

Optimization of the Linopristin / Flopristin Dose Ratio in NXL103

M. RANGARAJU¹, A. TARRAL¹, H. MERDJAN¹, P. LEVASSEUR¹, D. CHASSARD², N. AUDONNET³

¹Novexel S.A., Romainville, France, ²SGS Aster, Paris, France, ³Synexel, Poitiers, France



A1-1943

ABSTRACT

Background: 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). NXL103 was initially developed as a 30:70 fixed dose combination and simulations suggested that a dose ratio of 40:60 to 45:55 may achieve equivalent activity at a lower total dose.

Methods: This was an open, randomized, cross-over study to assess the PK and ex-vivo bactericidal activity of 6 different combinations of the 2 active components of NXL103.

30 young male subjects received a single dose of 500 to 650 mg NXL103, with linopristin/flopristin dose ratios of 33:67 to 46:54. Subjects were randomized in 3 groups of 10 and received 2 of the 6 different combinations, in a cross-over design with a 7-day washout.

Linopristin, flopristin and a metabolite of linopristin, were quantified in plasma by LC-MS/MS; non-compartmental analysis was used. Ex-vivo plasma bactericidal activity was measured against strains of *S. pneumoniae* (SP) and *S. aureus* (SA).

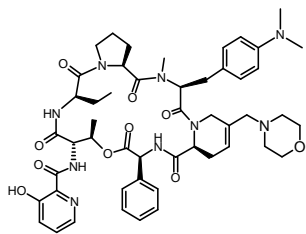
Results: 32 subjects were randomized and 30 completed the study. One subject withdrew due to vomiting and one for abnormal laboratory values. There were no severe adverse events. All formulations were safe and well tolerated.

The dose consisting of linopristin 250 mg (~42%) and flopristin 350 mg (~58%) gave a low PK variability and least effect of linopristin on flopristin PK and flopristin on linopristin PK, with a mean total AUC of 8.31 µg.h/mL. All subjects receiving this formulation achieved bactericidal activity against strains of SP and SA with activity lasting up to 5 h post-dose. The linopristin/flopristin AUC ratio at this dose was 26/74, in the middle of the efficacy range determined by in vitro and in vivo studies.

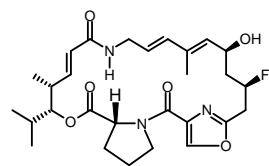
Conclusions: The dose consisting of linopristin 250 mg (~42%) and flopristin 350 mg (~58%) was considered optimal as it gave low PK variability and ex-vivo plasma bactericidal activity in all subjects.

CHEMICAL STRUCTURES

LINOPRISTIN "PI"



FLOPRISTIN "PII"



BACKGROUND AND OBJECTIVE

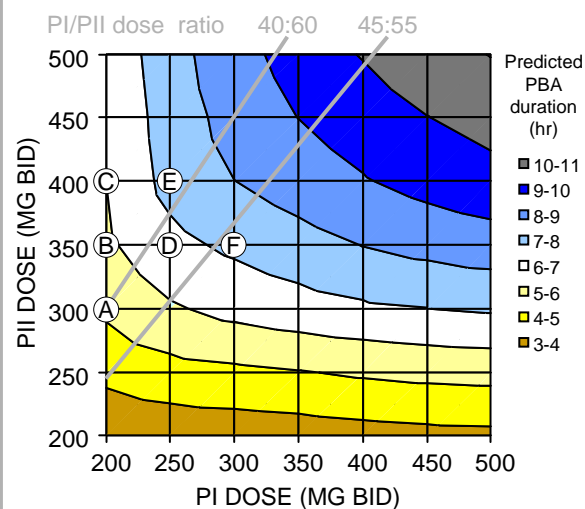
NXL103 is a novel oral streptogramin, a combination of linopristin ("PI") and flopristin ("PII"). Antibacterial activity covers *S. pneumoniae* (including multidrug resistant strains), *S. aureus* (including MRSA), *H. influenzae*, and atypical pathogens.

NXL103 was initially developed as a combination of PI and PII in a 30:70 dose ratio (w/w).

PK/PD models have previously been developed and validated for the relationships between plasma concentrations and plasma bactericidal activity (PBA). According to the models, bactericidal activity on *S. pneumoniae* was predicted for concentrations of PI > 0.175 mg/L and PII > 0.523 mg/L. Breakpoints for *S. aureus* were lower at 0.123 mg/L and 0.081 mg/L, respectively¹.

The duration of PBA against *S. pneumoniae* was simulated over 24 hours by varying PI and PII doses independently between 200mg BID and 500mg BID.

Figure 1: Simulated duration (hr) of PBA against *S. pneumoniae* at steady-state for PI and PII doses of 200 mg BID to 500 mg BID. Two-dimensional projection of a 3D response surface. Letters A to F refer to the 6 formulations tested.



The response surface was convex as a result of the synergistic bactericidal activity between components. The simulations suggested that the synergy may be optimal along the crest of the response surface, allowing achievement of equivalent activity at a lower total dose.

This corresponded to PI to PII dose ratios estimated between 40:60 and 45:55.

The study objective was to assess the PK and ex-vivo bactericidal activity of 6 combinations of the 2 active components of NXL103.

MATERIALS AND METHODS

This was an open, randomized, cross-over study.

Thirty young male subjects were randomized in 3 groups of 10, and received a single dose of 2 out of 6 different formulations (either A and D, or B and E, or C and F), in a cross-over fashion with a 7-day washout period.

