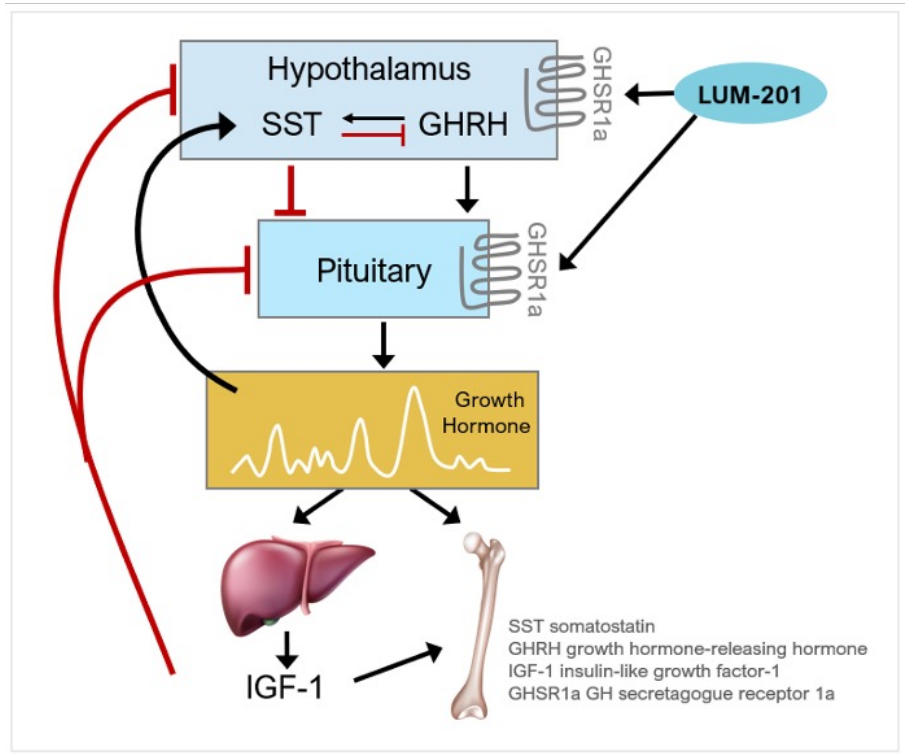
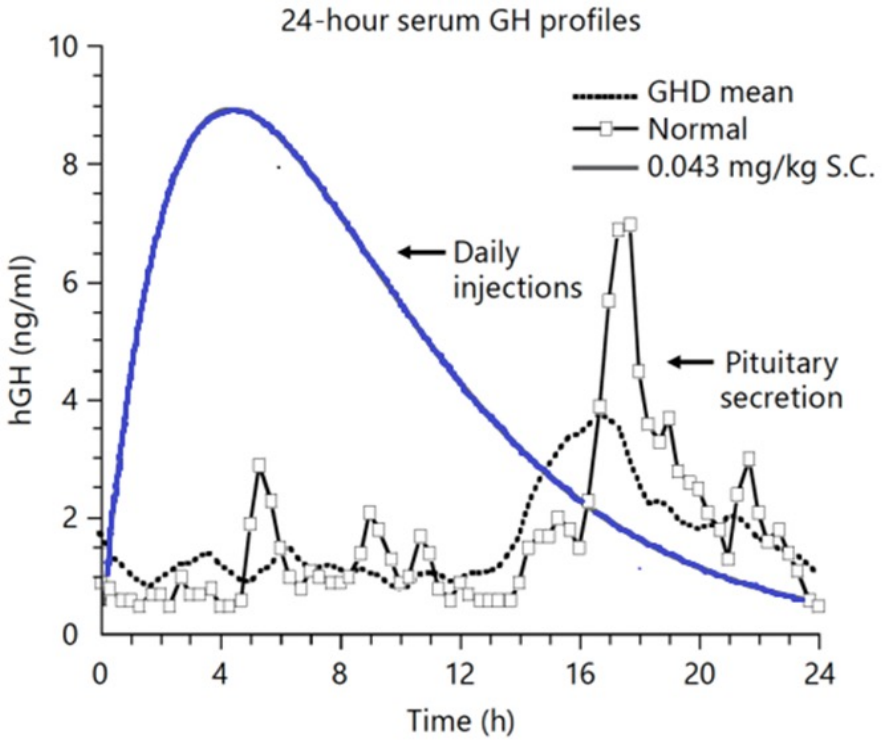
# LUM-201 Stimulates Endogenous GH Secretion




