MODULE 2.6.4. PHARMACOKINETICS WRITTEN SUMMARY

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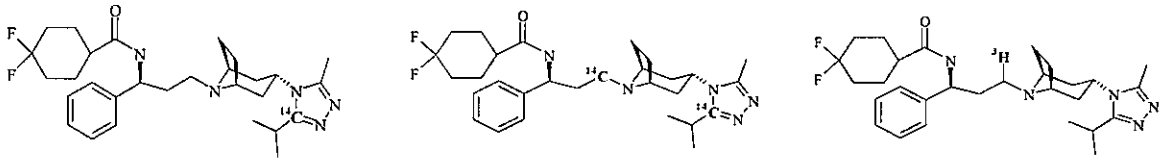
2.6.4. PHARMACOKINETICS WRITTEN SUMMARY

2.6.4.1. Brief Summary

In terms of physiochemical properties, maraviroc is a moderately lipophilic and basic molecule with a log $D_{7.4}$ of 1.9, pKa 7.7 and a molecular weight of 513.7 (Figure 1).

Figure 1. Structure of [^{14}C]-labelled and [^{3}H]-labelled maraviroc

[^{14}C]-Maraviroc Single label **[^{14}C]-Maraviroc Dual label** **[^{3}H]-Maraviroc**



Bioavailability and pharmacokinetic studies have been conducted in animals and human using specific validated chromatographic (HPLC) methods with mass spectrometric detection for analysis of drug and metabolites UK-408,027 and UK-463,977 in biological fluids. Strains of mouse, rat and dog used in single dose pharmacokinetic studies have corresponded to those used in toxicology and pharmacology studies. In addition, mdr 1a/1b knockout and FVB wild type mice were used to investigate the role of P-glycoprotein in compound disposition. The pharmacokinetic program was supplemented by sampling during repeat dose toxicology studies in mouse, rat, dog and cynomolgus monkey. In addition, the tissue distribution, metabolism and excretion of maraviroc in mouse, rat, rabbit, dog, cynomolgus monkey and human has been studied using three radiolabelled forms of maraviroc – tritium (^{3}H) and both single and dual carbon-14 labelled material (Figure 1). The carbon-14 studies are considered to be definitive since they provided a more comprehensive metabolism profile due to some metabolic loss of the [^{3}H] label.

The intravenous pharmacokinetics of maraviroc in rats and dogs have been determined following solution administration. The vehicle of choice for these studies was 5% DMSO/ 94.5% saline/ 0.5% 1M HCl. For oral administration, the vehicle of choice was 5% DMSO/ 94.5% water/ 0.5% 1M HCl. For the excretion and metabolism studies, [^{14}C]-labelled maraviroc has been administered orally in 0.2M lactate buffer pH range 3-3.85.

Following oral administration maraviroc was absorbed rapidly with a T_{max} of 4h or less across species. Bioavailability was low in the rat at 5% and absorption was judged to be incomplete based upon hepatic portal vein concentration data. In dogs bioavailability was higher at around 41% and absorption was also judged to be high based upon anticipated first-pass extraction. In humans, due to non-proportionality of pharmacokinetics, absolute bioavailability is dose dependent (23% at 100 mg).

Maraviroc has a volume of distribution in rats, dogs and humans which is significantly above that of total body water (>0.7 L/kg) indicating extensive tissue distribution. Maraviroc, however, shows limited penetration into the brain with a cerebrospinal fluid (CSF) to plasma concentration ratio of 0.01 for unbound drug in the rat. Tissue distribution studies showed that following [^{3}H]-labelled maraviroc administration to pigmented rats, there was significant binding of drug-related material to melanin in the eye. Such melanin binding is often observed for lipophilic and basic compounds and is not generally associated with any toxicological consequences. In addition, radioactivity was shown to be associated with lymph nodes (including gut-associated lymphoid tissues, GALT) following administration of [^{14}C]-maraviroc to rats.

The plasma protein binding of maraviroc is moderate across species with values of 58.0%, 51.0%, 66.0%, 63.7%, 48.4% and 75.5% in mouse, rat, rabbit, dog, cynomolgus monkey and human, respectively. Maraviroc shows some partitioning into red blood cells with partition ratios less than unity in all species except rat.

Unchanged drug was the major excreted component in all species, with combined urine and faecal excretion ranging from 33% of total administered dose in humans to 79% in rat. Metabolism was responsible for the remaining clearance of maraviroc with a high degree of commonality observed across species. The major metabolic pathways involve oxidation of the triazole moiety, N-dealkylation adjacent to the tropane ring, and oxidation in the difluorocyclohexyl ring. The major circulating component was unchanged maraviroc in all species. In addition to unchanged maraviroc (33%), significant metabolites detected in human plasma were a secondary amine product of N-dealkylation (UK-408,027; 22%) and a hydroxylated analogue (11%). All human metabolites were identified in at least one of the toxicology species indicating that animals were exposed to these metabolites in repeat dose safety studies.

Investigations using human liver microsomes and recombinant enzymes have shown that maraviroc is predominantly metabolised by CYP3A4. Consequently its pharmacokinetics may be altered by co-administered drugs that inhibit or induce this enzyme. Maraviroc itself does not inhibit the activity of any of the major cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) at clinically relevant concentrations (IC_{50}>30μM).

Toxicokinetic investigations show that at the NOAEL doses in toxicology studies animals were exposed to similar or several-fold higher unbound concentrations of maraviroc than humans at the maximum expected clinical dose (300 mg BID).

2.6.4.2. Methods of Analysis (Module 2.6.5 Tabulated Summaries, Section 2, Study nos. DM1, DM2, DM4, DM11, DM25, DM26, DM27, DM28, DM29, DM30, DM31)

The perfomrance of analytical methods used in determining the pharmacokinetics of maraviroc and UK-463,977 in mouse, rat, rabbit, dog and cynomolgus monkey are shown in Section 2.6.4.10.1 (Table 8). Maraviroc and UK-463,977 concentrations in plasma were determined using validated and specific HPLC mass spectrometry methods.

Following the identification of UK-463,977 and UK-408,027 as excreted metabolites, assays were developed to measure their concentrations in urine from mouse, rat, dog, cynomolgus

monkey and human following administration of maraviroc. The concentrations of UK-463,977 and UK-408,027 were determined in urine using validated and specific HPLC mass spectrometry and are shown in Secton 2.6.4.10.1 (Tables 9 and 10).

In addition, the tissue distribution, excretion and metabolism of maraviroc has been studied following administration of tritium and [^{14}C]-labelled compound. At all times the radiochemical purity of the material used was greater than 95%.

2.6.4.3. Absorption

2.6.4.3.1. Single dose pharmacokinetics

Data on the single dose pharmacokinetics of maraviroc in mouse, rat, dog and human are summarised in Table 1 of this module. Following intravenous administration to rat and dog, the elimination phase half-life values were 0.9 and 2.3h with plasma clearance values of 74 and 21.4 mL/min/kg, rat and dog respectively. Volumes of distribution were 6.5 and 4.3 L/kg, rat and dog respectively.

2.6.4.3.1.1. Mouse (Module 2.6.5. Tabulated Summaries, Section 3, Study No. DM2)

The pharmacokinetics of maraviroc in male mice have been studied following single oral administration of 16 mg/kg. A strain of Mdr1a/b double knockout mouse which is deficient in both Mdr1a and Mdr1b genes which encode murine P-glycoprotein was studied and compared with a wild-type fvb strain. Pharmacokinetic parameters were derived from drug concentrations in plasma pooled from groups of 2 animals per time point.

Following single oral (16 mg/kg) administration to mdr1a/b knockout and fvb wild type mice plasma C_{max} values of 1119 and 536 ng/mL (respectively), were achieved at 0.5h post dose, with $AUC_{0-\infty}$ values of 1247 and 440 ng.h/mL, respectively.

2.6.4.3.1.2. Rat (Module 2.6.5. Tabulated Summaries, Section 3, Study No. DM1)

The pharmacokinetics of maraviroc in male rats have been studied following single intravenous (1 mg/kg) and oral (3 and 10 mg/kg) administration. Following intravenous administration, the elimination half-life value was 0.9h. Plasma clearance was 74 mL/min/kg with a volume of distribution of 6.5 L/kg. Following single oral (3 and 10 mg/kg) administration, both hepatic portal and systemic blood was collected for analysis. At 3 mg/kg, systemic plasma concentrations were below the limit of quantitation and absorption was estimated to be 20% based on hepatic portal vein concentrations. Following a 10 mg/kg dose,a plasma C_{max} of 55 ng/mL was achieved at 2h post-dose and absorption had increased to 30%. Apparent oral bioavailability relative to the intravenous dose was 5%.

