Population Pharmacokinetic Analysis for Lefamulin Using Phase 1 Data and Assessment of Optimal PK Sampling Strategies for a Phase 3 Community-Acquired Bacterial Pneumonia Study

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ABSTRACT

Background: Lefamulin, a semi-synthetic intravenous (IV) and oral (PO) pleuromutilin antibiotic with activity against pathogens commonly associated with community-acquired bacterial pneumonia (CABP), including multi-drug resistant *Streptococcus pneumoniae* and *Staphylococcus aureus*, is currently in Phase 3 development for the treatment of patients with CABP. The objectives of these analyses were to refine a previously-developed PPK model using Phase 1 data and to assess optimal sampling strategies (OSS) for implementation in Phase 3.

Methods: Lefamulin PK data were obtained from healthy subjects who received single 150 mg IV and 600 mg PO lefamulin doses under fed and fasted conditions. Using parameter estimates from the final PPK model, lefamulin $AUC_{0\text{-}24}$ at steady-state ($AUC_{0\text{-}24,SS}$) was determined for 1,000 simulated patients after administration of lefamulin 600 mg PO Q12h for 5 days. Multiple linear regression-based OSS determination was then conducted to identify informative sampling times for predicting $AUC_{0\text{-}24,SS}$. OSS were evaluated with fixed sampling times or sampling windows in all simulated patients. A mix of different scenarios (i.e., an unbalanced design) among simulated patients was also evaluated.

Results: The PPK analysis dataset contained 959 lefamulin plasma concentrations from 20 (8 female and 12 male) fasted and fed healthy subjects. A three-compartment model with nonlinear protein binding and two parallel first-order absorption processes provided precise and unbiased estimates of lefamulin plasma exposure (Figure 1). Covariate analyses demonstrated that the absorption rate was slower and bioavailability was decreased after a high fat/high calorie meal compared to the fasted condition. OSS assessments demonstrated that a minimum of 4 samples at fixed times provided accurate $AUC_{0\text{-}24,SS}$ estimates, regardless of fed or fasted status. Additionally, a 3- or 4-sample scheme or an unbalanced design, each based on sampling windows, provided acceptably precise estimates of $AUC_{0\text{-}24,SS}$ under fed and fasted conditions (R^2>0.77, Figure 2).

Conclusions: The refined PPK model provided precise and unbiased fits to lefamulin PK data after IV and PO administration. Application of this model identified an OSS which should allow for reliable $AUC_{0\text{-}24,SS}$ estimates for patients who received lefamulin 600 mg PO Q12h in a Phase 3 CABP trial.

INTRODUCTION

- Lefamulin is an antimicrobial agent from the pleuromutilin class with *in vitro* activity against pathogens associated with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI), including multi-drug resistant *Streptococcus pneumoniae* and *Staphylococcus aureus.*
- Lefamulin is being developed for intravenous (IV) and oral (PO) administration, thus potentially allowing for IV to PO step-down therapy in patients with CABP or ABSSSI.
- The objectives of these analyses were to refine a previously-developed population pharmacokinetic (PK) model using pooled IV and PO PK data from healthy subjects in a Phase 1 study and to assess optimal PK sampling strategies (OSS) for implementation in a planned Phase 3 study evaluating patients with CABP.

METHODS

Data

- Data were obtained from Study NAB-BC-3781-1107 (Study 1107), a Phase 1, single cohort, randomized, four-period crossover study that was carried out to assess the bioavailability of lefamulin [Data on file, Nabriva; ClinicalTrials.gov Identifier: NCT02557789]. Heathy subjects received a single PO or IV dose of lefamulin in four study sessions at least four days apart:
  Cohort A: 600 mg PO tablet in the fasted state;
  Cohort B: 600 mg PO in capsule (3 x 200 mg capsules) in the fasted state;
  Cohort C: 150 mg IV infused over 1 hour; and
  Cohort D: 600 mg PO tablet administered 1 hour after a high fat/high calorie meal.
- Population PK model refinement was conducted using data from healthy subjects in study sessions A, C, and D only.

Population PK Model Development

- The population PK model was developed in a sequential manner:
  - A previously-developed population PK model developed by Rubino *et al.* (AAC 2015;59:282-8) was first fit to the IV data, and then fit to the pooled IV and PO data to develop the final model.
  - If the previously-developed population PK model did not describe the Phase 1 data well, a series of two- or three-compartment models with more complex atypical protein binding and absorption were evaluated.
- Once an appropriate structural model was identified, a covariate model was developed using forward selection followed by a backward elimination procedure.

