

Multiple-dose Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of NXL103

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ABSTRACT

Objective:

NXL103 is a novel oral streptogramin, a combination of linopristin and flopristin with activity against *S. pneumoniae* (including MDRSP), *H. influenzae*, atypical pathogens and *S. aureus* (including MRSA). We investigated the safety, PK and plasma bactericidal activity of NXL103 (linopristin/flopristin in a 30/70 ratio) after 10 days repeated oral dosing.

Method:

This was a randomized, double blind, placebo-controlled parallel group study with 4 escalating oral doses of NXL103 (500 mg twice daily [*b.i.d.*], 750 mg *b.i.d.*, 1500 mg once daily [*o.d.*], 1000 mg *b.i.d.*) or placebo with 8 NXL103 and 2 placebo subjects per cohort. Linopristin, flopristin and a metabolite of linopristin were quantified in plasma by LC-MS/MS; non-compartmental analysis was used.

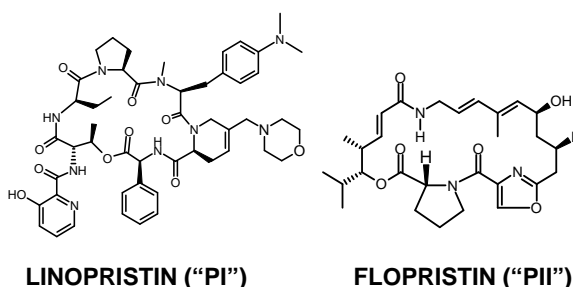
Results:

43 healthy adult male volunteers (mean ± SD age 31.9 ± 6.5 years) were randomized; 37 completed the study. There were no clinically relevant abnormalities in laboratory parameters, ECGs or vital signs. There were no severe or serious adverse events (AE). 4 subjects discontinued due to nausea/vomiting (2 on 1500 mg *o.d.* and 2 on 1000 mg *b.i.d.*). The most common AEs were gastrointestinal (loose stools, nausea, vomiting and abdominal pain) and were dose-dependent. In groups receiving 500, 750 and 1000 mg, the plasma sample of, 6/8, 8/8 and 8/8 subjects, respectively, achieved bactericidal activity against *S. pneumoniae* (starting as early as 30 min and lasting up to 4 h post-dose). See table Pharmacokinetics.

Conclusion:

NXL103 was generally well tolerated up to 750 mg *b.i.d.* for 10 days. Exposure to NXL103 increased in relation to the dose up to 1500 mg *o.d.* inclusive, steady state was achieved on Day 2. NXL103 gave good ex-vivo plasma activity against *S. pneumoniae*.

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), *H. influenzae*, *M. catarrhalis*, and *Legionella* and other atypicals (*Chlamydia* and *Mycoplasma*).

MATERIALS AND METHODS

Study Objectives:

To determine safety tolerability and pharmacokinetics after single and *b.i.d.* (12 hrs interval) dosing for 10 days.

Formulation:

125 mg capsules
Doses tested: 500 mg *b.i.d.*, 750 mg *b.i.d.*, 1500 mg *o.d.* and 1000 mg *b.i.d.*

Study design:

Dose escalation using a randomised, double-blind, placebo-controlled, parallel groups design. Single (D1) and multiple *b.i.d.* dosing for 10 days.

Study evaluations:

Sampling for PK:

- ✓ D1 and D10 : 10 samples → 12 h
- ✓ D1 evening dose (*b.i.d.*): 3 samples
- ✓ D4, D6 and D8 morning dose: 3 samples.

ECG recording: same time as for PK and double-blind re-reading of ECG digital files.

Vital signs: same time as for PK.

