Pharmacokinetics of Omadacycline (PTK0796) in Subjects with Hepatic Impairment

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ABSTRACT

Background Omadacycline (PTK796) is a novel aminomethylcyline that has activity against gram positive, gram negative, anaerobic, and atypical organisms. Potential indications include intravenous and oral therapy of CABP and ABSSSI. This study characterized the pharmacokinetics (PK) of omadacycline in subjects with varying degrees of hepatic impairment.

Methods The study enrolled 18 subjects with various degrees of hepatic impairment (by Child-Turcotte-Pugh score) and 12 healthy subjects to match mild or moderate hepatic impairment subjects. In period 1, the mild hepatic impairment group was given a single dose of omadacycline 100 mg IV; moderate and severe groups were given 50 mg IV. In period 2, mild and moderate groups were given a single oral dose of 300 mg and 150 mg omadacycline, respectively. Plasma PK samples were collected up to 90 hours post-dose, and Child-Turcotte-Pugh score was used to correlate liver function with dose normalized PK exposure. Safety assessments included monitoring of hematology, blood chemistry and urinalysis, vital signs, and physical conditions.

Results Omadacycline was well-tolerated, and exposures were similar between subjects with hepatic impairment and matching healthy subjects. Pooled analysis of dose normalized PK parameters across all study groups after IV dosing showed no clear relationship between exposure and degree of hepatic impairment.

Conclusions Omadacycline exposures were similar in subjects with hepatic impairment, regardless of severity, compared with healthy subjects following IV or oral dosing. No dose adjustment is warranted with hepatic impairment.

STUDY DESIGN

This was an open-label fixed-sequence study in subjects with mild, moderate, and severe hepatic impairment categorized according to the Child-Turcotte-Pugh scoring method and healthy subjects. The groups were matched based on sex, age (±10 years), weight (±10 kg) and smoking status. Peripheral blood samples were collected for determination of plasma omadacycline (OMC) concentrations at specified times up to 96 hours after dose administration.

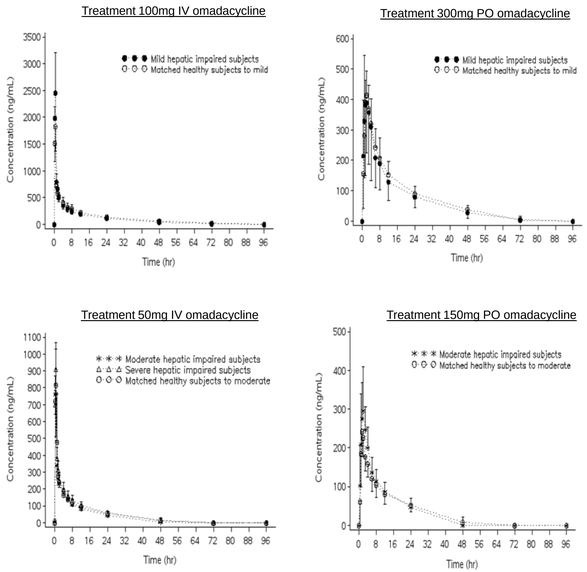
Table 1. Study treatment groups

Group	Liver Impairment	N	Treatment		
			Period 1 Single IV Dose OMC	Washout Period	Period 2 Single PO Dose OMC
Group 1	Child-Turcott Pugh A	6	100mg IV	≥7	300mg PO
Group 2	Child-Turcott Pugh B	6	50mg IV	≥7	150mg PO
Group 3	Child-Turcott Pugh C	6	50mg IV	-	-
Group 4	Health Subjects (Match to Group 1)	6	100mg IV	≥7	300mg PO
Group 5	Health Subjects (Match to Group2)	6	50mg IV	≥7	150mg PO