LUM-201 is an <u>oral</u> ***growth hormone (GH) secretagogue***

Targeted to those with moderate GH deficiency, and identified by a Predictive Enrichment Marker (PEM) test:

**PEM Positive Responders** [1]

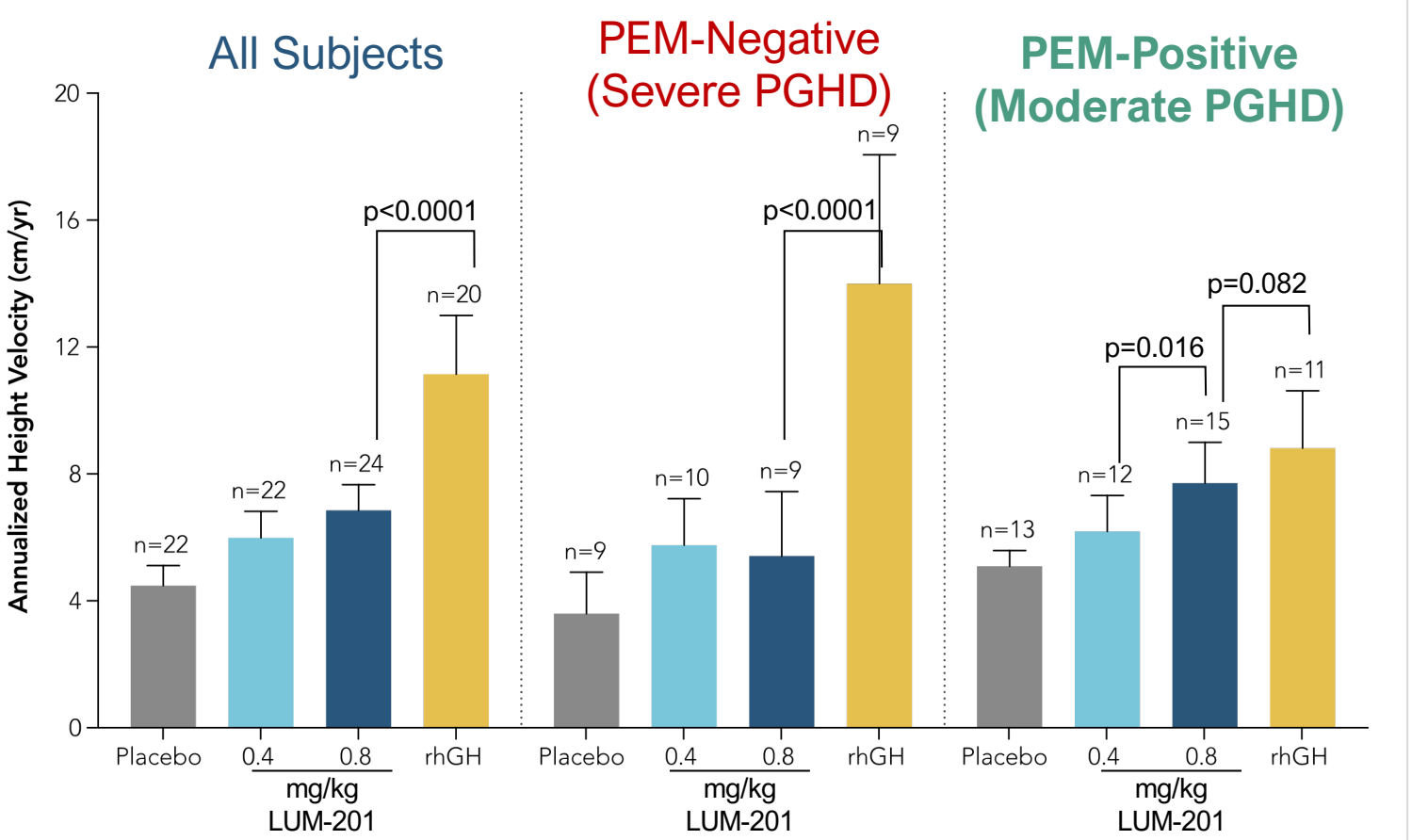
- Baseline IGF-1 > 30 ng/ml
- Stimulation LUM-201 0.8mg/kg peak GH ≥ 5 ng/ml
- Functional but reduced HP-GH axis


