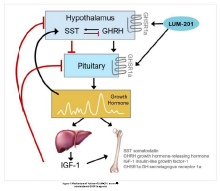
OraGrowtH210 Trial (Phase 2): Oral LUM-201 Shows Similar Annualized Height Velocity to Daily rhGH in Moderate Pediatric Growth Hormone Deficiency (PGHD) with a 1.6mg/kg/day Dose and a Promising Investigational Safety Record

Andrew Dauber, MD, MMSc, Children's National Hosp., Washington, DC, US; Beata Wikiera, MD, PhD, Dept of Pediatrics, Endocrinology, Diabetes & Metabolic Diseases, Wroclaw, Poland; Renata Stawerska, MD, Dept of Paediatric Endocrinology, Medical Univ. of Lodz, Lodz, Poland; Alison Lunsford, MD, Texas Tech HSC Amarillo, Amarillo, TX, US; Maria Conteras, MD, Texas Tech HSC Amarillo, Amarillo, TX, US; Artur Bossowski, MD, PhD, Medical Univ. in Białystok, Dept of Paediatric, Endocrinology and Diabetes Białystok, Poland; Michael Tansey, MD, Univ. of Iowa, Iowa City, IA, US; Sasigarn Bowden, MD, Nationwide Children's Hosp., Columbus, OH, US; Beata Pyrzak, MD, Dept of Pediatric and Endocrinology Medical Univ. of Warsaw, Warsaw, Poland; Michael Everett Gottschalk, MD, PhD, Rady Children's Hosp., San Diego, CA, US; Leslie Soyka, MD, UMass Chan Medical School, Worcester, MA, US; Elżbieta Petriczko, MD, Sonomed Clinic, Szczecin, Poland; Sunil Nayak, MD, Pediatric Endocrine Assoc., Greenwood, CO, US; Monica Marin, MD, Oklahoma Children's Hosp. OU Health, Oklahoma City, OK, US; Matthew Feldt, DO, Children's Mercy Hospital and Clinics, Kansas City, MO, US; Oscar Escobar, MD, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, US; M. Jennifer Abuzzahab, MD, Children's Hospitals, Minneapolis, MN, US; Bhuvana Sunil, MD, Mary Bridge Children's Hospital and Health Center, Tacoma, WA, US; Kupper Wintergerst, MD, MBA, Norton Children's Hosp., Univ. of Louisville, Louisville, KY, US; Paul Thornton, MD, Cook's Children Medical Center, Fort Worth, TX, US; Mark Harris, MD, Queensland Children's Hosp., South Brisbane, Australia; Elżbieta Moszczynska, MD, Memorial Inst. Children's Health Center, Warsaw, Poland; Lumos Pharma, Inc., Austin, TX, United States: Aleksandra Bruchey, PhD; Christopher Smith, MS; Erik Brincks, PhD; John C McKew, PhD; Michael Thorner, MB BS, DSc, FRCP, MACP, Pisit "Duke" Pitukcheewanont, MD

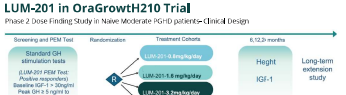
LUM-201 (ibutamoren)

- **Oral Secretagogue:** Agonist of the growth hormone (GH) Secretagogue Receptor 1a (GHSR1a)
- **Mechanism of Action:** Figure 1: LUM-201 acts on the GHSR1a which is expressed in the hypothalamus and anterior pituitary (ref 1). LUM-201 enhances the amplitude of pulsatile releases of GH and normalizes GH levels after 6 months of therapy, while simultaneously acting as a functional antagonist at the somatostatin receptor (ref 2,3,4). In turn, these effects increase the levels of IGF-1, which together with GH, reach the open growth plates and stimulate growth.



