Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of a Novel Aminomethylcycline Antibiotic, KBP-7072, in the Neutropenic Murine Pneumonia Model Against S. aureus (SA) and S. pneumoniae (SPN)

Alexander J. Lepak1, Miao Zhao1, Qingmei Liu2, Ping Wang2, Yanli Wang2, Justin C. Bader3, Paul G. Ambrose3, and David R. Andes1

(1)Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI; (2)KBP Biosciences Co. Ltd., Jinan, China; (3)CIDP, Schenectady, NY

ABSTRACT

Background: KBP-7072 is a novel aminomethylcycline antibiotic with broad-spectrum activity that includes organisms with drug resistance to beta-lactams and tetracyclines. We examined its PK/PD in vivo dose-response relationships using the neutropenic murine pneumonia model to define therapeutic targets and susceptibility.

Methods: The PK/PD of KBP-7072 was evaluated in mice following intraperitoneal (IP) and subcutaneous (SC) administration. KBP-7072 concentrations were determined by GLC methods. PKs and ELF PKs were determined after SC dosing (range 1-5 mg/kg). Three groups of mice were infected with each of the strains included in the study. Animals were euthanized and lungs aseptically removed, homogenized, and plated for CFU determination. No treatment and zero-hour controls were included. Therapeutic plasma AUC and ELF AUC targets for stasis, 1-log kill, and 2-log kill were determined in the Neutropenic Murine Pneumonia Model using efficacy and safety analyses.

Results: KBP-7072 PK in mice was linear over the dose range (R2 0.999) and demonstrated enhanced ELF penetration (>100%) when examined in relation to free plasma drug levels. The median plasma free drug AUC/MIC targets for stasis, 1-log kill and 2-log kill was 1.1, 3.7, and 13.1 for SPN. The ELF targets for these ranges were 4.4 and 18.8.

Conclusions: KBP-7072 PK/PD studies in mice demonstrated dose-response relationships using the PK/PD model. Therapeutic targets were identified for the in vivo PK/PD relationship between KBP-7072 drug exposures and treatment effect using a R2=0.89, SPN R2 0.80). Median static, 1- and 2-log kill AUC/MIC values are shown in the table.

Table 2. PK/PD target exposures associated with net stasis, 1-log kill and 2-log kill

RESULTS (cont.)

Plasma and ELF pharmacokinetics of KBP-7072 in mice

In vivo PK/PD studies for KBP-7072 against select SA strains

In vivo PK/PD studies for KBP-7072 against select SPN strains

BACKGROUND

• KBP-7072 is a novel aminomethylcycline antibiotic with broad-spectrum activity that includes organisms with drug resistance to beta-lactams and tetracyclines.

• Previous studies with the tetrasaccharide class, including aminomethylcyclines, have demonstrated time-dependent activity with prolonged post-antibiotic effects.

• This study was designed to investigate the pharmacokinetics of KBP-7072 in vivo dose-response studies: Dose-response experiments using the pneumonia model were performed for all strains. The dose range was between those measured kinetics and linear extrapolation for dose levels greater than or less than the highest and lowest dose values with kinetic measurements. The protein binding rate in murine pneumonia model (77.5% bound) was used for all dose levels. The PK/PD relationship between KBP-7072 drug exposures and treatment effect using a R2=0.89, SPN R2 0.80). Median static, 1- and 2-log kill AUC/MIC values are shown in the table.

METHODS

Plasma and ELF pharmacokinetics of KBP-7072 in mice

In vivo PK/PD studies for KBP-7072 against select SA strains

In vivo PK/PD studies for KBP-7072 against select SPN strains

RESULTS

Plasma and ELF pharmacokinetics of KBP-7072 in mice

In vivo PK/PD studies for KBP-7072 against select SA strains

In vivo PK/PD studies for KBP-7072 against select SPN strains

Table 2. PK/PD target exposures associated with net stasis, 1-log kill and 2-log kill

<table>
<thead>
<tr>
<th>Organism Group</th>
<th>Dose 24h (mg/kg)</th>
<th>AUCf/MIC (mg*h/L)</th>
<th>AUCt/MIC (mg*h/L)</th>
<th>1-log10kill</th>
<th>2-log10kill</th>
<th>24h Plasma AUC/MIC (mg*h/L)</th>
<th>24h ELF AUC/MIC (mg*h/L)</th>
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<tr>
<td>SA</td>
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1) KBP-7072 demonstrated potent in vivo and in vitro activity against a diverse group of SA strains, including MRSA, and SPN strains, including those with penicillin and vancomycin resistance.

2) The PK/PK index AUC/MIC was a robust predictor of therapeutic efficacy with R² = 0.80.

3) The median plasma free drug AUC/MIC targets for stasis, 1-log kill and 2-log kill were 1.7, 4.4, and 7.9.

4) The median plasma free drug AUC/MIC targets for stasis, 1-log kill and 2-log kill were 1.7, 4.4, and 7.9.

5) The median plasma free drug AUC/MIC targets for stasis, 1-log kill and 2-log kill were 1.7, 4.4, and 7.9.

6) These studies should prove very useful for optimization of KBP-7072 dosing strategies and examining preliminary breakpoints.