METHODS

- Covariate screening involved graphical examination of plots of PK parameters versus demographic characteristics and food effects.
- Visual predictive checks (VPC) were used to evaluate the final model.

Optimal Sampling Stategy

- Using the final population PK model, a Monte Carlo simulation was conducted to generate plasma concentration-time profiles for 1,000 simulated subjects after administration of 600 mg PO Q12h for 5 days.
- Total-drug area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24}$; "true" $AUC_{0\text{-}24}$) values were calculated by integrating the PK profile in very small time increments for each subject in NONMEM v7.1.2.
- Using the "true" $AUC_{0\text{-}24}$ value on Day 1 or 5 as the dependent variable and the simulated plasma concentration values as independent variables, multiple linear regression (MLR) was carried out to identify the OSS that would allow for adequate estimation of $AUC_{0\text{-}24}$.
- Precision, as assessed by the r^2 for the relationship between fitted $AUC_{0\text{-}24}$ and true $AUC_{0\text{-}24}$, was computed for each OSS.
- OSS were evaluated for simulated subjects under fed and fasted conditions using a balanced design in which all subjects were sampled as described below:
  - Fixed sampling time: Fitted $AUC_{0\text{-}24}$ values were generated for 1,000 simulated subjects using MLR for schemes that included 3 or 4 samples taken at fixed time points.
  - Fixed sampling window: The simulated concentrations were subset so that 1,000 simulated subjects had a sample drawn at a randomly selected time point within each of the sampling windows. Fitted $AUC_{0\text{-}24}$ values were generated for each simulated subject using MLR for OSS that included 2, 3, or 4 samples taken during the fixed sampling windows. The process was repeated 500 times for each OSS.
- As described below, OSS were evaluated for simulated subjects under fed and fasted conditions using an unbalanced design in which all subjects were not sampled completely.
  - 200 simulated subjects were randomly selected from the fixed sampling window simulation, with 40% of subjects using the 2-sample scheme, 40% using the 3-sample scheme, and 20% using the 4-sample scheme.
  - The process was repeated 500 times to generate a distribution of r^2 values.

RESULTS

Analysis Data

- The PK population consisted of 20 subjects (8 female and 12 male) and 959 plasma concentration records. All records were available for the final analysis dataset.

Development of Structural and Covariate Models

- After an appropriate structural model was identified, subsequent covariate screening based on this model revealed statistically significant relationships between subject descriptors and primary PK parameters.
  - Oral absorption rate, where both the immediate and delayed rate constants were faster when lefamulin was administered under fasted conditions compared to administration after a high fat/high calorie meal.

Final Population PK Model

- The final population PK model for describing lefamulin after IV and PO administration was a three-compartment disposition model with nonlinear protein binding, two parallel first-order absorption processes, and an absorption delay for the second absorption process occurring though multiple transit compartments. Parameter estimates and associated standard errors are shown in **Table 1**.

RESULTS

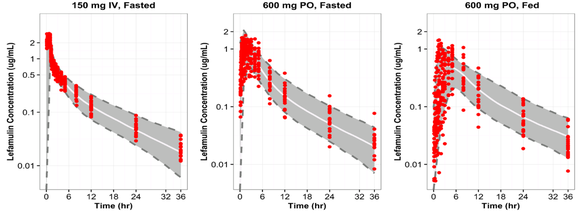
Table 1. Final population PK model parameter estimates and standard errors

Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	% SEM	Final estimate	%SEM
CL (L/hr)	159	5.61	16.1	57.7
Vc (L)	53.1	9.66	13.4	Fixed
CLd1 (L/hr)	86.6	42.1	37.1	77.5
Vp1 (L)	656	27.4	24.7	Fixed
CLd2 (L/hr)	199	16.1	23.5	69.1
Vp2 (L)	259	8.17	NE	NA
Ka (1/hr)	1.20	11.6	108.2	38.5
Ka2 (1/hr)	2.12	26.0	54.8	63.3
F_{tot}	0.24	7.99	22.8	84.6
FS	0.80	8.35	55.7	74.2
Proportion of Ka under Fed	0.04	14.7	NE	NA
Proportion of Ka2 under Fed	0.44	3.55	NE	NA
Proportion of Ftot under Fed	0.81	9.13	NE	NA

CL: total clearance of free-drug; Vc: volume of the central compartment; CLd1: distributional clearance to 1st peripheral compartment; Vp1 Volume of 1st peripheral compartment ; CLd2: distributional clearance to 2nd peripheral compartment; Vp2: volume of 2nd peripheral compartment; Ka: immediate absorption rate constant; Ka2: delayed absorption rate constant; F_{tot}: total bioavailability; FS: fraction of delayed absorption bioavailability

- As shown by the VPC plots in **Figure 1**, since the bulk of the observed data was within the prediction interval, the final model provided precise and unbiased estimates of lefamulin plasma exposure.

