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

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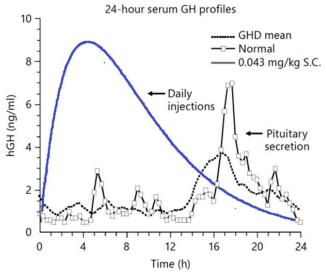
OraGrowtH TRIALS
oral therapy to release natural GH secretion

GH Profiles in a Normal and a GHD subject compared to exogenous GH injection over 24 hours



Advanced Therapies http://www.drugs.com/pro/nutropin.html Holl RW, et al. J Clin Endocrinol Metab, 77:216, 1993. Pediatric Endocrinology and Diabetology. Endocr Dev. Basel, Karger, 2016

LUM-201 Mechanism of Action

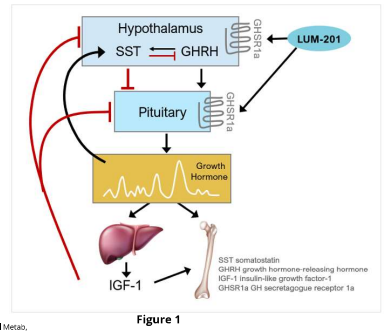


Figure 1

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.

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"

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

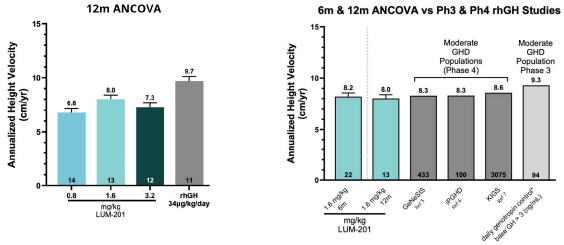
OraGrowtH210 TRIAL

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)

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

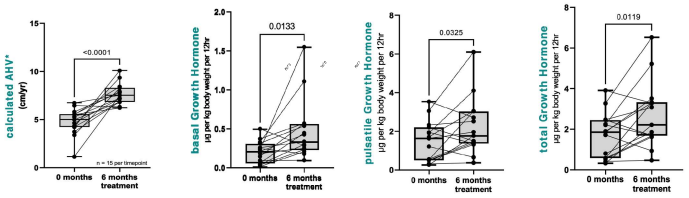
Normalisation of growth to levels, near those achieved with daily rhGH



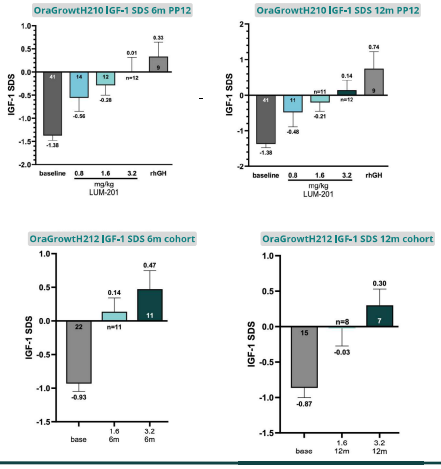
AHV ANCOVA Model Terms for AHV grpstrt: Treatment, Age at dose 2, Sex, Baseline HT SDS, Baseline BMI SDS, Baseline IGF-1 SDS, LUM-201, PGH, Baseline BA Delay, HT SDS*HPH SDS. Bars represent Least Squares Mean (LSM). Error bars represent the Standard Error of LSM. rhGH equates to 0.24 mg/kg/wk (approved rhGH dose range 0.17–0.24 mg/kg/wk for Nordiscrips).

* 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

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

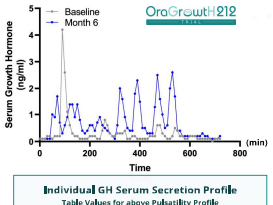


LUM-201 Normalised IGF-1 Values: OraGrowtH 210 and OraGrowth212



Example of an individual subject's GH profile and growth response

Q10m-12 hour : Baseline vs Treatment



Individual GH Serum Secretion Profile
Table Values for above Pulsatility Profile

		Baseline	6 months LUM-201 1.6-3.2 mg/kg/d
IGF-1 (ng/ml)		48	111
	% change from baseline **		131%
Q 10m 12h GH	AUC 0-12 (ng*hr/ml)	252.9	481.8
	% change from baseline **		91%
Height velocity (cm/yr)		4.4	9.4

**Percent change from baseline calculated as: (6mo value – baseline value) / (baseline value)

Combined Safety Data from Ph2 Trials

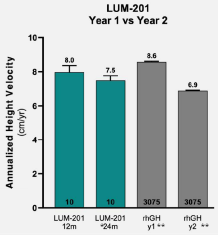
	PEM	0.8 mg/kg	1.6 mg/kg	3.2 mg/kg	rhGH
	N =129	N =18	N =33	N=33	N =20
Number of AEs	38	59	155	150	54
Subjects with AE (%)	24 (18.6%)	14 (77.8%)	31 (93.9%)	30 (90.9%)	16 (80.0%)
Treatment Related AEs *	7	2	16	19	6
Subjects with Treatment Related AEs (%)	4 (3.1%)	1 (5.6%)	13 (39.4%)	13 (39.4%)	5 (25.0%)
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%)

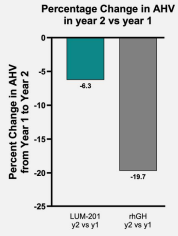
- No meaningful treatment-related Serious Adverse Events (SAEs)–No drop-outs due to SAEs or AEs
- No meaningful safety signals observed in laboratory values, adverse events data, or in EKG values to date
- *Treatment related AEs in 1.6 and 3.2 groups: Increased appetite (23), Pain in extremity (7), Arthralgia (5)
- # One subject had SAE between PEM dose and randomized dose. ## Subject had SAE between PEM dose and randomized dose

Phase 2 Combined Data LUM-201

OraGrowtH210 TRIAL + OraGrowtH212 TRIAL

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





•**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 near normal levels via pulsatile secretion

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 (IC-GH‡)	Untreated GHD (IC-GH‡)	LUM-201 (baseline GH)*	LUM-201 (treat 6M GH)*	Comparator arm rhGH 34µg/kg/day
	Zadik†		N=22		Albertsson-Wikland††
12h (day) 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	1.27-1.52	--

‡ IC-GH: integrated concentration of Growth Hormone; data represent mean + standard deviation
* GH concentrations from the combined 1.6 and 3.2 mg/kg/day cohorts of the OraGrowthH212 Trial
¥ 24-hr GH concentration for LUM-201 calculated from 12-hr data using published conversion ratios
† Zadik et al Horm Res 1992
†† Adapted from data in Albertsson-Wikland et al JCEM 1994; 24h exposures listed reflect absorbance/bioavailability of ~60% of the administered dose

References
1. Howard 1996 Science
2. Ness 2008 Ann Intern Med
3. Chapman 1997 J Clin Endocrinol Metab
4. Supported by Lumos Pharma Topline Phase 2 Data
5. Blum 2021 JES
6. Lechuga-Sancho et al JPEM 2009
7. Ranke et al JCEM 2010

lumos PHARMA

AHV values from the OraGrowth studies are based on ANCOVA model
* At 24 months, data include a subset of subjects from OraGrowthH210 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