

# Effect of Age and Gender on the Pharmacokinetics (PK) and Safety of NXL104 in Healthy Subjects (Protocol NXL104/1004)

Antoine Tarral<sup>1</sup>, Joy Lipka<sup>1</sup>, Shwe Gyaw<sup>2</sup>, Pepi Pencheva<sup>2</sup>, Henri Merdjan<sup>1</sup>, Walter Heber<sup>2</sup>, Victoria Cheung<sup>3</sup>, Rachael Garner<sup>2</sup>, Carole Sable<sup>1</sup>

<sup>1</sup> Novoxel SA, Romainville, France, <sup>2</sup> PAREXEL International, Baltimore, MD, <sup>3</sup> Quotient Bioresearch, Fordham, UK



Contact Information: antoine.tarral@novoxel.com

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## ABSTRACT

**Background:** NXL104 is a novel, non  $\beta$ -lactam,  $\beta$ -lactamase inhibitor with a spectrum of activity encompassing both class A and class C  $\beta$ -lactamases. NXL104 is being developed in combination with ceftazidime (CAZ). CAZ/NXL104 has been shown to be active against strains expressing a combination of  $\beta$ -lactamase types, as well as strains concomitantly resistant to other antibacterial classes.

**Methods:** NXL104/1004 was a Phase I open label study in which 33 healthy subjects were enrolled in 4 cohorts based on age and gender. All subjects received a single 500 mg IV infusion of NXL104. Blood was collected at 13 timepoints over 24 h to give a full PK profile; 3 urine fractions were collected over 24 h. Subjects were followed for safety for 14 days after dosing.

**Results:** As shown in the table, the PK of NXL104 was similar in the cohorts, regardless of age and gender. There was a slight trend towards lower plasma and renal clearance in elderly women. There was no serious adverse event (AE) in any subject, and no discontinuation due to AE. The most common AEs (regardless of drug relationship) were application site bruising (4/33; 12%) and headache (2/33; 6%). Three subjects (9%) experienced 6 AEs considered drug-related, including dry mouth, feeling hot, feeling jittery, dysgeusia, headache, and hyperhidrosis; each event was mild in intensity.

Cohort	Demographics		PK Parameters						
	Statistic	Age	Statistic	$C_{max}$ (µg/mL)	$T_{max}$ (h)	$t_{1/2}$ (h)	CL (L/h)	$AUC_{0-\infty}$ (µg·h/mL)	$CL_R$ (L/h)
Young Men (n=9)	Mean	28.7	Mean	33.83	0.542	2.093	10.16	49.86	9.19
	SD	8.24	SD	4.24	0.080	0.636	1.23	6.27	4.02
	Median	34.19	Median	34.19	0.520	1.770	10.21	48.97	8.96
Young Women (n=8)	Mean	30.9	Mean	36.86	0.536	1.709	10.34	49.75	8.59
	SD	12.44	SD	9.31	0.087	0.089	1.82	9.10	1.55
	Median	34.77	Median	34.77	0.500	1.685	10.48	47.74	8.28
Elderly Men (n=8)	Mean	68.8	Mean	68.45	0.596	3.165	9.82	52.40	6.93
	SD	15.74	SD	5.73	0.185	0.654	1.81	9.38	3.58
	Median	62.59	Median	62.59	0.500	2.965	9.69	51.63	5.78
Elderly Women (n=8)	Mean	69.1	Mean	68.41	0.509	2.433	7.98	66.23	4.49
	SD	10.76	SD	15.51	0.012	0.469	2.22	14.97	1.83
	Median	63.97	Median	63.97	0.500	2.625	7.21	69.71	3.76

**Conclusion:** NXL104 was generally well tolerated across all cohorts. No dose adjustment is required based on age or gender, given the marginal differences in PK parameters and the good systemic tolerance of NXL104 across all cohorts.