Figure 1. VPC plots of the observed and simulated lefamulin PK data from fed and fasted healthy subjects, stratified by treatment arm. The solid white line and grey shaded area represent the median and the 90% confidence interval , respectively, based on simulated PK data, while the circles represent the observed PK data from the Phase 1 healthy volunteers



Optimal Sampling Strategy

- The results of the MLR-based OSS analysis based on the fixed sampling time points are shown in **Table 2**.
  - The 4-sample OSS provided the most accurate estimates of $AUC_{0\text{-}24}$, regardless of sample day and fed or fasted status (mean $r^2 \geq 0.962$).
  - The 4-sample OSS was expected to provide precise estimates of key PK parameters, with CL and F_{tot} expected CV% values < 20%.
  - On Day 5, the most informative sampling time points were pre-dose, 1.5, 3.5, and 9 hours after the dose, regardless of fed or fasted status.
- The results of the MLR-based OSS analysis based on the fixed sampling windows on Day 5 are shown in **Table 3**.
  - The balanced 3- and 4-OSS provided the most accurate estimates of $AUC_{0\text{-}24}$ (mean $r^2 \geq 0.854$) regardless of fed or fasted status.

RESULTS

Table 2. Summary of the performance of OSS based on fixed sampling time points, as assessed by r^2 values

Number of samples	Food status	Day	PK sampling time points (hr)				Mean r^2 value
4	Fasted	1	0.5	1.5	3.5	9	0.995
		5	Pre-dose	1.5	3.5	9	0.962
	Fed	1	0.5	1.5	3.5	9	0.977
		5	Pre-dose	1.5	3.5	9	0.998
3	Fasted	1	0.5	3.5	9	--	0.933
		5	Pre-dose	3.5	9	--	0.723
	Fed	1	0.5	3.5	9	--	0.976
		5	Pre-dose	3.5	9	--	0.657

Table 3. Summary of the performance of OSS based on fixed sampling windows on Day 5, as assessed by r^2 values

Fed status	Number of samples	PK sampling scheme	r^2 values		
			Mean	5th percentile	95th percentile
Fasted	2	Pre-dose, 1-2 hr	0.658	0.638	0.677
	3	Pre-dose, 1-2, 3-4 hr	0.854	0.846	0.864
	4	Pre-dose, 1-2, 3-4, 7-9 hr	0.914	0.909	0.92
Fed	2	Pre-dose, 1-2 hr	0.585	0.568	0.603
	3	Pre-dose, 1-2, 3-4 hr	0.859	0.85	0.868
	4	Pre-dose, 1-2, 3-4, 7-9 hr	0.963	0.96	0.965

- The unbalanced OSS provided an acceptable prediction of the $AUC_{0\text{-}24}$ value at steady-state, regardless of food status, with mean r^2 values of 0.791 and 0.772 for simulated subjects studied under fasted and fed conditions, respectively.

CONCLUSIONS

- The final population PK model, a three-compartment disposition model with nonlinear protein binding, two parallel first-order absorption processes, and an absorption delay for the second absorption process occurring though multiple transit compartments, provided precise and unbiased fits to lefamulin PK data after IV and PO administration.
- The covariate analyses showed that a high fat/high calorie meal resulted in slower absorption rate compared to those under the fasted condition.
- Results of OSS analyses indicated that a balanced 3- or 4-sample scheme based on fixed sampling windows provided the most accurate estimates of $AUC_{0\text{-}24}$.
  - Evaluation of an unbalanced scheme indicated that use of the 4-sample fixed window scheme in a clinical trial setting with less than optimal sampling compliance would still result in acceptably precise estimates of lefamulin $AUC_{0\text{-}24}$ at steady state.
- Application of the population PK model allowed for the identification of OSS, the implementation of which in Phase 3 will allow for pharmacometric evaluations of PK data from patients.