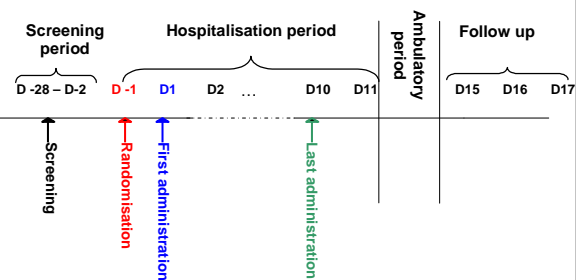
Safety lab: haematology and biochemistry, screening, D-1, D3, D11 and at follow-up visit.

Bioanalysis:

PII, PI and RPR208880 (a metabolite of PI) were analyzed by LC-MS/MS with a lower limit of quantification of 5 ng/mL.

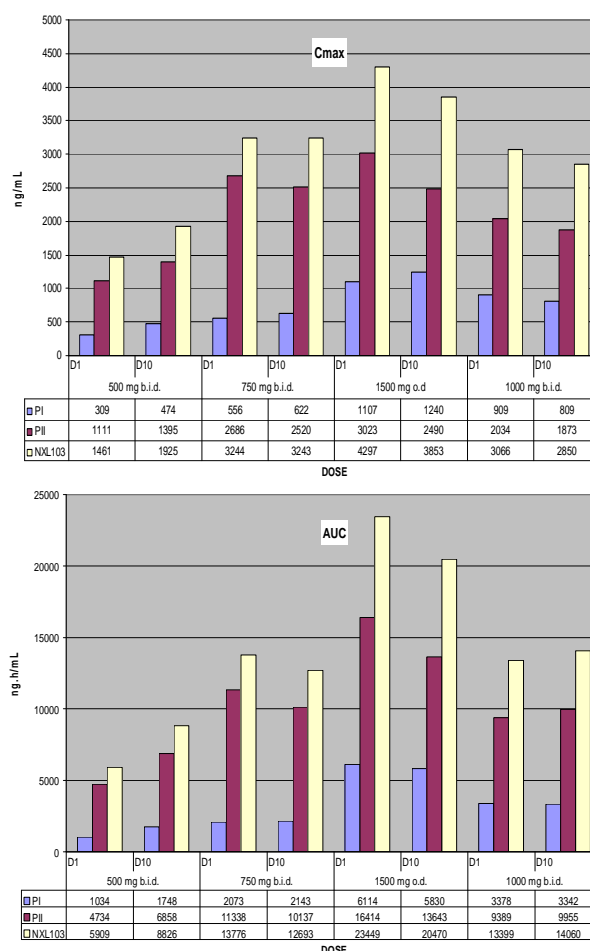
Population:

4 cohorts of 10 healthy subjects (8 active, 2 placebo).

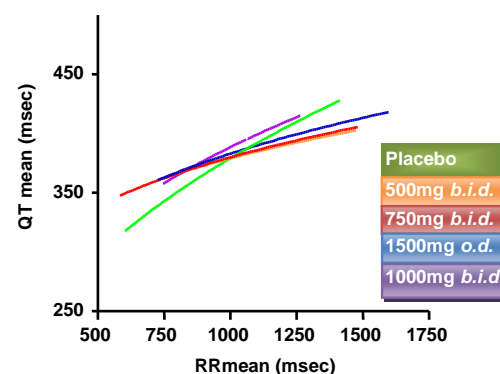


RESULTS

C_{max} and AUC of PI and PII and NXL103



ECG: QT/RR relationship



Demographics and Subject Disposition

(Mean ± SD)	500 mg <i>b.i.d.</i> (n=8)	750 mg <i>b.i.d.</i> (n=8)	1500 mg <i>o.d.</i> (n=10)	1000 mg <i>b.i.d.</i> (n=9)	Placebo (n=8)
Age (years)	31.8 ± 7.7	33.4 ± 6.6	28 ± 2.4	34 ± 6.9	33.1 ± 7.5
BMI	23.8 ± 2.8	24.2 ± 2.1	23.7 ± 1.8	23.8 ± 2.3	23.3 ± 2.6
Origin:					
Caucasian	6	6	9	7	8
Black	1	1	0	1	0
Other	1	1	1	1	0

