

Deconvolution Analysis:

Oral GH secretagogue (LUM-201) enhances growth in individuals with moderate Pediatric Growth Hormone Deficiency (PGHD) by enhancing endogenous GH secretion and increasing IGF-1

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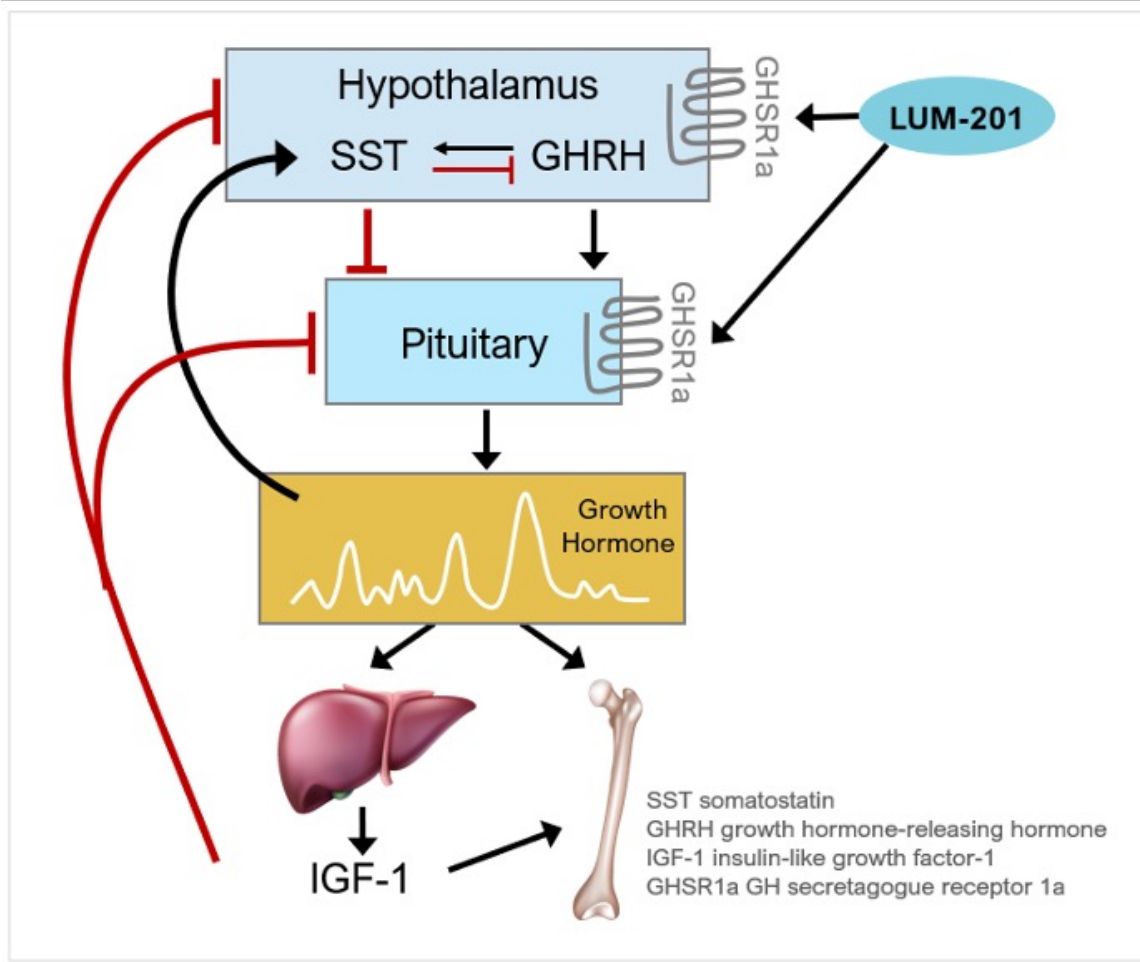
Disclosure

Dr. Cassorla is an investigator for clinical studies with LUM-201 at the University of Chile (Sponsor - Lumos Pharma, Inc.) and has previously acted as a consultant for Debiopharm, Pfizer, Merck, Novo Nordisk and Sandoz.