Table 1. Single dose intravenous and oral pharmacokinetics of maraviroc in animals

Species (Study No.)	Male Mouse[a] (DM2)	Male Mouse[b] (DM2)	Male Rat (DM1)	Male Rat (DM1)	Dog (DM4)	Dog (DM4)	Human (1009, Cohort 2)
Parameter							
Intravenous Dose (mg/kg)	-	-	1	-	0.5	-	0.4[c]
n	-	-	2	-	4	-	12
Elimination half-life (h)	-	-	0.9	-	2.3	-	12.0
$AUC_{0-\infty}$ (ng.h/mL)	-	-	227	-	396	-	656
Plasma Clearance (mL/min/kg)	-	-	74	-	21.4	-	11.0
Blood to Plasma ratio (DM16, DM32)	-	-	1.08	1.08	0.89	0.89	0.59
Blood Clearance (mL/min/kg)	-	-	68.5	-	24.0	-	-
Volume of Distribution (L/kg)	-	-	6.5	-	4.3	-	2.6[d]
Oral Dose (mg/kg)	16	16	3	10	1	2	1.4[c]
N[e]	2	2	2	2	2	2	12
C_{max} (ng/mL)	1119	536	ND	54.8	82	256	122
T_{max} (h)	0.5	0.5	ND	2	1.5	0.75	3.08
$AUC_{0-\infty}$ (ng.h/mL)	1247	440	ND	124	335	583	506
Oral Bioavailability (%)	-	-	-	5	42	40	23
Free fraction in plasma (DM23)	0.42	0.42	0.49	0.49	0.36	0.36	0.25

[a] Strain; mdr 1a/ 1b ko
[b] Strain; fvb WT
[c] Human doses were administered in mg, 30 mg intravenously and 100 mg orally.
[d] Human volume of distribution is Vss
[e] For mouse blood samples were taken from 2 to 3 animals per time point and pooled for analysis
- = Not conducted
ND = Not determined

2.6.4.3.1.3. Dog (Module 2.6.5. Tabulated Summaries, Section 3, Study No. DM4)

The pharmacokinetics of maraviroc in male and female dogs have been studied following single intravenous (0.5 mg/kg) and oral (1 and 2 mg/kg) administration (DM4). Following intravenous administration pharmacokinetics were determined in 2 dogs from each sex and mean values derived from all 4 animals with no observed sex difference. The elimination half-life was 2.3h with a plasma clearance of 21.4 mL/min/kg and a volume of distribution of 4.3L/kg. Following single oral (1 and 2 mg/kg) administration pharmacokinetics were determined in 1 dog from each

sex and mean values derived from 2 animals with no observed sex difference. Plasma C_{max} values of 82 and 256 ng/mL were achieved at 1.5 and 0.75h post dose for 1 and 2 mg/kg administration respectively. The apparent oral bioavailability was 42 and 40% for 1 and 2 mg/kg administration respectively.

2.6.4.3.1.4. Human (Module 2.7.2. Summary of Clinical Pharmacology, Section 2.1., Study No. 1001, 1003 and 1009)

Maraviroc intravenous pharmacokinetics are approximately dose proportional (1009). Mean total clearance and steady state volume of distribution for a 30 mg dose were 46L/h and 182L (11 ml/min/kg and 2.6 L/kg, respectively, assuming a 70 kg body weight). The mean elimination half-life was 12 hours.

After single oral administration, maraviroc is rapidly absorbed in human with C_{max} achieved between 0.5 and 4 hours after dosing (1001, 1003). The oral pharmacokinetics of maraviroc are not dose proportional. The degree of non-proportionality decreases with increasing dose and is most evident at doses below 100 mg. Mean absolute bioavailability of the 100 mg oral dose was 23%.

2.6.4.3.2. Multiple dose pharmacokinetics

2.6.4.3.2.1. Human (Module 2.7.2. Summary of Clinical Pharmacology, Section 2.2., Study No. 1002 and 1019)

Multiple dose pharmacokinetic data suggest that maraviroc accumulates after both QD and BID oral dosing. The mean accumulation ratios for 300 mg BID and 600 mg BID were 1.21 and 1.20, respectively (1019). Absorption was rapid with T_{max} occurring at approximately 2 hours. Steady state was reached after 7 days of maraviroc dosing.

2.6.4.3.2.2. Plasma concentrations in toxicology studies

The maraviroc toxicokinetic data following oral administration to mouse, rat, dog and cynomolgus monkey are listed with the exposure at the human clinical dose in Section 2.6.4.10.2. There was no significant difference in the plasma concentrations between male and female animals so these values were combined. Plasma exposure (defined by C_{max} and AUC) increased with dose in all species.

In mice, the increase in exposure was approximately proportional with the increment in dose over the 200 to 750 mg/kg dose range (Study 03012). In rats (Study 911/092), C_{max} increased approximately proportionately with dose whereas AUC increased supra-proportionally and plasma concentrations were approximately 1.4 to 2.2-fold higher on Day 181 compared with Day 0. In cynomolgus monkeys (Study 911/102), the increase in mean AUC and C_{max} values was greater than the increment in dose over the 30 to 400 mg/kg/day dose range (as twice daily doses). Systemic exposure was similar over the duration of treatment except for the highest dose group in which the AUC values were 1.5-fold higher from day 133 and day 270 compared with day 0. There was a proportional increase in C_{max} and AUC in dogs with increasing dose and systemic exposure was similar on days 1 and 176 (Study 02073)..

2.6.4.3.2.3. Comparison of plasma concentrations in toxicology studies and in human

The maraviroc toxicokinetic data following oral administration to mouse, rat, dog and cynomolgus monkey are listed with the exposure at the human clinical dose in Section 2.6.4.10.2.. The exposure of animals in the toxicology studies at the reference dose are compared to the human clinical dose (300mg or 4.3mg/kg) in terms of dose, C_{max} and AUC (both total and unbound maraviroc) in Table 2 of this module. The reference dose has been defined as the no adverse effect level (NOAEL) in mouse (750mg/kg), rats (100mg/kg), dogs (5mg/kg) and cynomolgus monkeys (120mg/kg) in the repeat dose studies.

Table 2. Exposure multiples based on dose and NOAEL plasma concentrations in toxicology species

Maraviroc Toxicology Study	Reference dose (mg/kg)	Multiples over the 300mg (BID), (total dose 8.6mg/kg) (Study 1007[a])				
Species and Gender		Dose	C_{max} Total	C_{max} Unbound	AUC Total	AUC Unbound
Mouse (M + F)	750	87	27	45	41	68
Rat (M + F)	100	12	4.8	9	3.8	8
Dog (M + F)	5	0.6	1.4	2	0.5	1
Monkey (M + F)	120[b]	14	1.9	4	1.3	3

Studies used in the calculation of these multiples were mouse (03012, day 83), rat (911/092, day 181), dog (02073, day 176) and cynomolgus monkey (911/102, day 270).
[a] Human (Study 1007) mean Cmax 618 ng/mL and AUC_{24h} 5100 ng.h/mL.
[b] 60 mg/kg BID, total daily dose 120 mg/kg.

This comparison includes consideration of the effect of species differences in plasma protein binding. In the mouse, the multiples are large based on dose (87-fold) and the margins are high when C_{max} (27 to 45-fold) or AUC (41 to 68-fold) are considered. In the rat, the dose multiple is 12-fold whereas based on C_{max} and AUC they are 5 to 9-fold and 4 to 8-fold, total and unbound respectively. In the dog, the margins are similar irrespective of whether dose (0.6-fold), C_{max} (1.4 to 2-fold) or AUC (0.5 to 1-fold) are considered. In the cynomolgus monkey, the dose multiple is 14-fold whereas based on C_{max} and AUC they are 2 to 4-fold and 1.3 to 3-fold for total and unbound drug, respectively.

Since there is a 2-fold variation in unbound fraction of maraviroc across species (0.25 in human to 0.52 in cynomolgus monkey), unbound exposure is considered to be a more relevant comparison. Therefore overall, when unbound drug is considered, the exposure multiples for maraviroc indicate an acceptable multiple between C_{max} and AUC for the drug in humans and the equivalent values associated with no adverse effects in mouse, rat, dog and cynomolgus monkey.

2.6.4.4. Distribution

2.6.4.4.1. Tissue distribution (Module 2.6.5 Tabulated Summaries, Section 5, Study Nos. DM6 and DM46)

Tissue distribution was studied by dissection and combustion following single intravenous administration of [^{3}H]-labelled maraviroc(3 mg/kg) to male pigmented rats (DM6). Distribution throughout the body was assessed at 0.1, 1, 6, 24, 48 and 96h in individual animals.

Distribution of radioactivity following administration of [^{3}H]-labelled maraviroc was rapid. Shortly after dosing, the concentration of radioactivity in most tissues was similar to or higher than those in blood. Highest levels were detected in liver, kidney, small intestine, bladder, seminal vesicles, and prostate gland. Levels of tissue radioactivity had decreased by 2- to 13-fold 1 hour after dosing and were higher than blood in all tissues except brain which was 4-fold lower. Concentrations continued to decline at later time points and were below the limit of quantification (less than 0.01µg equivalents/g tissue) in most tissues by 96 hours post-dose. Low levels of radioactivity were still present in the thymus and testes but these only represented 0.25% and 0.14% of the administered dose, respectively. The highest concentration of radioactivity remained in the eye and was slowly eliminated with an estimated half-life of approximately 7 days. This is commonly observed for lipophilic and basic compounds and is due to reversible binding to melanin. Such binding has been shown to have no toxicological consequences *per se* (Leblanc, 1998).

In a separate study, tissue distribution was studied by WBAL following single intravenous (nominally 3 mg/kg) administration of [^{14}C]-labelled maraviroc to Long-Evans male rats (DM46). Distribution into the gut associated lymphoid tissue (GALT) was assessed at 1 and 4 hours in individual animals. At both time points, radioactivity was shown to penetrate into the GALT lymph nodes, as well as axial and sublingual lymph nodes, at concentrations that were 6 to 7 fold higher than those measured in blood.

2.6.4.4.2. Brain penetration (Module 2.6.5. Tabulated Summaries, Section 8, Study No. DM3)

The brain penetration of maraviroc has been studied in rats (n=4) following intravenous infusion administration of maraviroc. Following intravenous loading (1.3 mg/kg) and infusion (30 µg/min/kg) doses the mean concentration of unbound maraviroc in the cerebrospinal fluid (CSF) was approximately 10% of that in plasma (mean CSF:plasma ratio 0.01) indicating limited penetration across the blood-brain barrier.

2.6.4.4.3. Plasma protein binding (Module 2.6.5. Tabulated Summaries, Section 6, Study Nos. DM23 and DM18)

The plasma protein binding of maraviroc has been determined by equilibrium dialysis using plasma samples obtained during toxicology studies in mouse, rat, rabbit, dog and cynomolgus monkey, and using human plasma samples from a multiple dose clinical study (A4001002) (DM23). Analysis was performed by fortification with a small amount of [^{14}C]-labelled maraviroc (<10% of total drug measured). Results are summarised in Table 3.

Where both sexes were studied (mouse, dog and cynomolgus monkey) no difference in binding was observed. Maraviroc exhibits moderate plasma protein binding with mean values of 58.0%, 51.0%, 66.0%, 63.7%, 48.4% and 75.5% in mouse, rat, rabbit, dog, cynomolgus monkey and human respectively. The extent of binding was independent of concentration over the ranges studied.