LUM-201 in OraGrowtH210 Trial

Phase 2 Dose Finding Study in Naive Moderate PGHD patients– Clinical Design

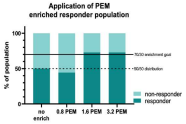


Study Objective:
To evaluate oral LUM-201 ibutamoren in children with moderate pediatric growth hormone deficiency (PGHD)

Primary Endpoints: Annualized Height Velocity (AHV)
Goals: Prospectively confirm utility of PEM strategy, Determine optimal Phase 3 dose

Study Information:
•45 trial sites US and International. • Trial duration: 24 months
• N = 81 subjects •Only PEM+ pre-pubertal PGHD subjects that are rhGH-treatment naïve
•Inclusion: Previous PGHD diagnosis, HTSDS less than or equal to −2.0, delayed bone age
PEM = Responders to PEM Test: LUM-201 stim GH ≥ 9 ng/ml, & baseline IGF-1 > 30 ng/ml.

Application of PEM enriched responder population

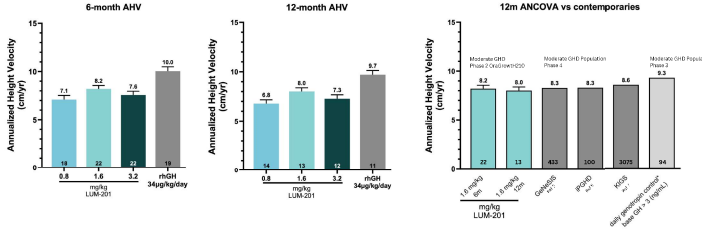


PEM Test Reproducibility Results:

- Subjects with Positive Agreement on PEM Tests: 70/76
- PEM positive classification was 100% reproducible and exceeded pre-specified statistical objective
- 95% Confidence Interval, (95.3%, 100%)
- Enrichment strategy demonstrated that >70% of PEM+ subjects met pre-specified target growth in 1.6 and 3.2 mg/kg/day cohorts

References
1. Howard 1996 Science
2. Nass 2008 Ann Intern Med
3. Chapman 1997 J Clin Endocrinol Metab
4. Supported by Lumos Pharma Topline Phase 2 Data
5. Laron 2004
6. Laron/Kauli et al JPEM 2009
7. Ranke et al JCEM 2010
8. Nass 2008 Ann Intern Med

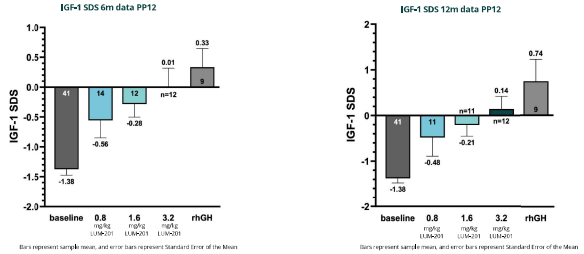
OraGrowtH 210 AHV Results



AHV ANCOVA Model Terms for AHV graphs: 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. rhGH equates to 0.24 mg/kg/wk (approved rhGH dose range: 0.17–0.24 mg/kg/wk for Nordiftropin).

* Daily Genotropin control group for Somatropin Ph3 dosed at 0.034 mg/kg/day (equates to 0.24 mg/kg/wk); subjects were stratified based on GH production during a standard stim test

OraGrowtH210: LUM-201 Normalized IGF-1 Values



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

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OraGrowtH 212: PK/PD Trial

Study Information:
Single specialized clinical site (University of Chile, Santiago) Open-label LUM-201 1.6mg/kg and 3.2mg/kg study; N = 22
•Inclusion Criteria: Height <2 SD, delayed bone age, serum IGF-1 below the mean for age, and peak GH response to a clonidine stimulation test between 3 and 10 ng/mL

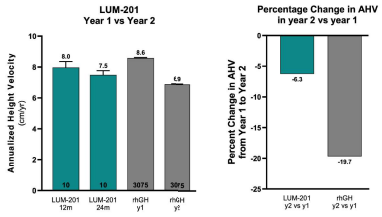
LUM-201 Normalizes GH Concentrations in Moderate PGHD
Increasing 24-hour pulsatile secretion, LUM-201 achieves comparable growth to exogenous injectable rhGH, with only 20% of GH concentration levels

