Poster # P1994

In vivo efficacy of TP-6076 in murine thigh and lung infection models challenged with *Acinetobacter baumannii*

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Introduction and Purpose

TP-6076 is a novel, fully synthetic tetracycline antibiotic developed for the treatment of life-threatening bacterial infections. It has demonstrated *in vitro* potency against carbapenem-resistant *Acinetobacter baumannii* (CRAB), with MIC_{90} value of 0.063 mg/L.[1-2] The current study examined the *in vivo* efficacy of TP-6076 in murine thigh and lung infection models challenged with *A. baumannii.*

Methods

Minimum inhibitory concentration (MIC) assay

The *in vitro* activity of TP-6076 against *A. baumannii* clinical isolates was tested in MIC assays conducted according to CLSI guidelines.[3] A total of 9 *A. baumannii* isolates were selected for TP-6076 *in vivo* efficacy studies.

Mouse infection models

Female CD-1 mice (22 ± 2 g) were quarantined at least 3 days prior to use and housed 5 per cage in accordance with approved IACUC protocols. Animals were rendered neutropenic by intraperitoneal injection of cyclophosphamide at 150 mg/kg (Day -4) and 100 mg/kg (Day -1) pre-infection. In the thigh infection model, mice were inoculated intramuscularly with 0.1 mL of the designated strain (6 log_{10} colony forming units (CFUs)). While, for the lung infection model, mice were inoculated intranasally (7 log_{10} CFUs).

Pharmacokinetics

Pharmacokinetics of TP-6076 were determined in the murine thigh infection model. The doses ranged from 0.25 to 40 mg/kg, and were administered by a single intravenous (IV) bolus injection. Both plasma and ELF PK samples were collected up to 24 hours after dosing, and TP-6076 concentrations were determined by a validated LC-MS/MS method. The AUCs for TP-6076 concentration-time profiles were calculated using non-compartmental analysis.

In vivo efficacy

For *in vivo* efficacy studies, TP-6076 was administered intravenously 2 hours post-infection at various dose levels. Mice were euthanized via CO_2 inhalation at 2 hours (baseline) or 26 hours post-infection, and CFUs in tissues were determined. A sigmoid model was used to describe the relationship between AUC and the average change of tissue bacterial burden (equation is shown below). Both plasma and ELF AUCs were evaluated in the lung infection model, while only plasma AUCs were evaluated in the thigh infection model.

$$E = E_0 - E_{max} \times X^H / (IX_{50}^H + X^H)$$

- E_0 is the top of the curve
- E_{max} is the maximum effect
- X is the plasma/ELF AUC_{24h}
- IX_{50} is the required value of PK/PD index to achieve 50% of the E_{max}
- H is the Hill slope of the curve

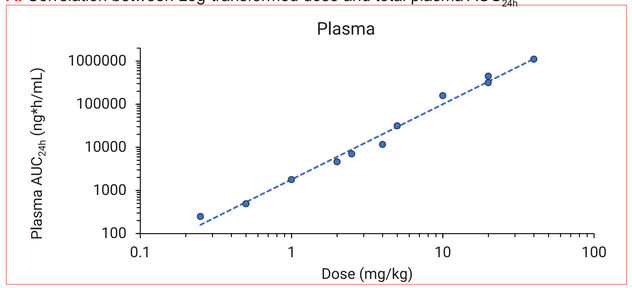
Results

Table 1. TP-6076 MICs for the tested *A. baumannii* strains

AB strains	TP-6076 MIC (mg/L)
AB1709	0.0078
AB3116	0.0312
AB3117	0.0625
AB3118	0.0312
AB3119	0.0156
AB3120	0.0156
AB3121	0.25
AB3122	0.0312
AB3123	0.0625

