Mechanistic PK/PD Modeling and Simulation of The Follistatin–Myostatin/Activin A–ActRIIB Pathway

Haojing Rong, Paul Jasper, Zhiwei Zhang, Andrea Iskenderian, David Ehmann, Qingwei Deng, Kathleen Palmieri, Bob Crooker, Dianna Lundberg, Chuan Shen, Angela Norton, Kening Song, John McNulty, Haobin Lou, John Tolsma, Devin Welty

1 Shire, 300 Shire Way, Lexington, MA 02421; 2 RES Group Inc, 75 2nd Ave #200, Needham Heights, MA 02494

Objectives: To predict the dose/exposure/biomarker response of follistatin fusion proteins using a mechanistic PK/PD modeling approach.

Methods: A mechanistic PK/PD model was constructed with the following steps. First, analyze relevant literature surrounding the pathway, and identify data that may be used for model parameterization, calibration, and validation. Secondly, develop a mechanistic model of myostatin/activin A binding and the effects of relevant therapies on PD endpoints including muscle mass increase and FSH modulation. The model was verified using preclinical and clinical exposure, biomarker and efficacy data from a tool molecule and myostatin antibody reported in the literature [2]. Lastly, the mechanistic PK/PD model was used to simulate dose-response relationships on various PD endpoints, including receptor occupancy (RO), muscle mass increase, and time to effect.

Results: A mechanistic PK/PD model, consisting of three compartments, plasma, pituitary, and muscle, was built to describe the biological processes of follistatin fusion protein and its interactions with myostatin and activin A. The biodistribution of follistatin fusion protein from serum to muscle and pituitary was estimated using the PBPK methodology [1]. The activin A inhibition in vivo was verified using FSH modulation in the ovariectomized rats. ActRIIB RO in muscle, driven by both myostatin and activin A binding, was linked to muscle mass increase. Clinical data of BMS-986089 was used to establish the threshold of ActIIB RO for muscle mass increase in human [2].

Conclusions: Applying the mechanistic PK/PD model, which incorporated ActRIIB RO for myostatin and activin A inhibition in muscles, the dose/exposure/biomarker response relationships with various dosing regimens of follistatin fusion protein were simulated to provide dose selection rationale for further clinical development.

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