Combined Population (Pop) Pharmacokinetic (PK) Analysis of 6 Phase I Studies with NXL103

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ABSTRACT

Background: NXL103 is a novel oral streptogramin, a combination of linopristin and flopristin with activity against *S. pneumoniæ* (plus MDR-SP), *H. influenzæ*, atypical pathogens and *S. aureus* (plus MRSA). This analysis was conducted to characterise the PK of linopristin and flopristin in healthy subjects, and identify the covariates that influence their PK parameters.

Methods: A Pop PK analysis was performed by combining the data from six Phase I studies totalling over 224 subjects. The dataset included some diversity with regard to age class, gender, unit doses, linopristin to flopristin dose ratio, dosing duration and frequency, dietary conditions, concomitant medications and formulation. Data were analyzed using the NONMEM software.

Results: The structural PK model was similar for both linopristin and flopristin. It was a one-compartment model with first order absorption (different Ka in the morning and in the evening), a lag-time and, for linopristin only, a different lag-time in the morning and in the evening. The key Pop PK parameters are listed in the table below:

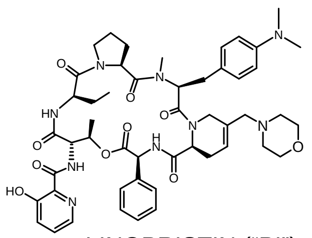
Parameter	Linopristin Estimate (SE)	Linopristin BSV (%)	Flopristin Estimate (SE)	Flopristin BSV (%)
CL/f (L/h)	176 (18.2)	53	65.2 (8.18)	65
V/f (L)	545 (50.3)	42	516 (66.7)	59
Ka,morning (h^{-1})	1.64 (0.18)	124	1.16 (0.147)	139
Tlag,morning (h)	0.1 (0)	155	0.100 (fixed)	130
Ka,evening (h^{-1})	0.523 (0.0528)	0 (fixed)	0.190 (0.0372)	104
Tlag,evening (h)	0.867 (0.0778)	0 (fixed)	-	-

BSV: between-subject variability; SE: standard error; CL/f and V/f: clearance and volume in fed condition; Ka: absorption rate constant; Tlag: lag time

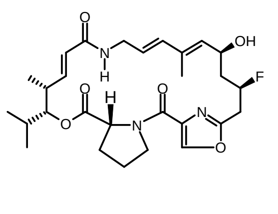
The most significant covariate was an effect of dietary conditions on clearance of both components. Other covariates influencing linopristin PK included dose and age class. Those influencing flopristin PK included dose, body weight and formulation. Validation tests demonstrated the descriptive performance of this Pop PK model despite some substantial residual variability.

Conclusions: This pop PK analysis done with Phase I data allows to use a sparse sampling approach for estimation of individual PK parameters for further studies. It demonstrated the importance of dietary conditions on NXL103 PK parameters.

CHEMICAL STRUCTURES



LINOPRISTIN ("PI")



FLOPRISTIN ("PII")

BACKGROUND AND OBJECTIVE

NXL103 is a novel oral streptogramin, a combination of linopristin ("PI") and flopristin ("PII").

Antibacterial activity covers *S. pneumoniæ* (including multidrug resistant strains), *S. aureus* (including MRSA). *H. influenzæ*, and atypical pathogens.

NXL103 was initially developed as a combination of PI and PII in a 30:70 dose ratio (w/w). The dose ratio was subsequently switched to ca 42:58[1].

NXL103 has completed six Phase I studies totalling 248 subjects, 224 and 226 being evaluable for the PK of PI and PII, respectively.

Some diversity was present in the Phase I dataset:

Sex:	231 males and 17 females
Age class:	87% [18-45 yrs] and 13% [65-77 yrs]
Body weight:	51 to 96 kg
Ethnic origin:	variable, mostly Caucasian
Unit doses:	125 mg to 2000 mg
PI/PII dose ratio:	mostly 30:70, also 33:67 to 46:54
Formulation:	capsules or tablets
Conditions:	fasted or fed
Duration:	single dose, or up to 10 days
Frequency:	q12h or q24h

The study objective was to develop and validate Pop PK models for PI and PII through a combined analysis of 6 Phase I studies.

MATERIALS AND METHODS

Separate models were built for PI and PII. The software was NONMEM version V. The first-order minimization method was used.

Potential covariates included: age category, body weight, body mass index, gender, ALAT, ASAT, co-medication, dose, dosing time, dietary conditions, ethnic origin, and formulation.

Covariates were tested one by one. The effect of a covariate was considered significant when its addition decreased the objective function by ≥3.84 units ($P<0.05$), and its subsequent deletion deteriorated the objective function by ≥7.88 units ($P<0.005$).

Comparison between models at each step of model building was via NONMEM's objective function, examination of confidence intervals (CI) around parameters, and standard diagnostic plots.

Validation of PK models was performed using diagnostic plots, bias and precision calculation, and visual and numerical posterior predictive checks (PPC).

RESULTS

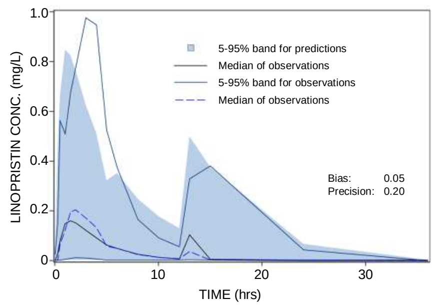
COMMON MODEL CHARACTERISTICS

Structural PK models: One-compartment disposition models with first order absorption with, in case of BID dosing, same bioavailability between the morning and evening doses, however different absorption rate constants and lag-times.

