

# A Phase II double-blind, double-dummy, multicenter study of two doses of linopristin/flopristin (NXL103) vs. amoxicillin in the treatment of mild to moderate community acquired pneumonia (CAP) in adults

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## ABSTRACT

**Background:** NXL103 is a novel, investigational, oral, bactericidal streptogramin with activity against *S. pneumoniae* (plus MDR-SP), *H. influenzae*, atypical pathogens and *S. aureus* (plus MRSA).

**Methods:** 302 adults with CAP were enrolled in 8 countries and randomized 1:1:1 to oral NXL103 500 mg bid or NXL103 600 mg bid or amoxicillin 1 gram tid, all for 7 days.

**Results:** Patients had similar demographics and severity of infection at baseline. Approximately 22% had microbiologically documented infections; *S. pneumoniae* and *H. influenzae* were most common. At test of cure (7 to 14 days post-therapy) clinical response in clinically evaluable patients was 91.4% in NXL103 500 mg, 94.7% in NXL103 600 mg, and 88.5% in amoxicillin. Favorable microbiological responses were high for all pathogens. NXL103 was generally well tolerated. Gastrointestinal adverse events (AEs) (nausea and vomiting) were most common in NXL103 groups. No drug-related serious AEs were reported; AEs leading to discontinuation were uncommon ( $\leq$  5% each group).

**Conclusions:** NXL103 at 500 mg or 600 mg bid is efficacious in the treatment of CAP with results similar to high dose amoxicillin. NXL103 was generally well tolerated. NXL103 may be an effective oral therapy for CAP and, based on its spectrum, for complicated skin and skin structure infections.

## INTRODUCTION

CAP continues to be a common and serious illness despite the availability of potent new antibacterial agents and effective vaccines. Most disease is mild and treated on an outpatient basis with a low mortality rate of < 5%. Streptococcus pneumoniae is the pathogen most frequently isolated from adults with CAP (up to 62%). Other pathogens implicated in CAP are *H. influenzae*, Mycoplasma, Chlamydia, Legionella, *S. aureus*, *M. catarrhalis*, and other *Streptococcus* spp. More recently MRSA has also been reported as an etiologic pathogen in CAP (6.2% to 8.9% of cases). The initial treatment is typically empirical. According to the ERS Task Force in collaboration with ESCMID, the preferred treatment for outpatient CAP is oral amoxicillin 1 g three times daily.<sup>1</sup>

Linopristin/flopristin (NXL103) is a new oral streptogramin antibacterial agent composed of a combination of two components in a 42/58 ratio (w/w) [PI: RPR202868 and PII: RPR132552] that individually exert only a limited antibacterial effect, but have potent bactericidal activity when administered together. It acts through inhibition of protein synthesis. Linopristin/flopristin has an *in vitro* spectrum of activity that includes aerobic Gram-positive cocci including multi-resistant *S. pneumoniae* and MRSA including CA-MRSA and those constitutively resistant to MLSB. It also has activity against *H. influenzae* and *M. catarrhalis* and atypical pathogens (Legionella, Chlamydia and Mycoplasma). Linopristin/flopristin is rapidly bactericidal and has a low potential *in vitro* to select resistant mutants in MSSA, MRSA, *S. pneumoniae* and *H. influenzae*. These characteristics make linopristin/flopristin a potential alternative therapy for oral treatment of CAP.

## MATERIALS AND METHODS

### Study Design:

Phase II, double-blind, multicenter, randomized, double-dummy, comparative study in adults with mild to moderate community acquired pneumonia.

41 centers in 8 countries participated: Croatia, Estonia, Germany, Peru, Poland, Romania, South Africa, Ukraine.

300 patients were to be randomized to one of three oral treatment arms (1:1:1):

NXL103 500 mg BID,  
NXL103 600 mg BID,  
Amoxicillin 1000 mg TID.

All patients received matching placebo to the other treatment arm. Treatment duration – 7 days.

### Endpoints:

Primary – clinical outcome at early follow up (Day 7-14d post therapy) [test of cure];

Secondary – clinical outcome at late post-therapy visit (Day 14 to 21d post therapy), microbiological outcome, safety.

### Key Inclusion Criteria:

Adult male aged 18 to 70; Female either post menopausal or surgically incapable of bearing children; outpatients; patients meeting the clinical definition of pneumonia by signs/symptoms/physical examination and radiographs.

### Key Exclusion Criteria:

Subjects with severe CAP; Nosocomial pneumonia; Received more than 24 hours of treatment with other antibiotics, within the 7 days prior to enrollment.

### Population Definitions:

Safety: All randomized subjects who received  $\geq$  1 dose of study drug.

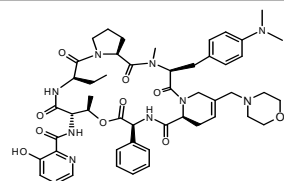
Modified Intention to Treat (mITT): All randomized subjects who received  $\geq$  1 dose of study drug and had signs, symptoms and radiologic findings supporting diagnosis of CAP.