1. Bright 2021 JES
2. Figure 'Long-Acting Growth Hormone: An Update' Paul H. Saenger & Jorge Mejia-Corletto In: Advanced Therapies in Pediatric Endocrinology and Diabetology. Endocr Dev. Basel, Karger, 2016, vol 30, pp 79–97

# Merck Study 020 Post-Hoc Analysis: PEM-Positive Patients Responsive to MK-0677 (LUM-201)

- Naïve PGHD, Study 020
  - N=68; three arms
  - Placebo patients switched to rhGH at 6 mos.
  - Annualized growth shown for each arm
- PEM-positive subset*: [1]
  - LUM-201 0.8 mg/kg not statistically different from rhGH
  - Dose response: 0.8 mg/kg statistically superior to 0.4 mg/kg

## Historical Phase 2a Data from 020 Trial in PGHD

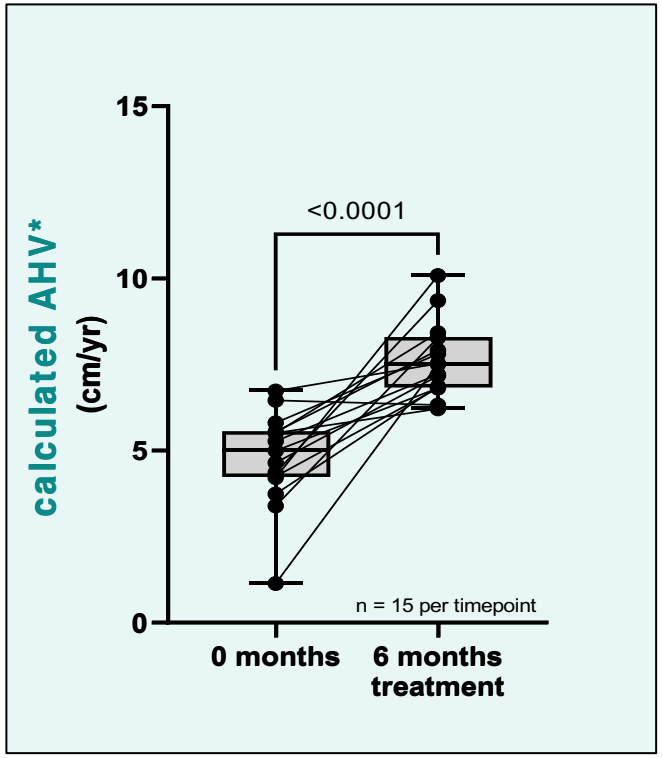



[1] Bright 2021 JES

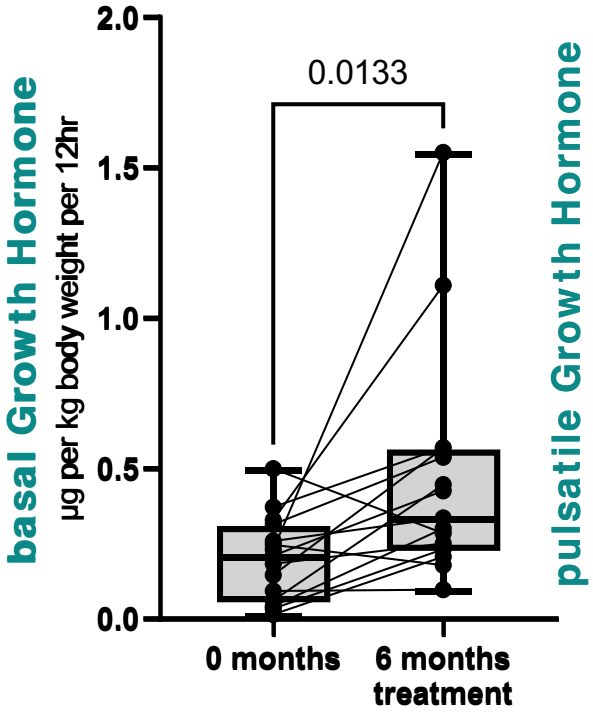
* PEM-positive (PEM+) = PGHD patients with baseline IGF-1 > 30 ng/ml & peak stimulation GH ≥ 5 ng/ml from single dose of LUM-201