	PI (mg)	PII (mg)	NXL103 (mg)	PI/PII dose ratio
A	200	300	500	40:60
B	200	350	550	36:64
C	200	400	600	33:67
D	250	350	600	42:58
E	250	400	650	38:62
F	300	350	650	46:54

Formulations A to F are reported on figure 1.

Blood samples were taken at 13 time-points until 12 hours post-dose for PK and PD evaluations.

Linopristin, flopristin and a metabolite of linopristin (RPR208880), were quantified in plasma by a validated LC-MS/MS method. The lower limit of quantification was 0.005 mg/L for each analyte. Between-day assay precision and inaccuracy were consistently < 9.57% and ≤ ±12.00%, respectively.

PK data interpretation was by conventional non-compartmental analysis.

Ex-vivo bactericidal activity was measured in PK plasma samples against strains of *S. aureus* and *S. pneumoniae*.

Thirty-two subjects were actually randomized and 30 completed the study. One subject withdrew due to abnormal laboratory values, and one for a vomiting episode 20 min after dosing with form A, thus possibly affecting the PK objective. There were no serious adverse events. All formulations were generally well tolerated.

CONCLUSION

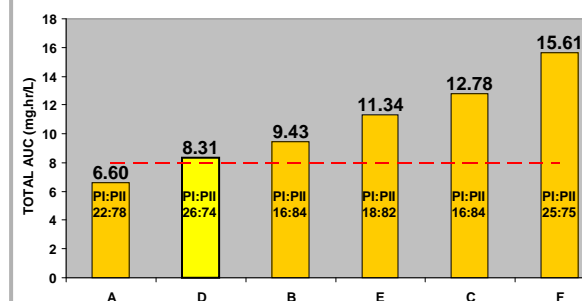
An optimum 40:60 to 45:55 PI/PII dose ratio has been suggested by PK/PD simulations. Formulation "D" was considered optimal for its absolute exposure to total NXL103, relative exposure to PI, acceptable PK variability, consistency of plasma bactericidal activity in all subjects, and onset and duration of activity. It contained 250 mg of PI and 350 mg of PII. This corresponds to a PI/PII dose ratio of exactly 5:7 or, after normalization, approximately 42:58. This was an experimental confirmation of PK/PD simulations.

REFERENCES

- MERDJAN H *et al.* Abstract P793, 17th ECCMID Meeting, Munich, Germany, 2007.
- ANDES D and CRAIG WA. *Antimicrob. Agents Chemother.* 2006,50(1):243-249.

RESULTS

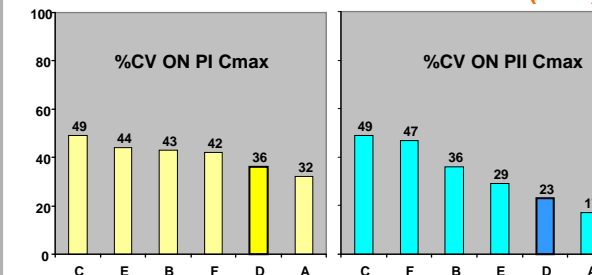
FIGURE 2: SINGLE DOSE EXPOSURE TO TOTAL NXL103 (ranking by increasing AUC) (Total AUC expressed as mg.hr/L of PI + PII + RPR208880)



All formulations but "A" achieved a target exposure of 8 mg.hr/L or above. Upon repeated BID dosing, the projected steady-state AUC₂₄/MIC will be ≥ 32, thus providing coverage for pathogens with an MIC up to 0.5 mg/L inclusive².

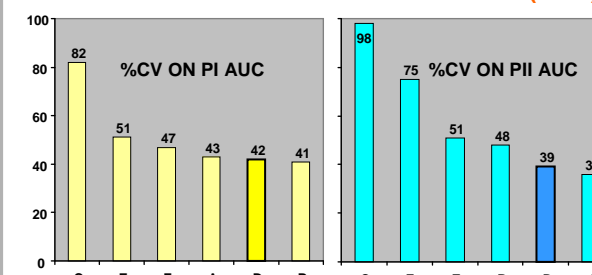
Formulation "D" exhibited the highest relative exposure to PI at 26%.

FIGURE 3: INTER-INDIVIDUAL VARIABILITY (%CV) ON Cmax (ranking by decreasing variability)



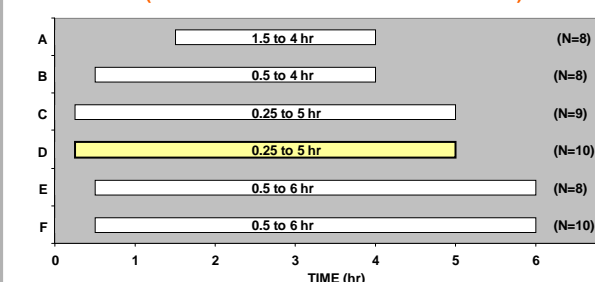
Formulation "D" was ranked second best with regard to inter-individual variability of Cmax for both components.

FIGURE 4: INTER-INDIVIDUAL VARIABILITY (%CV) ON AUC (ranking by decreasing variability)



Formulation "D" was ranked second best with regard to inter-individual variability of AUC for both components.

FIGURE 5: DURATION OF PLASMA BACTERICidal ACTIVITY AGAINST *S. pneumoniae* (RANGE AND NUMBER OF RESPONDERS)



Only formulations "D" and "F" resulted in plasma bactericidal activity in all 10 subjects.

This was achieved at lower NXL103 dose and exposure with formulation "D" than "F", and with a shorter onset of activity.