Per Protocol Clinical (PPC): All mITT subjects excluding major protocol violations.

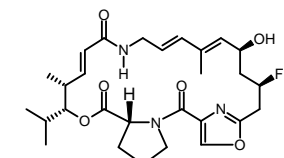
Per Protocol Bacteriological (PPB): All PPC subjects with bacteriologically proven infection.

## CHEMICAL STRUCTURES

Linopristin "PI"



Flopristin "PII"



## RESULTS

302 adults with CAP were randomized. Baseline characteristics were similar across treatment groups. Patients had mild to moderate CAP as defined by investigators and consistent with baseline CURB-65 scores. Twenty two percent had microbiologically confirmed infections.

### Demographics

	NXL103 500mg N = 98 n (%)	NXL103 600mg N = 99 n (%)	AMX 1g N = 105 n (%)
Gender			
Male	70 (71.4%)	64 (64.6%)	75 (71.4%)
Age			
Median	48	49	46
< 65	85 (86.7%)	82 (82.8%)	92 (87.6%)
$\geq$ 65	13 (13.3%)	17 (17.2%)	13 (12.4%)
Race			
White	74 (75.5%)	75 (75.8%)	75 (71.4%)
Black	20 (20.4%)	21 (21.2%)	21 (20.0%)
Other	4 (4.1%)	3 (3.0%)	9 (8.6%)
CURB 65 <sup>A</sup>			
0,1	94 (95.9%)	95 (96%)	101 (96.2%)
2	4 (4.1%)	4 (4%)	4 (3.8%)

<sup>A</sup>Calculated post hoc based on data collected from study entry

### Distribution of Baseline Pathogens

Number of isolate of each pathogen by treatment group at study entry

Pathogen	NXL103 500mg N* = 21	NXL103 600mg N = 14	Amoxicillin 1g N = 23
<i>S. pneumoniae</i>	12	6	13
<i>H. influenzae</i>	9	9	11
<i>H. parainfluenzae</i>	1	2	1
<i>M. catarrhalis</i>	4	1	4

\*N = number of patients from whom one or more pathogens was isolated

### Efficacy Data

Clinical cure rates were high for both doses of NXL103 and similar to high dose amoxicillin. Favorable responses in the PPb population were high regardless of pathogen identified.

### Favorable Clinical Outcome by Treatment Group at Test of Cure

Population	NXL103 500mg bid (A)	NXL103 600mg bid (B)	Amoxicillin 1g tid (C)	95% confidence intervals for differences in cure rates A to C	
mITT	80.6% (79/98)	75.8% (75/99)	76.2% (80/105)	4.4 (-7.9, 16.7)	-0.4 (-13.1, 12.3)
PPc	91.4% (74/81)	94.7% (72/76)	88.5% (77/87)	2.9 (-7.4, 13.1)	6.2 (-3.4, 15.8)
PPb	85.7% (18/21)	92.9% (13/14)	82.6% (19/23)	3.1 (-23.0, 29.2)	10.2 (-16.0, 36.5)

### Overview of Safety

- NXL103 was generally well tolerated. Most AEs in the 500mg NXL103 group were mild.
- SAEs were infrequent and none was considered drug-related.
- AEs leading to discontinuation were uncommon.
- Gastrointestinal events and increased hepatic enzymes AEs in NXL103.

	Number of subjects (%)		
Subjects with at least one:	NXL103 500mg bid N = 98	NXL103 600mg bid N = 99	Amoxicillin 1g tid N = 105
Treatment emergent adverse event	43 (43.9%)	50 (50.5%)	35 (33.3%)
Drug-related TEAE	28 (28.6%)	38 (38.4%)	16 (15.2%)
Serious adverse event	5 (5%)	0	4 (4%)
Drug-related serious adverse event	0	0	0
Discontinuation due to adverse event(s)	2 (2%)	5 (5%)	3 (3%)
Death <sup>A</sup>	1 (1%)	0	1 (1%)

<sup>A</sup>Deaths were due to *Pneumocystis jirovecii* pneumonia (n=1) and Mycobacterium tuberculosis (n=1)

### Treatment Emergent Adverse Events

	TEAEs in > 5% in any treatment group		
Adverse Event	NXL103 500mg N = 98	NXL103 600mg N = 99	Amoxicillin 1g N = 105
Nausea	11 (11.2%)	18 (18.2%)	2 (1.9%)
Vomiting	4 (4.1%)	9 (9.1%)	0
Hepatic enzyme increased	4 (4.1%)	6 (6.1%)	3 (2.9%)
Diarrhea	5 (5.1%)	2 (2%)	3 (2.9%)
Pneumonia worsening	1 (1%)	1 (1%)	5 (4.8%)

## CONCLUSIONS

**NXL103 at 500 mg or 600 mg bid is efficacious in the treatment of CAP with results similar to high dose amoxicillin. NXL103 was generally well tolerated. NXL103 may be an effective oral therapy for CAP and based on its spectrum for cSSSI.**

## REFERENCES

- Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005; 26:1138-1180.