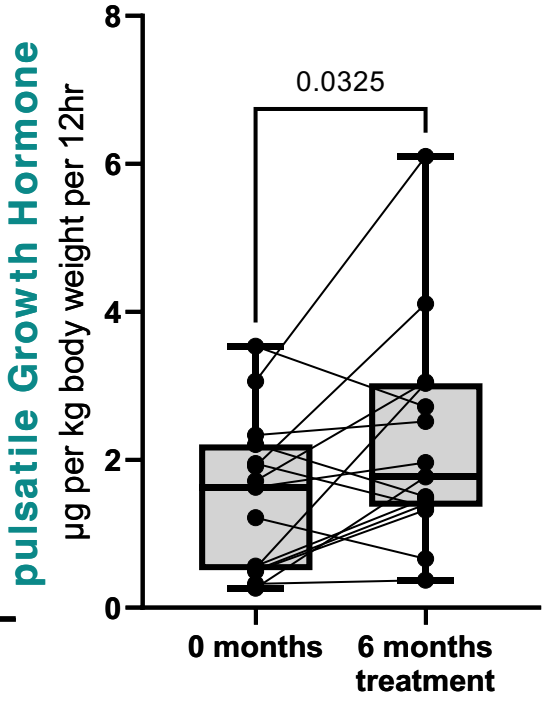
OraGrowtH212 TRIAL

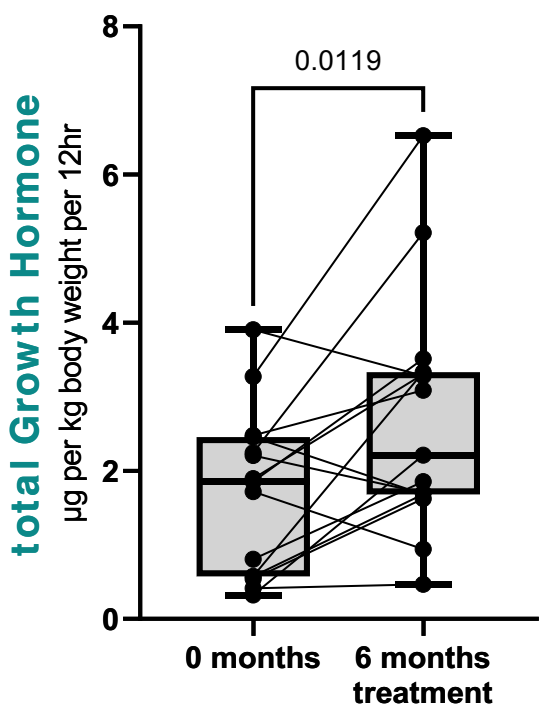
PK/PD: N=22, Open label LUM-201 1.6 & 3.2mg/kg daily
Objectives: Assess LUM-201 effect on endogenous GH pulsatility, Assess Height Velocity, Evaluate PK/PD




GH secretion at 0 vs 6 months of oral LUM-201 Treatment (1.6 & 3.2mg/kg/d combined), all variables from deconvolution based on 72 samples in 12 hours