The protein binding values in Table 3 have been used for the calculation of unbound concentrations and exposure multiples (Table 2)

Table 3. Plasma protein binding of maraviroc across species

Species and Gender	Conc range (μg/mL)	Mean percentage bound (fraction unbound*)
Mouse (M+F)	4.0 – 25.09	58.0 (0.42)
Rat (M)	1.06 – 8.82	51.0 (0.49)
Rabbit (F)	1.68 – 7.39	66.0 (0.34)
Dog (M+F)	0.47 – 18.65	63.7 (0.36)
Monkey (M+F)	0.2 – 10.88	48.4 (0.52)
Human (M)	0.12 – 1.72	75.5 (0.25)

* Fraction unbound = (100 - Percentage Bound)/100

In addition, the binding of [^{3}H]-labelled maraviroc to albumen and α-1-acid glycoprotein (constituents of human plasma) has been investigated over a range of drug concentrations (DM18, Table 4). Maraviroc exhibits moderate and similar binding to both human plasma protein albumen (56%) and α-1-acid glycoprotein (69%) at physiologic concentrations. The extent of binding was independent of drug concentration over the range studied.

Table 4. Binding of [^{3}H]-maraviroc to albumen and α-1-acid glycoprotein

Plasma Constituent	Mean percentage bound ± SD (n=5)		
	1 ng/mL	30 ng/mL	1000 ng/mL
Albumen	55.0 ± 2.3	55.6 ± 2.3	56.2 ± 1.1
α-1-acid glycoprotein	73.8 ± 1.2	69.6 ± 2.6	63.8 ± 6.4

2.6.4.4.4. Blood distribution (Module 2.6.5. Tabulated Summaries, Section 8, Study Nos. DM16 and DM32)

The *in vitro* whole blood to plasma concentration ratio for [^{3}H]-labelled maraviroc has been determined in fresh blood from rat, dog and human (DM16). The nominal concentration of maraviroc chosen was 100 ng/mL. The values for the ratio were 1.08, 0.89 and 0.66 for rat, dog and human blood respectively.

Low partitioning into human red blood cells was confirmed using [^{14}C]-labelled maraviroc (n=6 subjects) which provided a mean ratio of 0.59 (DM32).

2.6.4.4.5. Affinity for P-glycoprotein (Module 2.6.5. Tabulated Summaries, Section 8, Study No. DM21)

The affinity of maraviroc for the drug efflux transporter P-glycoprotein (P-gp) has been studied in vitro. The K_m value was 37 ± 6.4μM, with a V_{max} of 55 ± 3.4 nmol/mg/min. The low K_m value indicates that maraviroc is a substrate for P-gp.

2.6.4.4.6. Permeability in Caco-2 cells (Module 2.6.5. Tabulated Summaries, Section 8, Study Nos. DM20 and DM44)

The permeability of maraviroc has been studied across Caco-2 cell monolayers (DM20). The compound was fluxed with Papp values in the apical to basolateral direction (A-B) of $<1 \times 10^{-6}$ cm/sec and in the basolateral to apical direction (B-A) $>10 \times 10^{-6}$ cm/sec (drug concentration 25μM, pH 7.4). The compound exhibited an efflux ratio (B-A/A-B) of >10 reflecting polarised transport across the cell monolayer.

The transport of [^{14}C]-maraviroc across Caco-2 cell monolayers has been studied in the presence of a number of P-gp and MRP inhibitors. The P-gp inhibitors verapamil and CP-100,356, and the Multidrug Resistance Protein (MRP) inhibitor MK-571 all reduced the efflux ratio of maraviroc (DM20). In addition, the presence of a number of known P-gp substrates reduced the efflux of [^{14}C]-maraviroc to some extent (DM44). The rank order for efflux inhibition was ketoconazole > ritonavir > nelfinavir > saquinavir > indinavir, with IC_{50} values ranging from 2.25μM to >100μM.

2.6.4.5. Metabolism

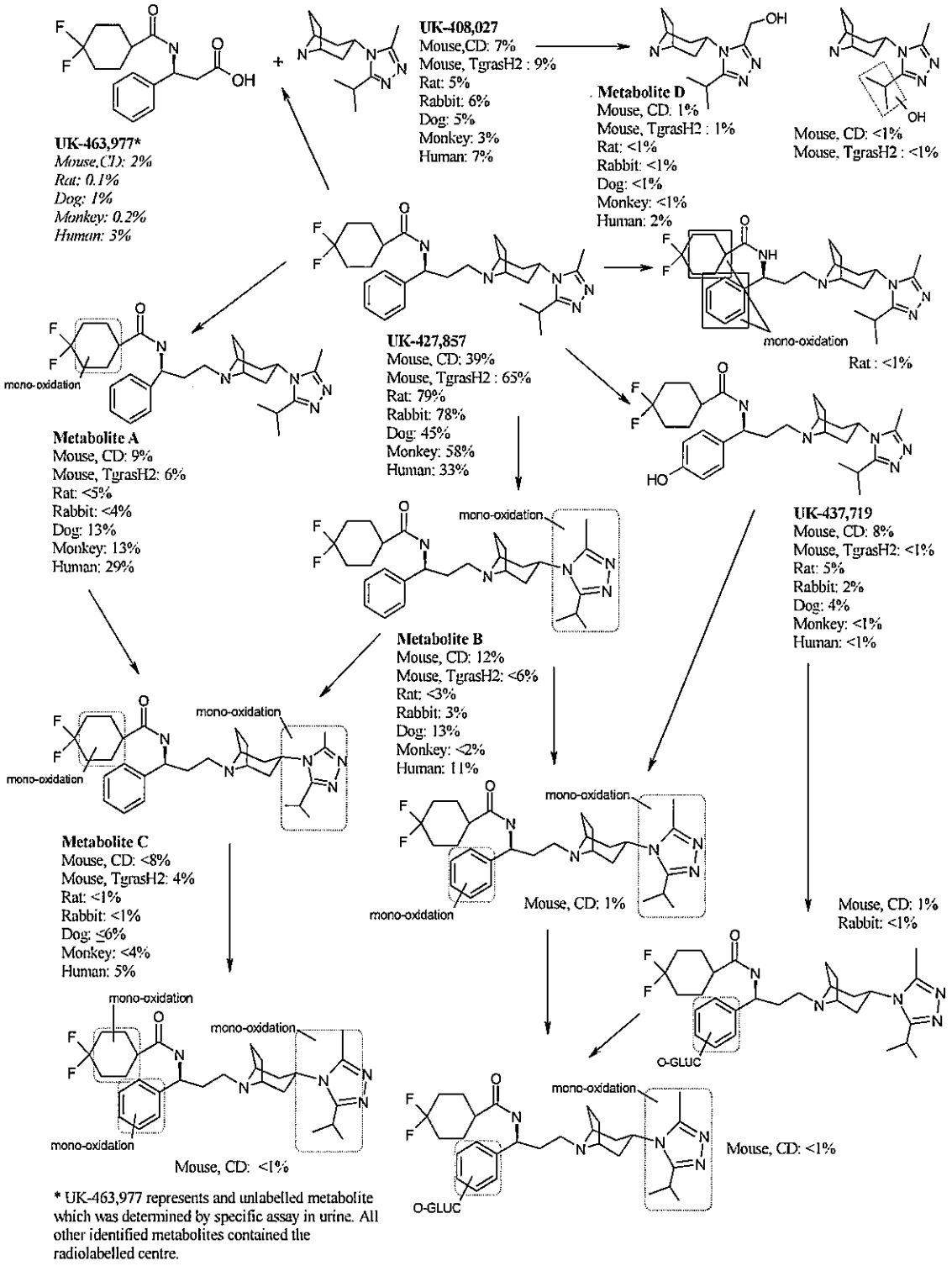
The metabolism of maraviroc in animals and human has been characterised from excretion studies using [^{14}C]-labelled maraviroc. Metabolite identification was carried out primarily using mass spectrometry combined with chromatographic retention time. NMR was also utilised to aid with structural elucidation when required. Where possible, authentic standards of each metabolite were synthesised for definitive identification.

2.6.4.5.1. In vivo metabolism (Module 2.6.5. Tabulated summaries, Section 9, Study Nos. DM25, DM29, DM36, DM37, DM38, DM39, DM40, DM41 and DM43)

The in vivo metabolism of maraviroc has been studied following oral administration of [^{14}C]-labelled drug. Preliminary studies were also performed using [^{3}H]-maraviroc in mouse, rat and dog (DM15, DM13, DM14) but the carbon-14 data are considered to be definitive since they provide a more comprehensive metabolism profile due to some metabolic loss of the [^{3}H] label.

A summary of the urinary and faecal excretion of maraviroc and its metabolites in animal species and human in terms of percentage dose are shown in Figure 2 of this module. In order to simplify the summary scheme, several metabolites have been combined and indicated by boxed structures within the figure (metabolites A, B & C). However, the actual site of oxidation has been fully elucidated in human samples using a combination of mass spetrometry and NMR analysis (DM25, DM43)

Figure 2: Excreted metabolites of maraviroc (as% of the dose) following administration of [^{14}C]-maraviroc to mouse, rat, rabbit, dog, cynomolgus monkey and human.



Note: Metabolites A, B & C – the actual site of oxidation has been determined in human samples by a combination of mass spectrometry and NMR (DM25, DM43).

2.6.4.5.1.1. Metabolism in mouse (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM27, DM38 and DM39)

The metabolite profile of maraviroc has been determined in two studies following oral administration of [^{14}C]-labelled maraviroc. In the first study (DM38) male CD1 mice received a single oral dose of [^{14}C]-labelled maraviroc (200 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (39%). Identified metabolites included the secondary amine resulting from N-dealkylation (UK-408,027; 7%), a product of mono-oxidation at the para position of the phenyl ring (UK-437,719; 8%), two products of oxidation in the triazole group (4 and 8%; labelled as metabolite B in Figure 2) and four metabolites involving mono-oxidation in the difluorocyclohexane ring which together accounted for 9% of the dose (labelled as metabolite A in Figure 2). Also identified in urine was UK-463,977, an acid metabolite of maraviroc (2%), (DM27).

