

Effect of Food, Age and Gender on NXL103 Pharmacokinetics (PK)

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ABSTRACT

Objective:

NXL103 is a novel oral streptogramin, a combination of linopristin and flopristin with activity against *S. pneumoniae* (plus MDR-SP), *H. influenzae*, atypical pathogens and *S. aureus* (plus MRSA). We investigated the effect of food, age and gender on the PK of NXL103 given as linopristin/flopristin in a 30:70 dose ratio.

Method:

This was an open, randomized, cross-over study of NXL103 single oral 500 mg dose administered to 48 healthy subjects: 3 cohorts of 16 young male adults, 16 elderly male and 16 postmenopausal female subjects. Cross-over design: fasted vs. fed separated by 7-day washout. Linopristin and flopristin and a metabolite of linopristin were quantified in plasma by LC-MS/MS; non-compartmental analysis was used.

Results:

49 subjects were included and 48 completed the study. One subject withdrew his consent due to nausea and vomiting. There were no serious adverse events. NXL103 was generally well tolerated by the 3 sub-populations.

Intake of food increased the exposure to linopristin and flopristin (+56% and +55% on AUC, respectively) and reduced the inter-individual variability of exposure. These effects were associated with a delayed plasma peak (+1.0 to 1.5 h for linopristin and +0.5 to 2.0 h for flopristin), and increases in C_{max} by 16% for linopristin or 41% for flopristin.

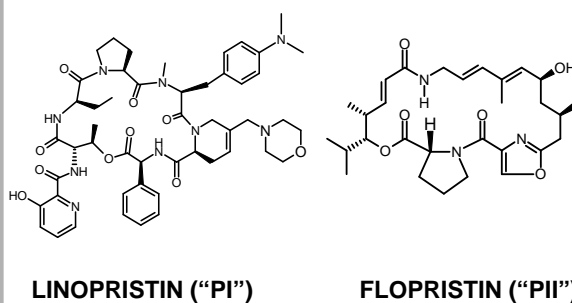
In males, elderly subjects had higher exposures (increased for linopristin and flopristin C_{max} by 64% and 33% and AUC by 65% and 56%, respectively) as compared to young subjects.

No statistically significant difference in PK parameters was found between elderly males and females.

Conclusion:

NXL103 showed a beneficial interaction with food (increased exposure and decreased PK variability). Although NXL103 exposures were higher in elderly than young subjects, adverse events and clinical laboratory values were similar, indicating that dose adjustment is not required. There was no significant gender effect in the elderly.

CHEMICAL STRUCTURES



BACKGROUND

NXL103 is an oral streptogramin comprised of two components: PI or linopristin and PII or flopristin. It has potent antibacterial activity against: MRSA, Multi-drug resistant *S. pneumoniae* (MDRSP), *S. pyogenes*, *H. influenzae*, *M. catarrhalis*, and *Legionella* and other atypicals (*Chlamydomydia* and *Mycoplasma*).

MATERIALS AND METHODS

Study Objectives:

Primary: Effect of food, age and gender in young males, elderly males and females

Secondary: Safety

Population:

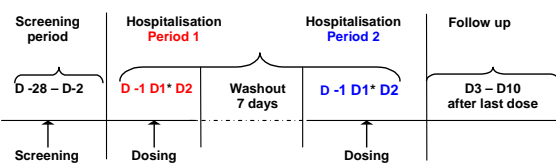
- 48 healthy subjects
- 16 young males (18-45 years old)
- 16 elderly males (>65 years old)
- 16 elderly females (>65 years old)

Bioanalysis:

Validated LC-MS/MS method.
Lower limit of Quantification (LOQ) 5.00 ng/mL

Study design:

Open, randomized, cross-over study
Single oral 500mg Tablets of NL103 combination of PI and PII in a 30:70 dose ratio (w/w)



- Blood PK: 15 samples over 24 hours
- Vital signs (BP/HR): 12 measurements over 24 hours
- ECG: 8 recordings over 24 hours
- Lab evaluations: screening D-1, D2 and follow up