## INTRODUCTION

Gram negative bacilli are important causative pathogens in a number of serious infections. The prevalence of multidrug resistance (MDR) strains among Gram-negative bacilli is increasing [1-4]. Compared to infections due to antimicrobial-susceptible Gram-negative bacilli, infections due to MDR Gram-negative bacilli lead to longer hospital stays, increased mortality, and greater costs of hospitalization [5,6]. The most common mechanism for resistance to  $\beta$ -lactams in Gram negatives is production of  $\beta$ -lactamases.

NXL104 is a novel, non  $\beta$ -lactam,  $\beta$ -lactamase inhibitor with a spectrum of activity encompassing both class A and class C  $\beta$ -lactamases. NXL104 when administered with

## INTRODUCTION (cont'd)

CAZ has been shown to be active against strains which express a combination of  $\beta$ -lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones.

NXL104 has a broader spectrum (including class C enzymes and class A carbenapenems) than the currently marketed  $\beta$ -lactamase inhibitors clavulanic acid, tazobactam and sulbactam. Unlike currently available  $\beta$ -lactamase inhibitors, NXL104 does not induce  $\beta$ -lactamase production.

The potent *in vitro* activity of the NXL104 and CAZ combination against *Enterobacteriaceae* producing class A, and importantly class C,  $\beta$ -lactamases has been confirmed *in vivo* in murine pneumonia, septicemia and pyelonephritis models.

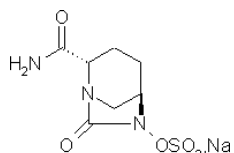
Currently, the options for the treatment of Gram-negative infections, especially MDR strains including Extended Spectrum  $\beta$ -lactamase (ESBL) producers, are extremely limited. There are no new classes in development specifically targeted to combat these organisms. Hence availability and development of new agents to treat these infections would be a welcome addition to the existing treatment.

## MATERIALS AND METHODS

NXL104/1004 was a Phase I study to evaluate the effect of age and gender on the PK and safety of NXL104 in healthy volunteers. This was an open label study in which 32 healthy subjects divided in 4 cohorts (8 young male adults, 8 elderly males, 8 elderly females, and 8 young females) were planned for enrollment. All subjects were to receive one single 500mg I.V. infusion of NXL104. Subjects participated in a 28-day screening period, followed by a baseline period (Day-1, start of hospitalization), followed by single I.V. dose (D1) and 24 hours post dosing follow-up (hospitalization up to 24h post dosing). An End of Study (EOS) visit was performed 3 to 7 days after dosing. Subjects were contacted by phone 14 days after dosing to assess for AEs.

In order to provide a full PK profile, blood was collected pre-dose and at 12 timepoints between 15min and 24h after the start of infusion. In addition, urine was collected before infusion, and at 0-6h, 6-12h, 12-24h post-dose. NXL104 was analyzed by validated LC-MS/MS methods, with limits of quantitation of 0.010 and 0.100 µg/mL in plasma and urine, respectively.

## CHEMICAL STRUCTURE



## RESULTS

### Demographics and Subject Disposition

Overall, 33 subjects were enrolled in 4 cohorts [young men (N=9); young women (N=8); elderly men (N=8); elderly women (N=8)] and received a single 500 mg I.V. dose of NXL104. The cohort of young men had one extra subject enrolled because one young male subject (AN101) did not return for follow up and a replacement subject (AN5101) was enrolled. Thus, 32 of the 33 subjects completed the study. The mean age of subjects enrolled was similar among the two young cohorts as well as the two elderly cohorts, as provided in Table 1.

### Safety

Table 2 provides a summary of treatment-emergent AEs by cohort. There were no serious AEs in any subject; no AEs led to discontinuation. Treatment-emergent AEs that occurred in more than one subject (regardless of relationship to study drug) were application site bruising (4/33; 12%) and headache (2/33; 6%). Three subjects (9%) experienced 6 treatment-emergent AEs considered to be drug-related, including dry mouth, feeling hot, feeling jittery, dysgeusia, headache, and hyperhidrosis; each event was mild in intensity.

