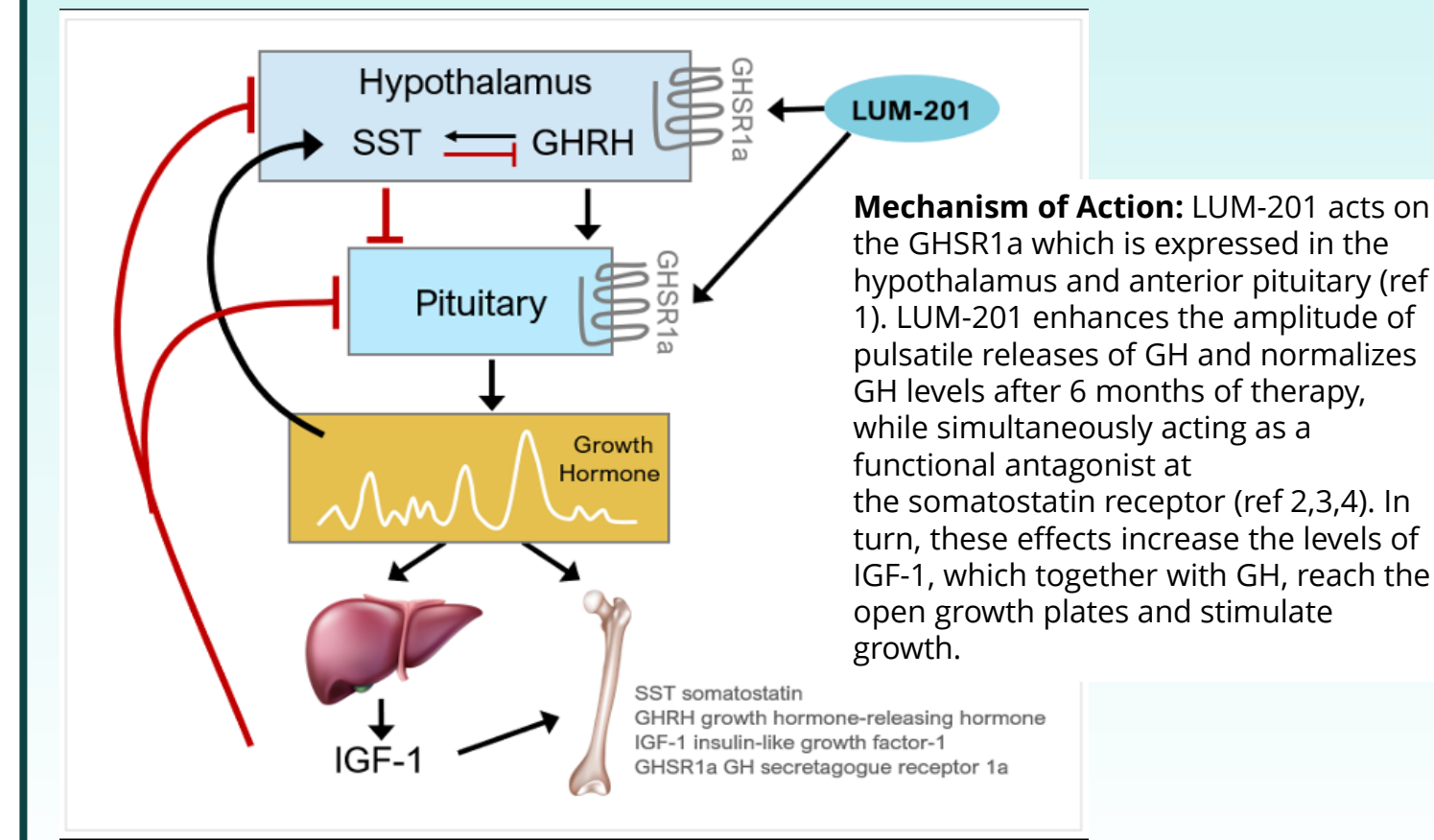


Growth Response to Oral Growth Hormone Secretagogue LUM-201 in Children with Moderate GH Deficiency (GHD) is Dependent on the Pattern of Pulsatile GH Secretion Stimulated by LUM-201