RESULTS (1)

Demographics and Subject Disposition

Total subjects	Young Males	Elderly Males	Elderly Femles
N= 49	N=16	N=16	N=17(1)
Age range (Yrs)	19-42	66-77	66-76
Mean	19.1 ±7.0	70.5 ±3.5	68.9 ±2.9
Origin:			
Black	4(25.0%)	1(6.3%)	-----
Caucasian	10 (62.5%)	14 (87.5%)	17(100.0%)
Other	2(12.5%)	1(6.3%)	-----

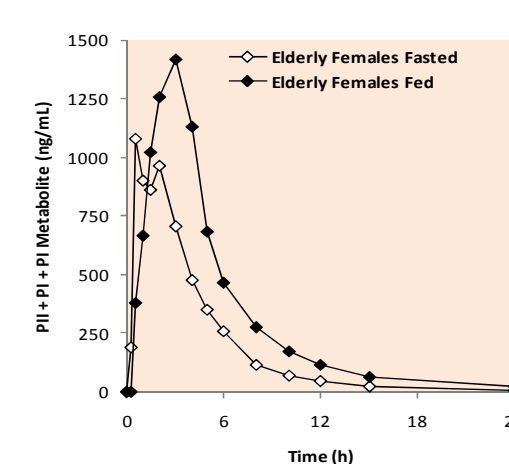
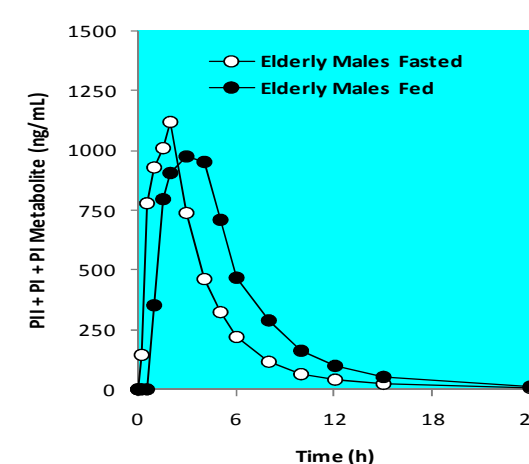
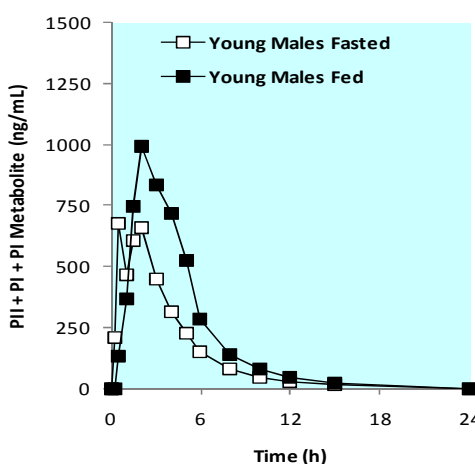
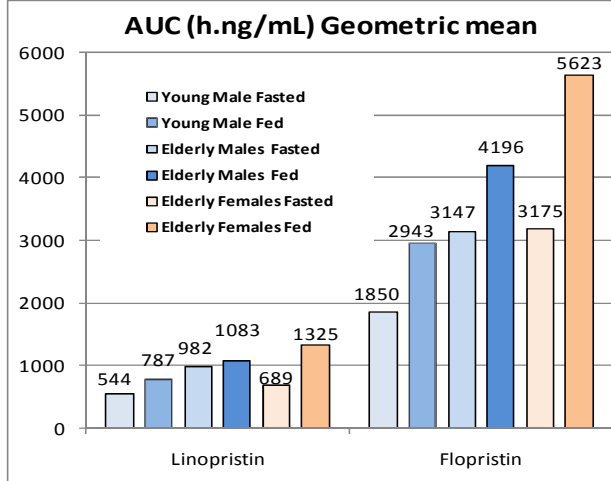
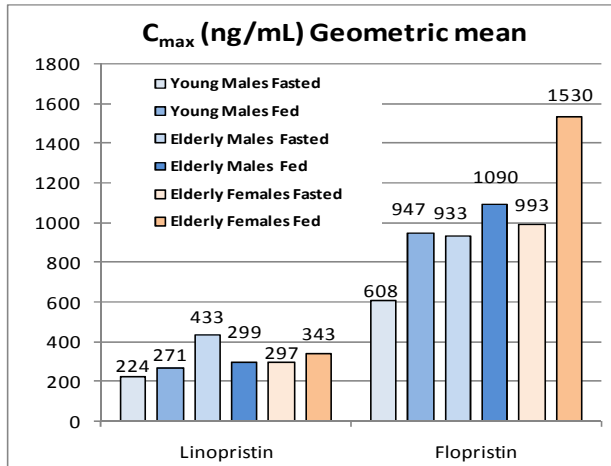
(1) One withdrawal due to vomiting within 20 min. after dosing and replaced.