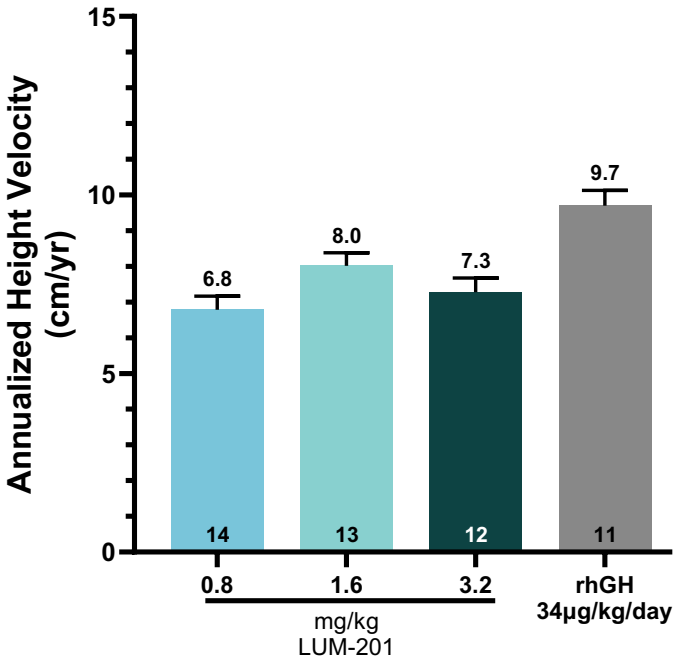




| Time period *24 hr GH Secretion* µg/kg/24hr | Normal healthy (IC-GH) *Zadik et al* | Untreated GHD (IC-GH) *Zadik et al* | LUM-201 (baseline GH) | LUM-201 (treat 6M GH) | rhGH 34 µg/kg/day |
|---|---|---|---|---|---|
| | **5.0 ± 1.3** | 1.4 ± 0.5 | 1.7 ± 1.3 | **3.3 – 4.0** | **~20** |

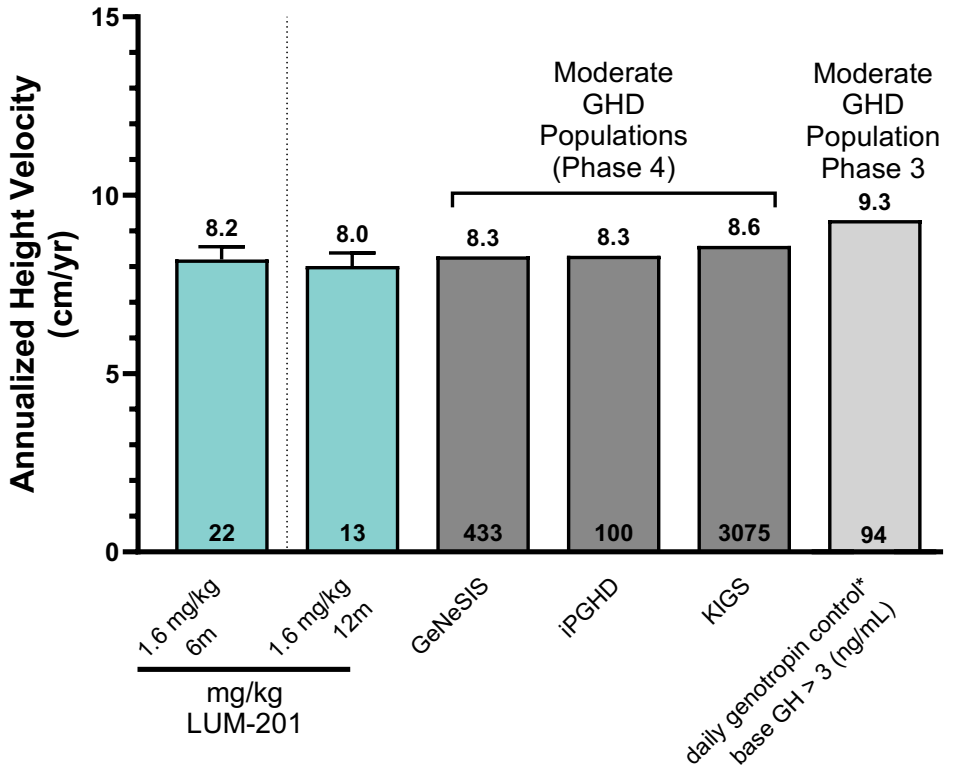
OraGrowtH210 TRIAL

Dose finding: N=82, randomised to LUM-201 0.8, 1.6 & 3.2mg/kg daily, or rhGH 34µg/kg daily
Objectives: Confirm PEM strategy, Assess Height velocity
(Not powered for non-inferiority)