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LUM-201 (ibutamoren) – Mechanism of Action



Oral LUM-201 is a **growth hormone (GH) secretagogue**

- Acts as a durable agonist of GH Secretagogue Receptor (GHSR1a) to stimulate GH release¹
- LUM-201 has been observed to **increase the amplitude of endogenous, pulsatile GH secretion over 24 hours**^{2,3}
- Another differentiating feature vs rhGH is the **natural negative feedback mechanisms, which limit the potential for hyperstimulation and excessive increases in IGF-1**
- LUM-201 promotes pulsatile GH secretion in a **selective PGHD Population**

Moderate PGHD - Axis Responsive

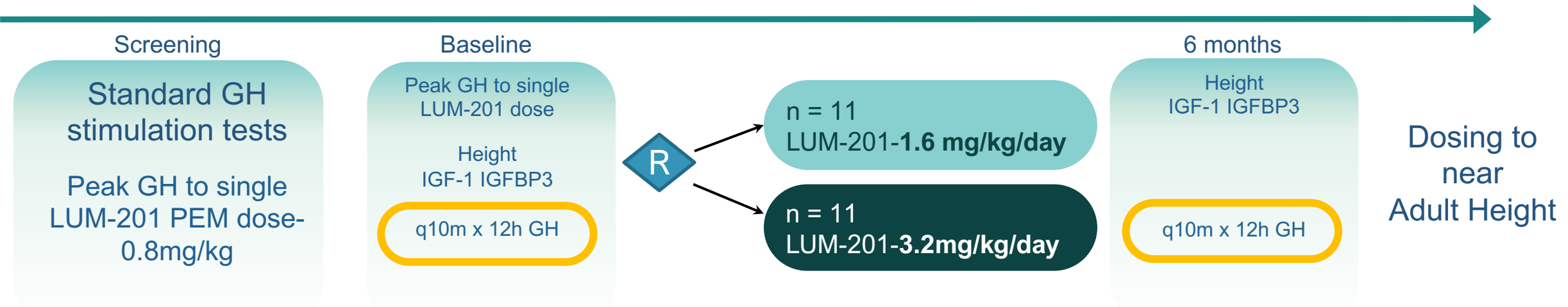
1. Howard 1996 Science 273:974-977
2. Nass 2008 Ann Intern Med 149:601-611
3. Chapman 1997 J Clin Endocrinol Metab 82:3455-3463



Phase 2- Pulsatility and PK/PD Study Design

Naive Moderate PGHD Patients

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Primary Endpoints:

- Assess LUM-201 effect on endogenous GH pulsatility and Annualized Height Velocity (AHV)
- Evaluate PK/PD in children

Use of PD Data to Combine Cohorts:

- GH responses to the PEM test dose 0.8 mg/kg (p=0.9)
- First treatment doses were not different between the groups (GH C_{max} 34.8±6.6ng/ml for 1.6mg/kg and 38.2±11.2 ng/ml for 3.2mg/kg, p=0.7).
- The groups were therefore combined for this analysis.

Baseline Data

Subjects N=15	1.6 mg N=8	3.2 mg N=7
	Mean (SD)	
Age (mos)	96.9 (11.9)	95.0 (22.7)
Height (cm)	115.2 (4.6)	113.1 (10.10)
Height SDS	-2.1 (0.3)	-2.3 (0.5)
IGF-1 SDS	-1.1 (0.5)	-0.8 (0.4)
MPH (cm)	161.8 (7.0)	160.8 (5.7)
MPH SDS Δ	0.7 (0.5)	0.8 (0.4)
BA Delay (yrs)	1.5 (0.3)	1.8 (0.9)
BMI (SDS)	-0.2 (1.0)	+0.5 (1.0)
Peak GH response to clonidine stim (ng/mL)	7.2 (2.4)	7.2 (2.3)
Peak GH response to LUM-201 stim (ng/mL)	25.3 (6.4)	25.4 (11.0)
Male/Female %	63/37	71/29

Minor differences between the two groups:

- Slight imbalance in age and gender
- Slight imbalance in delta below MPH, BMI, and bone age delay