Safety

Preferred term	Fasting	Fed
Young males		
- Nausea	-	2
- Abdominal Pain	-	1
Elderly male		
- Nausea	1	1
- Vomiting	1	1
Elderly female		
- Nausea	2	2
- Abdominal Pain	1	-
- Diarrhea	1	-
- Vomiting	1	2
- Headache	1	-

There were no clinically significant changes in the haematology or biochemistry parameters.

RESULTS (2)



Pharmacokinetics of NXL103 (based on PII + PI + PI metabolite)

Treatment		t _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (h*ng/mL)	t _{1/2} (h)	Frel
Young Male	Fasted	1.00	1010	2967	6.71	
	(N=16)		858	2395	5.98	
			54	74	51	
	Fed	2.00	1340	4511	3.63	1.81
	(N=16)		1240	3889	3.29	1.62
			49	55	39	48
Elderly Male	Fasted	1.75	1400	4652	5.03	
	(N=16)		1330	4282	4.63	
			35	38	40	
	Fed	2.50	1620	6227	4.00	1.51
	(N=16)		1470	5442	3.77	1.27
			46	48	29	55
Elderly Female	Fasted	1.00	1460	4704	6.99	
	(N=16)		1290	3988	5.54	
			45	60	114	
	Fed	3.00	2070	7813	4.66	2.23
	(N=16)		1910	7157	4.36	1.79
			37	44	46	71

Statistical assessment of Food, Age and Gender effects of PI and PII

FOOD EFFECT	(N=48)	PE	LINOPRISTIN (PI)			FLOPRISTIN (PII)		
			t _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (h*ng/mL)	t _{max} (h)	C _{max} (ng/mL)	AUC _{0-∞} (h*ng/mL)
		90% CI	p<0.05	1.16	1.56	NS (M)	1.41	1.55
				0.87-1.56	1.22-1.99	p=0.03 (F)	1.25-1.59	1.35-1.80
AGE EFFECT	Elderly males vs Young Males	PE	ND	1.64	1.65	ND	1.33	1.56
		90% CI		1.05-2.58	1.12-2.44		1.07-1.66	1.19-2.04
		p		NS	0.04		0.03	0.009
GENDER EFFECT	Elderly Females vs Elderly Males	PE	ND	0.78	0.88	ND	1.22	1.16
		90% CI		0.50-1.23	0.59-1.29		0.98-1.52	0.89-1.52
		p		NS	NS		NS	NS

PE Point estimate

CONCLUSION

- Food intake increased AUCs by ~55% compared to fasted conditions and reduced inter-individual variability of PK parameters.
- PI and PII AUCs were 65% and 56% higher in elderly than young males, but safety and tolerability were similar, indicating that dose adjustment is not required.
- No significant gender effect was present in elderly subjects.
- No serious nor severe adverse events were reported, treatment emergent adverse events were principally gastrointestinal and included nausea, vomiting, and abdominal pain.
- No clinically significant changes in the haematology or biochemistry parameters.