In a second study (DM39), male TgrasH2 wild type mice received a single oral dose of [^{14}C]-labelled maraviroc (200 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (65%). The major identified metabolites were the secondary amine resulting from N-dealkylation (UK-408,027; 9%), a product of mono-oxidation on the methyl group of the triazole ring (<6%; metabolite B in Figure 2), a product of oxidation on both the triazole and difluorocyclohexane moieties (4%; metabolite C in Figure 2). Minor components included a product of N-dealkylation together with oxidation of the methyl group on the triazole moiety, a component resulting from mono-oxidation at the para-position of the phenyl ring (UK-437,719) and multiple products of oxidation in the difluorocyclohexyl and triazole moieties.

2.6.4.5.1.2. Metabolism in rat (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM26 and DM36).

The metabolite profile of maraviroc has been determined in male and female rats following a single oral administration of [^{14}C]-labelled maraviroc (100 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (79% mean of both sexes). The secondary amine resulting from N-dealkylation (UK-408,027; 5%) and a metabolite resulting from mono-oxidation on the para position of the phenyl group (UK-437,719; 5%) were identified in excreta. In addition a number of minor metabolites were identified including an oxidated derivative that had undergone hydroxylation on the methyl group of the triazole moiety (<1%) and a number of faecal metabolites that were formed from multiple oxidation reactions on the difluorocyclohexyl, triazole and phenyl moieties. Also identified in urine was UK-463,977, an acid metabolite of maraviroc (<0.1%), (DM26).

2.6.4.5.1.3. Metabolism in rabbit (Module 2.6.5. Tabulated Summaries, Section 9, Study No. DM41)

The metabolite profile of maraviroc has been determined in female rabbits following a single oral administration of [^{14}C]-labelled maraviroc (30 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (78%). The secondary amine resulting from N-dealkylation (UK-408,027; 6%), a metabolite resulting from mono-oxidation on the para position of the phenyl group (UK-437,719; 2%), two products of

oxidation in the triazole group (2 and 1%; labelled as metabolite B in Figure 2), four metabolites involving mono-oxidation in the difluorocyclohexane ring (<4%; labelled as metabolite A in Figure 2) and three products of mono-oxidation in the tropane ring (combined <3%), were identified.

2.6.4.5.1.4. Metabolism in dog (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM30 and DM40)

The metabolite profile of maraviroc has been determined in male and female dogs following a single oral administration of [^{14}C]-labelled maraviroc (5 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (45%, mean of male and female). The secondary amine resulting from N-dealkylation (UK-408,027; 5%), four metabolites involving mono-oxidation in the difluorocyclohexane ring (between 1 and 7%; labelled as metabolite A in Figure 2) and three metabolites resulting from oxidation in the triazole group (2 to 8%; labelled as metabolite B in Figure 2), were identified. Also identified in urine was UK-463,977, an acid metabolite of maraviroc (1%), (DM30).

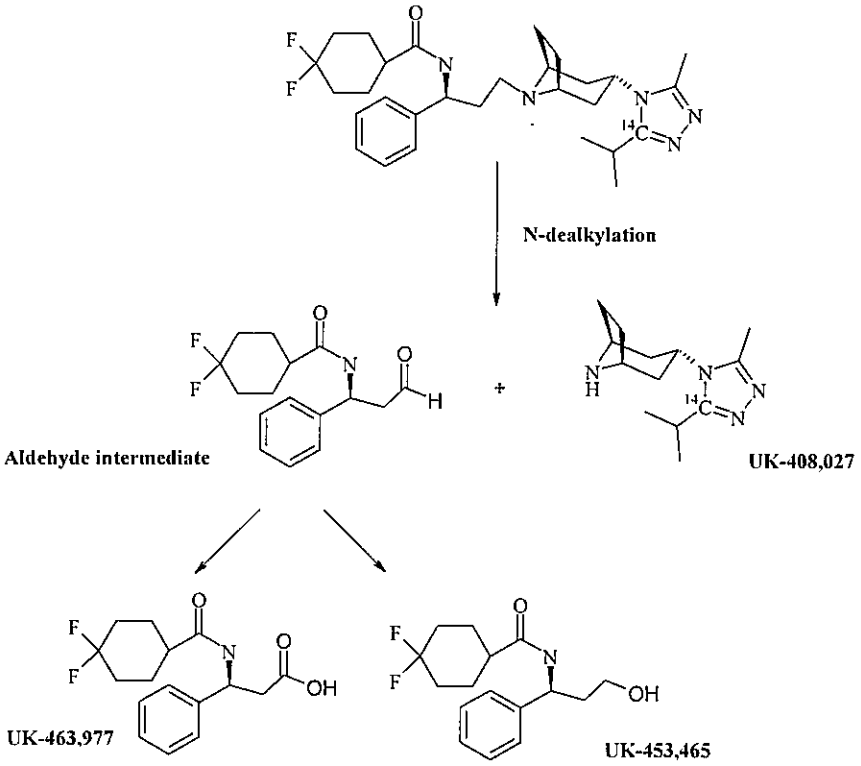
2.6.4.5.1.5. Metabolism in cynomolgus monkey (Module 2.6.5. Tabulated Summaries, Section 9, Study No. DM28 and DM37)

The metabolite profile of maraviroc has been determined in male cynomolgus monkeys following a single oral administration of [^{14}C]-labelled maraviroc (50 mg/kg). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (58%). The secondary amine resulting from N-dealkylation (UK-408,027; 3%), four metabolites involving mono-oxidation in the difluorocyclohexane ring (13%; labelled as metabolite A in Figure 2). Minor components included a product of N-dealkylation and oxidation of the methyl group of the triazole moiety, a component resulting from mono-oxidation at the para-position of the phenyl ring (UK-437,719) and multiple products of oxidation in the difluorocyclohexyl and triazole moieties. Also identified in urine was UK-463,977, an acid metabolite of maraviroc (0.2%), (DM28).

2.6.4.5.1.6. Metabolism in human (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM25, DM29 and DM43)

The metabolite profile of maraviroc has been determined in male human volunteers following oral solution administration of [^{14}C]-labelled maraviroc (300 mg single dose). Profiling by HPLC and LC-MS/MS analysis showed that unchanged maraviroc was the major excreted component (33%, mean of 3 subjects). The secondary amine resulting from N-dealkylation (UK-408,027; 7%), four metabolites involving mono-oxidation in the difluorocyclohexane ring (between 5 and 9% each; labelled as metabolite A in Figure 2) and two metabolites resulting from oxidation in the triazole group (10%and 1%; labelled as metabolite B in Figure 2) were identified. The N-dealkylation mechanism also yielded an unlabelled carboxylic acid metabolite (UK-463,977, Figure 3) which was quantified in urine and shown to be present at levels equivalent to 3% of the total dose (mean of 3 subjects).

Figure 3. Proposed Metabolites Arising from N-dealkylation of Maraviroc



2.6.4.5.1.7. Circulating metabolites

The plasma metabolite profiles of maraviroc in mouse, rat, rabbit, dog, cynomolgus monkey and human have been determined by mass spectrometry of plasma extracts following administration of [^{14}C]-labelled maraviroc. The concentrations of maraviroc and the metabolite UK-463,977 were also determined in rat, dog, cynomolgus monkey and human plasma using a validated specific assay (Table 5). A summary of the circulating metabolites in all species is presented as a percentage of circulating radioactivity in Figure 4. In order to simplify the summary scheme, several metabolites have been combined and indicated by boxed structures within the figure (metabolites A, B & C). However, the actual site of oxidation has been fully elucidated in human samples using a combination of mass spectrometry and NMR analysis (DM25, DM43)

Table 5. Circulating concentrations of UK-463,977 and maraviroc in plasma from rat, dog, cynomolgus monkey and human following oral administration of maraviroc

Species (Study No.)	Dose (mg/kg)	UK-463,977 C_{max} (ng/mL)	Maraviroc C_{max} (ng/mL)
Rat (DM26)	100	2.48	518
Dog (DM30)	5	10.8	273
Monkey (DM28)	50	45.2	934
Human (DM25, 1010)	300mg	37.3	496

2.6.4.5.1.8. Circulating metabolites in the mouse (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM38 and DM39)

The profile of circulating metabolites of maraviroc has been examined in two studies following oral administration of [^{14}C]-labelled maraviroc. In the first study (DM38) male CD1 mice received oral doses of 200 mg/kg [^{14}C]-labelled maraviroc. At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. Profiling by HPLC and LC-MS/MS analysis of precipitated plasma (0-7h) showed that unchanged maraviroc was the major circulating component (58%). The secondary amine resulting from N-dealkylation (UK-408,027; 6%), two analogues of the amine involving oxidation of the triazole moiety (6 and 1%) and two products of oxidation in the triazole moiety (5 and 8%; metabolite B in Figure 4) were also identified, in addition to multiple minor components involving oxidation in the triazole, phenyl and difluorocyclohexane moieties.

