An Open-Label, Single Dose Study Designed to Assess the Metabolism and Mass Balance Recovery for [14C]-Eravacycline in Healthy Male Subjects after Oral and Intravenous Dosing

QUOTIENT CLINICAL
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INTRODUCTION

Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broadspectrum activity in development as an IV and oral treatment for the treatment of infections caused by multidrug-resistant (MDR) Gram-negative bacteria. Phase 3 studies evaluating eravacycline for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) have been completed.

This study was conducted to assess the mass balance recovery, PK and metabolism of a single oral dose and single IV dose of carbon-14 [^{14}C]-eravacycline.

MATERIALS AND METHODS

This was a single center, open-label, non-randomized, single dose study in 10 healthy male subjects.

The study was approved by the UK, MHRA and an independent ethics committee prior to consenting and screening subjects. The radioactive doses for the study were approved by the Administration of Radioactivity Substances Advisory Committee (ARSAC).

The subjects were enrolled in 2 groups, each group containing 5 subjects with 1 group receiving Regimen A and the other group receiving Regimen B:

- Regimen A: 100 mg [^{14}C]-eravacycline as a single oral solution administration containing not more than (NMT) 4.8 MBq (130 µCi) ^{14}C.
- Regimen B: 60 mg [^{14}C]-eravacycline as a single IV dose by a 60 minute infusion containing NMT 3.8 MBq (105 µCi) ^{14}C.

For each regimen, blood samples were taken after dosing for the measurement of total radioactivity, eravacycline and two known metabolites (TP-498 and TP-6208) and for metabolite profiling and identification. Excreta were collected for the measurement of total radioactivity and for metabolite profiling and identification.

Safety assessments were performed at specified time points and adverse events (AEs) were monitored throughout the study.

Both oral and IV formulations were manufactured under full GMP conditions and dosed within 2 and 7 days of manufacture respectively using Quotient Clinical's integrated Translational Pharmaceutics® platform.

RESULTS AND DISCUSSION

Number of subjects:

Ten subjects were enrolled and ten subjects completed the study. All subjects were included in both the safety and PK populations. Nine subjects were included in the mass balance population. One subject did not meet the protocol-defined mass balance recovery criteria at discharge and was asked to continue home fecal collections but failed to do so and was excluded from the mass balance population.

Mass balance following oral administration of [^{14}C]- eravacycline (Regimen A)

Following a single oral dose of 100 mg [^{14}C]-eravacycline (Regimen A), between 80.46% and 85.89% of the radioactivity administered was recovered by the end of the sampling period (288 h). An average of 7.16% and 75.32% of total radioactivity were recovered from the urine and feces, respectively. Within the first 48 h post-dose, 5.19% and 6.33% of the total radioactivity were recovered from the urine and feces, respectively.

Table 1 Mean Mass Balance Recovery of Total Radioactivity Following a Single Oral Dose of [^{14}C]-Eravacycline: Mass Balance Population

Collection Time (h)	Mean Cumulative %Ae (%)	
	Urine (N = 5)	Feces (N = 5)
Pre-dose	NC	NC
0 – 6	1.32	NC
0 – 12	1.81	NC
0 – 24	3.64	NC
0 – 48	5.19	6.33
0 – 72	5.93	43.01
0 – 96	6.31	54.29
0-120	6.66	71.51
0-144	6.89	73.80
0-168	6.98	74.29
0-192	7.06	74.66
0-216	7.10	75.20
0-240	7.16	75.29
0-264	NC	75.30
0-288	NC	75.32
Total	**82.48**	

NC: Not calculated

Mass balance following intravenous administration of [^{14}C]-eravacycline (Regimen B)

Following IV administration of 60 mg [^{14}C]-eravacycline (Regimen B), between 77.45% and 88.19% of the radioactivity administered was recovered by the end of the sampling period (288 h). An average of 34.96% and 47.79% of the total radioactivity was recovered from the urine and the feces, respectively. Within the first 48 h post-dose, 27.13% and 0.34% of the total radioactivity was recovered in the urine and feces, respectively.

