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

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Objectives

LIPO-102 is a novel injectable pharmaceutical product designed to produce local, selective fat tissue reduction (pharmaceutical lipoplasty).

- Derive a model of human PK based on minipig PK data, supporting dose determination.
- Determine a maximal dose for humans subject to rule 505(b)(2) limits, using the fewest number of dose levels.

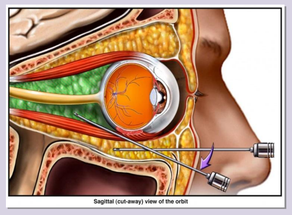
Background

LIPO-102 is a novel injectable combination of Salmeterol Xinafoate and Fluticasone Propionate.

LIPO-102 may provide a non-surgical treatment of diet- and exercise-resistant or pathological fat deposits.

Data from subcutaneous adminstration of LIPO-102 in 28 (14 male and 14 female) Gottingen minipigs were available.

An FIH dose that would be expected to give measurable analyte concentrations was sought, and the final dose had to have maximum analyte concentrations less than those produced by the currently marketed product ADVAIR DISKUS 500/50, to support an NDA meeting 505(b)(2) guidelines. A rapid (one-step) titration from FIH dose to a maximum dose was desired.



Methods

The plasma versus time data for the two components of LIPO-102 (salmeterol xinafoate and fluticasone propionate), administered to Gottingen minipigs, were modeled using the nonlinear mixed effects modeling program Monolix (Monolix group, Paris France, v 2.4) implemented in a Matlab computational environment (Mathworks, Natick, MA Ver7.5 R2007b).

The data were fit to a one-compartment and a two-compartment model. Absorption from the subcutaneous space to plasma was explored as a first-order and a zero-order absorption process. The intersubject parameter distributions model was chosen as log normal. The random residual error was modeled as an additive component to the model. This fit all data well, including concentration values shortly after drug administration because a primary objective in using the model to estimate FIH doses is to stay below a drug concentration range that has been shown to be safe in humans.

Selection of the best model to describe the data was based on minimization of the model objective function and overall visual inspection of the model fit to the data. This included inspection of the aggregate data fit and individual animal fits. In addition, using a Monte Carlo simulation method, the final parameters were simulated for a group of 28 estimates of their distribution to create a visual predictive check to compare with the actual measured data.

The pharmacokinetic model that best described the data from the minipig study was then scaled allometrically to reflect differences between Gottingen minipigs and humans.

Abstract

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 minipig 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 minipig 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 Cmax value) was identified directly from the modeling analysis and implemented. This dose gave the desired Cmax 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.

Results

Salmeterol Xinafoate

Minipig salmeterol plasma concentration versus time data are shown in Figure 1.

Data was best described by a two-compartment model with zero-order absorption (Figure 2).

The model parameters are given in Table 1 for salmeterol.

The initial distribution volume is large compared to total blood volume and body water for the minipig consistent with the high lipophilicity of salmeterol and its extensive volume of distribution.

These parameter values were simulated to create a population distribution of salmeterol concentration versus time as a visual predictive check.

The 90% distribution of these simulated profiles is shown in Figure 3 along with the measured data from the experiment.

The agreement of the predicted concentration range from the model with the range of measured data confirms the accuracy of the model.

Fluticasone Propionate

Minipig fluticasone propionate plasma concentration versus time data were analyzed (not shown) .

Data were best described by a one-compartment model with zero order absorption.

Analysis and evaluation of the model and model fit similar to that forsalmeterol were performed.

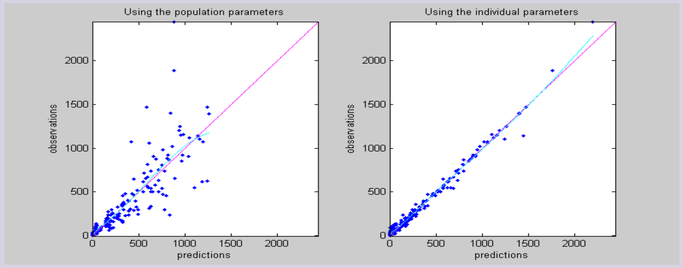


Figure 1. Plots of the predicted salmeterol concentration values (pg/mL) versus observed values (pg/mL) for the population model (left plot) and the individual animal parameters (right plot).

