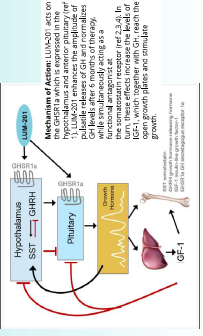


Introduction

The oral GH secretagogue, LUM-201 (butamoren mesylate), stimulates the secretion of growth hormone (GH) from the pituitary (see below for the mechanism of action). In Phase 2 trials, LUM-201 increases growth rates in children with moderate GHD (OraGrowthH210 and 212) (ENDO 2023, OR21-06). In OraGrowthH212, subjects underwent GH profiling over 12 hours at baseline (D1) and 6 months (M6). This provides an opportunity to evaluate the relationships between GH pulse profiles and growth response to LUM-201, taking account of both the increased GH secretion and the pattern of secretion.



### Phase 2 Pulsatility and PKPD Study Design



Ph 2 Pulsatility and PKPD Study – Baseline Demographics			
	LUM-201 1.6 mg	LUM-201 3.2 mg	
	Mean (SD)	Mean (SD)	
Age (months)	99.7 (15.2)	100.9 (21.1)	
Height SDS	-2.15 (0.28)	-2.26 (0.38)	
IGF-1 SDS	-1.01 (0.64)	-0.85 (0.50)	
MPH (cm)	162.6 (7.0)	160.3 (8.7)	
MPH SDS-A	-0.85 (0.53)	-0.73 (0.51)	
BA Delay (Yrs)	1.7 (0.86)	1.8 (0.96)	
BMI SDS	-0.07 (0.85)	0.28 (0.97)	

Correlation Matrix

A univariate Spearman's rank correlation matrix on all subjects was used to screen for relationships (marginally significant at  $p < 0.05$ ) between variables, with a focus on D1 characteristics.

D1 height velocity, 6m annualized height velocity, D1 GH pulse profile, D1 GH secretion at D1 and M6, and change in ANH.

Key findings:

1. Age was negatively associated with 6m ANH ( $r = -0.46$ ), D1 pulse profile, GH secretion was positively associated with D1 ANH ( $r = -0.53$ ), and negatively associated with change in ANH ( $r = -0.47$ ). However, GH secretion at D1 and M6 was not correlated with 6m pulse profile.

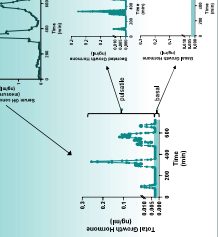
2. D1 GH pulse profile was positively associated with 6m pulse profile, D1 GH secretion was positively associated with 6m pulse profile, and D1 GH secretion was positively associated with change in total GH secretion ( $r = -0.47$ ).

### Principles of Deconvolution Analysis

1. Phases of GH concentration are identified and analyzed by combining these features:

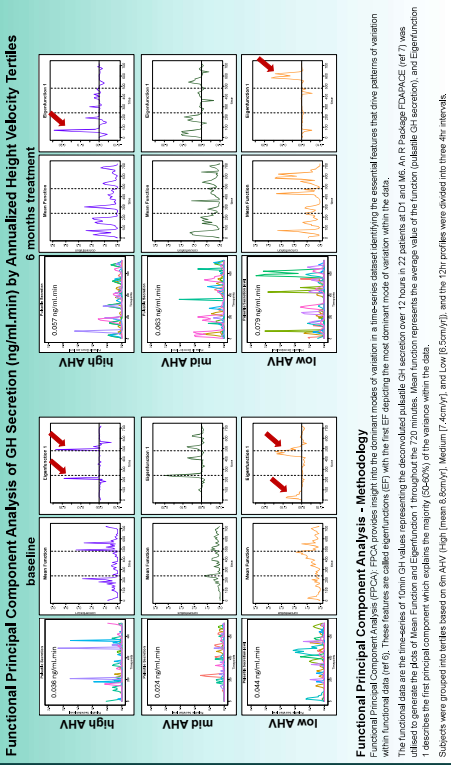
- a rapid increase representing secretion described as 'secretion' (secretion peak)
- a slow decay representing elimination based on the half-life of GH in the circulation

2. This generates episodes of secretion and elimination as right-mirrored (ref 5)

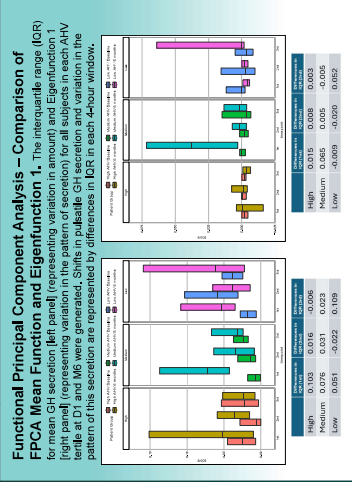
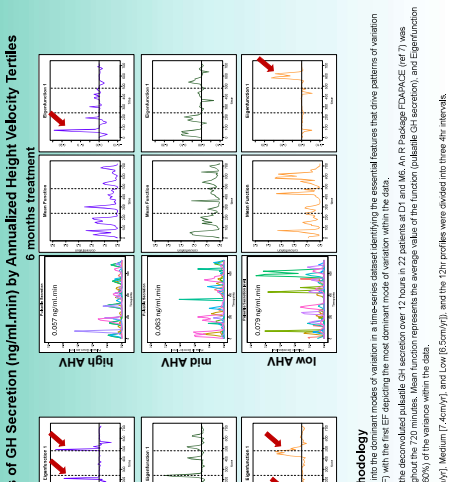
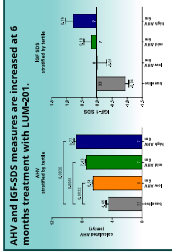
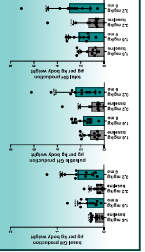


## Growth Response to Oral Growth Hormone Secretagogue LUM-201 in Children with Moderate GH Deficiency (GHD) is Dependent on the Pattern of Pulsatile GH Secretion Stimulated by LUM-201

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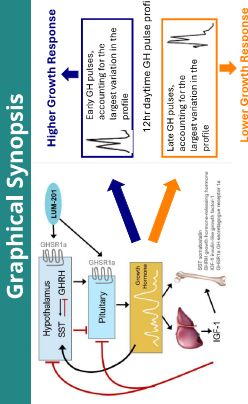


### Changes in GH secretion at baseline and at 6 months on LUM-201 treatment



Summary of Results

- Oral LUM-201 promotes significant increases in GH secretion over 6 months in children with moderate GH deficiency.
- Subjects treated with oral LUM-201 showed significant increases in growth rate and IGF-1 SDS.
- In the FPCA analysis, all three groups show an increase in mean GH secretion at 6m. There is more GH secretion in the first part of the profile at 6m for those in the high & medium tertiles, and more secretion in the later part of the profile for those in the low tertile.
- Subjects in the high tertile show the largest variation in the early GH pulses, while the lowest ANH tertile shows the largest variation in the late GH pulses (see Arrows on the FPCA figure).



Conclusions

- Complex relationships exist between growth response and both the amount and pattern of GH secretion, with the highest growth responses to LUM-201 associated with the greatest pulsatile activity early in the profile
- Restoring GH secretion with LUM-201 in moderate GHD results in both an increase in the overall amount of GH, and importantly an alteration in the pattern of the pulse profile, with distinct differences in these patterns between the best responders and the lower responders.

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