ABSTRACT

Objectives: PTK 0796 (omadacycline) is a first in class aminomethylenecycline antibiotic with activity against Gram-positive, Gram-negative, aerobic and anaerobic, and atypical bacteria. PTK 0796 is being developed for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community Acquired Bacterial Pneumonia (CABP) with once daily IV followed by oral dose administration. The bioavailability of two oral formulations (tablets) relative to the IV was investigated to select an optimal oral formulation for Phase 3 Studies. An oral solution was also included as an exploratory investigation.

Methods: This was an open-label, randomized, four period, complete cross-over study in healthy subjects with four treatment conditions (PTK0796 100 mg IV infusion, two 300 mg tablet formulations with different dissolution profiles, and a 300 mg oral solution for comparison to the tablets). A total of 24 subjects between the ages of 18-50 were randomized to the treatment groups. Routine safety and tolerability assessments were performed. Analysis of plasma PTK 0796 concentration was performed using a validated LC/MS/MS method.

Results: Twenty subjects completed all periods of the study. No SAEs were reported and only three AEs of mild intensity (dizziness, nausea, vomiting) were experienced by three subjects during the study. There were no clinically relevant changes in laboratory tests following dose administration. Among the oral formulations studied, the oral solution had the fastest rate of absorption as evident by the earlier Tmax. Both 300 mg tablet formulations produced equivalent total exposure relative to the 100 mg IV dose (9960 (690 ng/mL)*h) with geometric mean ratios of AUCinf (90% CI) of 1.00 (0.93,1.07) and 0.96 (0.90,1.03), respectively. The absolute bioavailability of the tablets was approximately 34%. Compared to the tablets, the oral solution yielded 19% higher total systemic exposure. The inter-subject variabilities were consistent among the oral formulation groups (~20-25%).

Conclusions: The two 300 mg tablet formulations of PTK 0796 produced equivalent total exposure as measured by AUC relative to the 100 mg IV dose. Single doses of PTK0796 administered orally (as different formulations) and 24 healthy subjects were enrolled. Pharmacokinetic assessments were conducted for up to 48 hours after each administered dose of PTK 0796. A washout period of at least 7 days separated each treatment period. Subjects underwent study completion evaluations and were discharged from the study, after 1 week (± 1 day) from the last drug administration. All completed subjects with evaluable pharmacokinetic (PK) parameter data were included in the pharmacokinetic data analysis. Routine safety and tolerability assessments were performed.

INTRODUCTION

PTK 0796 (omadacycline) is a first in class aminomethylenecycline antibiotic with activity against Gram-positive, Gram-negative, aerobic and anaerobic, and atypical bacteria. PTK 0796 is being developed for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community Acquired Bacterial Pneumonia (CABP) with once daily intravenous followed by oral dose administration. The bioavailability of two oral tablet formulations relative to the intravenous was investigated to select an optimal oral formulation for Phase 3 Studies. An oral solution was also included in this study as an exploratory investigation.

STUDY DESIGN

This was an open-label, randomized, four period, complete cross-over study in healthy subjects with four treatment which were:

Treatment 1 (T1): PTK 0796 IV 100 mg IV infusion
Treatment 2 (T2): PTK 0796 oral Tablet Formulation 1 (2 x 150mg tablets)
Treatment 3 (T3): PTK 0796 oral Tablet Formulation 2 (2 x 150 mg slower dissolution tablets)
Treatment 4 (T4): PTK 0796 oral 300 mg 3 (x 100 mg IV infusion solution)

24 healthy subjects were enrolled. Pharmacokinetic assessments were conducted for up to 48 hours after each administered dose of PTK 0796. A washout period of at least 7 days separated each treatment period. Subjects underwent study completion evaluations and were discharged from the study, after 1 week (± 1 day) from the last drug administration.

All completed subjects with evaluable pharmacokinetic (PK) parameter data were included in the pharmacokinetic data analysis. Routine safety and tolerability assessments were performed.

RESULTS

The geometric mean ratio for and 90% confidence intervals of PK parameters per treatment comparison are presented in Table 3. The geometric mean ratio and 90% confidence intervals for PK parameters (PK analysis set) are presented in Table 3. The mean (SD) plasma concentration time profiles for the different PTK 0796 treatment are presented in Figure 1. The summary of pharmacokinetic parameters for each dosage form is shown in Table 2. The two tablet formulations were equivalent for exposure (AUCinf) as compared to the IV exposure or each other, but the oral solution yielded 19% higher total exposure (AUCinf) than the tablet formulations.

The summary of pharmacokinetic parameters for each dosage form is presented in Table 2. The two tablet formulations were equivalent for exposure (AUCinf) as compared to the IV exposure or each other, but the oral solution yielded 19% higher total exposure (AUCinf) than the tablet formulations.

SAFETY

No deaths or SAEs were reported in this study. Only 3 mild AEs (dizziness, nausea, and vomiting) were experienced by three subjects during the study. There were no drug-related study discontinuations. A summary of adverse events by preferred term is shown in Table 4.

There were no clinically relevant changes in clinical laboratory tests or physical exam findings. Among vital signs a mild and transient effect on heart rate was noted. In addition a small transient effect on diastolic blood pressure (2-3mmHg) was noted, the interpretation or significance of which is unclear because of the lack of a placebo control group in the study.

CONCLUSIONS

• The two 300 mg tablet formulations of PTK 0796 produced equivalent total exposure as measured by AUC relative to the 100 mg IV dose.
• Single doses of PTK0796 were administered orally (as different formulations) and intravenously were safe and well tolerated in the subjects studied.
• Among the oral formulations studied, the oral solution had the fastest rate of absorption (as evident by the earlier Tmax) and yielded the higher exposure (19% higher AUCinf compared to 100mg IV infusion).