E 0032

In vivo activity and PK of the novel siderophore cephalosporin AR-2126 in a lethal lung infection model in mice infected with a carbapenem-resistant *Pseudomonas aeruginosa*

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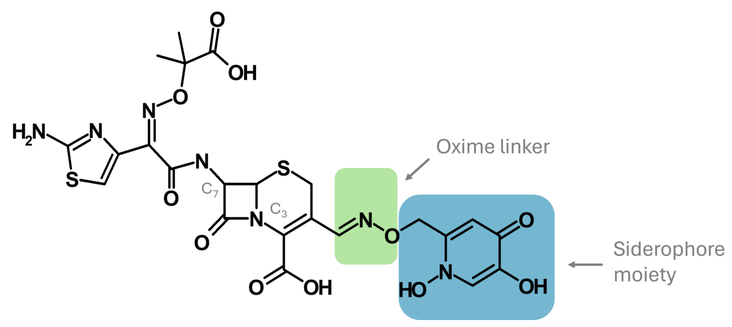
BACKGROUND:

- **AR-2126 is a novel siderophore-cephalosporin** with strong iron-chelating capabilities that promote entry into Gram-negative bacteria

Figure 1. Structure of AR-2126



- AR-2126 demonstrated **potent *in vitro* activity** [1]

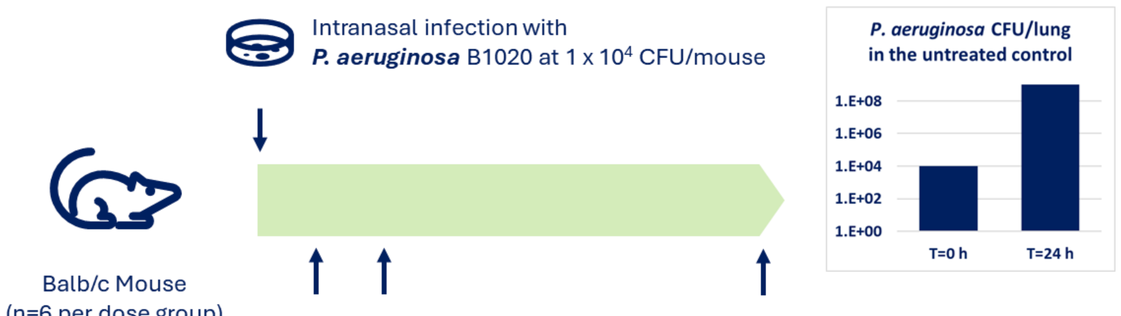
MIC$_{50/90}$	AR-2126 ID CAMHB	Cefider-ocol ID CAMHB	Cefepime CAMHB	Ceftazi-dime CAMHB	Ceftolo-zane-Tazobactam CAMHB	Meropenem / Imipenem[a] CAMHB
P. aeruginosa (n=25)	0.25 / 2	0.5 / 2	2 / 16	4 /32	0.5 / 4	4 / 16
A. baumannii (n=13)	0.12 / 0.5	0.12 / 1	8 / 16	8 / 16	1 / 2	0.5 / 1
B. cepacia complex (n=20)	≤0.03 / 0.12	≤0.03 / 0.12	16 / 32	4 / 8	4 / 16	8 / 32

1, Paukner S, Wicha W. Abstract EA043. ESCMID-ASM 2025, Porto, Portugal

- AR-2126 is intended for **IV and inhalation** treatment
- *In vivo* **PoE** demonstrated for **aerosolized AR-2126** in the **carbapenem-resistant *P. aeruginosa*** lung infection model following inhalation [1]
- This study evaluated the *in vivo* efficacy and PK in mice following SC administration

MATERIALS:

***In vivo* PoE in a carbapenem-resistant *P. aeruginosa* lung infection model in mice**



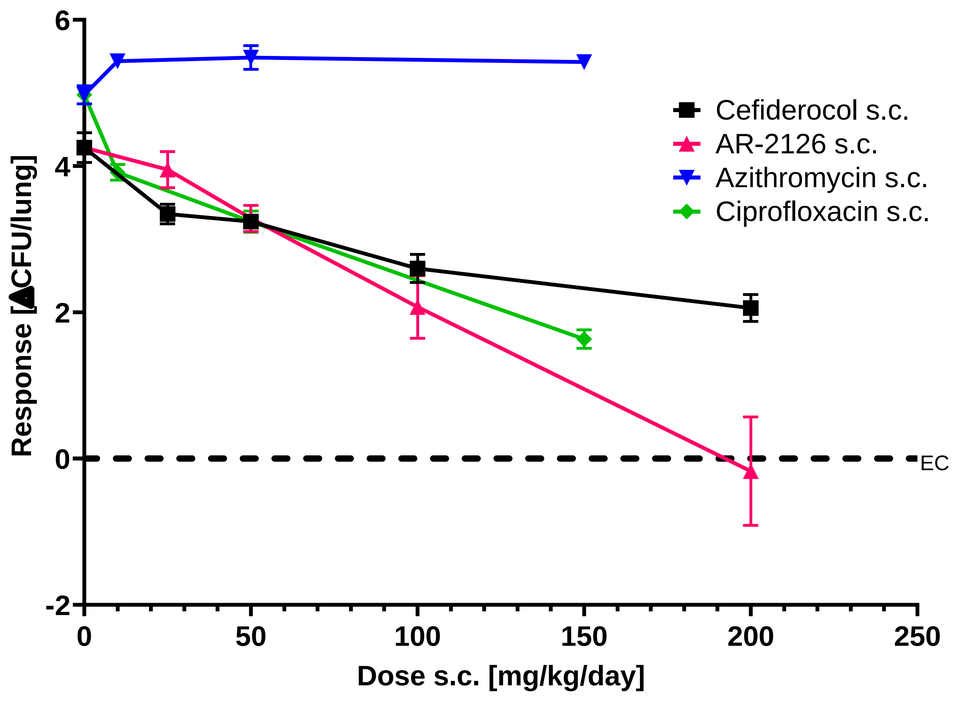
P. aer. B1020	MIC (mg/L)
AR-2126	0.25
Cefiderocol	0.5
Azithromycin	>32
Ciprofloxacin	1
Meropenem	16