Principles of Deconvolution Analysis¹

1. Peaks of GH concentration are identified and analyzed by combining these features:
 - a) a rapid increase representing **secretion** described by a Gaussian curve
 - b) a slow decay representing **elimination** based on the half-life of GH in the circulation
2. This generates episodes of GH secretion expressed as ng/ml/min
3. The distribution volume of GH in plasma is used to define secretion over 12 hours per ml of blood, which is then converted into secretion from the pituitary as $\mu\text{g}/\text{kg}$ body weight/12 hours

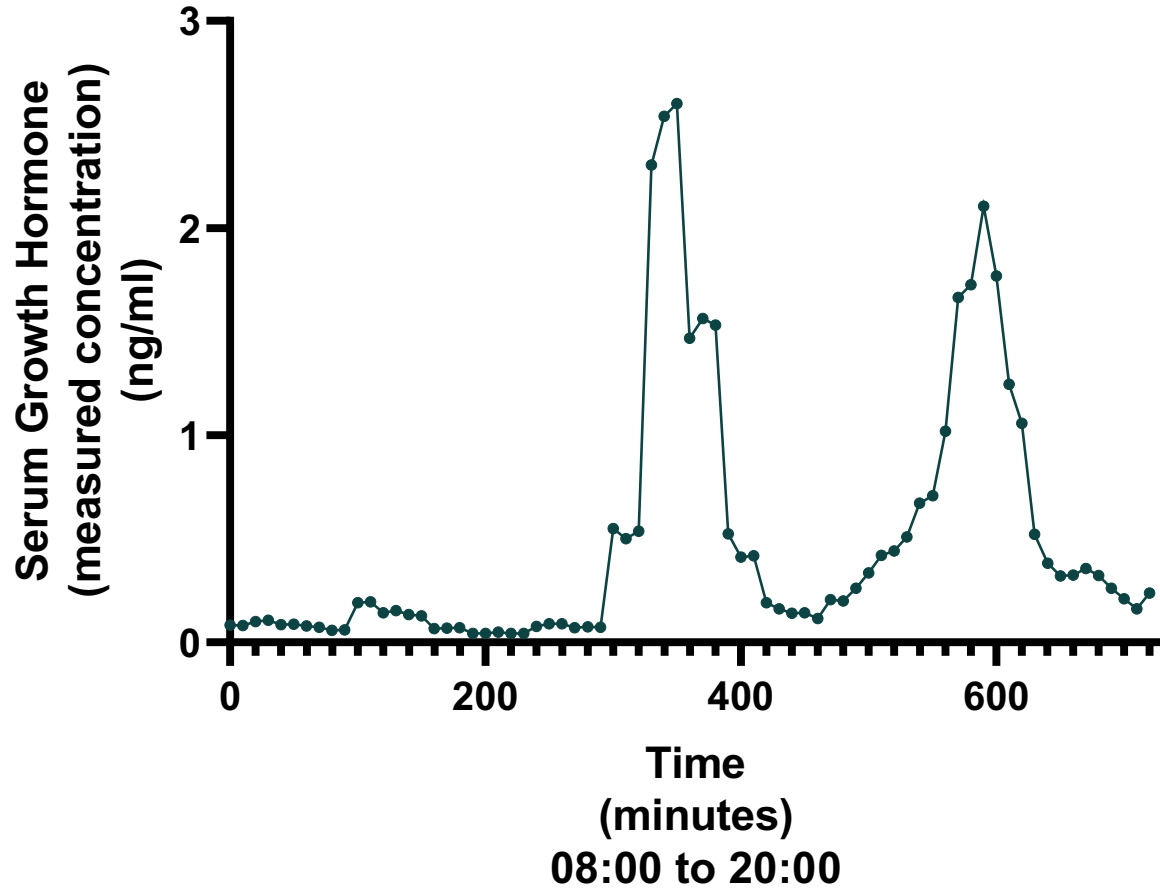
1. ML Johnson et al, "Signal-Response Modeling of Partial Hormone Feedback Networks", Journal of Diabetes Science and Technology 2009