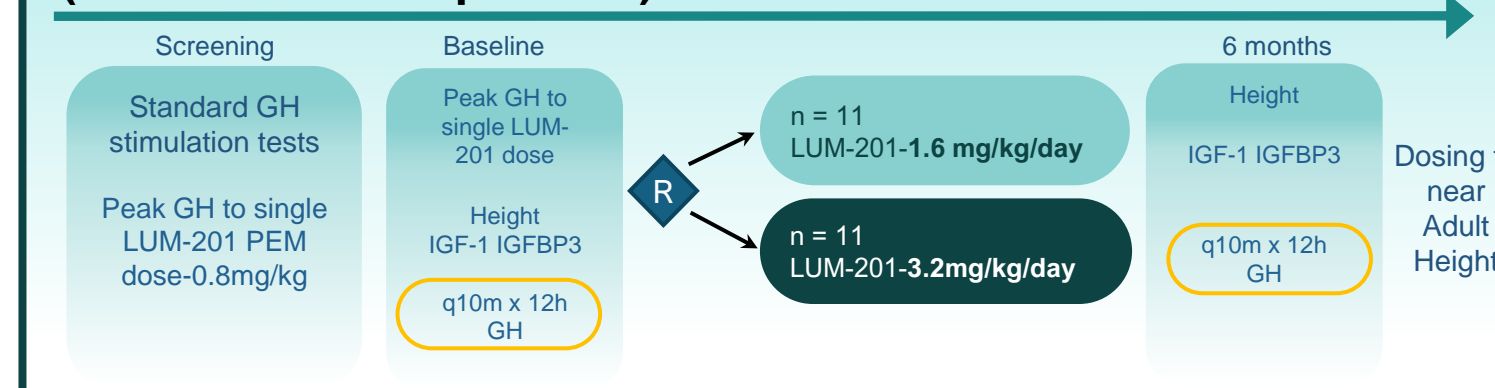
A. Roslan, MSc¹, R. Román, MD², A. Avila, RN², D. Said, RN², I. Baier, MD², E.L. Brincks, PhD⁴, A. Bruchey, PhD⁴, J.C. McKew, PhD⁴, P. Pitukcheewanont, MD⁴, M.L. Johnson, PhD³, T. Garner PhD¹, M.O. Thorner, MBBS, DSc⁴, P.E. Clayton, MB ChB, MD, A Stevens PhD¹, F. Cassorla, MD². ¹Developmental Biology and Medicine, Univ. of Manchester, UK ²Institute of Maternal and Child Research, Univ. of Chile, Santiago, Chile ³Univ. of VA - Emeritus, Charlottesville, VA, USA ⁴Lumos Pharma, Inc., Austin, TX, USA

Introduction

The oral GH secretagogue, **LUM-201 (Ibutamoren 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 (OraGrowth210 and 212) [ENDO 2023, OR21-06]. In OraGrowth212, 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.