## 12m ANCOVA




## 6m & 12m ANCOVA vs Ph3 & Ph4 rhGH Studies



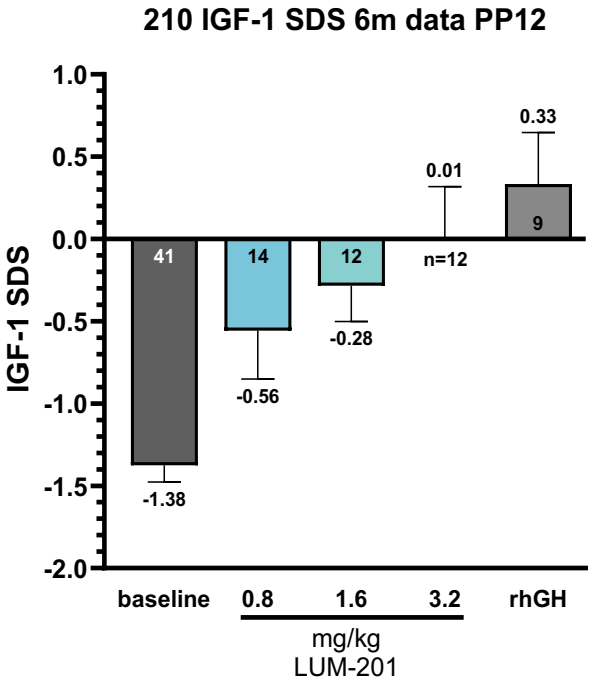

- 1.6 mg/kg best performing LUM-201 cohort
  - Growth of 8.0 cm comparable to historical 12-month AHV for moderate population
- 1.7 cm difference between 1.6mg/kg and rhGH cohorts at 12 months
  - Differences less than 1.8 – 2.0 cm have been the historical Phase 3 non-inferiority margin for rhGH approvals

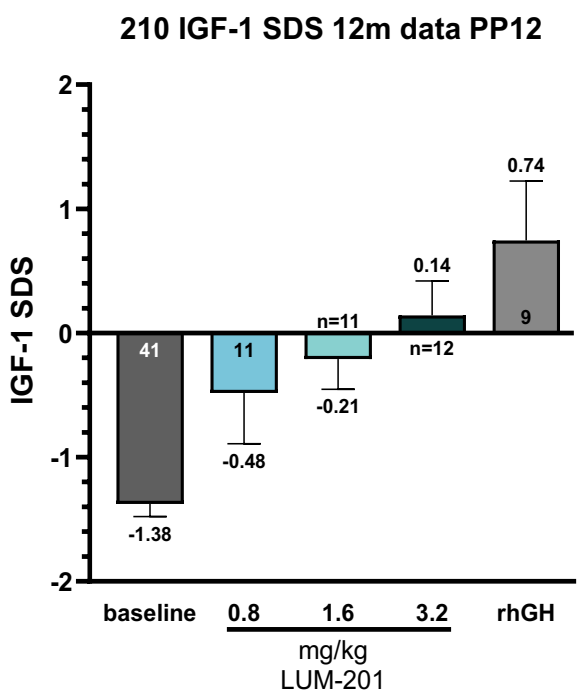
AHV ANCOVA Model Terms: treatment, Age at dose 1, Sex, Baseline HT SDS, Baseline BMI SDS, Baseline IGF-1 SDS, LUM-201 PEM, Baseline BA Delay, HT SDS-MPH SDS
Bars represent Least Squares Mean (LSM), Error bars represent the Standard Error of LSM

** Equates to 0.24 mg/kg/wk (approved rhGH dose range: 0.17-0.24 mg/kg/wk for Norditropin)

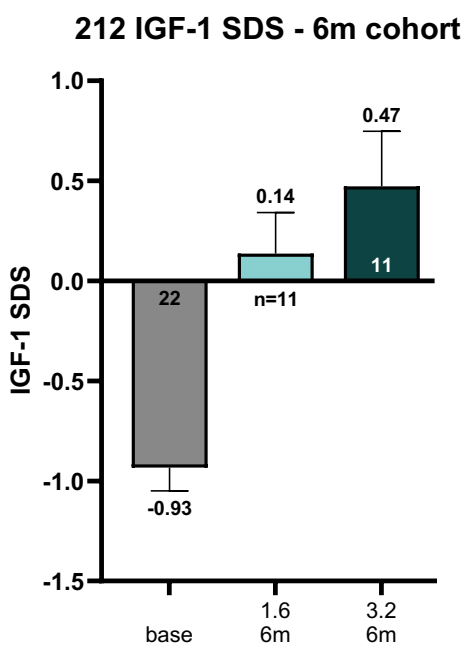
# LUM-201 Normalizes IGF-1 SDS with Durable Effect Out to 12 Months

