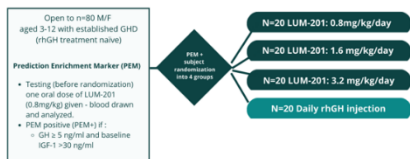# OraGrowtH210 TRIAL

LUM-201 in Idiopathic Pediatric Growth Hormone Deficiency (iPGHD) Interim Analysis on Baseline Demographics, Safety Profile and 6 month Annualized Height Velocity (AHV)

A Lunsford[1], B Wikiera[2], A Dauber[3], B Pyrzak[4], A Bossowski[5], M Tansey[6], E Petriczko[7], R Stawerska[8,3], S Bowden[10], M Feldt[11], M Everett Gottschalk[12], M Marin[13], S Nayak[14], B Sunil[15], E Moszczynska[16], D Repaske[17], L Soyka[18], J Fuqua[19], O Escobar[20], D Bowlby[21], P Y Fechner[22], E Wiltshire[23], M Harris[24], K Wintergest[25], A R Lafferty[26], B S Miller[27], P Simm[28], A Bruchey[29], C Smith[29], D B Karpf[29], C McKew[29], MO Thorner[29]

LUM-201 (ibutamoren) in OraGrowtH210 Trial

Investigational oral GH secretagogue tablet (once daily) studied in iPGHD Phase 2 trial - 24 months

Open to n=80 M/F aged 3-12 with established GHD (rhGH treatment naive)

Prediction Enrichment Marker (PEM)
- Testing (before randomization) one oral dose of LUM-201 (0.8mg/kg) given - blood drawn and analyzed.
- PEM positive (PEM+) if:
  - GH ≥ 5 ng/ml and baseline IGF-1 >30 ng/ml

PEM + subject randomization into 4 groups

- N=20 LUM-201: 0.8mg/kg/day
- N=20 LUM-201: 1.6 mg/kg/day
- N=20 LUM-201: 3.2 mg/kg/day
- N=20 Daily rhGH injection

Primary Endpoint:
Annualized Height Velocity (AHV)

Goals:
- Prospectively confirm utility of PEM strategy
- Determine optimal dose for Phase 3

LUM-201 (ibutamoren) Mechanism of Action and Pharmacodynamics

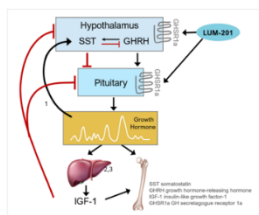**Oral Secretagogue:** Agonist of the growth hormone (GH) Secretagogue Receptor 1a (GHSR1a)

Mechanism of Action:
Figure 1: LUM-201 acts on the GHSR1a which is expressed in the hypothalamus and anterior pituitary. LUM-201 enhances the amplitude of pulsatile releases of GH over 24 hours, while simultaneously acting as a functional antagonist at the somatostatin receptor. In turn, these effects increase the levels of IGF-1, which together with GH, reach the open growth plates and stimulate growth

Figure 1 Mechanism of Action of LUM-201, an orally administered GHSR1a agonist

Pharmacodynamics (PD): Figure 2: PD curve shows potential for LUM-201 doses in OraGrowtH210 Trial to produce greater GH response

- 200 mg adult (5.6 mg/kg PGHD)
- 100 mg adult (2.8 mg/kg PGHD)
- 50 mg adult (1.4 mg/kg PGHD)
- 25 mg adult (0.7 mg/kg PGHD)
- 10 mg adult (0.3 mg/kg PGHD)
- 5 mg adult (0.1 mg/kg PGHD)
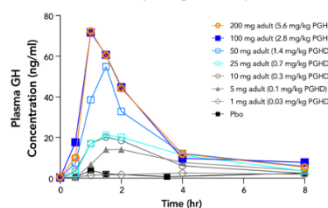- 1 mg adult (0.03 mg/kg PGHD)
- Pbo

Figure 2: Merck Study 001 in healthy adult subjects, results based on single LUM-201 dose administered. Pharmacodynamic (PD) graph- PD plateau possible ≥ 2.8 mg/kg PGHD dose equivalent (based on AUC equivalence)