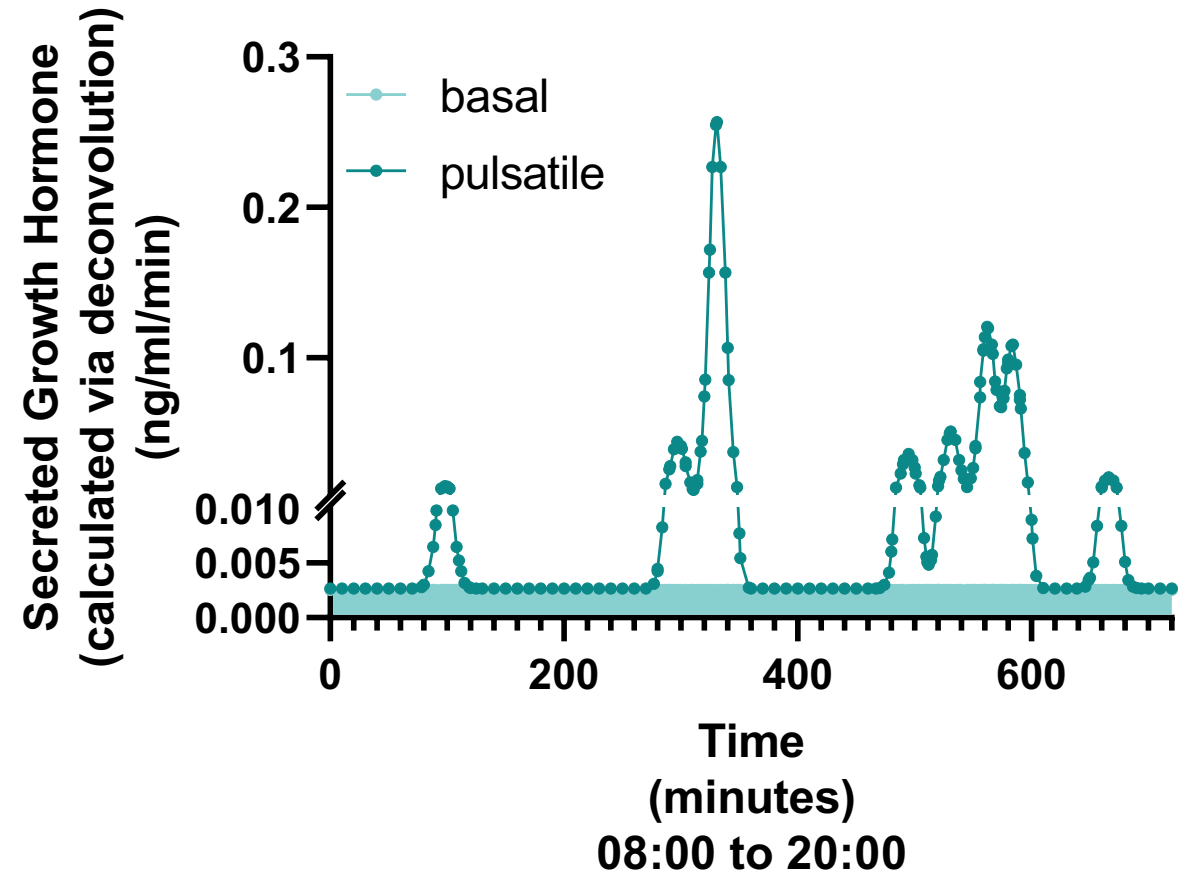
Deconvolution Analysis of Serum GH Pulsatility