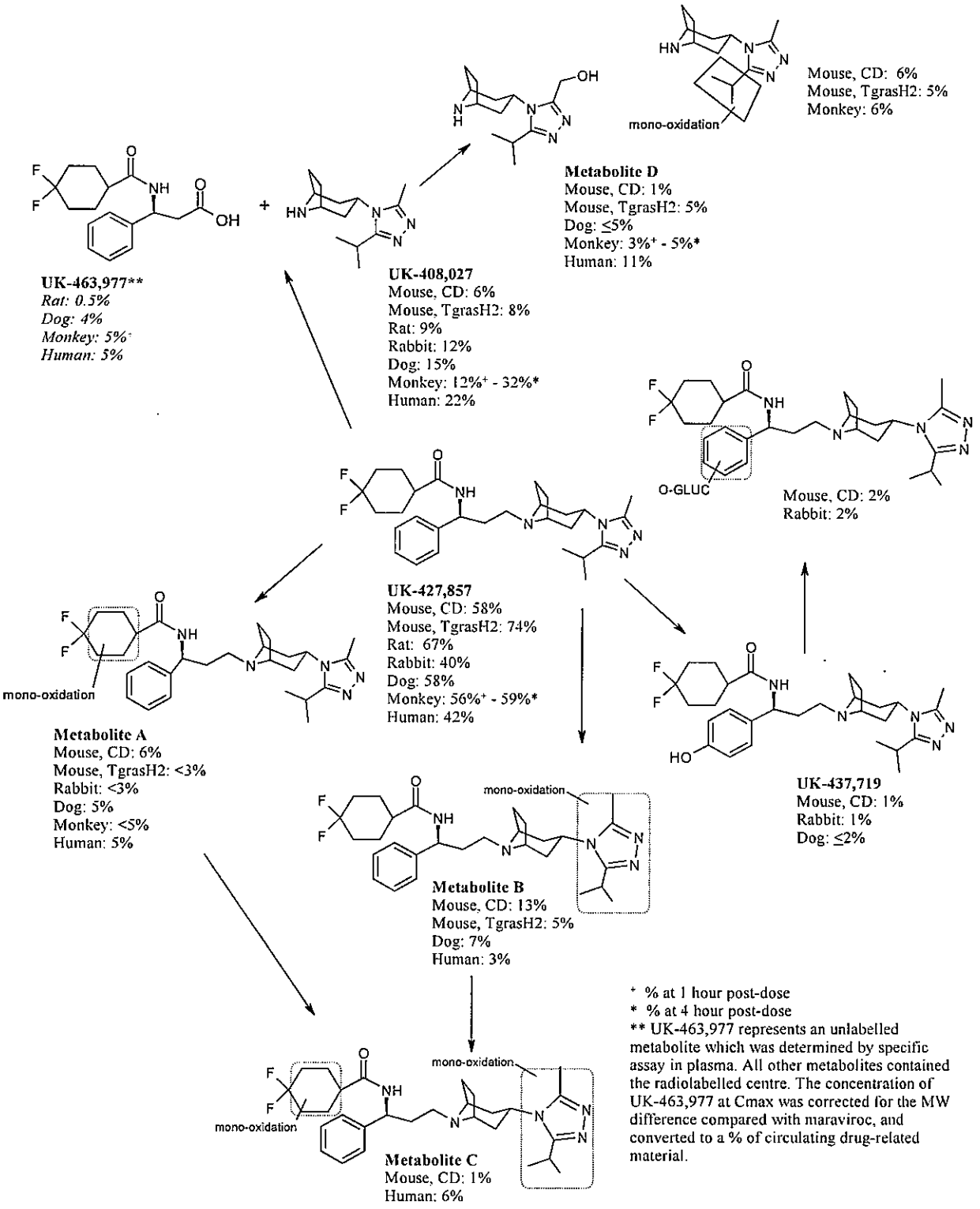
In a second study (DM39) male TgrasH2 wild type mice received oral doses of 200 mg/kg [^{14}C]-labelled maraviroc. At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (0-7h) showed that unchanged maraviroc was the major circulating component (74%). The secondary amine resulting from N-dealkylation (UK-408,027; 8%), two analogues of the amine involving oxidation of the triazole moiety (5% each) were also indentified, in addition to four minor components involving oxidation in the triazole and difluorocyclohexane moieties.

2.6.4.5.1.9. Circulating metabolites in the rat (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM26 and DM36)

The profile of circulating metabolites of maraviroc has been examined following oral (100 mg/kg) administration of [^{14}C]-labelled maraviroc to male and female rats (DM36). At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (0-7h and 0-24h, male and female respectively) showed that unchanged maraviroc was the major circulating component (mean 67%). The secondary amine resulting from N-dealkylation (UK-408,027; 9%) and an uncharacterised polar metabolite (23%) were also identified.

The concentration of the carboxylic acid metabolite (UK-463,977) was determined by specific assay (this module, Table 5). A mean C_{max} concentration of 2.48 ng/mL was achieved at 2 hours post-dose (DM26).

Figure 4. Circulating metabolites of maraviroc following administration of [^{14}C]-maraviroc to mouse, rat, rabbit, dog, cynomolgus monkey and human



Note: Metabolites A, B & C – the actual site of oxidation has been determined in human samples by a combination of mass spectrometry and NMR (DM25, DM43).

2.6.4.5.1.10. Circulating metabolites in the rabbit (Module 2.6.5. Tabulated Summaries, Section 9, Study No. DM41)

The profile of circulating metabolites of maraviroc has been examined following oral (30 mg/kg) administration of [^{14}C]-labelled maraviroc to female rabbits (DM41). At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (0-8h) showed that unchanged maraviroc was the major circulating component (40%). The secondary amine resulting from N-dealkylation (UK-408,027; 12%), the product of mono-oxidation at the para position of the phenyl ring (UK-437,719; 1%), a metabolite resulting from oxidation and glucuronidation of the phenyl ring (2%) and three minor components involving oxidation in the difluorocyclohexane ring (<3%) were identified. The major circulating rabbit metabolite remained unidentified (38%).

2.6.4.5.1.11. Circulating metabolites in the dog (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM30 and DM40)

The profile of circulating metabolites of maraviroc has been examined in male and female dogs following oral (5 mg/kg) administration of [^{14}C]-labelled maraviroc (DM40). At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (0-8h) showed that unchanged maraviroc was the major circulating component (58%; mean of male and female). The secondary amine resulting from N-dealkylation (UK-408,027; 15%) and the product of mono-oxidation at the para position of the phenyl ring (UK-437,719; ≤2%) were also identified, in addition to three minor components involving oxidation.

The concentration of the carboxylic acid metabolite (UK-463,977) was determined by specific assay (Table 5). A mean C_{max} concentration of 10.8 ng/mL was achieved at 1.25 hours post-dose (DM30).

2.6.4.5.1.12. Circulating metabolites in the cynomolgus monkey (Module 2.6.5. Tabulated Summaries, Section 9, Study Nos. DM28 and DM37)

The profile of circulating metabolites of maraviroc has been examined in male cynomolgus monkeys following oral (50 mg/kg) administration of [^{14}C]-labelled maraviroc (DM37). At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (1 and 4h) showed that unchanged maraviroc was the major circulating component (58%; mean of both time points). The secondary amine resulting from N-dealkylation (UK-408,027; mean 22%) and an analogue of the amine involving oxidation of the methyl group of the triazole moiety (mean 4%; metabolite D in Figure 4) were identified, in addition to three products of mono-oxidation in the difluorocyclohexyl ring and a product of N-dealkylation and oxidation identified as minor components.

The concentration of the carboxylic acid metabolite (UK-463,977) was determined by specific assay. A mean C_{max} concentration of 45.2ng/mL was achieved at 1 hour post-dose (DM28).

2.6.4.5.1.13. Circulating metabolites in human (Module 2.6.5. Tabulated Summaries, Section 9, Study No. DM25)

The profile of circulating metabolites of maraviroc has been examined in male human volunteers following oral (300 mg) administration of [^{14}C]-labelled maraviroc (DM25, Study 1010). At all times following dosing concentrations of radioactivity were higher than those of unchanged maraviroc, indicating the presence of circulating metabolites. HPLC profiling and LC-MS/MS analysis of precipitated plasma (0-18h) showed that unchanged maraviroc was the major circulating component (42%). The secondary amine metabolite resulting from N-dealkylation (UK-408,027) and an analogue of the amine involving oxidation of the methyl group on the triazole moiety (metabolite D, Figure 4) were also identified and accounted for 22% and 11% of circulating radioactivity, respectively. Other identified minor radiolabelled metabolites involved oxidation in the difluorocyclohexyl ring (5%; three components identified as metabolite A in Figure 4), oxidation of the triazole moiety (3%; metabolite B in Figure 4) and four products of oxidation in both the difluorocyclohexyl ring and the triazole moiety (6%; labelled as metabolite C in Figure 4).

The concentration of the carboxylic acid metabolite (UK-463,977) was determined by specific assay. A mean C_{max} of 37.3 ng/mL was achieved at 1.5 hours after dosing (Table 5).

2.6.4.5.2. *In vitro* metabolism

2.6.4.5.2.1. Enzymology (Module 2.6.5. Tabulated Summaries, Section 10, Study Nos. DM5, DM19, DM24, DM35 and DM42)

The *in vitro* metabolism of maraviroc has been studied in hepatic microsomes from human livers with varying CYP3A4, 2C9 and 2D6 activities and in microsomes prepared from cells expressing individual cytochrome P450 enzymes. Maraviroc was slowly metabolised in human liver microsomes with disappearance half-life values of 80 ± 5 min for HM/29 and >120 min in livers HM/28 and HM/9-2. In microsomes prepared from cells expressing individual cytochrome P450 enzymes, it was only possible to detect metabolism in incubations with CYP3A4 and CYP2D6 (DM5). In further studies using human hepatic microsomes, maraviroc had a disappearance half-life of 13.1 min. This was extended to 79 min in the presence of the specific CYP3A4 inhibitor, ketoconazole. The inhibitors sulphaphenazole (CYP2C9), and quinidine (CYP2D6) had no effect on the rate of metabolism. The use of recombinant enzyme systems confirmed a role for CYP3A4 (and its orthologue, CYP3A5) in the metabolism of maraviroc, and showed that neither of the polymorphic P450 enzymes CYP2C19 or CYP2D6 contribute significantly to its metabolism (DM24).

The formation of the circulating N-dealkylated metabolite UK-408,027 has been shown to be mediated by CYP3A4 in human liver microsomes (DM35). The metabolic pathway in vitro was characterised by single enzyme kinetics, with a K_m of 23μM and V_{max} of 154 pmol/mg/min. In incubations with individual CYPs only CYP3A4 gave substantial metabolite formation, with a K_m value of 13μM.

Following incubation of [^{3}H]-maraviroc for 2 hours with dog, cynomolgus monkey and human hepatocytes, the major radioactive component was unchanged parent (DM19). In addition, small

quantities of monohydroxylated metabolites were detected, consistent with hydroxylation in the difluorocyclohexyl ring and on the substituted triazole moiety.