PHARMACOKINETIC RESULTS

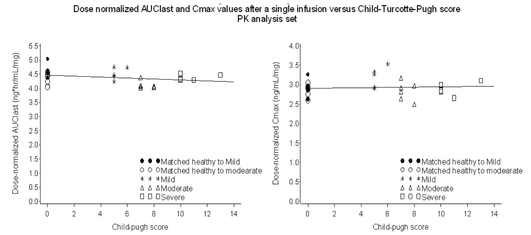
All 30 subjects enrolled in the study were included in the safety analysis set and 28 subjects were included in the PK analysis set. Of the 30 subjects (12 healthy subjects and 18 subjects with hepatic impairment) enrolled, 29 subjects completed the study according to the protocol. A total of 23 subjects received a single oral and single intravenous dose of omadacycline in the study on separate occasions. The six subjects with severe hepatic impairment received only a single intravenous dose of omadacycline by protocol. The mean age of subject was 54.7 years (range: 46-64 years). All subjects were Caucasians. The means of height, weight and BMI across all treatment groups were comparable.

Figure 1. Arithmetic mean (SD) plasma PK concentration-time profiles (per omadacycline dose group)



PHARMACOKINETIC RESULTS (cont.)

Figure 2. Dose-normalized AUClast and Cmax vs. Child-Turcotte-Pugh score, IV infusion. Healthy subjects were assigned a score of zero



Note:Solid line represents regression line.
Log transformed AUClast and Cmax values are plotted.

Table 2. Geometric mean ratio comparison of and 90% confidence intervals for primary PK parameters (hepatic impaired subjects / healthy subjects)

	Group 1[1]		Group 2[2]		Group 3[3]
Parameter (unit)	**100 mg IV OMC**	**300 mg oral OMC**	**50 mg IV OMC**	**150 mg oral OMC**	**50 mg IV OMC**
AUClast (hr*ng/mL)	0.89 (0.70, 1.14)	0.78 (0.42, 1.42)	0.83 (0.70, 0.97)	1.01 (0.71, 1.42)	1.08 (0.88, 1.33)
AUCinf (hr*ng/mL)	0.89 (0.70, 1.12)	1.21 (0.91, 1.60)	0.80 (0.63, 1.01)	*	0.97 (0.79, 1.18)
Cmax (ng/mL)	1.37 (1.03, 1.81)	0.96 (0.62, 1.47)	0.98 (0.81, 1.18)	1.24 (0.94, 1.65)	1.03 (0.86, 1.24)

* AUCinf parameter not available for 150 mg oral omadacycline (OMC) due to insufficient data.
[1] Group 1: mild hepatic impairment vs. Matched healthy subjects
[2] Group 2: moderate hepatic impairment vs. Matched healthy subjects
[3] Group 3: Severe hepatic impairment) vs. healthy subjects matched to group 2, receiving 50 mg IV omadacycline

SUMMARY OF SAFETY RESULTS

- Single doses of omadacycline administered orally and intravenously were safe and well tolerated in both healthy and hepatically impaired subjects in the study.
- There were no clinically relevant changes in clinical laboratory tests or physical examination findings.
- All treatment groups on average experienced a heart rate increase following dose administration. The interpretation or significance of the heart rate effect is unclear due to the lack of placebo control.
- A single subject with moderate hepatic impairment experienced serious adverse events of alcohol poisoning, angina pectoris, hypocalcemia, hypotension and rhabdomyolysis during this study. None of the events was considered related to the study medication.
- One subject was discontinued from the study due to an AE of mild rash, which was considered possibly related to the study medication.
- The commonly reported AEs were headache (13.3%), nausea (6.7%), infusion site pain (6.7%), contusion (6.7%) and dizziness (6.7%).

CONCLUSION

- Overall, omadacycline exposures were similar in subjects with hepatic impairment, regardless of severity, compared with healthy subjects following IV or oral administration.
- The pooled analysis of dose normalized omadacycline AUC or Cmax across all study groups showed no clear relationship between exposure to omadacycline and Child-Turcotte-Pugh score.
- Single doses of omadacycline administered orally and intravenously were safe and well tolerated in the subjects studied.
- The data from this study suggest no dose adjustment for omadacycline in subjects with hepatic impairment is warranted.

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