Safety: Summary of all treatment emergent adverse events (TEAEs)

	500 mg <i>b.i.d.</i>	750 mg <i>b.i.d.</i>	1500 mg <i>o.d.</i>	1000 mg <i>b.i.d.</i>	Placebo
Subjects with at least 1 TEAE	5/8	8/8	9/10	7/9	2/8
List of events					
Abdominal pain (upper)			1	1	
Vomiting		3	6	1	
Nausea	1	4	6	2	
Loose stools	2	4	3	5	
Pharyngitis	1				
Headache	1			1	
Heat rash		1			
Orthostatic hypotension	2		1	1	2
Total number of events	7	12	17	11	2

Pharmacokinetics of NXL103 (PII + PI + PI metabolite)

PK Parameters (mean and range)	500 mg <i>b.i.d.</i> (n=8)		750 mg <i>b.i.d.</i> (n=7)		1500 mg <i>o.d.</i> (n=7)		1000 mg <i>b.i.d.</i> (n=7)	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
C _{max} (µg/mL)	1.46	1.93	3.24	3.24	4.30	3.85	3.07	2.85
	0.91-2.18	1.51-2.58	1.08-4.10	1.80-4.98	2.70-5.52	2.78-4.84	1.96-4.10	2.18-3.49
T _{max} (h)	3	3	3	2	4	3	3	3
	1.5-4	2-4	2-4	1.5-4	1.5-4	2-4	1.5-4	1.5-4
AUC _{0-t} (µg.h/mL)	5.91	8.83	13.8	12.7	23.4	20.5	13.4	14.1
	3.35-10.0	5.56-12.4	4.10-20.8	7.50-20.4	7.50-38.9	9.72-31.0	7.32-17.3	8.93-18.0
C _{24h} (ng/mL) mean	98	129	216	144	35	26	161	190
	7-378	34-281	16-433	47-277	0-102	0-56	45-216	48-434
R _{ss} Geometric Mean	NA	1.53	NA	0.97	NA	0.93	NA	1.03

AUC_{0-t} was calculated from 0-12h data for *b.i.d.* administrations and 0-24h data for *o.d.* administration

Plasma bactericidal activity against *S. pneumoniae* (SP) and *S. aureus* (SA): (range of bactericidal titers on day 10)

Time (hr)	500 mg <i>b.i.d.</i>		750 mg <i>b.i.d.</i>		1500 mg <i>o.d.</i>		1000 mg <i>b.i.d.</i>	
	SP	SA	SP	SA	SP	SA	SP	SA
1	0-2	0-2	0-4	0-4	0-4	0-4	0-4	0-2
2	2-4	0-2	2-8	2-8	4-16	4-16	0-8	2-8
3	0-4	0-4	2-8	0-8	4-16	8-32	0-8	2-8
4	0-2	0-2	0-4	0-4	4-16	4-16	0-8	0-8
6	0-0	0-0	0-0	0-2	0-16	0-16	0-2	0-4
8	0-0	0-0	0-0	0-0	0-4	0-8	0-0	0-2

CONCLUSION

- NXL103 was rapidly absorbed with a median T_{max} of 3 hours (1.5 to 4 hours). The mean terminal T_{1/2} was short (2.04 to 3.23 hours).
- Steady state was reached around day 2.
- Based on PK/PD of AUC/MIC a dose of NXL103 of 500 mg *b.i.d.* should provide adequate exposures to treat pathogens with MICs ≤ 0.5 µg/mL.
- NXL103 was generally well tolerated at doses up to 750 mg *b.i.d.*: gastrointestinal adverse events occurred most commonly and appeared dose related. There were no significant changes in ECG parameters. Isolated increases in ALAT and/or ASAT were seen at D11 (most less than twice the ULN).