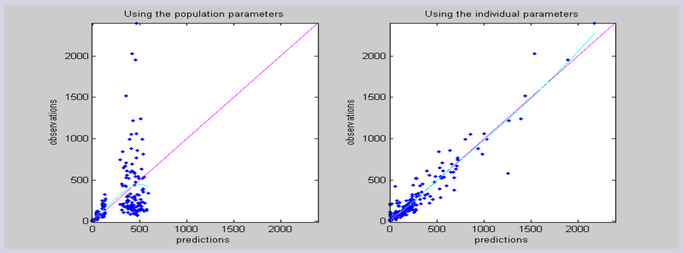


Figure 2. Plots of the predicted fluticasone propionate concentration values (pg/mL) versus observed values (pg/mL) for the population model (left plot) and the individual animal parameters (right plot).

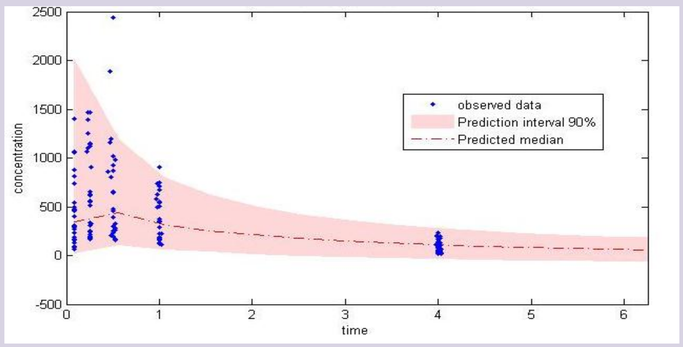


Figure 3a. A visual predictive check of the two-compartment, zero-order absorption model for salmeterol and measured data.

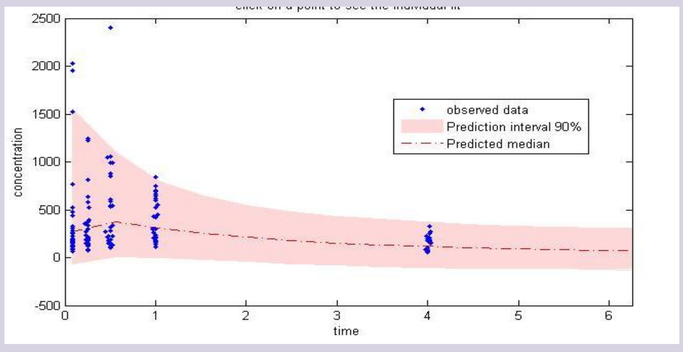


Figure 3b. A visual predictive check of the two-compartment, zero-order absorption model for fluticasone propionate and measured data.

Conclusions

- The FIH LIPO-102 dose determined using the minipig model scaled to humans was four times that originally envisioned, preventing many analyte concentrations from being below the lower limit of quantitation (LLOQ).
- The actual clinical PK results were within 10% of those predicted by the scaled model.
- FIH data and the model allowed a rapid, one-step titration to final maximal doses of salmeterol and fluticasone propionate that fell within 505(b)(2) criteria.
- Modeling provided a more accurate estimate of FIH doses than allometric scaling and permitted efficient, cost-effective dose escalation. The trial duration was cut at least by half (two dose levels versus four or more).