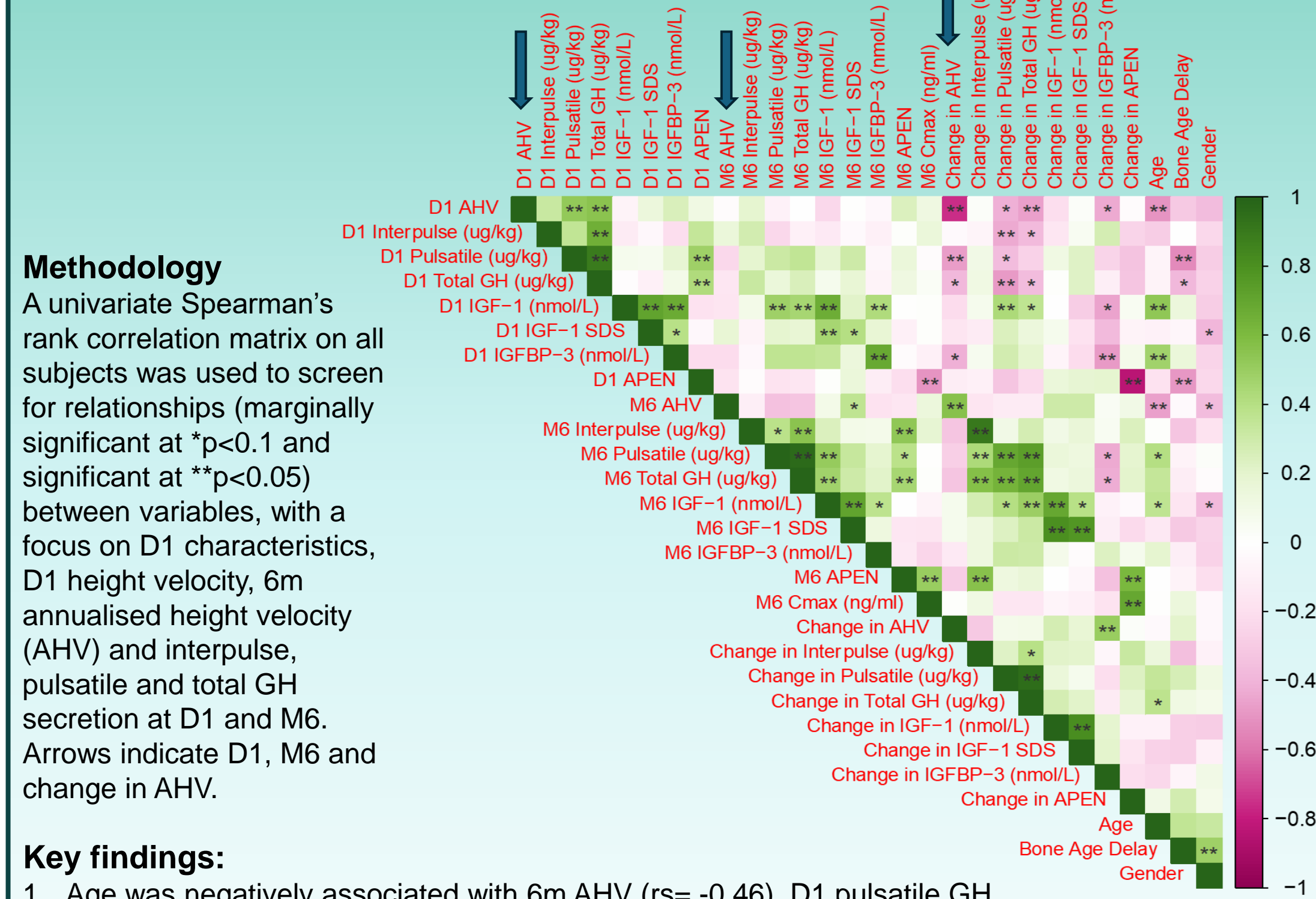
Phase 2 Pulsatility and PK/PD Study Design (Moderate PGHD patients)



Ph 2 Pulsatility and PK/PD Study – Baseline Demographics

	LUM-201 1.6 mg Mean (SD) N=11	LUM-201 3.2 mg Mean (SD) N=11
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 Δ	-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