The *in vitro* metabolism of [^{14}C]-dual-labelled maraviroc has been studied in human liver microsomes and hepatocytes (DM42). In vivo studies using [^{14}C]-single-labelled maraviroc showed that N-dealkylation adjacent to the tropane ring was a significant pathway, resulting in unlabelled metabolic components (Sections 2.6.4.5.1 and 2.6.4.5.2.). The in vitro data showed that this N-dealkylation pathway occurred in both microsomes and hepatocytes. In microsomes, the previously unlabelled portion of the molecule formed an alcohol, whilst the presence of cytosolic enzymes (such as aldehyde dehydrogenase) in hepatocytes promoted the formation of a carboxylic acid, UK-463,977. In hepatocytes, the alcohol and acid metabolites together accounted for approximately the same amount of radioactivity as UK-408,027, also suggesting that no other metabolic components are formed from the N-dealkylation pathway.

2.6.4.5.2.2. Inhibition (Module 2.6.5. Tabulated Summaries, Section 12, Study Nos. DM7, DM22 and DM33)

The potential for maraviroc to inhibit the activity of five drug metabolising cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) has been studied using recombinant enzymes (DM7) and human liver microsomes (DM22, DM33). In the recombinant enzyme systems, maraviroc did not inhibit any of the cytochrome P450 enzymes investigated except for weak inhibition of CYP2D6 (IC_{50} 87$\pm$2 μM). A slight increase in potency (<2-fold) upon pre-incubation of maraviroc with CYP2D6 was observed.

However, the human liver microsome studies are considered definitive since this matrix has the greater relevance to the *in vivo* situation. The potential for maraviroc to inhibit the activity of seven drug metabolising cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) has been studied in human liver microsomes (DM22, DM33). Maraviroc was demonstrated to be a weak inhibitor of cytochrome P450 activity with estimated IC_{50} values of >30μM against each enzyme investigated. Maraviroc is unlikely to inhibit the metabolism of other cytochrome P450 substrates in the clinic.

2.6.4.6. Excretion

2.6.4.6.1. Excretion into urine and faeces (Module 2.6.5. Tabulated Summaries, Section 13, Study Nos. DM25, DM26, DM27, DM28, DM30, DM31 and DM34)

The excretion of orally administered [^{14}C]-labelled maraviroc has been investigated in the animal species used in toxicology studies (DM26, DM27, DM28, DM30, DM31 and DM34), and also in male human volunteers (DM25). Although [^{3}H]-maraviroc was also administered to mouse, rat and dog (DM9, DM10, DM11), the carbon-14 data is considered to be definitive since it provided a more comprehensive metabolism profile. The results are summarised in Table 6 of this module.

The major route of excretion in all species was in the faeces with 76 to 95% of the dose recovered by this route. In contrast from 4 to 20% of the dose was recovered in the urine. In all

species, the excretion of radioactivity was rapid and the majority of dosed radioactivity was recovered within the first 48h after administration (57-100%).

Table 6. Excretion of radioactivity after single oral doses of [^{14}C]-maraviroc to mouse, rat, rabbit, dog, cynomolgus monkey and human

Species (Study No.)	Dose (mg/kg)	Sex (n)	t (h)	Percentage of dose recovered in: Urine 0-t	Faeces 0-t	Total Recovery 0-48h	Total Recovery 0-t
Mouse (CD1) (DM27)	200	3M	96	10.0	86.9	96.0	97.5
Mouse (TgrasH2) (DM34)	200	3M	96	11.6	88.9	100.1	100.5
Rat (DM26)	100	2M/2F	96	6.0	91.1	96.9	97.1
Rabbit (DM31)	30	3F	120	4.6	94.6	75.8	104.9
Dog (DM30)	5	1M/1F	168	11.7	79.0	69.5	91.3
Monkey (DM28)	50*	2M	120	4.0	78.9	76.8	92.1
Human (DM25)	4**	3M	168	19.6	76.4	57.0	96.0

* cage wash and cage debris accounted for 9% of total recovery.
** human study was a single solution administration of 300mg [^{14}C]-maraviroc.

2.6.4.6.2. Biliary secretion (Module 2.6.5. Tabulated summaries, Section 14, Study Nos. DM8 and DM17)

Maraviroc (1 mg) has been administered to an isolated perfused male rat liver (DM8). Hepatic extraction was moderate (extraction ratio 0.4), in keeping with the high systemic clearance in this species (Section 2.6.4.3.1.2). During the 90 minute period of the experiment a total of 34% of the dose was recovered as unchanged maraviroc in the bile.

In a further study [^{3}H]-labelled maraviroc was administered intravenously (3 mg/kg) to male bile duct cannulated rats (DM17). Recovery of total radioactivity in the bile (0 to 6 h) was 64% of the dose indicating that the high proportion of the dose excreted in the faeces of the rat (Table 6) is probably mediated by biliary secretion. Four drug-related components were present in the bile, the major being unchanged maraviroc. In addition, 15% of dosed radioactivity was secreted directly into the gastrointestinal tract as parent compound.

2.6.4.6.3. Excretion into milk (Module 2.6.5. Tabulated Summaries, Section 7, Study No. DM45)

The excretion of maraviroc and its metabolites into milk of lactating female rats has been studied following oral administration of 100mg/kg [^{14}C]-maraviroc. At all times following dosing, concentrations of radioactivity could be measured in the milk indicating that drug-related material was excreted in milk (Table 7). The major component of drug related material present in the milk was identified as unchanged maraviroc representing 86% of the total radioactivity. In addition, 4% of drug related material present in milk was identified as the secondary amine resulting from N-dealkylation (UK-408,027).

Table 7. Concentrations of total radioactivity in milk and plasma following administration of [^{14}C]-maraviroc

Time post dose (h)	Concentrations (µg equiv/mL)		Ratio
	Plasma	Milk	Milk:Plasma
1	1.13 ± 0.25	2.73 ± 0.19	2.5 ± 0.6
4	0.80 ± 0.16	2.07 ± 0.25	2.6 ± 0.2
12	0.06 ± 0.02	0.16 ± 0.04*	2.7 ± 0.2*
24	BLQ	BLQ	BLQ

* Mean includes results calculated from data less than 30dpm above background
BLQ = below limit of quantification
Data represent mean ± standard deviation of 3 animals

2.6.4.7. Pharmacokinetic Drug Interactions

Not applicable because no such studies have been performed.

2.6.4.8. Other Pharmacokinetic Studies

Not applicable because no such studies have been performed.

2.6.4.9. Discussion and Conclusions

Pharmacokinetic analysis has established the absorption, metabolism, distribution and elimination profile of maraviroc in animals and humans. The pathways of maraviroc metabolism in human were all represented in toxicology species. The main circulating metabolites in human plasma were the secondary amine UK-408,027 and a hydroxylated metabolite which arose by further metabolism of the amine. All human circulating metabolites were identified in the plasma of at least one of the toxicology species indicating that animals were exposed to these metabolites in repeat-dose safety studies. Consequently, the choice of animal species for the evaluation of maraviroc toxicology was appropriate and relevant to human safety.

Although the major excreted and circulating component is unchanged maraviroc, the drug has been shown to be a substrate for CYP3A4 in vitro. Maraviroc is also a substrate for P-glycoprotein. Therefore its pharmacokinetics are likely to be affected by co-administration of inhibitors and inducers of these proteins. Maraviroc is not an inhibitor of the 7 major cytochrome P450 enzymes and is therefore unlikely to affect the metabolism of other co-administered P450 substrates at clinical doses.

Toxicokinetic investigations show that at the NOAEL doses in toxicology studies animals were exposed to similar or several-fold higher unbound concentrations of maraviroc than humans at the maximum expected clinical dose (300 mg BID).

2.6.4.10. Tables and Figures

2.6.4.10.1. Performance of analytical methods used for determination of maraviroc, UK-408,027 and UK-463,977 in biological fluids

Table 8. Determination of maraviroc in animal plasma

Species (Study No.)	Maraviroc		
	LOQ (ng/mL)	Concn. (ng/mL)	Imprecision (%)
Mouse (DM2)	10	20	17
		200	9.2
		2000	1.8
Mouse (DM27 & DM34)	10	10	1.3
		16	1.6
		20	1.3
		80	1.2
		180	0.9
Rat (DM1)	1	20	15
		200	1.3
		2000	2.3
Rat (DM26)	10	10	1.4
		16	5.0
		100	0.6
		128	0.3
		180	1.6
Rabbit (DM31)	10	10	4.1
		16	3.0
		80	2.6
		180	1.2
Dog (DM4)	25	25	8.0
		250	2.8
		500	2.3
Dog (DM11)	1.25	2.5	12*
		5.0	2.0*
		25	1.8*
		50	2.6*
		75	3.3*
		125	15.2*
Dog (DM30)	4	4	2.0
		10	0.7
		16	1.2
		100	1.5
		180	1.0
Monkey (DM28)	10	10	2.2
		16	0.9
		20	0.7
		100	1.1
		180	0.9

Method of detection mass spectrometry
LOQ = limit of quantification
* As only single measurements were made the values quoted are inaccuracy values.

