Utilizing Modeling and Simulation to Inform Dose Selection, Titration Algorithms, and Trial Design of Oral Testosterone (T) Products for Testosterone Replacement therapy (TRT) in Hypogonadal Men

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Objectives: The key primary efficacy and safety regulatory endpoints for T trials are ≥75% subjects with T Cavg within 300–1000 ng/dL; ≤15% and 0% subjects with T Cmax >1500 and >2500 ng/dL respectively. With these criteria multiple intramuscular injection and transdermal products have been approved for TRT in hypogonadal men. However, there are currently no approved oral testosterone products in USA. Oral T products may have potential challenges in simultaneously achieving both endpoints due to PK characteristics of high peak-to-trough ratios along with possibly substantial inter- and intra-subject/inter-occasion variability. These factors put the onus on appropriate selection of dosing regimen and titration algorithm to successfully design trials. Here, we evaluate how various product PK profiles can influence design decisions for dose, regimen (QD/BID/TID) and titration algorithm for pivotal phase 3 trials.

Methods: A linear one-compartment population PK model with oral administration and a negative feedback for suppression of endogenous testosterone was built (NONMEM v7.3) and used for clinical trial simulations (R v3.1.2). Different magnitudes of inter-occasion variability (0 to 100%) and clearance-volume of distribution combinations that would support QD or BID dosing were simulated. Also, various titration algorithms were considered and the resulting Cavg and Cmax were compared with regulatory endpoints.

Results: The simulations showed that with high inter-occasion variability (≥45%) there is minimal chance of achieving both regulatory endpoints with QD or BID dosing irrespective of choice of titration algorithm, but with smaller inter-occasion variability (≤20%), the regimen was able to achieve the endpoints. In situations involving high intra-subject variability, more frequent dosing may be needed to satisfy both endpoints rather than relying on a titration algorithm.

Conclusions: Understanding the magnitude of variability (intra- and inter-subject) is key to the successful trial design of oral T products. Simulations, combined with collected intensive PK and assessment of product variability, can help with arriving at important trial design elements for reasonable chance of success of pivotal trial or go/no-go decision.