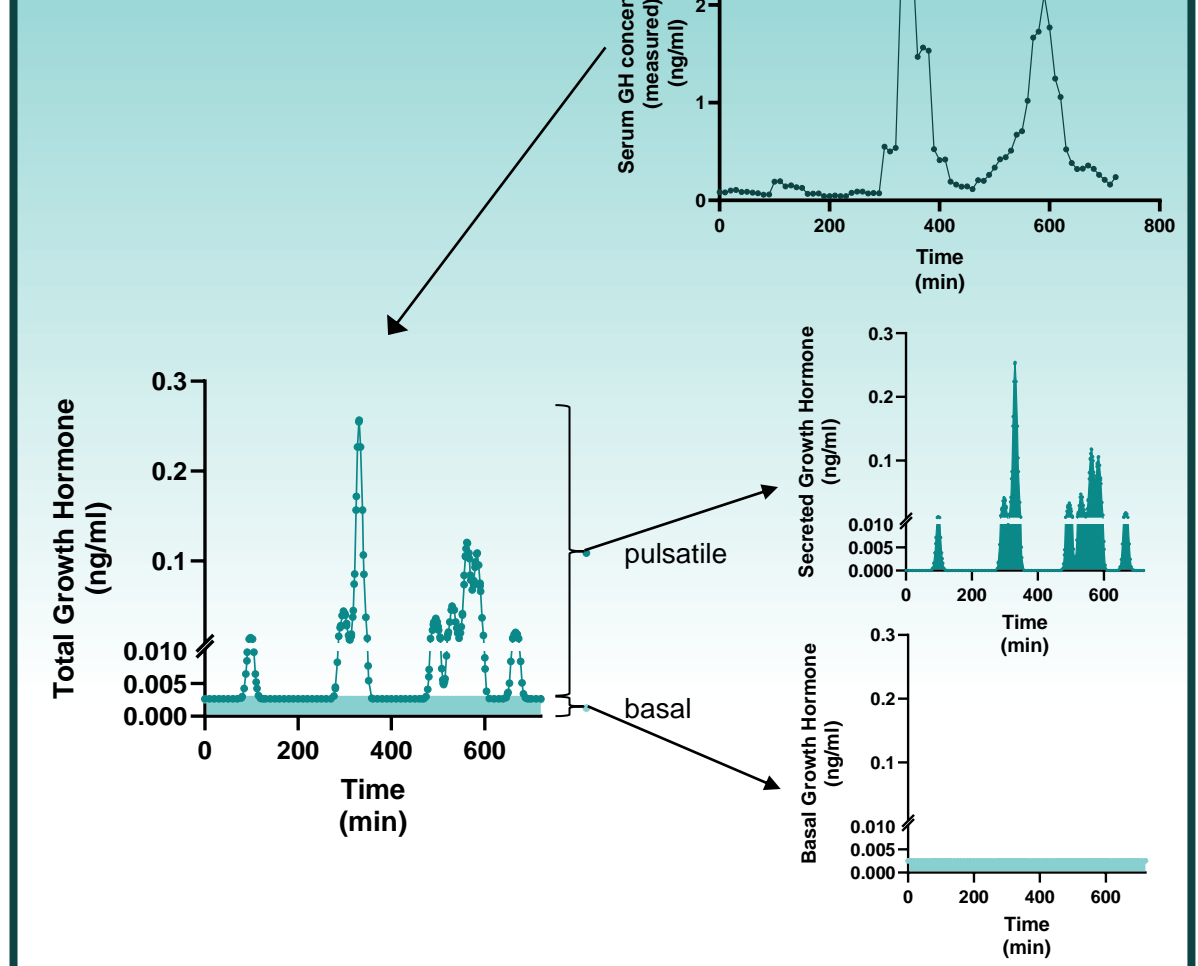
Methodology
A univariate Spearman's rank correlation matrix on all subjects was used to screen for relationships (marginally significant at *p<0.1 and significant at **p<0.05) between variables, with a focus on D1 characteristics, D1 height velocity, 6m annualised height velocity (AHV) and interpulse, pulsatile and total GH secretion at D1 and M6. Arrows indicate D1, M6 and change in AHV.

Key findings:

- Age was negatively associated with 6m AHV (rs= -0.46). D1 pulsatile GH secretion was positively associated with D1 AHV (rs=+0.53), and negatively associated with change in AHV (rs=-0.47). **However, GH secretion at D1 and M6 was not correlated with 6m AHV.**
- D1 serum IGF-I concentration was positively associated with 6m pulsatile and total GH secretion (rs=+0.49). 6m serum IGF-1 concentration was positively associated with change in total GH secretion (rs=+0.47).

