LUM-201 Elicits Greater GH Response Than Standard GH Secretagogues in Pediatric Growth Hormone Deficiency

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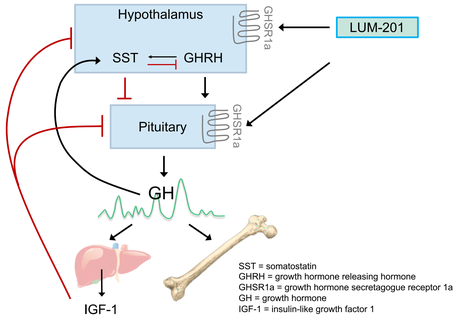
Background

Objective
To compare GH responses to an oral GH secretagogue, LUM-201 (ibutamoren, formerly MK-0677) and standard GH stimulation tests used for diagnosis of pediatric growth hormone deficiency (PGHD)

Introduction
LUM-201 is an orally administered agonist of the growth hormone secretagogue receptor (GHSR1a). A clinical study is underway (NCT04614337) to determine if LUM-201 is a safe and effective alternative to injections of recombinant human growth hormone (rhGH) in PGHD.

LUM-201 is an agonist of the growth hormone secretagogue receptor (GHSR1a) in the hypothalamus that diminishes inhibitory signals via somatostatin and increases stimulatory signals via GHRH to augment endogenous GH pulsatility (Fig 1).



Methods

- GH responses measured to a single, oral 0.8 mg/kg dose of LUM-201 and to two standard GH stimulation tests (arginine, clonidine, glucagon, insulin, L-Dopa)
- 68 subjects (40 M, 28 F) had GH responses measured to a single, oral 0.8 mg/kg dose of LUM-201 and to two standard GH stimulation tests (arginine, clonidine, glucagon, insulin, L-Dopa)
- Median (interquartile range) values for patient characteristics are shown in Table 1

Table 1 Baseline Characteristics

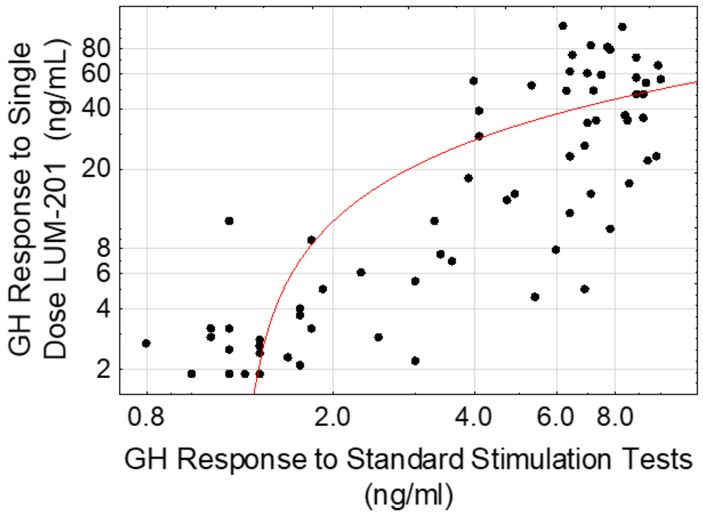
	Age (years)	Bone Age (years)	HT-SDS (cm)	Pretreatment Height Velocity (cm/year)	GH Stimulation Tests (ng/mL)	IGF-1 (ng/mL)
Median	9.2	6.0	-3.3	4.0	5.4	51
IQR	7.2, 10.8	4.5, 7.9	-4.5, -2.5	3.2, 4.6	1.8, 7.6	24, 111

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

Results

The null hypothesis of no difference in GH responses to LUM-201 and standard GH stimulation tests was rejected ($p < 0.00001$).
The median (IQR) response to LUM-201 was 15.0 (3.5,49) and to two standard GH stimulation tests was 5.4 (1.8, 7.6).
The subject-level data are shown below in Figure 2.

Fig 2. Comparison of GH Responses to LUM-201 and to two standard GH stimulations test (Note both parameters are displayed on logarithmic scales)



The differential GH responses, **shown in Fig 3 and Fig 4,** is defined as the difference between GH response to a single oral dose of LUM-201 and the GH response to two standard GH stimulation tests.

In a forward stepwise model of the differential response as dependent variable and including age, height SD and weight as potential covariates, standard stimulated GH ($p = 0.036$) and baseline IGF-I ($p < 0.000001$) were most strongly correlated (model r-square = 0.736).

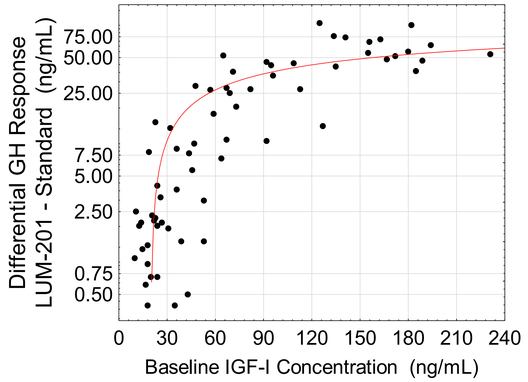


Fig 3. Dependence of differential GH response on baseline IGF-I concentration

(Note the differential response is displayed on a logarithmic scale)

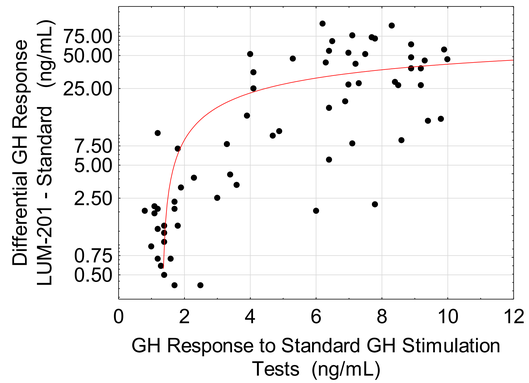


Fig 4. Dependence of differential GH response on standard GH stimulation test results

(Note the differential response is displayed on a logarithmic scale)

Summary and Conclusion

In prepubertal subjects diagnosed with Pediatric Growth Hormone Deficiency

- GH responses to single, oral doses of LUM-201 are substantially higher than observed in two standard GH stimulation tests.
- The difference in GH responses increases with higher baseline concentrations of IGF-I and higher GH stimulation test results.
- A differential response between LUM-201 and standard GH stimulation tests is more likely in patients with more moderate forms of PGHD.

References

Smith RG, Development of Growth Hormone Secretagogues, Endocrine Reviews, 2005; 26: 346-360

Bright, GB, Development of a Predictive Enrichment Marker for the Oral GH Secretagogue LUM-201 in Pediatric Growth Hormone Deficiency, J Endocrine Society, 2021, doi/10.1210

Disclosures
The authors are consultants to Lumos Pharma, Inc. Dr Thorner has equity in Lumos Pharma, Inc.