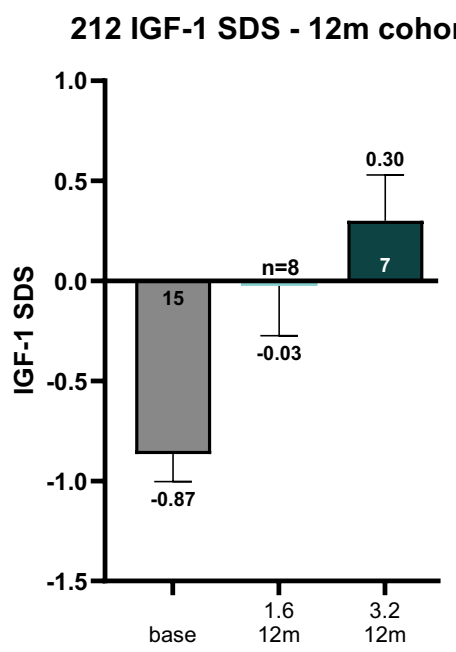
OraGrowtH210 TRIAL




OraGrowtH212 TRIAL



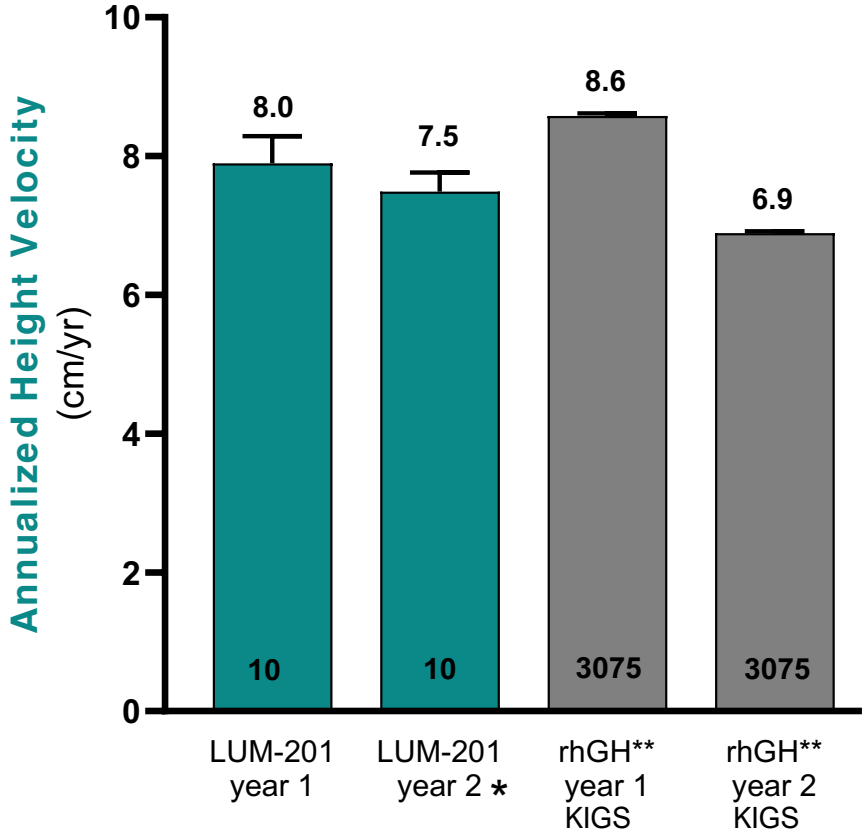

Bars represent sample mean, and error bars represent Standard Error of the Mean

OraGrowtH210 TRIAL + OraGrowtH212 TRIAL

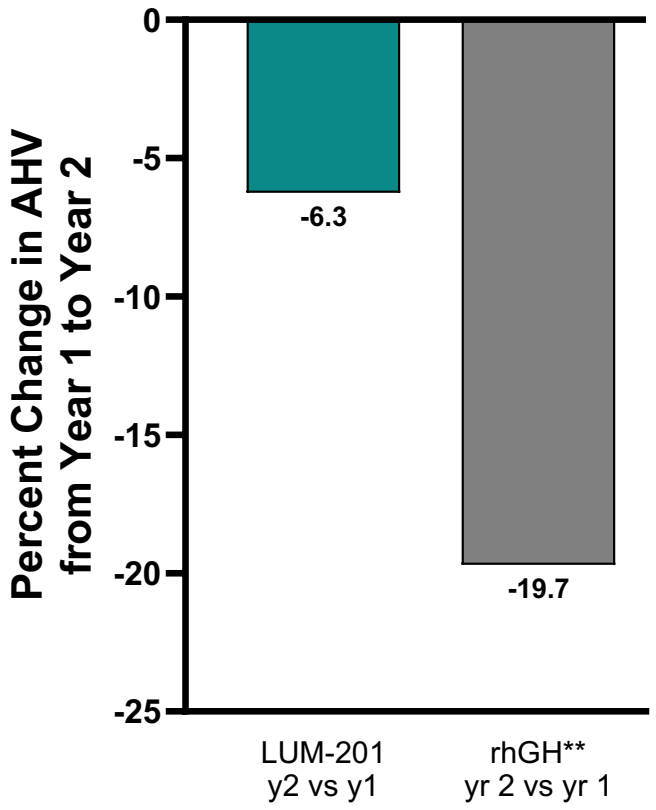
# LUM-201 Data Suggests Potential for Greater Durability of Response than rhGH to 24 Months