### Pharmacokinetics

Plasma PK parameters and renal clearance (CL<sub>R</sub>) are provided in Table 3. In the young men, the mean half life of NXL104 was 2.09 hours with AUC (0-inf) 49.86 µg·hr/mL and C<sub>max</sub> 33.83 µg/mL; clearance was ~10L/hour. In the young women, the mean half life of NXL104 was 1.71 hours with AUC (0-inf) 49.75 µg·hr/mL and C<sub>max</sub> 36.86 µg/mL; clearance was ~10L/hour. In the elderly men, the mean half life of NXL104 was 3.17 hours with AUC (0-inf) 52.4 µg·hr/mL and C<sub>max</sub> 26.45 µg/mL; clearance was ~10L/hour. In the elderly women, the mean half life of NXL104 was 2.43 hours with AUC (0-inf) 66.23 µg·hr/mL and C<sub>max</sub> 38.41 µg/mL; clearance was ~8L/hour. Figure 1 provides the mean NXL104 plasma concentration over time by cohort. The renal clearance value observed at 0-24 hours in each cohort was as follows: young men: 9.19 L/hour, young women: 8.59 L/hour, elderly men: 6.93 L/hour, and elderly women: 4.49 L/hour. Overall, the PK (total plasma clearance, C<sub>max</sub>, AUCs, and half-life) of NXL104 is similar in the cohorts, regardless of age and gender. There is a slight trend towards lower plasma and renal clearance in elderly women.

Table 1 – Demographics

	Young men N=9	Young women N=8	Elderly Men N=8	Elderly women N=8
Age range (Years)				
Mean	28.7	30.9	68.8	69.1
Min	20	23	65	65
Max	37	44	74	76
Race				
African American	6 (66.7%)	5 (62.5%)	1 (12.5%)	2 (25.0%)
Caucasian	3 (33.3%)	3 (37.5%)	7 (87.5%)	6 (75.0%)

Table 3 – PK Parameters

Cohort	Statistic	PK Parameters					
		$C_{max}$ (µg/mL)	$T_{max}$ (h)	$t_{1/2}$ (h)	CL (L/h)	$AUC_{0-\infty}$ (µg·h/mL)	CL <sub>R</sub> (L/h)
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	SD	15.51	0.012	0.469	2.22	14.97	1.83
	Median	33.97	0.500	2.625	7.21	69.71	3.76

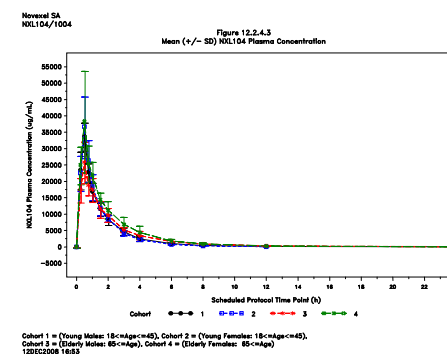
$C_{max}$  = maximum plasma concentration;  $T_{max}$  = time to maximum plasma concentration;  $t_{1/2}$  = terminal half-life; CL = total plasma clearance;  $AUC_{0-\infty}$  = Area under the plasma concentration versus time curve from time zero to infinity; CL<sub>R</sub> = renal clearance

Table 2 – Treatment Emergent AE Summary

	Young men N=9	Young women N=8	Elderly Men N=8	Elderly women N=8
Subjects with one or more TEAE	1 (11.1%)	3 (37.5%)	2 (25.0%)	4 (50.0%)
Drug-related TEAE	1 (11.1%)	0	0	2 (25.0%)
TEAE Leading to Discontinuation	0	0	0	0
Serious TEAE	0	0	0	0
Death	0	0	0	0

TEAE = Treatment-emergent adverse event

Figure 1 – NXL104 Plasma Concentration



## CONCLUSION

NXL104 was generally well tolerated across all cohorts. No dose adjustment is required based on age or gender, given the marginal differences in PK parameters and the good systemic tolerance of NXL104 across all cohorts.

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