Parameter	Mean value	% Relative Standard Error
V1 (L)	69.8	29%
Cl (L/hr)	124	6%
V2 (L)	172	12%
Q (L/hr)	1210	30%
Duration (hr)	0.27	10%

Table 1. Population pharmacokinetic parameters for salmeterol after subcutaneous injection in minipigs

Parameter	Mean value	% Relative Standard Error
V1 (L)	118	19%
Cl (L/hr)	37.9	13%
Duration (hr)	0.13	39%

Table 2. Population pharmacokinetic parameters for fluticasone propionate after subcutaneous injection in minipigs

Typical Monte Carlo trial simulations predicting human results for Salmeterol and Fluticasone Propionate

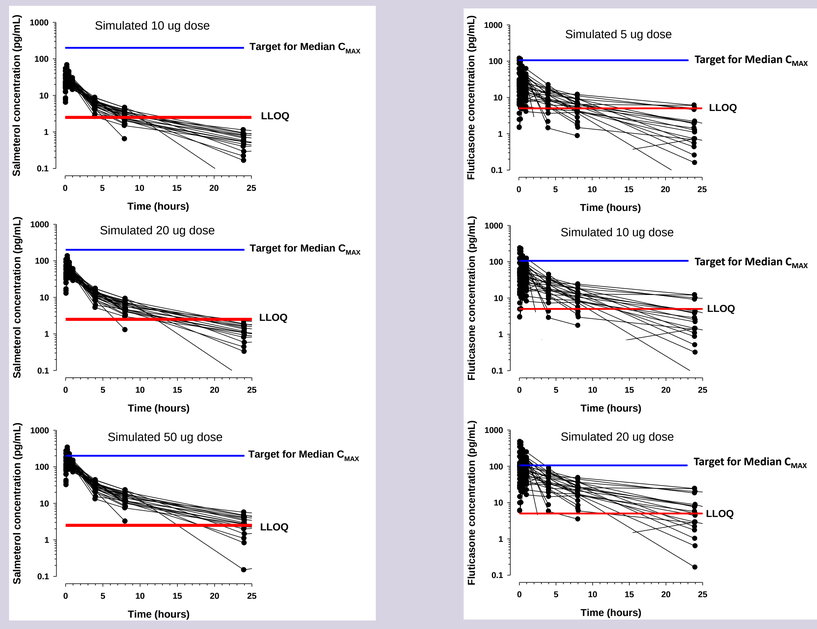


Figure 4. Initial dose predictions for humans were made by Monte Carlo simulations (above) of the minipig model which had been scaled to humans. Simulations of the doses slated for FIH prior to modeling, for both compounds, showed many points would be expected to be below the LLOQ (top two graphs). Likewise, a high dose bound was established by the 505(b)(2) limits and the lower two graphs show the expect doses to reach those limits. The middle plots showed predictions for the recommended FIH dose.

Human Clinical Trial Data – Mean Salmeterol and Fluticasone Propionate Plasma Concentrations

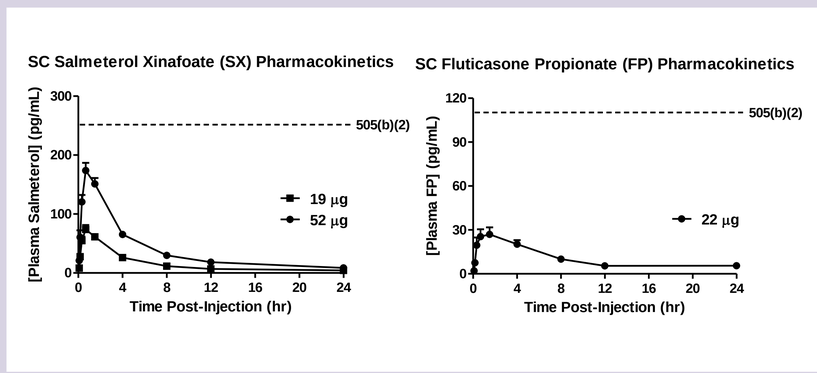


Figure 5. Human FIH dose time vs. concentration, showing that the mean Cmax for the FIH dose of salmeterol xinafoate matched within 3 percent of the predicted value. Likewise, the fluticasone propionate concentration observed agreed well with the predicted value. The second salmeterol dose was estimated from the first dose, and allowed titration to the final dose without an intervening dose.

Stephen Kern, PhD, contributed to this work while a Senior Consulting Scientist with Rosa and is now affiliated with Novartis Pharmaceuticals.

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