Table 2 Mean Mass Balance Recovery of Total Radioactivity Following a Single Intravenous Dose of [^{14}C]-Eravacycline: Mass Balance Population

Collection Time (h)	Mean Cumulative %Ae (%)	
	Urine (N = 4)	Feces (N = 4)
Pre-dose	NC	NC
0 – 6	7.49	NC
0 – 12	12.73	NC
0 – 24	19.00	0.02
0 – 48	27.13	0.34
0 – 72	30.35	16.02
0 – 96	32.05	27.47
0-120	33.25	35.04
0-144	33.97	40.97
0-168	34.39	42.54
0-192	34.64	45.14
0-216	34.82	45.38
0-240	34.96	47.01
0-264	NC	47.07
0-288	NC	47.70
Total	**82.75**	

NC: Not calculated

Pharmacokinetic results

Following a single oral dose of 100 mg [^{14}C]-eravacycline (Regimen A), maximum plasma concentrations occurred between 2.00 h and 3.00 h, and then declined in a biphasic manner. Plasma eravacycline remained quantifiable for between 36 h and 72 h post-dose.

Following IV administration of 60 mg [^{14}C]-eravacycline (Regimen B), maximum plasma concentrations of eravacycline occurred by the end of the infusion (T_{max} ranged from 0.55 h to 1.00 h) and then declined in a biphasic or triphasic manner, remaining quantifiable for around 73 h post-dose in the majority of subjects.

Table 3 Key PK Parameters for Eravacycline

Parameter	Oral dose (100mg, Regimen A) (n = 5)	IV dose (60mg, Regimen B (n = 5)
T_{lag} (h) [a]	0.00 (0.00-0.00)	NC
T_{max} (h)[a]	2.03 (2.00-3.00)	1.00 (0.55-1.00)
C_{max} (ng/mL)	81.5 (32.3)	1100 (13.5)
$AUC_{0\text{-}last}$ (ng.h/mL)	983 (38.9)	4360 (9.8)
$AUC_{0\text{-}24}$ (ng.h/mL)	783 (29.6)	3330 (10.0)
$AUC_{0\text{-}inf}$ (ng.h/mL)	803 [n=1]	4380 (11.4) [n=2]
$AUC_{\%extrap}$ (%)	15.26 [n=1]	4.04 (34.2) [n=2]
$T_{1/2}$ (h)	14.06 [n=1]	18.23 (5.0) [n=2]
$MRT_{0\text{-}inf}$ (h)	NC	15.86 (8.9) [n=2]
$MRT_{0\text{-}last}$ (h)	NC	14.08 (16.3)
CL (mL/min)	NC	228 (13.8) [n=2]
CL_R (mL/min)	49.1 (4.6)	41.9 (16.6)
V_{ss} (L)	NC	217 (4.9) [n=2]

[a] Median (range) NC: Not calculated

Following oral administration there were no quantifiable concentrations of TP-498 in plasma. Maximum concentrations of TP-6208 in plasma occurred between 6.00 h and 8.07 h and TP-6208 remained quantifiable for 48 h post-dose in the majority of subjects. Plasma concentrations of total radioactivity reached maximum concentrations between 2.00h and 5.00h post-dose with concentrations remaining quantifiable up to 120-144h post-dose.

Following IV administration, maximum plasma concentrations of TP-498 occurred between 0.55 h and 1.00 h and TP-498 remained quantifiable for between 37 h and 49 h post-dose. Plasma TP-6208 concentrations reached a maximum between 9.03 h and 13.03 h and remained quantifiable for between 49 h and 73 h post-dose. Plasma concentrations of total radioactivity reached maximum concentrations between 0.55 h and 1.00 h post-dose with concentrations quantifiable up to 241 h post-dose in the majority of subjects.

Following oral dosing, whole blood concentrations of total radioactivity were quantifiable after 0.5 h in most subjects, and maximum concentrations occurred between 3.48 h and 5.00 h and remained quantifiable between 5 h and 24 h post-dose. Following IV administration, whole blood concentrations of total radioactivity reached maximum concentrations between 0.55 h and 1.00 h post-dose and remained quantifiable between 49 h and 73 h post-dose.

CONCLUSIONS

- After oral administration, an average of 82.48% of the total radioactive dose was recovered during the 288 h collection period, with approximately half of the dose recovered within the first 72 h.
- After IV administration, an average of 82.75% of the total radioactive dose was recovered during the 288 h collection period, with approximately half of the dose recovered within the first 72 h.
- Following IV administration, the majority of total recovered radioactivity was in the feces suggesting biliary elimination is the major route of excretion for eravacycline and/or its metabolites.
- Following IV and oral administration, total radioactivity and eravacycline was recovered in urine, demonstrating evidence of renal clearance of eravacycline, although to a lesser extent than biliary elimination.

The combination of intravenous and oral mass balance in a single study has enabled a more thorough understanding of the absorption, IV and oral pharmacokinetics of eravacycline providing insights to absolute bioavailability, fraction absorbed and drug disposition.

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