

Safety, Single Dose Pharmacokinetics, and Pharmacodynamics of Beta-Lactamase Inhibitor NXL104 in Healthy Young Male Adults.

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ABSTRACT

Background: NXL104 is a novel broad spectrum beta-lactamase inhibitor covering both class A and class C enzymes. This first-in-Man study investigated the safety, pharmacokinetics (PK) and pharmacodynamics of single doses in healthy male volunteers, alone or in combination with ceftazidime (CAZ).

Methods: 70 subjects were randomized in 7 cohorts (8 active + 2 placebo) to receive single ascending doses of 50, 100, 250, 500, 1000, 1500 and 2000mg NXL104 by 30-min intravenous infusion. The 2 cohorts who received 250 or 500mg also participated in a second session after a washout period of one week to receive 250mg NXL104 + 1g CAZ or 500mg NXL104 + 2g CAZ, respectively. Assessments included clinical and laboratory safety, and ECG recordings. NXL104 and CAZ were measured in plasma and urine. In subjects receiving a NXL104/CAZ combination, plasma bactericidal activity was assessed against a CAZ-sensitive (CAZ-S) and a CAZ-resistant strain (CAZ-R, AmpC and SHV-11) of *Klebsiella pneumoniae*.

Results: Adverse events (AEs) were rare and no serious AEs were recorded. No clinically significant results were observed. Peak plasma concentrations of NXL104 increased in direct proportion to dose: 2.7 to 124 mg/l from 50 to 2000mg. Plasma clearance averaged 10.4 to 13.8 l/h. The volume of distribution (Vss) was 20 to 24 l. The terminal half-life was 1.5 to 2.7 hours. NXL104 PK at 250 and 500mg was unaffected by CAZ. Plasma bactericidal activity was observed against both CAZ-S and CAZ-R strains of *K. pneumoniae* for up to 8 hours (250mg NXL104 + 1g CAZ) or 12 hours (500mg NXL104 + 2g CAZ) after the start of infusion.

Conclusion: Single intravenous doses of NXL104 were well tolerated in healthy male subjects. The maximum tolerated dose was above 2000mg. NXL104 PK was linear and unaffected by CAZ co-administration. Single doses of 250mg and 500mg NXL104 restored bactericidal activity of CAZ (1g and 2g, respectively) against a CAZ-R pathogen.

BACKGROUND

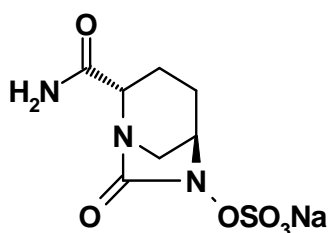
In vitro NXL104 is a potent broad spectrum beta-lactamase inhibitor. Although virtually devoid of antibacterial activity, NXL104 efficiently protects beta-lactams from hydrolysis in a variety of class A and class C producing strains, including ESBL producers.

In vivo the ceftazidime / NXL104 combination showed therapeutic activity in a variety of animal models of infection due to CAZ resistant strains¹⁻³.

The objectives of the present First-In-Man study were:

- to investigate the safety and tolerability of escalating single intravenous doses (from 50 to 2000 mg) of NXL104 administered alone and in combination with ceftazidime (2 doses) in healthy volunteers.
- to investigate the pharmacokinetics of NXL104 administered alone and in combination with ceftazidime in healthy volunteers.

STRUCTURE OF NXL104



REFERENCES

- Borgonovi M *et al.*, 17th ECCMID, abstract P794, 2007
- Levasseur P *et al.*, 45th ICAAC, abstract F-0127, 2005
- Cottagnoud P *et al.*, 47th ICAAC, abstract F1-321, 2007

METHODS

Clinical study design

- Single administration, dose escalation study using a randomized, double blind, placebo-controlled design in one center
- Administrations were by 30-min intravenous infusions
- Subjects: 70 healthy young male adults
- Cohorts: 7 cohorts of 10 subjects each (8 active + 2 placebo)

| Cohort | Period | Doses (mg) | |
|--------|--------|------------|------|
| | | NXL104 | CAZ |
| 1 | 1 | 50 | 0 |
| 2 | 2 | 100 | 0 |
| 3 | 3 | 250 | 0 |
| 4 | 4 | 250 | 1000 |
| | 5 | 500 | 0 |
| 5 | 6 | 500 | 2000 |
| | 7 | 1000 | 0 |
| 6 | 8 | 1500 | 0 |
| 7 | 9 | 2000 | 0 |

- In cohorts 3 and 4, a 7-day washout period separated the administrations of NXL104 alone and in combination with CAZ.