Figure 1. Nonlinear Pharmacokinetics for TP-6076 in female CD-1 mice

A. Correlation between Log-transformed dose and total plasma AUC_{24h}



B. Correlation between Log-transformed dose and ELF AUC_{24h}

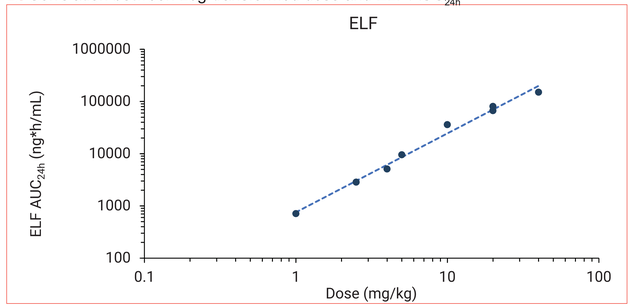
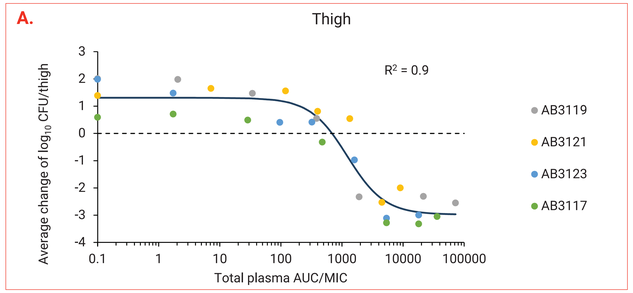


Figure 2. *In vivo* exposure-response relationship of TP-6076 against *A. baumannii*

A.



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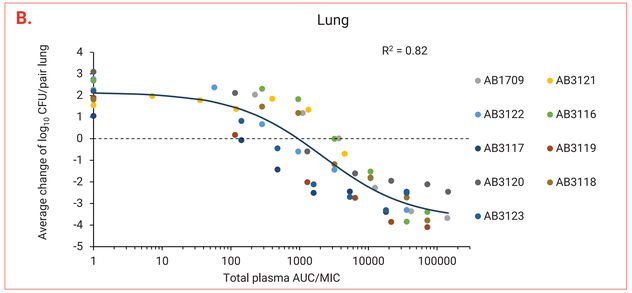
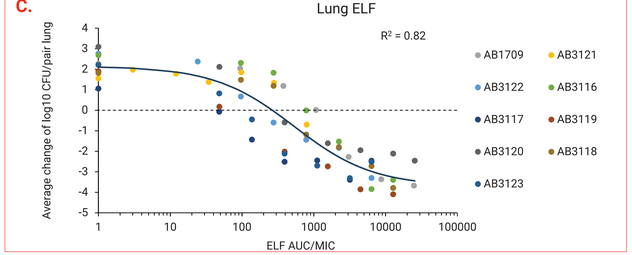


C.



Conclusions

- Nonlinear TP-6076 pharmacokinetics was observed in female CD-1 mice with single IV bolus injection. The increase in total plasma/ELF AUCs was more than dose-proportional over the 0.25 to 40 mg/kg dose range. The relationship between Log-transformed plasma/ELF exposures and dose levels can be described by a linear equation, which was used to predict AUCs for other dosing levels within the range.
- TP-6076 demonstrated potent in vivo efficacy against *A. baumannii* in murine neutropenic thigh/lung infection models. Full exposure-response relationships were obtained in both models, and the profiles were comparable.
- Since the determination of TP-6076 free fraction has proven challenging, only total plasma and ELF exposures were used in the current study. A better understanding of TP-6076 protein binding relationships in mouse and human plasma is needed before the results can be used to predict outcomes in patients.

Disclaimer

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References

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2. C. Fyfe, R. Barry, B. Close, K. Kerstein, P. Nordmann, J. Newman. 2018. TP-6076 is active against bacterial isolates carrying emergent resistance types. ASM Microbe, Atlanta, Georgia.
3. CLSI 2017. Performance standards for antimicrobial susceptibility testing, 27th edition, supplement M100. Clinical and Laboratory Standards Institute.