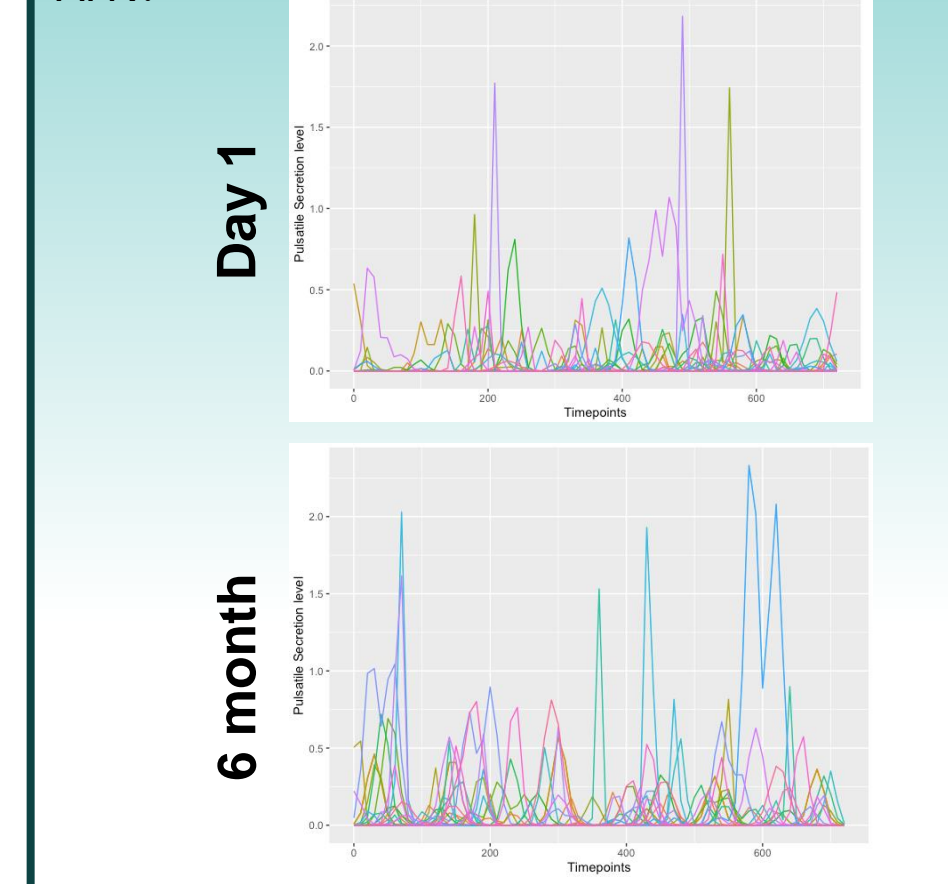
Principles of Deconvolution Analysis

- Peaks of GH concentration are identified and analyzed by combining these features:
 - a rapid increase representing secretion described by a Gaussian curve
 - a slow decay representing elimination based on the half-life of GH in the circulation
- This generates episodes of GH secretion expressed as ng/ml/min (ref 5)