Safety evaluation

- Safety was assessed via AEs, physical examination, clinical laboratory data, 12-lead ECG recordings, cardiac monitoring and vital signs (blood pressure and heart rate).
- Local tolerance at injection site was monitored and recorded.
- Treatment-Emergent Adverse Events (TEAEs) were defined as AEs that developed or worsened during the on-treatment period (*i.e.*: within 48 hours post-dose).

PK evaluation

- Two 5-ml blood samples were taken predose, then 10min, 30min, 40min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 36h and 48h after the start of infusion.
- Urine fractions were collected predose, then at [0-6h], [6-12h], [12-24h], [24-48h] post dosing.
- NXL104 and CAZ in plasma and urine were determined by validated LC-MS/MS methods. The lower limits of quantitation (LOQ) in plasma were 0.01 and 0.05 mg/l, respectively.
- Data analysis was by conventional non-compartmental methods using the WinNonlin[®] software version 5.01.

Pharmacodynamic evaluation

- Plasma samples from NXL104/CAZ combination groups were assessed for bactericidal activity against two strains of *Klebsiella pneumoniae*:

| Strains | MICs / MBCs (mg/l) - CLSI technique | |
|--|-------------------------------------|------------------|
| | CAZ | CAZ/NXL104 (4:1) |
| <i>K. pneumoniae</i> 283GR4 | 0.25 / 0.25 | 0.25 / 0.25 |
| <i>K. pneumoniae</i> 283KB5 (AmpC, SHV-11, non-ESBL) | 32 / 64 | 0.5 / 0.5 |

MICs and MBCs were not affected in the presence of 50% human plasma.

- Plasma bactericidal test: equal volume of test plasma were mixed with pooled human control plasma; 2-fold serial dilutions were carried out; an equal volume of Mueller-Hinton medium containing the test strains (5×10^5 cfu/ml) was then added to each well.
- Plasma bactericidal activity: after overnight incubation at 37°C, all wells were sampled and 10 μ l streaked onto solid agar medium. The highest dilution of plasma which suppressed 99.9% of the original inoculum was defined as the plasma bactericidal activity; thus growth of 5 colonies or less was considered as bactericidal.

Statistical methods

- Summary statistics for PK parameters were calculated by dose level.
- The dose-Cmax and dose-AUC relationships were characterized by unweighted linear regression.
- The possible influence of CAZ on NXL104 PK parameters (Cmax and AUCs) was assessed by a paired Student's t test.
- Statistical significance was set at $p < 0.05$.

RESULTS

1. NXL104 PHARMACOKINETICS

Table 1: Mean PK parameters of NXL104 when given alone or in combination with CAZ (grey background)