Provides a measure of pituitary secretion of GH

GH concentration

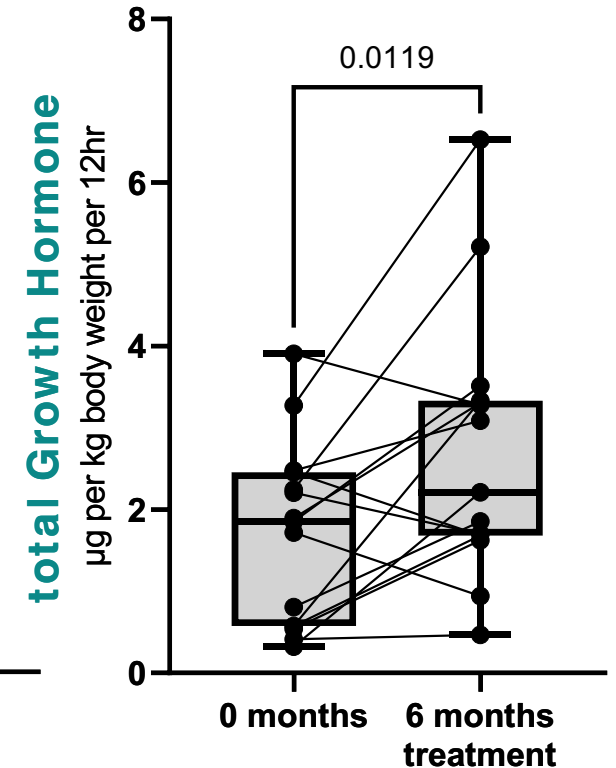
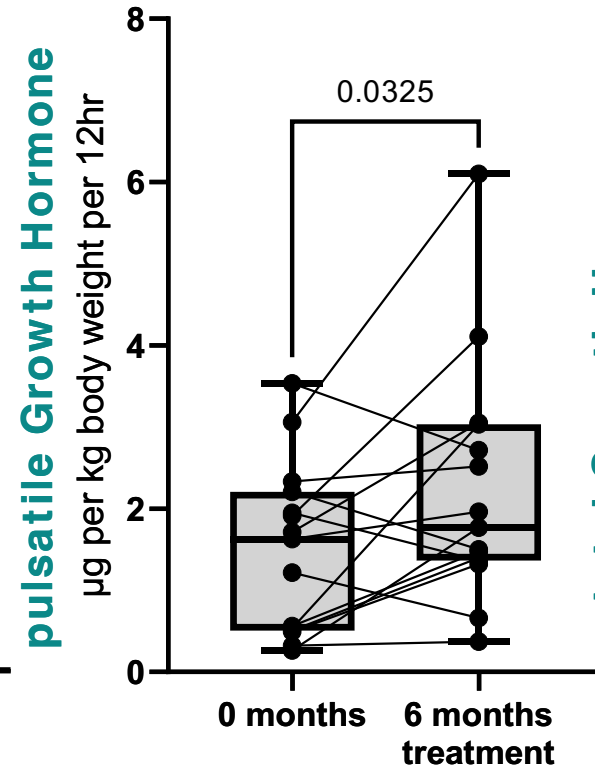
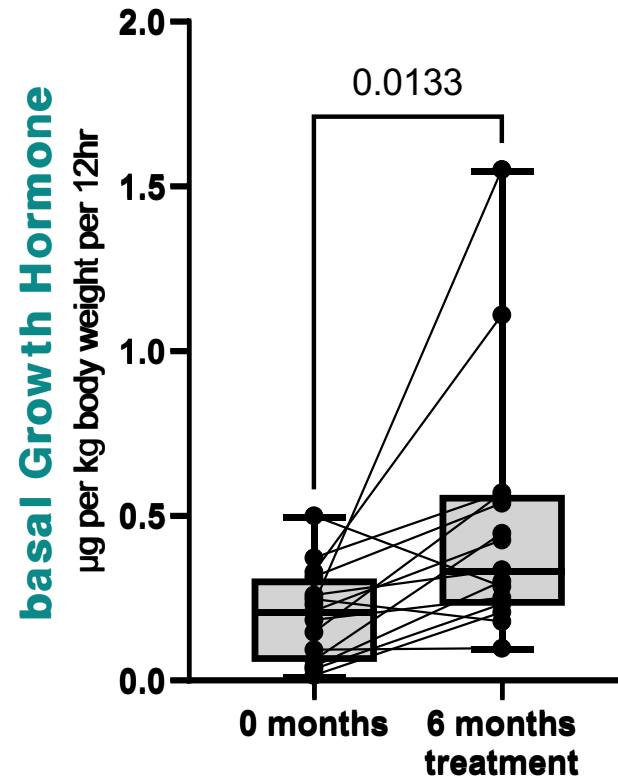
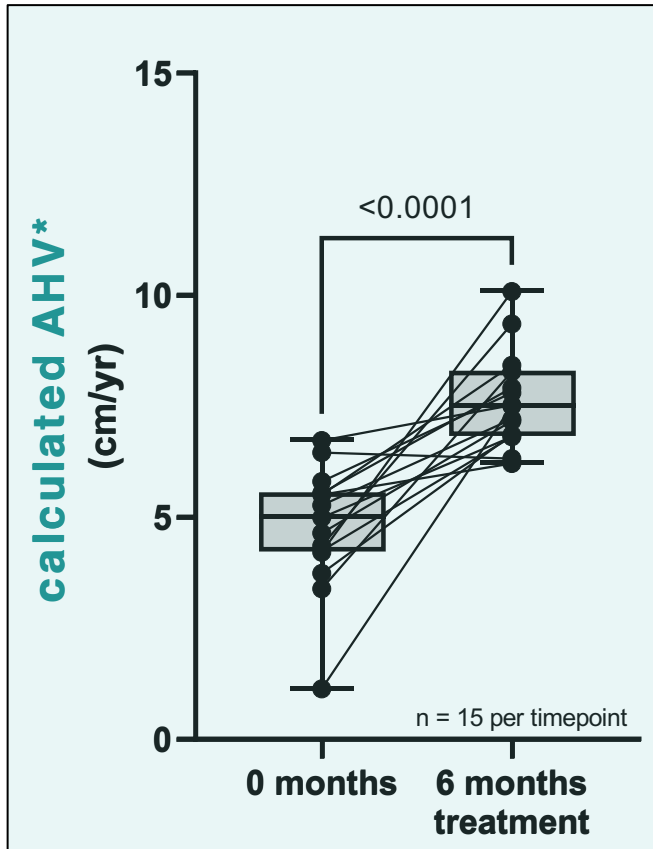