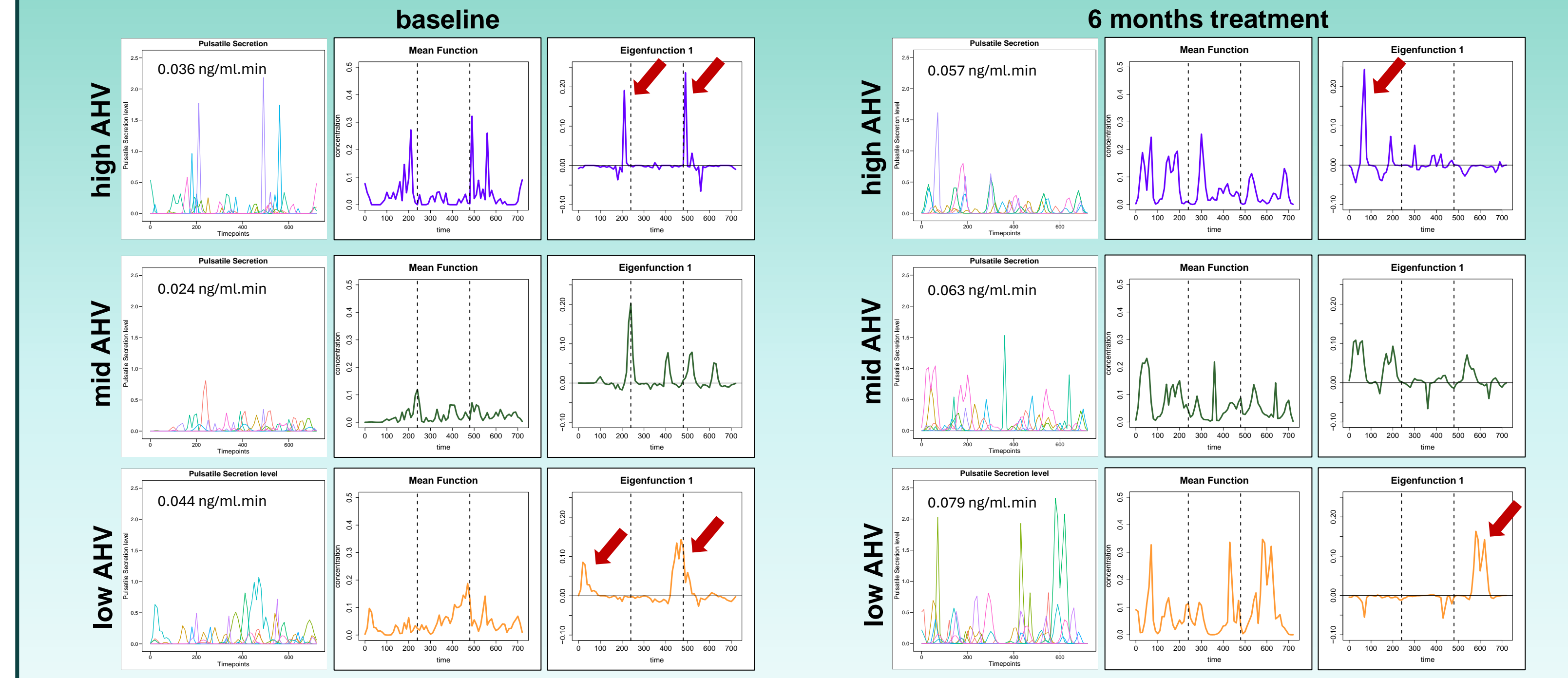


Deconvolution Analysis – Secretion patterns of GH in all 22 patients at D1 and after 6m treatment with LUM-201.

The increase in pulsatile secretion over 12hrs in the figure below is seen in the overall profiles. To explore the complexity of these data, we used FPCA (see next section) to identify the key patterns in subjects, divided into tertiles by their 6m AHV.



Functional Principal Component Analysis of GH Secretion (ng/ml.min) by Annualized Height Velocity Tertiles



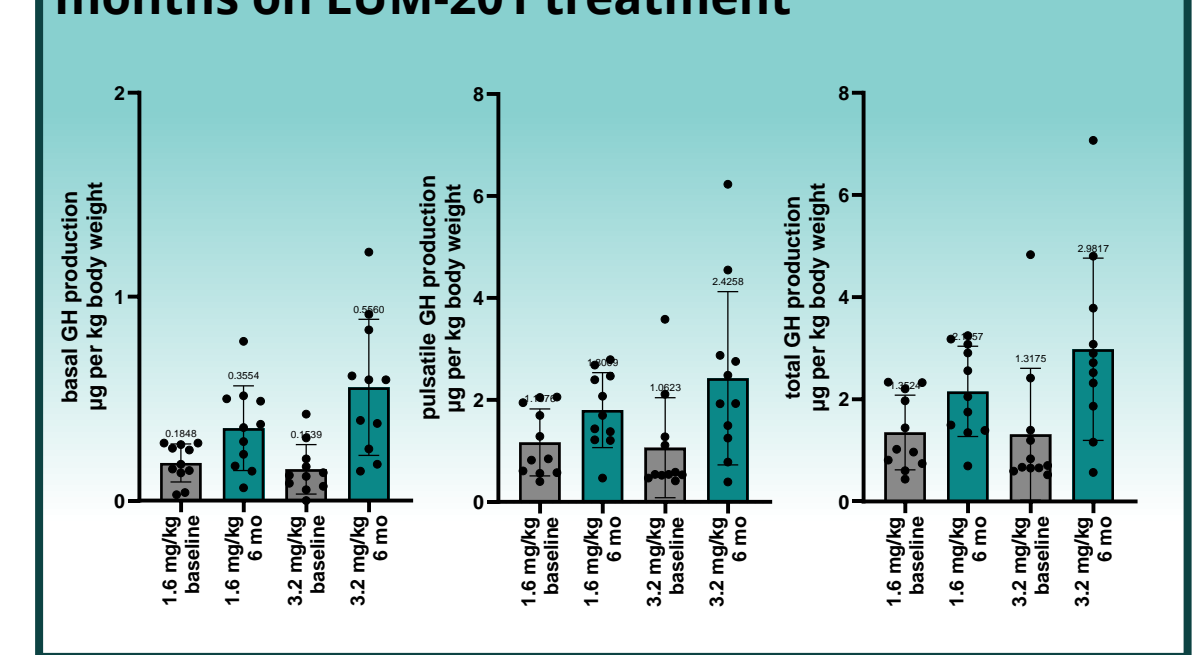
Functional Principal Component Analysis - Methodology

Functional Principal Component Analysis (FPCA): FPCA provides insight into the dominant modes of variation in a time-series dataset identifying the essential features that drive patterns of variation within functional data (ref 6). These features are called eigenfunctions (EF) with the first EF depicting the most dominant mode of variation within the data.