Table 9. Determination of UK-463,977 in animal and human plasma and urine

Species (Study No.)	UK-463,977 in plasma			UK-463,977 in urine		
	LOQ (ng/mL)	Concn. (ng/mL)	Imprecision (%)	LOQ (ng/mL)	Concn. (ng/mL)	Imprecision (%)
Mouse	-	-	-	10	10	7.3
(DM27)	-	-	-		100	2.6
	-	-	-		1000	3.9
Rat	0.5	0.5	7.0	10	10	12.8
(DM26)		1	7.2		20	3.1
		5	4.0		100	1.1
		50	4.2		1000	4.2
Dog	0.2	0.2	6.0	10	10	14.4
(DM30)		2	1.3		20	7.2
		20	1.8		100	6.2
	0.5	0.5	5.9		1000	2.8
Monkey		1	5.3	40	40	5.9
(DM28)		5	2.8		400	2.0
		50	3.2		4000	5.1
Human	0.1	0.1	11.3	10	10	2.0
(DM25)		0.5	7.6		100	4.2
		5	2.2		1000	1.4

Method of detection was mass spectrometry
LOQ = limit of quantification
- = not measured in this species

Table 10. Determination of UK-408,027 in human urine

Species (Study No.)	UK-408,027		
	LOQ (ng/mL)	Concn. (ng/mL)	Imprecision (%)
Human	5	5	13.2
(DM29)		10	6.6
		50	3.3
		500	3.3
		1000	3.5

Method of detection was mass spectrometry
LOQ = limit of quantification

2.6.4.10.2. Maraviroc toxicokinetic data

Table 11. Maraviroc plasma pharmacokinetics and exposure multiples in male and female mice

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
5-day pilot	01017	500	5	6311	2651	17	5160	24510	10294	8	
M		1000	5	6164	4027	26	7839	36050	15141	12	
		2000	5	21917	9205	60	17919	76630	32185	25	NOAEL
F		500	5	9588	4027	26	7839	33330	13999	11	
		1000	5	6752	2836	18	5520	26560	11155	9	
		2000	5	30346	12745	82	24811	94030	39493	31	NOAEL
2-week	01-2120-03	20	1	178	75	0,5	146	1950	819	0,6	
M		200	1	4900	2058	13	4006	18080	7594	6	
		1000	1	10738	4510	29	8779	139610	58636	46	
		2000	1	21931	9211	60	17931	239680	100666	79	
		20	13	250	105	1	204	1030	433	0	
		200	13	2379	999	6	1945	12660	5317	4	NOAEL
		1000	13	6560	2755	18	5364	45750	19215	15	
		2000	13	11806	4958	32	9652	132070	55469	44	
		20	1	1962	824	5	1604	5390	2264	2	
F		200	1	1558	654	4	1274	15920	6686	5	
		1000	1	11384	4781	31	9307	95780	40228	32	
		2000	1	14708	6177	40	12025	218920	91946	72	
		20	13	365	153	1	298	920	386	0,3	
		200	13	2017	847	5	1649	13770	5783	5	NOAEL
		1000	13	7382	3100	20	6036	59160	24847	19	
		2000	13	12360	5191	34	10106	236150	99183	78	
1-month	02002	200	26	5551	2331	15	4538	31640	13289	10	
M		500	26	10032	4214	27	8202	79410	33352	26	
		750	26	13033	5474	35	10656	126090	52958	42	NOAEL
		200	26	8267	3472	22	6759	35720	15002	12	
F		500	26	12777	5366	35	10446	106600	44772	35	
		750	26	13933	5852	38	11391	110360	46351	36	NOAEL
3-month	03012	200	83	3925	1648	11	3209	15169	6371	5	
M		500	83	19251	8086	52	15740	58927	24749	19	
		750	83	17933	7532	49	14662	250851	105357	83	NOAEL
		200	83	3674	1543	10	3004	10925	4588	4	
F		500	83	10084	4235	27	8245	52124	21892	17	
		750	83	15152	6364	41	12388	163855	68819	54	NOAEL
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Mice 0.42, Human 0.25
Molecular weight: 513.7 daltons
For the 5-pilot study, values in italics show AUC calculated over a 1-5h time period.

Table 11. Maraviroc plasma pharmacokinetics and exposure multiples in male and female mice (continued)

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
1-month Tg (ras H2)	2003-0392	500	28	11100	4662	30	9075	28100	11802	9	
M	Hemizygous	1000	28	18400	7728	50	15044	95400	40068	31	
		1500	28	54500	22890	148	44559	671000	281820	221	NOAEL
	Wild type	500	28	5850	2457	16	4783	31100	13062	10	
		1000	28	15200	6384	41	12427	118000	49560	39	
		1500	28	52700	22134	143	43087	650000	273000	214	
F	Hemizygous	500	28	8980	3772	24	7342	51800	21756	17	
		1000	28	11700	4914	32	9566	95100	39942	31	
		1500	28	22700	9534	62	18559	259000	108780	85	NOAEL
	Wild type	500	28	16600	6972	45	13572	44600	18732	15	
		1000	28	33100	13902	90	27062	415000	174300	137	
		1500	28	36300	15246	99	29679	504000	211680	166	
6-month Tg (ras H2)	2004-0091	200	184	4640	1949	13	3794	22500	9450	7	
M		800	184	2890	1214	8	2363	33400	14028	11	
		1500	184	8540	3587	23	6982	117000	49140	39	
F		200	184	4810	2020	13	3933	29000	12180	10	
		800	184	10600	4452	29	8667	71600	30072	24	
		1500	184	16000	6720	43	13082	213000	89460	70	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Mice 0.42, Human 0.25
Molecular weight: 513.7 daltons

Table 12. Maraviroc plasma pharmacokinetics and exposure multiples in mice

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
5-day pilot M+F	01017	500	5	7950	3339	22	6500	28920	12146	10	
		1000	5	9195	3862	25	7518	31310	13150	10	
		2000	5	26132	10975	71	21365	85330	35839	28	NOAEL
2-week M+F	01-2120-03	20	1	1070	449	3	875	3670	1541	1	
		200	1	3229	1356	9	2640	17000	7140	6	
		1000	1	11061	4646	30	9043	117695	49432	39	
		2000	1	18319	7694	50	14978	229300	96306	76	
		20	13	308	129	1	251	975	410	0	
		200	13	2198	923	6	1797	13215	5550	4	NOAEL
		1000	13	6971	2928	19	5700	52455	22031	17	
		2000	13	12083	5075	33	9879	184110	77326	61	
1-month M+F	02002	200	26	6909	2902	19	5649	33680	14146	11	
		500	26	11405	4790	31	9324	93005	39062	31	
		750	26	13483	5663	37	11024	118225	49655	39	NOAEL
3-month M+F	03012	200	83	3799	1596	10	3106	13047	5480	4	
		500	83	14668	6160	40	11992	55525	23321	18	
		750	83	16543	6948	45	13525	207353	87088	68	NOAEL
1-month Tg (ras H2) M+F	2003-0392 Hemizygous	500	28	10000	4200	27	8176	39900	16758	13	
		1000	28	15000	6300	41	12264	95200	39984	31	
		1500	28	35100	14742	95	28698	466000	195720	154	NOAEL
	Wild type	500	28	11200	4704	30	9157	38800	16296	13	
		1000	28	19200	8064	52	15698	267000	112140	88	
		1500	28	44000	18480	120	35974	577000	242340	190	
6-month Tg (ras H2) M+F	2004-0091	200	184	4510	1894	12	3687	25800	10836	8	
		800	184	6470	2717	18	5290	52500	22050	17	
		1500	184	12000	5040	33	9811	165000	69300	54	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Mice 0.42, Human 0.25
Molecular weight: 513.7 daltons
For the 5-pilot study, values in italics show AUC calculated over a 1-5h time period.

Table 13. Maraviroc plasma pharmacokinetics and exposure multiples in rats

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
1-month	02072	100	1	687	336	2	655	4766	2335	2	
M		300	1	2378	1165	8	2268	21285	10430	8	
		1500	1	7264	3559	23	6928	84550	41430	32	
		100	23	1145	561	4	1092	7388	3620	3	
		300	23	4293	2104	14	4095	31217	15296	12	NOAEL
		1500	23	7333	3593	23	6995	88759	43492	34	
6-month + 3-month reversibility	911/092	30	0	265	130	1	253	1334	654	0,5	
		100	0	1427	699	5	1361	12511	6130	5	
M+F		300	0	2995	1468	9	2857	38568	18898	15	
		900	0	7045	3452	22	6719	97178	47617	37	
		30	181	604	296	2	576	2831	1387	1	
		100	181	2981	1460	9	2843	19966	9783	8	NOAEL
		300	181	5973	2927	19	5697	65926	32304	25	
		900	181	9349	4581	30	8918	133605	65466	51	
Investigation (thyroid and Liver) 27 or 28 days M+F	03165	900	27	2994	1467	9	2856	34894	17098	13	
24-month	2003-0446	50	198	477	234	2	455	3520	1725	1	
M		100	198	839	411	3	800	9820	4812	4	
		500	198	2740	1343	9	2614	40700	19943	16	
		900	198	3570	1749	11	3405	46900	22981	18	
F		50	198	459	225	1	438	2550	1250	1	
		100	198	1700	833	5	1622	10100	4949	4	
		500	198	4260	2087	14	4063	38700	18963	15	
		900	198	4120	2019	13	3930	63100	30919	24	
M+F		50	198	468	229	1	446	3030	1485	1	
		100	198	1270	622	4	1211	9970	4885	4	
		500	198	3490	1710	11	3329	39700	19453	15	
		900	198	3840	1882	12	3663	54700	26803	21	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Rat 0.49, Human 0.25
Molecular weight: 513.7 daltons

Table 14. Maraviroc plasma pharmacokinetics and exposure multiples in dogs

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
4-day	00095										
M		25	1	3376	1225	8	2386	7880	2860	2	
F		50	1	6445	2340	15	4554	24450	8875	7	
M		500	4	14775	5363	35	10441	178480	64788	51	
F		250	4	5588	2028	13	3949	23040	8364	7	NOAEL
2-week	01-2120-05	10	1	1084	394	3	766	2369	860	0,7	
M+F	01059	50	1	2306	837	5	1630	9373	3402	3	
		250	1	3831	1391	9	2707	32176	11680	9	
		10	13	817	297	2	577	2152	781	0,6	NOAEL
		50	13	2831	1027	7	2000	9250	3358	3	
		250	13	4414	1602	10	3119	25653	9312	7	
1-month	02003	5	1	996	362	2	704	2926	1062	1	
M+F		50	1	6994	2539	16	4942	26643	9671	8	
		150	1	9396	3411	22	6640	61862	22456	18	
		5	19	974	354	2	688	6023	2186	2	NOAEL
		50	19	8813	3199	21	6228	35194	12775	10	
		150	19	9686	3516	23	6845	99732	36203	28	
6-month	02073	5	1	959	348	2	678	3009	1092	1	
M+F		15	1	2803	1018	7	1981	8317	3019	2	
		40	1	4441	1612	10	3138	18016	6540	5	
		5	5	972	353	2	687				
		15	5	3300	1198	8	2332				
		40	5	5925	2151	14	4187				
		5	54	859	312	2	607				
		15	54	3355	1218	8	2371				
		40	54	5333	1936	13	3768				
		5	110	752	273	2	532				
		15	110	3016	1095	7	2131				
		40	110	4769	1731	11	3370				
		5	173	938	340	2	663				
		15	173	2476	899	6	1749				
		40	173	4186	1520	10	2958				
		5	176	878	319	2	620	2661	966	1	NOAEL
		15	176	2612	948	6	1846	8534	3098	2	
		40	176	4002	1453	9	2828	19819	7194	6	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Dog 0.363, Human 0.25
Molecular weight: 513.7 daltons
Light shaded area: Plasma drug concentrations measured 1 hour post dosing during cardiovascular examination

