

Title: Modeling Supports Determination of First-In-Human Dosing and Rapid Titration to Final Dose for Subcutaneous Administration of LIPO-102

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Objectives: Lithera is developing (LIPO-102) as a novel injectable pharmaceutical product designed to produce local, selective fat tissue reduction (pharmaceutical lipoplasty). Using a combination of FDA-registered drugs approved for use in other indications, LIPO-102 targets and stimulates natural fat tissue metabolism to achieve non-ablative, non-surgical fat tissue reduction in specific locations. LIPO-102 is currently under development for the treatment of symptomatic exophthalmos (protrusion of the eye from the orbit) associated with thyroid-related eye disease (Graves' disease) and the reduction of abdominal adiposity. Objectives subsequent to obtaining human data were: 1) to titrate rapidly to a maximum dose meeting the 505(b)(2) limit, and 2) to analyze the relevant aspects of drug pharmacokinetics (PK) for this formulation and dosing. Key objectives in this first-in-human (FIH) trial were to ensure that plasma drug concentrations were above the lower limit of quantitation, but below specified maximum values to satisfy the requirements of the 505(b)(2) rule.

Methods: A population PK compartmental analysis of mini-pig data was performed using Monolix software. The best agreement with data was obtained using a two-compartment model with zero-order absorption from the subcutaneous depot. The resulting model was allometrically-scaled using standard body weight-related techniques and a first-in-human dose was determined. This dose was implemented in a trial and the resulting human concentration data were analyzed using a like modeling analysis. This analysis allowed titration to a final maximum dose, which was then implemented in a subsequent trial step. Analyses of dose-proportionality, drug-drug interactions, single vs. repeat dosing and single vs. multiple site dosing were also performed.

Results: The dose recommendation based upon mini-pig PK modeling was four times that originally envisioned. The measured concentrations from the recommended FIH dose were within 10 percent of those predicted by the scaled model. Drug concentrations resulting from the initial dose estimation may have been below the lower limit of quantitation. Rather than titrating the dose in limited steps, the final dose (which was designed to result in a specified mean C_{max} value) was identified directly from the modeling analysis and implemented. This dose gave the desired C_{max} results without additional incremental dose changes.

Conclusions: Modeling analysis and allometric scaling enabled accurate determination of an appropriate first-in-human dose for LIPO-102. This dose resulted in human concentrations very close to the target levels. These concentrations were within desired limits, and yielded data above the lower limit of quantitation. From the identified first dose, a final dose was determined rapidly without intervening titration steps. Modeling steamlined this FIH trial and eliminated unneeded titration steps.