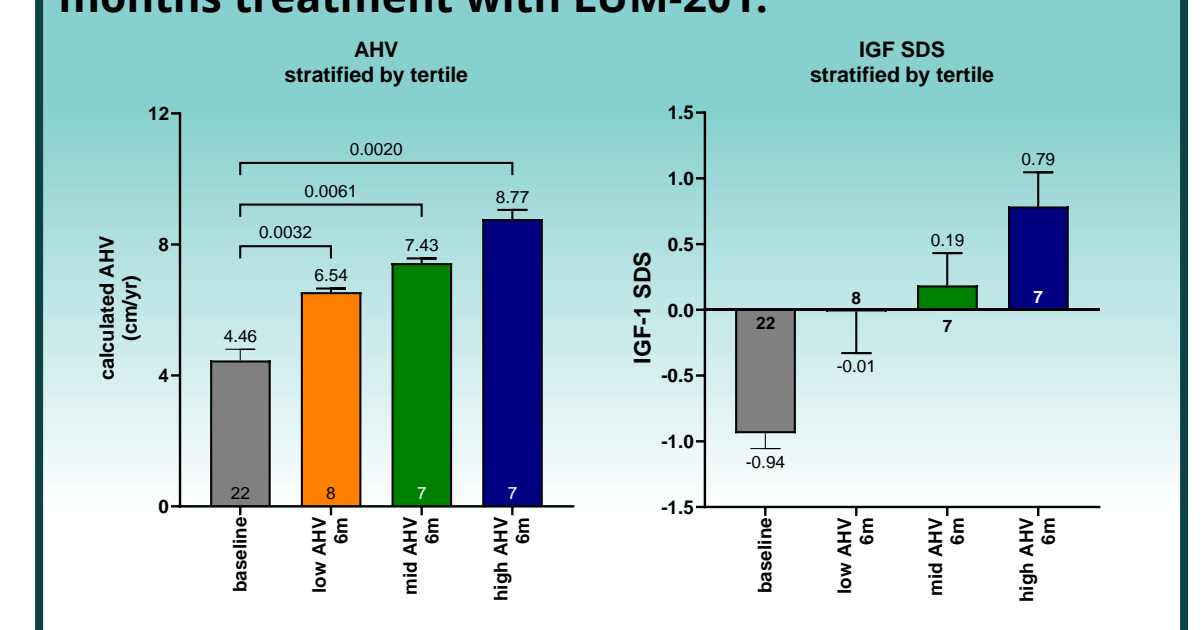
The functional data are the time-series of 10min GH values representing the deconvoluted pulsatile GH secretion over 12 hours in 22 patients at D1 and M6. An R Package FDAPACE (ref 7) was utilised to generate the plots of Mean Function and Eigenfunction 1 throughout the 720 minutes. Mean function represents the average value of the function (pulsatile GH secretion), and Eigenfunction 1 describes the first principal component which explains the majority (50-60%) of the variance within the data.

Subjects were grouped into tertiles based on 6m AHV (High [mean 8.8cm/yr], Medium [7.4cm/yr], and Low [6.5cm/yr]), and the 12hr profiles were divided into three 4hr intervals.

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



AHV and IGF-SDS measures are increased at 6 months treatment with LUM-201.