RESULTS:

***In vivo* results**

- ***In vivo* proof of efficacy (PoE)** was demonstrated in a murine **carbapenem-resistant *P. aeruginosa* lung infection model**
- When compared with the untreated control, 100 and 200 mg/kg/day **AR-2126** resulted in **a ΔCFU/lung of -2 and -4 log10,**
- ΔCFU/lung by **SC cefiderocol** at 200 mg/kg/day was at max. **-2 log10**
- Azithromycin and ciprofloxacin served as controls (Figure 2A)

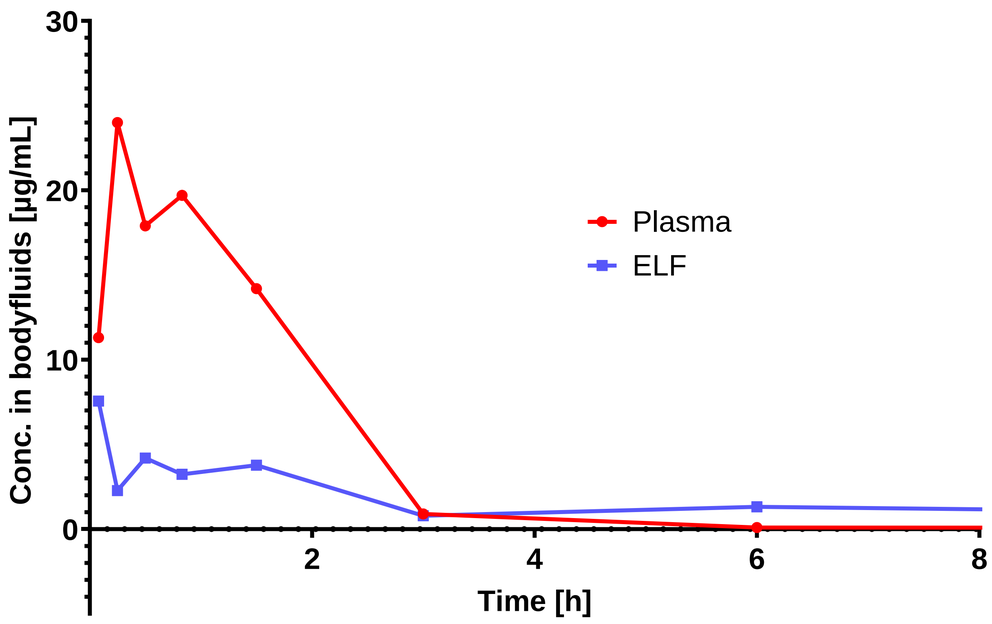
Figure 2A. *In vivo* activity of AR-2126 (SC) and comparators in the carbapenem-resistant *P. aeruginosa* B1020 lung infection model



Pharmacokinetics

- In the PK analysis, AR-2126 maintained a T>MIC of approximately 5 hours in both, plasma and ELF, following a 15 mg/kg SC dose which already started to translate into efficacy
- C_{max} in plasma and ELF were 24 µg/mL and 7.56 µg/mL, respectively
- Elimination rate from ELF follows the rate in plasma

Figure 2B. PK of AR-2126 (15 mg/kg SC) in infected mice in the same model assessed in plasma and epithelial lining fluid (ELF, n=3 per time point)



CONCLUSIONS:

- The novel siderophore cephalosporin AR-2126 showed significant *in vitro* and *in vivo* efficacy against carbapenem-resistant *P. aeruginosa*, a top priority pathogen as defined by the WHO and CDC
- This study in mice infected with lethal doses of *P. aeruginosa*, indicated a favorable outcome for AR-2126 (SC), and demonstrated promising PK/PD correlations
- These results position AR-2126 as a strong candidate for further development aimed at addressing urgent medical needs in conditions such as ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), and bronchiectasis linked to *P. aeruginosa* infections