Effect of intravenous rifampin as an organic anion transporting polypeptide 1B1/1B3 inhibitor on the pharmacokinetics of oral trazpiroben (TAK-906) in healthy adults

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Introduction

Gastroparesis is a chronic, morbid disorder characterized by delayed gastric emptying in the absence of mechanical obstruction.1,2 General symptoms include early satiety, postprandial fullness, nausea, vomiting and bloating.3 Despite the associated patient burden, current therapeutic options for gastroparesis are limited, and there are no approved pharmaceutical interventions for the long-term treatment of the disease.4,5 Previous studies have suggested that gastric emptying in vivo primarily occurs via the organic anion transporting polypeptide (OATP) 1B1 and 1B3,6 which is known as an important mediator of drug-drug interactions (DDIs).7

Participants with gastroparesis and a history of gastroparesis episodes, uncontrolled body weight, or concomitant medications known to affect the disposition of the study drugs were not eligible for this study.

Aims

• To evaluate the impact of rifampin, a potent OATP1B1/1B3 inhibitor, on the single-dose pharmacokinetics (PK) and safety profile of trazpiroben.
• To assess the potential utility of coproporphyrin (CPI) and CPIII as biomarkers of inhibition.

Methods

Study design

This was a phase 1, open-label, randomized, two-way crossover study conducted in healthy adults (NCT04121078, Figure 1). Participants were randomized 1:1 into two treatment sequences (AB or BA). Participants received each treatment on one occasion. Treatment A consisted of a single oral dose of trazpiroben 25 mg. Treatment B consisted of a single oral dose of trazpiroben 25 mg immediately following a single 30-minute IV dose of rifampin 600 mg.

PK sampling and safety monitoring

PK samples were collected using a pharmacokinetic sampling pattern at specified time points following dose administration (Table 1). Participants received each treatment on one occasion.

Safety assessment

Safety monitoring included laboratory, vital signs, clinical examinations, 12-lead electrocardiography, and symptom diaries.

Statistical analysis

• To determine the effect of rifampin on trazpiroben and CPII PK parameters, an analysis of variance (ANOVA) was performed on the natural log-transformed AUC and Cmax for trazpiroben, and CPII.• Geometric mean ratios (GMRs; trazpiroben with rifampin relative to trazpiroben alone) and their associated 90% confidence intervals (90% CIs) were calculated from the ANOVA model parameters. LSM, least-squares means; MSE, mean square error.

Results

Participant disposition and baseline characteristics

In total, 12 participants (88% male) were included in the study and had a mean (standard deviation) age of 37.3 (10.8) years and a BMI of 28.9 (2.3) kg/m2. There were no statistically significant differences or day-to-day variations on any polysubstance drugs or demographic characteristics between study groups.

Pharmacokinetics of trazpiroben and CPII

Following administration of the study drugs, all 12 participants had an evaluable PK profile and were included in the analysis.

• The median plasma trazpiroben concentrations were highest following treatment with trazpiroben and rifampin (AUC and Cmax), followed by trazpiroben alone (AUC and Cmax), and then rifampin alone (AUC and Cmax).
• Following co-administration of trazpiroben and rifampin, the geometric mean plasma trazpiroben AUC and Cmax values were 61% and 23% higher, respectively, in participants treated with trazpiroben alone (10.60 ng*h/mL and 1.20 ng/mL, respectively, Figures 5A and B). Co-administration of trazpiroben and rifampin also increased trazpirbene CPIII AUC and Cmax compared with trazpiroben alone, resulting in a GMR of 0.98 (CV% of values: 0.16 (0.07-0.59) and 0.17 (0.10-0.39), respectively).
• Similarly, plasma CPII AUC and Cmax were higher in participants treated with trazpiroben and rifampin than with trazpiroben alone, with respective GMR values of 15.98 (2.53-98.40) and 16.38 (5.47-50.71) (Figure 3).

Safety

In total, 12 participants were included in the safety analysis. There were no deaths, serious adverse events or discontinuations due to adverse events (AEs) during this study. One participant (8%) reported a headache, with an abnormal pain, sensory disturbances and skin congestion was reported by one participant (8%).

Table 1: Geometric LSM and GMR of trazpiroben PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM (ng*h/mL)</th>
<th>GMR (90% CI)</th>
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<tbody>
<tr>
<td>AUC</td>
<td>101.7 (76.0-139.3)</td>
<td>1.64 (1.17-2.30)</td>
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<tr>
<td>Cmax</td>
<td>61.94 (39.99-96.60)</td>
<td>1.07 (0.79-1.46)</td>
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Table 2: Baseline-adjusted plasma CPI parameters for CPI and CPIII

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<tr>
<td>CPIII</td>
<td>5.7 (2.6-12.1)</td>
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Conclusions

• Trazpiroben exposure increased following co-administration with rifampin, an OATP1B1/1B3 inhibitor, compared with trazpiroben alone, confirming trazpiroben as a substrate of OATP1B1/1B3.
• Both treatments were well tolerated by healthy participants in this study.

References

3. Jatinder K Mukker,1 George Dukes,1 Max Tolkoff,1 Lisi Wang,1 Cristina Almansa,2 Susanna Y Huh,1 Mitsubishi Nishihara,2 Diane Ramsden,1 Chunlin Chen1

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Disclosures

Adverse events are defined according to the World Health Organization (WHO) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A participant may have two or more adverse events. AEs are presented in terms of the organ system involved.

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Plasma pharmacokinetics of CPI and CPIII

Both treatments were well tolerated by healthy participants in this study.

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