OraGrowtH210 & OraGrowtH212 Combined (1.6 and 3.2 mg/kg LUM-201)

**210 & 212 combined LUM-201**
**Year 1 vs Year 2**




**210 & 212 combined LUM-201**
**24m AHV PP24**



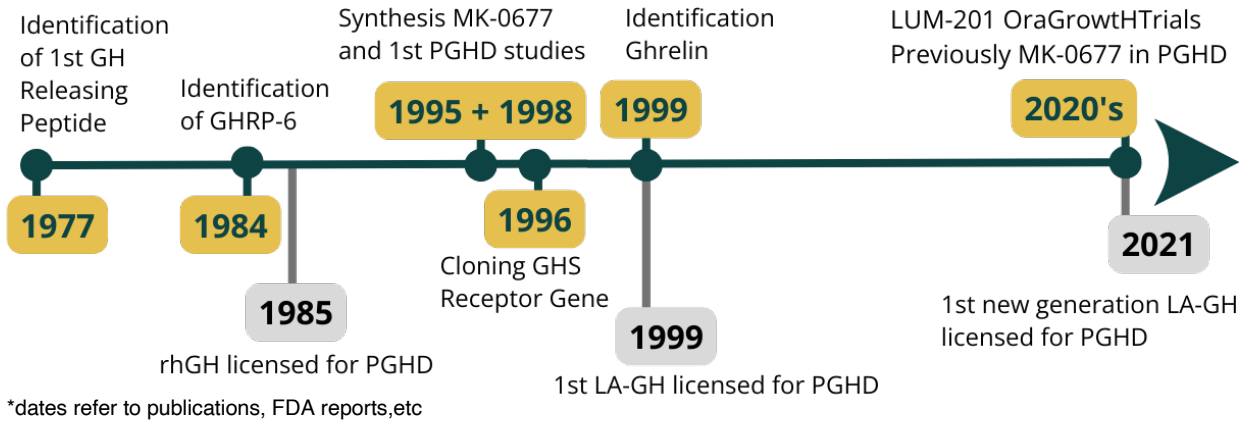

- **Preliminary** data demonstrated LUM-201 AHV durable to 24 months
- More moderate year 2 AHV decline than rhGH likely due to LUM-201 restoration of GH and IGF-1 to normal levels via pulsatile secretion

AHV values from the OraGrowth studies are based on ANCOVA model
* At 24 months, data include a subset of subjects from OraGrowtH210 trial who met protocol criteria to continue past 12 months.
** Ranke et.al. 2010 – rhGH treated cohort of moderate GHD children; mean AHV for the moderate GHD cohorts were 8.58 cm/yr in year 1 and 6.89 cm/yr in year 2.

# LUM-201 Summary

Restoration of approximately normal pulsatile endogenous GH secretion
Similar growth to that achieved with daily pharmacological rhGH
Maintenance of normal IGF-I levels
Maintenance of growth response over 2 years
Favorable investigational safety profile to date

***Timeline* for key events in the development of GH Secretagogues and rhGH in PGHD***

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*Is restoring physiological GH secretion a better approach to treating moderate paediatric GHD than using exogenous rhGH?*

Is it *time* for an innovative approach to treating moderate PGHD?

- Removes the burden of frequent injections
- Potential to achieve physiological GH profiles, meeting the core objectives of all endocrine therapies to restore normal hormonal homeostasis
- Stimulates rethinking on the etiology and management of moderate GHD – Should we consider a new term? “GH secretagogue responsive short stature”