Ascending Dose Safety, Tolerability, and Pharmacokinetics of KBP-7072, a Novel Third Generation Tetracycline

Fred Yang PhD1, Yanli Wang MS2, Ping Wang MS2, Mei Hong MS2, Vincent Benn PhD1
KBP Biosciences USA Inc. Princeton NJ USA1, KBP Biosciences Co. Ltd. Jinan China2

ABSTRACT

Ascending Dose Safety, Tolerability, and Pharmacokinetics of KBP-7072, a Novel Third Generation Tetracycline

BACKGROUND
KBP-7072 is a novel broad spectrum aminomethylcycline antibiotic exhibiting broad-spectrum activity against Gram-positive and Gram-negative bacteria including multiring resistant isolates and strains. Previously, KBP Biosciences completed a single ascending dose (SAD) study of KBP-7072 resulting in approximately linear pharmacokinetics (PK) and good tolerability up to 300 mg in healthy adults.

METHODS
This was a randomized, single-blind, placebo-controlled, sequential parallel-group, multiple ascending dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of KBP-7072 in healthy adults. Safety, tolerability, and PK were evaluated for each cohort.

RESULTS
16 subjects (male: 87.5%; 18-55 years of age) were enrolled including 8 in each of the two dose escalation cohorts (100 mg QD and 200 mg QD). After the results of the first two cohorts (100 mg QD and 200 mg QD) were analyzed, it was determined that the therapeutic dose of KBP-7072 was likely to be less than 200 mg/day. All treatment-emergent adverse events (TEAEs) were of mild intensity, resolved without intervention, and most TEAEs were assessed as either unrelated or probably unrelated to treatment.

CONCLUSIONS
This study demonstrated that KBP-7072 was safe and generally well-tolerated at doses up to and including 200 mg QD.

Pharmacokinetic Results
Figure 1 displays Day 1 mean KBP-7072 plasma concentrations vs. time for each of the 2 doses, plotted on a semi-log scale. Figure 2 shows corresponding Day 10 plasma concentration profiles.

Figure 1. Day 1 Mean (SD) KBP-7072 Plasma Concentrations vs. Time by Treatment, PK Population

Figure 2. Day 10 Mean (SD) KBP-7072 Plasma Concentrations vs. Time by Treatment, PK Population

PK parameters for KBP-7072 on Day 1 are shown in Table 1. Corresponding Day 10 PK parameters are shown in Table 2.

Table 1. Day 1 KBP-7072 Plasma PK Parameters by Treatment, PK Population

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Statistic</th>
<th>KBP-7072 100 mg QD (N = 6)</th>
<th>KBP-7072 200 mg QD (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>4038 (1159)</td>
<td>9224 (2798)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>415.7 (68.13)</td>
<td>846.0 (397.6)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>Median (range)</td>
<td>1.50 (1,4)</td>
<td>2.0 (1,4)</td>
</tr>
</tbody>
</table>

Table 2. Day 10 KBP-7072 Plasma PK Parameters by Treatment, PK Population

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Statistic</th>
<th>KBP-7072 100 mg QD (N = 6)</th>
<th>KBP-7072 200 mg QD (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>8274 (1440)</td>
<td>3563 (875)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>1377.5 (378.5)</td>
<td>2741.0 (496.0)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>Median (range)</td>
<td>2.0 (1,4)</td>
<td>3.0 (1,4)</td>
</tr>
</tbody>
</table>

PK-7072 was well-tolerated at a dose of 100 mg QD and generally tolerated at a dose of 200 mg QD for 10 days. Four subjects in the 200 mg QD cohort had elevated liver enzymes that were considered clinically significant by the Investigator, although one of these was not related to treatment. There were no clinically significant changes or trends in other safety assessments.

CONCLUSIONS
No serious adverse events were reported. Elevated alanine aminotransferase was reported in 4 subjects (all in the 200 mg QD cohort) who were asymptomatic and recovered without intervention. PK data suggests that exposure is approximately dose proportional.

Methods
This was a randomized, single-blind, placebo-controlled, sequential parallel-group, multiple ascending dose (MAD) study to evaluate the safety, tolerability, and pharmacokinetics (PK) of KBP-7072 in healthy adults. Four cohorts were planned with 8 subjects (6 randomized to active drug, 2 randomized to placebo) in each cohort in order to evaluate KBP-7072 100 mg QD, 200 mg QD, 300 mg QD, and 200 mg BID for 10 days. Dose escalation stopped following completion of the 200 mg QD cohort. Safety, tolerability, and PK were evaluated for each cohort.

RESULTS
Study Completion
A total of 16 subjects were enrolled in the study including 8 subjects (6 randomized to active drug, 2 in placebo) in each of the two dose escalation cohorts. Fourteen (14) subjects completed the study.

Demographics
Subjects were representative of a healthy adult male (N=14, 87.5%) and female (N=2, 12.5%) population ranging from 23 to 51 years of age. Overall mean (standard deviation [SD]) age was 35.0 (9.77) years and mean (SD) BMI was 26.45 (1.943) kg/m<sup>2</sup>. Racial composition was 90.6% Caucasian and 7 (43.8%) Black/African-American.

Safety Results
A total of 15 treatment-emergent AEs (TEAEs) were reported among 6 subjects during the study and all occurred in the 200 mg QD dosing cohort. Of the 15 TEAEs, 4 were assessed as probably related to treatment and 3 were assessed as related to treatment. All other TEAEs were assessed as probably not related or not related. All TEAEs were of mild to moderate intensity.

The most commonly reported TEAE was elevated liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and elevated lactate dehydrogenase (LDH). No elevation of total bilirubin was observed in the study. The elevated liver enzymes occurred in 4 subjects in the 200 mg QD dosing cohort and were related to treatment, except for one subject who consumed alcohol during the study. In addition, all serum aminotransferase elevations were mild in intensity, except one moderately elevated AST level. All 4 subjects were asymptomatic and recovered without intervention.

With the exception of the investigations noted for elevations of ALT, AST and LDH, there were no clinically significant findings from clinical laboratory tests (hematology, chemistry and urinalysis), vital signs, ECGs and physical examinations.

No deaths or SAEs occurred in the study.