Pharmacokinetics of [14C]-labeled Omadacycline (PTK 0796) in Healthy Male Subjects.

Sun H, Ting L, Flarakos J, Dole K, Praestgaard J, Kovacs SJ, Stein DS, Sunkara G, Tanaka SK.

Novartis Institute for Biomedical Research, East Hanover, NJ. Paratek Pharmaceuticals Inc. Boston, MA

75 Kneeland Street
Boston, MA 02111
617.275.0040
ktanaka@paratekpharm.com

Presentation Session 162
Poster A-1281

ABSTRACT

Background: Omadacycline (OMC), formerly PTK 0796, 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 assessed the absorption, distribution, metabolism and excretion, and identification of metabolites, from a single oral dose of [14C]OMC in humans. **Methods:** Six healthy male subjects were administered a single oral dose of 300mg [14C]OMC (mean radioactivity 36.6 µCi) under fasting conditions, and observed for 7 days post-dose during which plasma samples, and excreta samples of urine and feces, were collected. Parent plasma OMC concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Excretion and mass balance of radioactivity were determined with liquid scintillation; metabolites were characterized by HPLC with radioactivity detection and metabolite identification performed by LC-MS/MS. Safety assessments included hematology, blood chemistry and urinalysis, vital signs, and adverse events. **Results:** The maximum OMC plasma concentration was reached between 1 and 4 h; the mean half-life was 17.6 h, the mean apparent clearance was 32.8 L/h and the apparent volume of distribution was 827.8 L. Recovery of the radioactive dose was complete after 7 days (mean 95.5%) and no metabolites were detected. The C-4 epimer of OMC, a spontaneous conversion product present in the oral dose, was observed in all biofluids. The main route of OMC elimination was via the fecal route; feces accounted for 81.1±2.34% of the radioactivity, while 14.4±2.33% of the radioactivity was recovered in urine. Based on prior estimates of 30% oral bioavailability these data suggest that >40% of the absorbed dosed is eliminated in the urine. In plasma, OMC and its C-4 epimer accounted for 100% of the radioactivity exposure. Radiolabeled OMC was safe and well-tolerated. **Conclusion:** Oral OMC is excreted in the feces (81.1%) and urine (14.4%) as unchanged drug and as C4-epimer, and does not undergo metabolism in humans.

INTRODUCTION

Omadacycline is a novel aminomethylcycline and the first member of this class of tetracyclines to enter clinical development. Omadacycline is a broad spectrum antibacterial agent being developed as a once daily intravenous and oral therapy for the treatment of community acquired acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.

Previous studies (Hanna et al)) have shown that omadacycline is metabolically stable in *in vitro* studies using human hepatocytes, subcellular fractions, and purified cytochrome P450 enzymes.

The human volunteer study reported herein confirms the metabolic stability of omadacycline and describes the paths of elimination from the body following a single oral dose of 14C-omadacycline.

STUDY DESIGN

This was an open-label, single-dose, absorption, distribution, metabolism and excretion (ADME) study conducted in healthy male subjects.

The study design schema is shown below. The minimum stay for this study was anticipated to be 8 days (168 h), however, if subjects did not reach at least 85% recovery of the administered radioactive dose, then they could be confined to the clinical site until they met the discharge criteria or up to Day 10 (216 h).

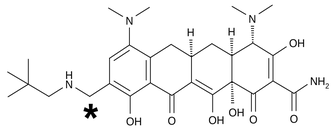
*Follow up period could have been extended up to Day 10.

METHODS

6 healthy male subjects who met eligibility criteria at screening were admitted to clinic on Day -1 for baseline evaluations. All baseline safety evaluation results were available prior to dosing. Each subject received a total of 300 mg OMC on the morning of Day 1 as a mixture of radiolabeled (actual dose was 36.6 µCi of ^{14}C) and nonlabeled drug. Subjects were required to fast overnight prior to the dose and until 4 h after dose administration.

Radiolabeled 14C-Omadacycline

Omadacycline was labeled with ^{14}C in the specified (*), metabolically stable position as shown



Chemical and radiochemical purity ≥90% (with no unspecified impurity >1.0%) was verified by HPLC. The stability ascertained for the period from manufacturing to dose administration.

The radiolabeled study drug was provided as individually packaged doses of 2 x 150 mg capsules with planned specific activity of 4.33 kBq/mg.

Free acid specific activity was 0.122 µCi/mg.

Radioactivity was determined by liquid scintillation counting. Plasma, whole blood, feces, and urine samples were analyzed by HPLC-MS/MS with or without radiodetection for parent omadacycline and metabolites.

RESULTS

Of the 6 subjects, 5 (83.3%) subjects completed the study. Subject 5104 withdrew consent due to a family emergency on Day 7, one day prior to the official end of study date. All scheduled end of study assessments were performed prior to dismissing this subject from the clinic.