| Cmax (mg/l) | Mean | %CV | 0 | | 1000 | | 2000 | | 0 | | 0 | |
|--------------------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| | | | 50 | 100 | 250 | 250 | 500 | 500 | 1000 | 1500 | 2000 | 2000 |
| AUC ₍₀₋₂₄₎ (h*mg/l) | Mean | 3.68 | 8.3 | 19.6 | 20.9 | 38.3 | 37.9 | 86.9 | 146 | 185 | | |
| | %CV | 11 | 20 | 11 | 15 | 27 | 22 | 16 | 10 | 15 | | |
| AUC (h*mg/l) | Mean | 3.72 | 8.36 | 19.7 | 21 | 38.5 | 38.2 | 87.1 | 146 | 186 | | |
| | %CV | 11 | 20 | 11 | 15 | 27 | 22 | 16 | 10 | 15 | | |
| t _{1/2,z} (h) | Mean | 1.48 | 1.8 | 1.7 | 1.8 | 1.83 | 1.8 | 2.17 | 2.65 | 2.71 | | |
| | %CV | 24 | 20 | 11 | 10 | 13 | 10 | 28 | 6 | 5 | | |
| V _{ss} (l) | Mean | 21.1 | 24.3 | 22.9 | 21.8 | 23.9 | 26.2 | 22.1 | 19.5 | 21.1 | | |
| | %CV | 16 | 26 | 12 | 32 | 37 | 26 | 12 | 14 | 20 | | |
| CL (l/h) | Mean | 13.6 | 12.4 | 12.9 | 12.2 | 13.8 | 13.6 | 11.8 | 10.4 | 11 | | |
| | %CV | 13 | 20 | 11 | 18 | 25 | 19 | 17 | 10 | 14 | | |
| CL _R (l/h) | Mean | 12.4 | 11.4 | 15.9 | 12.3 | 13.1 | 13 | 11.4 | 8.69 | 10.8 | | |
| | %CV | 14 | 22 | 16 | 32 | 27 | 22 | 18 | 21 | 21 | | |

Figure 1: Mean plasma concentration-time profiles of NXL104 (LOQ = 0.01 mg/l) when given alone or in combination with CAZ

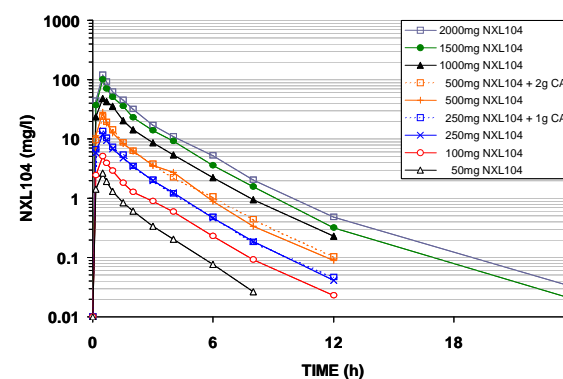
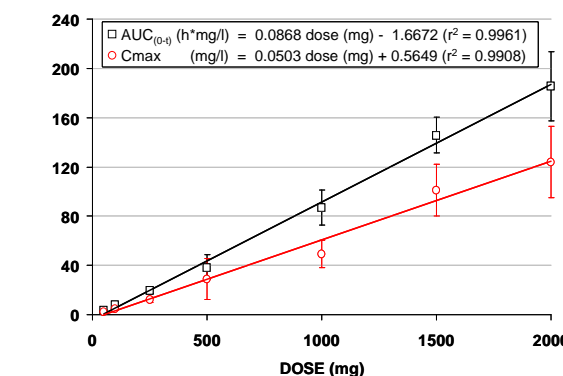