	Normal Healthy (Control)	Untreated GHD (Control)	LUM-201 (Baseline GHD)*	LUM-201 (Treat 6M GHD)*	Comparator arm rhGH 34µg/kg/day
	Zadeh		N=22		Albertsson-Wikland 07
12h AUC µg/kg.12h	3.3 ± 1.3	1.1 ± 0.5	1.3 ± 1.0	2.6 ± 1.4	-
24h µg/kg.24h	5.0 ± 1.3	1.4 ± 0.5	1.7 ± 1.3	3.3 – 4.0	~20
Ratio 24/12 (Day)	1.52	1.27	1.27	1.25-1.52	-

† LUM-201 integrated concentration of Growth Hormone data represent mean ± standard deviation.
*Six concentrations from the combined 1.6 and 3.2 mg/kg/day cohorts, 1 bottle at 18:00h (to 19h).
†† Adapted from data in Albertsson-Wikland et al. JCEM 1994. 20 subjects received their absolute individual daily dose of ~60% of the administered dose

OraGrowtH210 and 212: Combined (1.6 & 3.2 mg/kg)

LUM-201 values are from combined OraGrowtH210 and OraGrowtH212 per protocol 24 month cohort.
rhGH values are from moderate GHD children from the Ranke 2008 +KIGS data base.



Favorable Safety Data from Combined Phase 2 Trials

	PEM	0.8 mg/kg	1.6 mg/kg	3.2 mg/kg	rhGH
	N =129	N =18	N =33	N=33	N =20
Number of AEs	38	59	155	150	54
Subjects with AE (%)	24 (18.8%)	14 (77.8%)	31 (93.9%)	30 (90.9%)	16 (80.0%)
Treatment Related AEs *	7	2	16	19	6
Subjects with Treatment Related AEs (%)	4 (3.1%)	1 (5.6%)	13 (39.4%)	13 (39.4%)	5 (25.0%)
Subjects with SAEs (%)	0 (0%)	#2 (11.1%)	1 (3.0%)	0 (0%)	##1 (5.0%)
Subject with Treatment Related SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)

Topline Safety Results

- No meaningful treatment-related Serious Adverse Events (SAEs)
- No drop-outs due to SAEs or AEs
- No meaningful safety signals observed in laboratory values, adverse events data, or in EKG values to date

*Treatment related AEs in 1.6 and 3.2 groups: Increased appetite (13), Pain in extremity (7), Arthralgia (5)

One subject had SAE between PEM dose and randomized dose

Summary

OraGrowtH210

- Oral LUM-201 cohort 1.6 mg/kg shows best performing AHV from the 3 LUM-201 cohorts evaluated in the OraGrowtH210 trial.
- LUM-201 AHV of 8.0 cm at 12 months is comparable to historical rhGH AHV for moderate GHD population (8.3-8.6 cm)

Combined 24 month OraGrowtH210 and 212 Data

- Preliminary data demonstrate LUM-201 AHV durable to 24 months
- Oral LUM-201 shows a more moderate year 2 AHV decline than rhGH likely due to LUM-201's restoration of GH and IGF-1 to normal levels via endogenous pulsatile secretion

OraGrowtH212

- LUM-201 stimulates the secretion of endogenous GH by restoring the pulsatility of GH release within the standard physiological spectrum, resembling the pattern seen in typical children.
- Even though LUM-201 only triggers 20% of the GH concentration attained through its own administration, it exhibits growth velocity comparable to that induced by supraphysiological GH levels from subcutaneous GH injections. This suggests that LUM-201 might be more efficient in stimulating growth compared to daily GH injections.

Conclusions

Oral LUM-201 enables the restoration of normal endogenous pulsatile GH secretion, promoting growth comparable to that achieved through daily pharmacological rhGH.
This approach preserves the normal GH-IGF-1 feedback mechanisms in moderate PGHD, offering an alternative to rhGH injections.

By providing an oral therapy that attains physiologic GH profiles, investigational LUM-201 treatment aligns with the fundamental objectives of endocrine therapies—specifically, the restoration of normal hormonal homeostasis.

The OraGrowtH210 and OraGrowtH212 Trials are sponsored by Lumos Pharma, Inc.
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