Functional Principal Component Analysis – Comparison of FPCA Mean Function and Eigenfunction 1

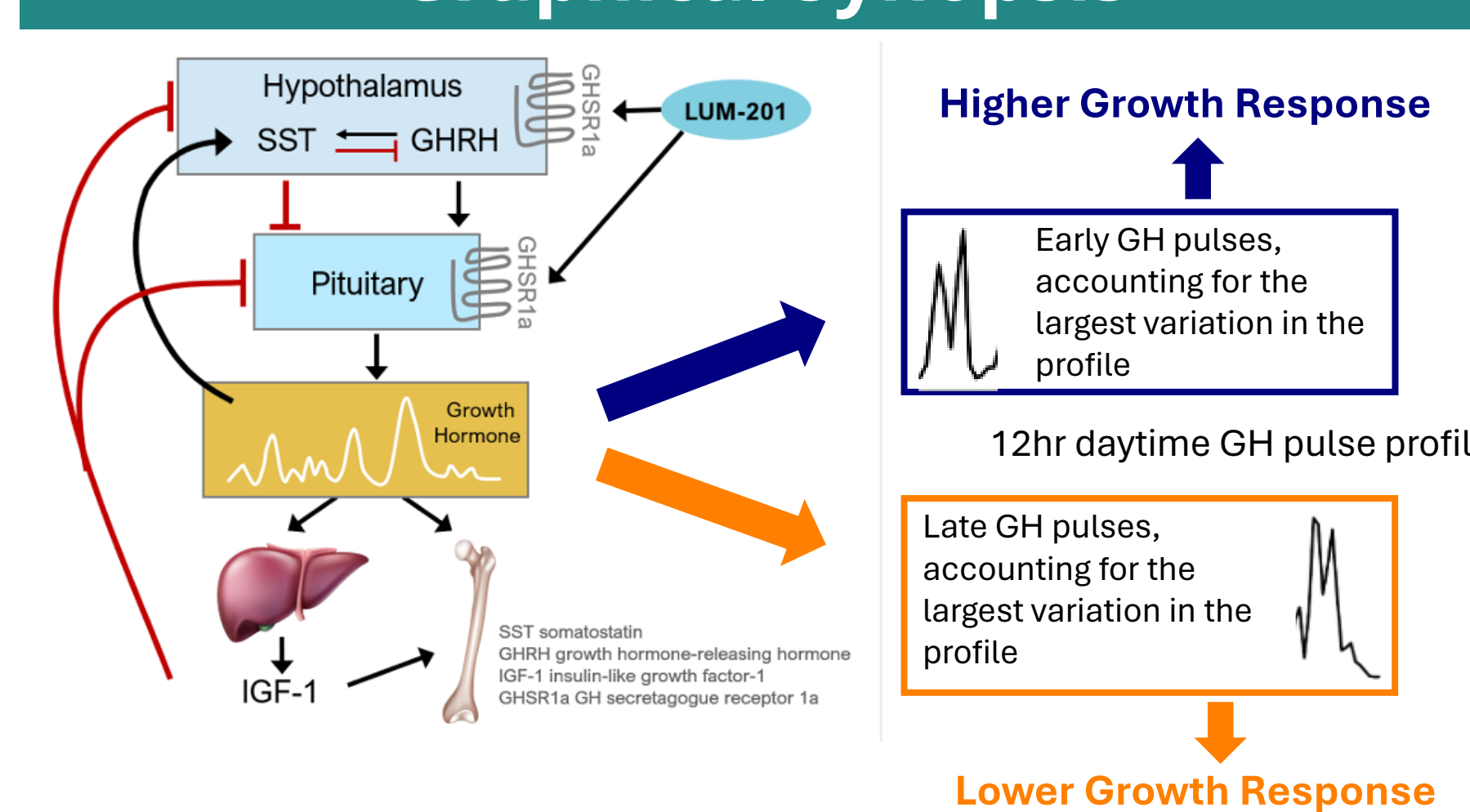
The interquartile range (IQR) for mean GH secretion [left panel] (representing variation in amount) and Eigenfunction 1 [right panel] (representing variation in the pattern of secretion) for all subjects in each AHV tertile at D1 and M6 were generated. Shifts in pulsatile GH secretion and variation in the pattern of this secretion are represented by differences in IQR in each 4-hour window.



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.
- Variation in GH secretion patterns changes between D1 and 6m; the high AHV tertile shows the largest variation in the **early** GH pulses, while the lowest AHV tertile shows the largest variation in the **late** GH pulses (see Arrows on the FPCA figure).

Graphical Synopsis



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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