GH secretion



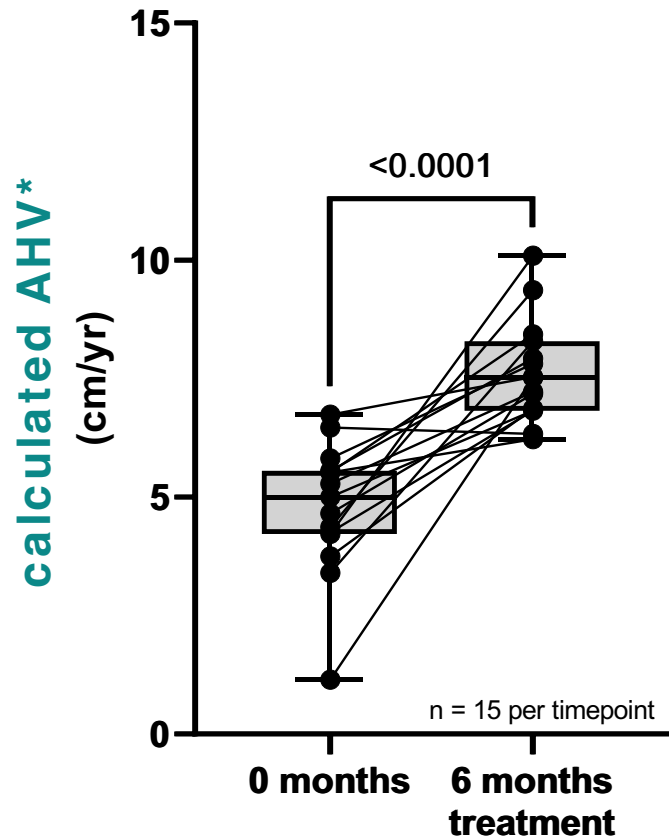
Growth Hormone secretion at 0 vs 6 months of oral LUM-201 Treatment

