INTRODUCTION

TNP-2092 (CB29-2092) is a non-cleavable, hydrophobic diketopiperazine antibiotic composed of a rifampin and a quinolone pharmacophore. Previous studies indicated that TNP-2092 is a potent and balanced inhibitor of bacterial RNA polymerase, DNase, gyrase and aminoglycoside phosphotransferase. TNP-2092 exhibits low plasma exposure, but has an elevated concentration within gastric mucosal layers that is in excess of its MIC against H. pylori. TNP-2092 exhibits high exposure in the reduced form of the H. pylori bacterial cells to below the detection limit of 7 days after treatment of TNP-2092 as a microarray appeared to be equally efficacious as PrevPac and superior to Helicobacter pylori in mouse model of infection. Reviewers.

MATERIALS & METHODS

Animals: Female C57BL/6J mice, 5-6 weeks of age and 18-22 grams in weight.

Bacterial strain: H. pylori SS1 (CagA+, VacA+).

Infection: All animals were infected prior to infection with 10^7 CFU of the H. pylori SS1 culture twice at 48 hr intervals.

Test articles: TNP-2092 was administered at 45 mg/kg and Clarithromycin + Amoxicillin + Omeprazole (TNP-2092 + Clarithromycin 10 mg/kg + Amoxicillin 20 mg/kg + Omeprazole 10 mg/kg) (TNP-2092) was administered at 10 mg/kg. Rifampin was administered at 45 mg/kg.

Treatment: Infected mice were treated with the test article for 7 days, starting the day after the last administration of the SS1 culture. The control group was infected with the SS1 culture.

Assessment: The gastric mucosal lining was histologically evaluated, and the stomach was isolated and homogenized, serially diluted and plated on solidified agar for H. pylori detection.

RESULTS

TNP-2092 exhibited high exposure in the gastric mucosal layer with drug levels in excess of the MIC against H. pylori 24-36 hours after oral administration at 45 mg/kg. This high exposure resulted in the reduction of the H. pylori bacterial cells to below the detection limit after 7 days of treatment with TNP-2092 as a miniarray appeared to be equally efficacious asPrevPac and superior to Helicobacter pylori in mouse model of infection.

PHARMACOKINETICS OF TNP-2092

In mice infected with C57BL/6J mice following oral administration

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tmax (h)</th>
<th>T1/2 (h)</th>
<th>Area Under the Curve (AUC) (h)</th>
<th>Maximum plasma concentration (Cmax) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNP-2092</td>
<td>2.00</td>
<td>3.25</td>
<td>1.22</td>
<td>0.90</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2.00</td>
<td>3.25</td>
<td>1.22</td>
<td>0.90</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>2.00</td>
<td>3.25</td>
<td>1.22</td>
<td>0.90</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>2.00</td>
<td>3.25</td>
<td>1.22</td>
<td>0.90</td>
</tr>
</tbody>
</table>

DISCUSSION

The results of this study indicate that TNP-2092 is a potent and balanced inhibitor of bacterial RNA polymerase, DNase, gyrase and aminoglycoside phosphotransferase. TNP-2092 exhibits low plasma exposure, but has an elevated concentration within gastric mucosal layers that is in excess of its MIC against H. pylori. TNP-2092 exhibits high exposure in the reduced form of the H. pylori bacterial cells to below the detection limit of 7 days after treatment of TNP-2092 as a miniarray appeared to be equally efficacious as PrevPac and superior to Helicobacter pylori in mouse model of infection.

CONCLUSION

TNP-2092 is a potential new therapeutic for the treatment of Helicobacter pylori infection.