Figure 2: Dose-Cmax and dose-AUC relationships of NXL104 when given alone

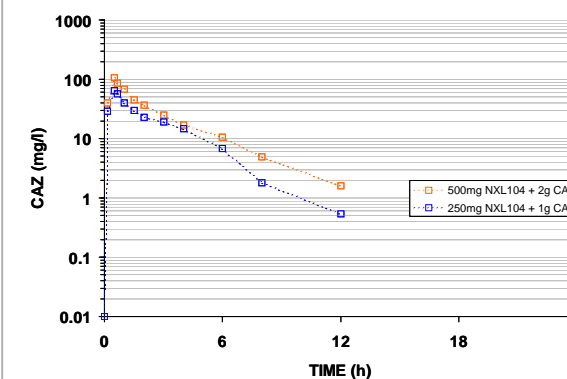


2. CAZ PHARMACOKINETICS

Table 2: Mean PK parameters of CAZ when given in combination with NXL104

| Cmax (mg/l) | Mean | %CV | CAZ (mg) | |
|--------------------------------|------|------|----------|------|
| | | | 1000 | 2000 |
| AUC ₍₀₋₂₄₎ (h*mg/l) | Mean | 65.3 | 144 | 224 |
| | %CV | 24 | 15 | 25 |
| AUC (h*mg/l) | Mean | 146 | 228 | 226 |
| | %CV | 15 | 26 | 26 |
| t _{1/2,z} (h) | Mean | 1.82 | 3 | 3 |
| | %CV | 26 | 61 | 61 |
| V _{ss} (l) | Mean | 17.3 | 26.4 | 26.4 |
| | %CV | 23 | 33 | 33 |
| CL (l/h) | Mean | 7.03 | 9.27 | 9.27 |
| | %CV | 18 | 23 | 23 |
| CL _R (l/h) | Mean | 6.75 | 10 | 10 |
| | %CV | 20 | 26 | 26 |

Figure 3: Mean plasma concentration-time profiles of CAZ (LOQ = 0.05 mg/l) when in combination with NXL104



3. SAFETY

- A total of 56 subjects were exposed to NXL104 alone, of which 16 were also exposed to CAZ.
- No serious or severe Adverse Event was reported.
- No TEAEs were reported in any of the subjects belonging to 50, 100, 1000, and 1500 mg cohorts, nor in the combination cohorts 250 mg NXL104 + 1000 mg CAZ and 500 mg NXL104 + 2000 mg CAZ. A total of 6 TEAEs were reported from 4 subjects dosed with 250, 500, and 2000 mg doses.
- Of the 6 TEAEs reported, 5 were of mild intensity (abdominal pain, sense of oppression, somnolence, anxiety, postural dizziness) and one was of moderate intensity (orthostatic hypotension).
- No clinically significant abnormal values were observed for blood chemistry, hematology, vital signs and ECG parameters.

CONCLUSION

NXL104 administered alone (up to 2000 mg) or in combination with CAZ was safe and well tolerated, both systemically and locally.

When given alone, dose-Cmax and dose-AUC relationships of NXL104 were described by straight lines over the whole dose range. Plasma clearance was 10.4 to 13.8 l/h and renal excretion of the unchanged drug represented the predominant elimination pathway. In subjects who received NXL104 both alone and in combination with CAZ, the pharmacokinetic parameters of NXL104 (Cmax and AUCs) were not statistically affected by CAZ co-administration.

Single doses of 250mg and 500mg NXL104 restored bactericidal activity of CAZ (1g and 2g, respectively) against a CAZ-R pathogen. Plasma concentrations which were bactericidal to both CAZ-S and CAZ-R strains of *K. pneumoniae* were achieved in all volunteers. The bactericidal activity was observed for up to 8 hours (250mg NXL104 + 1g CAZ) or up to 12 hours (500mg NXL104 + 2g CAZ) after the start of infusion.

4. PHARMACODYNAMICS

Figure 4: Individual plasma bactericidal titres in 8 subjects dosed with 250 mg NXL104 + 1g CAZ

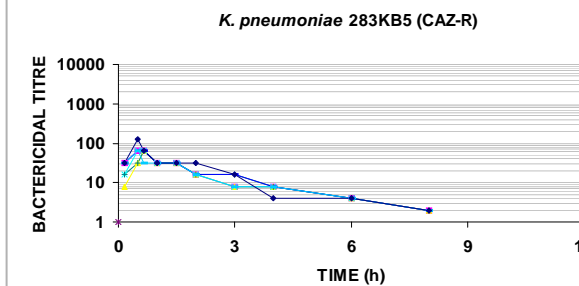
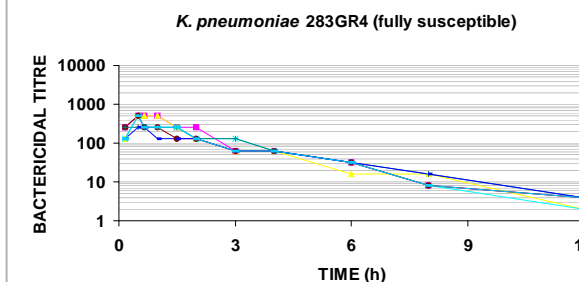


Figure 5: Individual plasma bactericidal titres in 8 subjects dosed with 500 mg NXL104 + 2g CAZ