All variables from deconvolution based on 72 samples in 12 hours

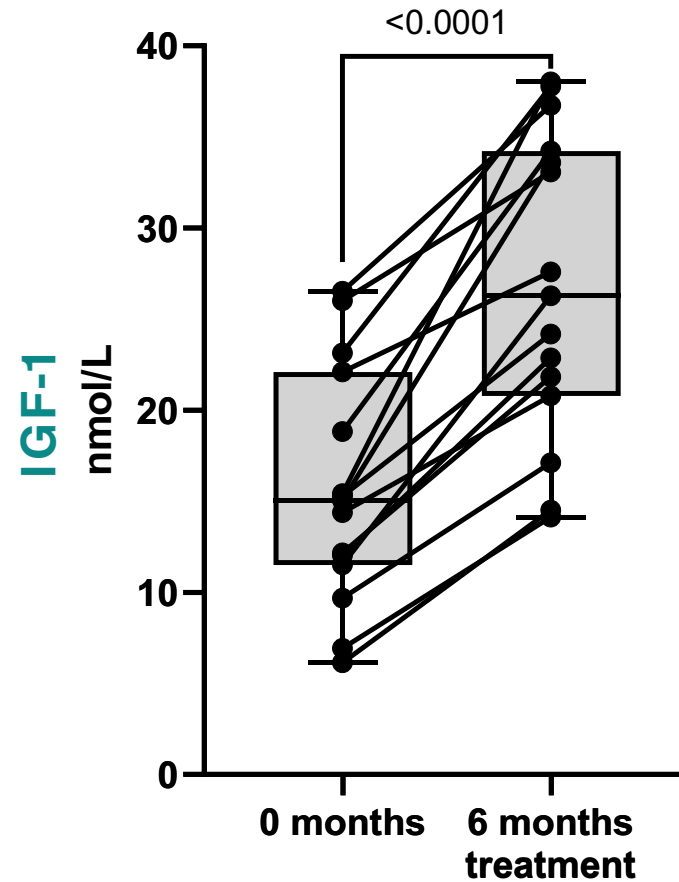


AHV*, IGF-1, and IGFBP-3 at 0 vs 6 months oral LUM-201 (n=15)

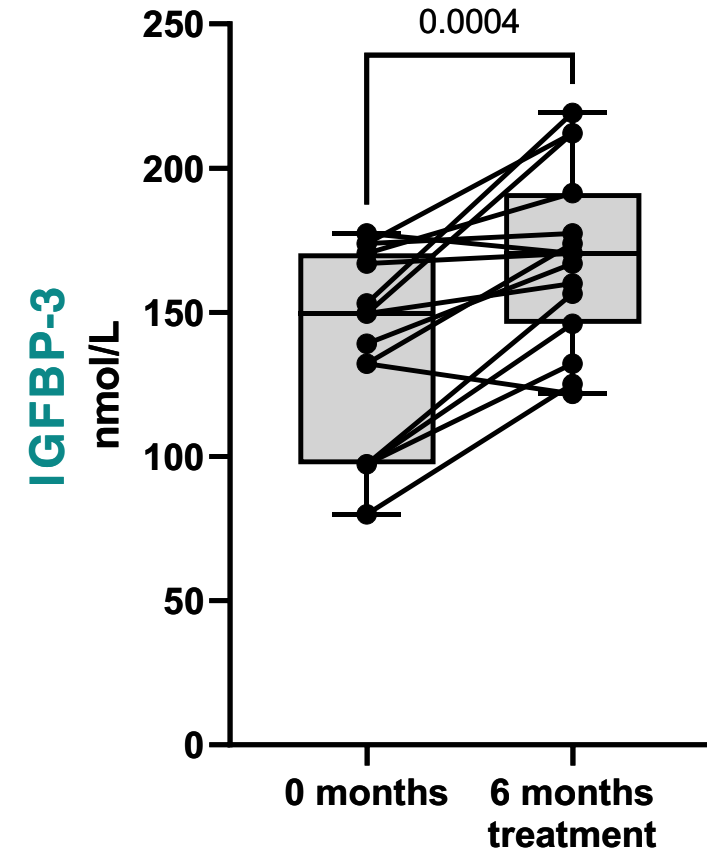
Annualized Height Velocity



IGF-1



IGFBP-3



Summary

After 6 months of treatment with oral once-a-day LUM-201

- Annualized Height Velocity increased by approximately 62% compared to baseline
- Total GH secretion, determined by deconvolution analysis, increased by 60%
- Serum IGF-1, after 6 months of LUM-201 administration increased by approximately 80%



Conclusion

LUM-201 in the potential treatment of moderate PGHD has the advantages of:

- being taken orally once-a-day
- enhancing endogenous pulsatile GH secretion
- maintaining normal feedback mechanisms
- restoring normal growth

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