TP-434 is a novel broad-spectrum fluoroquinolone antibiotic with potent activity and efficacy against multidrug-resistant (MDR) gram-negative and gram-positive aerobic and anaerobic pathogens, including Enterobacteriaceae expressing extended-spectrum β-lactamases (ESBL) and/or carbapenemases, MRSA, and VRE. It has limited activity against Pseudomonas spp. TP-434 is currently being evaluated intravenously (IV) in a phase 1 study for the treatment of commonly-complicated intra-abdominal infections. The current phase 1 study investigated the safety, tolerability and pharmacokinetic (PK) profile of TP-434 when administered orally once multiple daily doses.

Methods: Unformulated TP-434 was administered orally as single daily doses of 50, 100, 200 and 300 mg in a gelatin capsule for 7 days. Routine safety assessments and blood samples for PK analyses were obtained. The 100 mg dose was also administered as a single dose in both the fasting and fed states to determine the effect of food on the PK parameters. One group received 100 mg twice daily for 7 days. Results: AUC and C_max are listed below; T_max was 12-21 hours on Day 1 and 17-36 hours on Day 7.

Demographics: Mean (range) and Safety: No significant safety signals were identified following review of clinical chemistry, hematology, urinalysis, coagulation, liver function, renal function, vital signs, electrocardiograms and adverse events. Adverse Events Reported by 2 or More Subjects in any Dose Group: TP-434 is orally bioavailable, indicating the potential for IV/oral step-down therapy, or oral therapy alone. Adverse Events: The study was conducted at a single phase 1 unit in the UK with healthy subjects. For all dosing cohorts, TP-434 was administered as simple powder in hard gelatin capsules. TP-434 is currently being evaluated intravenously (IV) in a phase 2 study for the treatment of complicated intra-abdominal infections. Results: AUC and C_max are listed below; T_max was 12-21 hours on Day 1 and 17-36 hours on Day 7.

PHARMACOKINETICS, SAFETY AND TOLERABILITY OF A NOVEL FLUOROCYCLINE, TP-434, FOLLOWING MULTIPLE DOSE ADMINISTRATION

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Methods

Dose Group (n=6) C_max (ng/mL) AUCinf (ng·h/mL) 1/2 (hr) 100 mg q12h 200 ± 22 1001 ± 224 10 ± 2 164 ± 39 3079 ± 703 18 ± 3 300 mg q24h 206 ± 38 3154 ± 981 14 ± 3 342 ± 81 9511 ± 2450 36 ± 8 400 mg q24h 158 ± 101 3183 ± 910 13 ± 2 * Value reported is the AUCinf from the time of the last dose administered. For 100 mg q12h Dose Group, only 12 hours of dosing were included in the calculation.

Safety Findings: No safety signals were identified following review of clinical chemistry, hematology, urinalysis, coagulation, liver function, renal function, vital signs, electrocardiograms and physical examination findings.

Conclusions

• TP-434 is orally bioavailable and plasma levels likely to be therapeutic were observed following doses that were generally well tolerated in healthy subjects.
• Oral bioavailability of TP-434 is reduced following administration to fed subjects (AUCinf reduced ~62%).
• Urine concentrations of TP-434 above MICs for the majority of urinary tract pathogens were observed following oral administration of a single 100 mg dose.
• No significant safety signals were observed in this phase 1 study.

Day 1

Day 7

TP-434

Dose Group

100 mg q12h

300 mg q24h

400 mg q24h

100 mg q12h

300 mg q24h

400 mg q24h

Food Effect

TP-434 Multiple Dose

Age (yrs) 27.8 (18-44) 25.1 (18-34) 27.5 (18-47) 33.5 (18-47) 32.7 (22-46) 29.6 (22-46) Height (m) 1.8 (1.7-1.9) 1.8 (1.6-2.0) 1.8 (1.7-1.9) 1.8 (1.7-1.9) 1.8 (1.7-1.9) 1.8 (1.7-1.9) Weight (kg) 72.5 (69.0 - 84.0) 71.9 (60.4-79.3) 77.7 (74.2-83.6) 75.9 (71.4-82.1) 78.8 (69.3-86.4) 71.9 (69.0-86.4) Gender (% M) 100 100 100 100 100 100

No safety signals were observed.

• TP-434 is orally bioavailable, indicating the potential for IV/oral step-down therapy, or oral therapy alone.

Effect of Food on the Pharmacokinetics of TP-434

TP-434 Following Oral Administration of 100 mg

Conclusions

Urine Concentrations of TP-434 Following Oral Administration of 100 mg

Pharmacokinetics of TP-434 Following Multiple Dose Administration

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