Interim Analysis: Baseline Demographics, Safety Profile and 6 month AHV

Baseline Demographics Table

Predictors of growth response:
- Younger age
- Height (shorter stature)
- Lower height and IGF-1 standard deviation scores (SDS)
- Greater distance from mid-parental height (MPH)
- Higher body mass index standard deviation score (BMI SDS)

| Subjects (41)	0.8mg/kg N=11	1.6mg/kg N=10	3.2mg/kg N=10	rhGH N=10
Below Values are Denoted: Mean (SD)				
Age (mos)	95.5 (28.2)	99.3 (28.3)	96.1 (21.7)	90.3 (26.7)
Height (cm)	113.8 (12.6)	114.6 (9.6)	113.8 (8.8)	111.6 (11.9)
Height SDS	-2.31 (0.32)	-2.35 (0.62)	-2.30 (0.48)	-2.28 (0.43)
IGF-1 SDS	-1.24 (0.570)	-1.17 (0.72)	-1.39 (0.61)	-1.37 (0.48)
MPH (cm)	164.47 (6.44)	166.98 (7.15)	166.20 (8.06)	168.78 (8.54)
MPH SDS Δ	1.29 (0.62)	1.76 (0.60)	1.96 (0.83)	1.76 (0.73)
BA Delay (yrs)	1.89 (1.07)	1.91 (0.53)	2.19 (0.86)	1.78 (0.96)
BMI SDS	-0.29 (1.10)	-0.35 (0.79)	-0.70 (0.48)	+0.31 (1.05)
Male/Female (%)	64/36	60/40	40/60	70/30

Interim Safety Profile

- No treatment-related Serious Adverse Events (SAEs)
- No drop-outs due to SAE's
- No meaningful safety signals observed in either laboratory values, adverse event data, or in electrocardiogram values.

Annualized Height Velocity (AHV)

Reading the graphs from left to right:
- Previous LUM-201 study (Merck 020) using two lower doses (blue bars) vs rhGH (grey bar) with 6 month AHV data
- Followed by rhGH subjects from historical data bases with 12 month AHV data (grey bars outlined in blue)
- Ending with OraGrowtH210 Interim Analysis with 6 month AHV data.

LUM-201 Cohort Growth Consistent with Historical Norms: rhGH Arm Growth an Outlier

Merck 020 data[7]
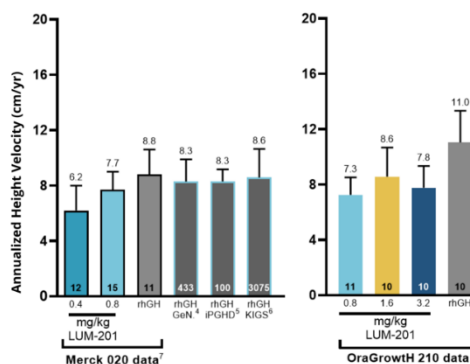
OraGrowtH 210 data

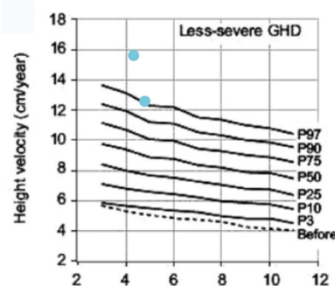**First-year Growth on rhGH for Moderate PGHD KIGS Database Analysis**

Figure 3: ● shows growth outliers in the OraGrowtH210 rhGH cohort (2 of 3 subjects under age 5 were randomized to rhGH), P lines = Growth percentiles and "Before" line marks height velocity before rhGH treatment. Ref: Ranke, et al 2010 JCEM

Conclusions

- LUM-201 1.6 mg/kg/day cohort grew 8.6 cm/year, in line with the expected rate of ~ 8.3 - 8.6 cm/year from prior data

- rhGH cohort grew at a much faster rate than historical data for first year growth data in moderate PGHD

- Cohort baseline differences predict faster first-year growth in the rhGH arm

- Baseline balance factors that predict faster growth should improve in the full data set

- No treatment-related Serious Adverse Events (SAEs) and no meaningful safety signals observed in either laboratory values, adverse event data, or in electrocardiogram values.

References
1. Howard 1996 Science
2. Nass 2008 Ann Intern Med
3. Chapman 1997 J Clin Endocrinol Metab
4. Blum et al JES 2021
5. Lechuga-Sancho et al JPEM 2009
6. Ranke et al JCEM 2010
7. Bright et al JES 2021

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