Models for between-subject variability (BSV): exponential models were used, unless otherwise specified.

Models for residual variability: mixed error model, comprising both a proportional and an additive term.

FIGURE 1: LINOPRISTIN MODEL VALIDATION



The Pop PK models tended to slightly underestimate the time to peak (tmax) and the peak plasma concentrations (Cmax) after administration of the morning doses.

Bias and precision were 0.05 and 0.20, respectively for linopristin, and 0.01 and 0.20, respectively for flopristin.

FIGURE 2: FLOPRISTIN MODEL VALIDATION

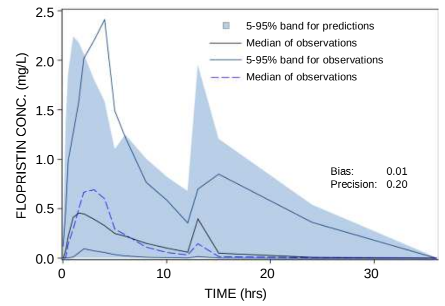


TABLE 1: FINAL POPULATION PK MODEL FOR LINOPRISTIN

PARAMETER (Unit)	ESTIMATES	SE	BSV	SE	BSV(%)
θ_1: CL/F (L/h)	176	18.2	0.278	0.0505	53
θ_2: V/F (L)	545	50.3	0.178	0.0374	42
θ_3: Ka PM (1/h)	0.523	0.0528	-	-	-
θ_4: TLAG PM (h)	0.867	0.0778	-	-	-
θ_5: Ka AM (1/h)	1.64	0.18	1.55	0.283	124
θ_6: TLAG AM (h)	0.1	(fixed)	2.41	0.749	155

Between-subject variability was exponential for all parameters but θ_3 and θ_4.

COVARIATES	ESTIMATES	SE	RELATIONSHIPS
θ_7: Food-effect on CL/f	0.234	0.101	$TVCL=[\theta_1*(1+(\theta_7*Food))]*exp(\theta_8*dose)$
θ_8: Dose-effect on CL/f	-0.864	0.378	
θ_9: Dose-effect on V/f	-0.851	0.336	$TVV = \theta_2*exp(\theta_9*dose)$
θ_{10}: Effect of age category on Ka AM	0.624	0.58	$TVKa = \theta_5+(\theta_{10}*Cage)$

With Food: 0 (fed) and 1 (fasted) – PI Dose in g and Cage: 0 (<65 years), 1 (>65 years)
The 95% confidence interval on θ10 included 0.

RESIDUAL VARIABILITY	ESTIMATES	SE
Multiplicative term	0.537	0.056
Additive term	14.7	2.73

TABLE 2: FINAL POPULATION PK MODEL FOR FLOPRISTIN

PARAMETER (Unit)	ESTIMATES	SE	BSV	SE	BSV(%)
θ_1: CL/F (L/h)	65.2	8.18	0.417	0.101	65
θ_2: V/F (L)	516	66.7	0.349	0.087	59
θ_3: Ka PM (1/h)	0.19	0.0372	1.09	0.481	104
θ_4: Tlag (h)	0.1	fixed	1.68	0.571	130
θ_5: Ka AM (1/h)	1.16	0.147	1.93	0.37	139

Between-subject variability was exponential for all parameters but θ_4.

COVARIATES	ESTIMATES	SE	RELATIONSHIPS
θ_6: Food-effect on CL/f	0.6	0.139	$TVCL=[\theta_1*(1+(\theta_6*Food))]$
θ_9: Effect of body weight on CL/f	1.38	0.455	$+ (\theta_9*(WT-70))$
θ_{10}: Effect on ethnic origin on CL/f	16.7	9.89	$+ (\theta_{10}*Race)$
θ_{12}: Effect of age category on CL/f	-5.57	11.3	$+ (\theta_{12}*Cage)$
θ_8: Effect of formulation on V/f	-0.375	0.0607	$TVV = \theta_2*[(1+ \theta_8)*Form]$
θ_7: Dose-effect on Ka AM	0.267	0.1	$KAM = \theta_5*+ (\theta_7*Dose)$
θ_{11}: Effect of age category on Ka AM	1.09	0.598	$+ (\theta_{11}*Cage)$

With Food: 0 (fed) and 1 (fasted) – PI Dose in g and Cage: 0 (<65 years), 1 (>65 years)
The 95% confidence interval on θ9, θ10, θ11 and θ12 included 0.

RESIDUAL VARIABILITY	ESTIMATES	SE
Multiplicative term	0.343	0.05
Additive term	77.7	30

CONCLUSION

Pop PK models were built for linopristin and flopristin data collected in six Phase I studies. Validation tests demonstrated the descriptive performance of these models despite some substantial residual variability. The most significant covariate was the influence of food on the oral bioavailability of both NXL103 components. Other covariates influencing linopristin PK included dose and age class. Those influencing flopristin PK included dose, body weight and formulation. This analysis will allow the use of a sparse sampling approach for estimation of individual PK parameters in further studies.

REFERENCE

1. MERDJAN H *et al*. Abstract A1-1943, 49th ICAAC Meeting, San Francisco CA, USA, September 2009.

Presented at 49th ICAAC, San Francisco September 2009