Subjects	OMC 300 mg N=6 (%)
Completed	5 (83.3)
Subject withdrew consent	1 (16.7)

		OMC 300 mg N=6
Age (years)	Mean (range)	25.7 (21-32)
Predominant race - n(%)	Caucasian	6 (100%)
Ethnicity - n(%)	Other	6 (100%)
Weight - (kg)	Mean (range)	75.5 (71-91)
BMI - (kg/m^2)	Mean (range)	24.4 (22.8-29.7)

Pharmacokinetics

Following a single oral dose of radiolabeled [^{14}C]OMC, the mean AUClast of total radioactivity in plasma was 3096.1±1547.7 ngEq•h/mL. The mean terminal half-life of radioactivity in plasma was 11.1 h (Table 1).

Table 1. PK parameters of [^{14}C]OMC for total radioactivity in plasma or whole blood

Matrix		Tmax* (h)	Cmax (ngEq/mL)	AUC0-8 (ngEq·h/mL)	AUClast (ngEq·h/mL)
Plasma	Mean	2.5 (1 – 3)	612	3142.5	3096.1
	SD	N/A	81.5	804.3	1547.7
Blood	Mean	2.75 (1.5 – 4)	608	N/A	1867
	SD	N/A	74	N/A	1322

*Tmax presented as median (range)

The pharmacokinetics of parent OMC is shown in Table 2.

Table 2. PK parameters in plasma following a single oral dose of 300 mg of [^{14}C]OMC

Subject ID	Tmax* (h)	Cmax (ng/mL)	AUC0-8h (ng· h /mL)	AUClast (ng· h /mL)	AUCinf (ng· h /mL)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
Mean	2.3	563	3019.3	8573	9418	17.6	32.8	827.8
SD	1-4	79.5	482.4	1941	1857	1.45	5.90	132.9

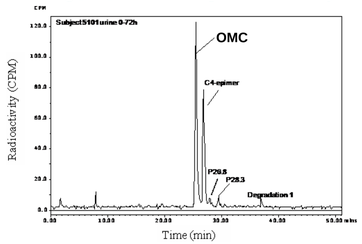
*Tmax presented as median and range

Comparison of total plasma radioactivity exposure and parent drug plasma exposure suggests little or no metabolites were present in plasma. AUC0-8h for total plasma radioactivity and OMC in plasma (HPLC-MS/MS) were comparable (3142.5 ngEq*h/mL and 3019.3 ng*h/mL, respectively).

Metabolism

No metabolites were detected in plasma, feces, or urine. The components (impurities including the C-4 epimer, degradants, and the 4-keto species) detected in all excreta were also detected in the dosing solution at similar levels (Figure 1).

Figure 1. Peak profiles in pooled human urine (0-72 h) after a single oral dose of 300 mg [^{14}C] OMC in a representative subject



Excretion

In all of the six subjects similar excretion profiles were seen. OMC related components (OMC and C-4 epimer) were primarily eliminated through biliary excretion (Table 3). 43.2 mg (14.4% of the administered oral dose) was excreted in the urine. This would represent approximately 40% of the 100 mg intravenous dose and the fraction of the absorbed oral dose, assuming 35% oral bioavailability demonstrated in previous human studies.

Table 3. Excretion of total radioactivity (% of dose) following an oral dose of 300 mg [^{14}C]OMC

	Subject							
	5101	5102	5103	5104	5105	5106	Mean	SD
Urine	16.2	14.6	17.4	10.7	14.4	13.3	14.4	2.33
Feces	82.1	80.0	77.5	80.1	82.8	84.0	81.1	2.34
Total	98.3	94.6	94.9	90.8	97.2	97.3	95.5	2.73

Safety

There were no serious adverse event (SAE) reported in the study. No subjects experienced AEs that led to the subject's discontinuation from the study.

There were no deaths, SAEs reported during the study. None of the subjects were discontinued from the study due to any AE. All AEs were mild in intensity.

All six subjects experienced mild gastrointestinal AEs that were suspected to be related to the study drug and consistent with the known profile of the drug following oral administration. The most frequently reported AEs were diarrhea (5, 83.3%), dyspepsia (2, 33.3%) and nausea (2, 33.3%), which resolved without intervention.

There were no clinically relevant changes in biochemistry, hematology parameters, blood pressure, or physical exam findings. Asymptomatic increases in heart rate following dose administration were observed in all subjects.

CONCLUSION

- The mass balance achieved in this study on average was 95.5% of the administered OMC radioactivity in the excreta (urine plus feces) of all subjects after 7 days.
- No metabolites were detected. Several impurities and degradation products were characterized in both the dosing solution and biological samples (plasma, urine and feces).
- In urine, the % mean total radioactivity administered was 14.4±2.33 with 100% being OMC and its C-4 epimer. This represents 43.2 mg or approximately 40% of the absorbed dose.
- In feces, the % mean total radioactivity was 81.1±2.34 with 100% being OMC and its C-4 epimer.
- OMC in plasma reached Cmax between 1 and 4 h. The mean half-life was 17.6 h, the mean apparent clearance was 32.8 L/h and the apparent volume of distribution was 827.8 L.
- Overall oral administration of OMC 300 mg was safe with acceptable tolerability.

REFERENCES

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