Table 15. Maraviroc plasma pharmacokinetics and exposure multiples in Cynomolgus monkeys

Study Duration	Study Number	Daily Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
7 or 8 days M+F	911/089	5	0	145	75	0,5	146	237	122	0,1	
		15	0	280	145	1	282	502	259	0,2	
		50	0	1590	820	5	1597	3725	1922	2	
		150	0	5971	3081	20	5998	19622	10125	8	
		5	6	169	87	0,6	170	254	131	0,1	
		15	6	621	321	2	624	1007	520	0,4	
		50	6	1388	716	5	1394	3744	1932	2	
		150	6	4274	2205	14	4293	15558	8028	6	NOAEL
Immunotoxicity 4-week	911/096	30*	23	262	135	1	263	948	489	0,4	
		100*	23	1683	869	6	1691	6657	3435	3	NOAEL
M+F		300*	23	4336	2237	14	4356	40098	20691	16	
1-month M+F	911/097	100*	0	1249	644	4	1254	5423	2798	2	
		200*	0	2967	1531	10	2980	19232	9924	8	
		400*	0	6786	3502	23	6816	66007	34060	27	
		800*	0	8704	4491	29	8743	84662	43686	34	
		100*	1	1191	614	4	1196				
		200*	1	2309	1191	8	2319				
		400*	1	3908	2016	13	3925				
		800*	1	12832	6621	43	12889				
		100*	26	1389	716	5	1395				
		200*	26	3518	1815	12	3534				
		400*	26	10381	5357	35	10428				
		800*	Euthanized on Day 1								
		100*	27	809	418	3	813	4212	2173	2	NOAEL
		200*	27	3095	1597	10	3108	19000	9804	8	
		400*	27	8338	4303	28	8376	68174	35178	28	
		800*	Euthanized on Day 1								
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

* given as a divided dose
Free fraction: Monkey 0.516, Human 0.25
Molecular weight: 513.7 daltons
Light shaded area: Plasma drug concentrations measured at the end of post-dosing cardiovascular examination (1 hour after the first daily dose at 100 and 200 mg/kg and 3 hours at 400 and 800 mg/kg)

Table 15. Maraviroc plasma pharmacokinetics and exposure multiples in Cynomolgus monkeys (continued)

Study Duration	Study Number	Daily Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
9-month M+F	911/102	30*	0	185	95	0,6	186	487	251	0	
		120*	0	1322	682	4	1328	7817	4034	3	
		400*	0	5529	2853	18	5553	57301	29567	23	
		30*	1	145	75	0	146				
		120*	1	1290	666	4	1296				
		400*	1	4087	2109	14	4106				
		30*	88	263	136	1	265				
		120*	88	1384	714	5	1390				
		400*	88	8522	4397	28	8560				
		30*	133	153	79	1	154	344	178	0,1	
		120*	133	1621	836	5	1628	7560	3901	3	
		400*	133	11462	5914	38	11513	86692	44733	35	
		30*	176	149	77	0	150				
		120*	176	1216	627	4	1221				
		400*	176	5915	3052	20	5942				
		30*	267	126	65	0	127				
		120*	267	1393	719	5	1399				
		400*	267	3330	1718	11	3345				
		30*	270	100	52	0,3	100	370	191	0,1	
		120*	270	1153	595	4	1158	6500	3354	3	NOAEL
		400*	270	10428	5381	35	10475	90605	46752	37	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

* given as a divided dose
Free fraction: Monkey 0.516, Human 0.25
Molecular weight: 513.7 daltons
Light shaded area: Plasma drug concentrations measured at the end of post-dosing cardiovascular examination (1 hour after the first daily dose at 30 and 120 mg/kg and 3 hours at 400 mg/kg)

Table 16. Maraviroc plasma pharmacokinetics and exposure multiples in rat reproductive studies

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/mL	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/mL	AUC 24h (free) ng.h/mL	Exposure Multiple AUC (free)	
Embryofoetal	02028	100	17 p.i.	1865	914	6	1779	15411	7551	6	
Day 6 to 17 p.i.		300	17 p.i.	4535	2222	14	4325	45520	22305	17	NOAEL (Fo females)
F		1000	17 p.i.	7566	3707	24	7217	102001	49980	39	
Pre-post natal	02-2120-10	100	4 p.p.	810	397	3	773	4127	2022	2	
Day 6 p.i. to 20 p.p.		300	4 p.p.	3496	1713	11	3335	22490	11020	9	NOAEL (Fo females & F1developmental tox)
F		1000	4 p.p.	7754	3800	25	7397	71438	35005	27	NOAEL (Reproduction)
Fertility	02133	100	15	1602	785	5	1528	9685	4746	4	
M 63-66 days		300	15	4068	1993	13	3880	35770	17527	14	NOAEL (Fo Males and Females)
F 23-28 days M+F		1000	15	6871	3367	22	6554	100306	49150	39	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Rat 0.49, Human 0.25
Molecular weight: 513.7 daltons
p.i: post insemination; p.p: post partum

Table 17. Maraviroc plasma pharmacokinetics and exposure multiples in rabbit reproductive studies

Study Duration	Study Number	Dose mg/kg	Day of treatment	Cmax (total) ng/ml	Cmax (free) ng/mL	Exposure Multiple Cmax (free)	Cmax (free) nM	AUC 24h (total) ng.h/ml	AUC 24h (free) ng.h/ml	Exposure Multiple AUC (free)	
Embryofoetal	02029	30	19 p.i.	1872	636	4	1239	5347	1818	1	
Days 7 to 19 p.i.		75	19 p.i.	5847	1988	13	3870	27128	9224	7	NOAEL (Fo females)
F		200	19 p.i.	10107	3436	22	6689	127540	43364	34	
Escalating Dose	01096	250	1	10604	3605	23	7018	120113	40838	32	
Range Finding		500	1	41480	14103	91	27454	516744	175693	138	
5 or 6 days		1000	1	68277	23214	150	45190	672178	228541	179	
F		125	3 or 4	16673	5669	37	11035	134374	45687	36	
Human Study	1007	600 mg (300 BID)		618	155		301	5100	1275		

Free fraction: Rabbit 0.34, Human 0.25
Molecular weight: 513.7 daltons
p.i : post insemination

2.6.5.1. Pharmacokinetics: overview Overview (1/5) Test Article: UK-427,857

Type of Study	Test System	Method of Administration	Dose/Spiked Concentration	Testing Facility	Study Number	Location
2.6.4.3 Absorption						
(1) Single Dose Pharmacokinetics	Mouse (mdr1a/1b ko)	po	16 mg/kg	[redacted](UK)	DM2	
	Mouse (fvb WT)	po	16 mg/kg	[redacted](UK)	DM2	
	Rat	iv	1 mg/kg	[redacted](UK)	DM1	
	Rat	po	3 mg/kg	[redacted](UK)	DM1	
	Rat	po	10 mg/kg	[redacted](UK)	DM1	
	Dog	iv	0.5 mg/kg	[redacted](UK)	DM4	
	Dog	po	1 mg/kg	[redacted](UK)	DM4	
	Dog	po	2 mg/kg	[redacted](UK)	DM4	
(2) Multiple Dose Pharmacokinetics	Not applicable					
(3) Toxicokinetics	See xxxxxx Toxicokinetic summary. Toxicokinetic data are summarised in this section					
(4) Distribution						
1) Tissue Distribution	Rat	iv	3 mg/kg	[redacted](UK)	DM6	
	Rat	iv	3 mg/kg	[redacted](US)	DM46	
2) Plasma Protein Binding	Mouse, Rat Rabbit, Dog Human	*In vitro*	1, 30 &1000 ng/mL	[redacted](UK)	DM12	
	Mouse, Rat Rabbit, Dog Monkey, Human	*Ex vivo*	C_{max} of *in vivo* study	[redacted](UK)	DM23	
	Human	*In vitro*	1,30&1000 ng/mL	[redacted](UK)	DM18	
3) Blood Distribution	Rat, Dog, Human	*In vitro*	100 ng/mL	[redacted](UK)	DM16	
	Human	*In vitro*	100 ng/mL	[redacted](UK)	DM32	

2.6.5.1. Pharmacokinetics: overview (continued) Overview (2/5) Test Article: UK-427,857

Type of Study	Test System	Method of Administration	Dose/Spiked Concentration	Testing Facility	Study Number	Location
4) Other Distribution Study;						
Brain penetration	Rat	iv	1.3 mg/kg	[redacted](UK)	DM3	
Permeability CACO-2	Human	*In vitro*	25 µmol/L	[redacted](UK)	DM20	
Affinity for P-GP	Human	*In vitro*		[redacted](UK)	DM21	
Permeability P-GP/CACO-2	Human	*In vitro*		[redacted](UK)	DM44	
2.6.4.5 Metabolism						
(1) Circulating Metabolites	Mouse	po	20 mg/kg	[redacted](UK)	DM15	
	Mouse (CD1)	po	200 mg/kg	[redacted](UK)	DM38	
	Mouse (TgrasH2)	po	200 mg/kg	[redacted](UK)	DM39	
	Rat	po	10 mg/kg	[redacted](UK)	DM13	
	Rat	po	100 mg/kg	[redacted](UK)	DM36	
	Rabbit	po	30 mg/kg	[redacted](UK)	DM41	
	Dog	po	10 mg/kg	[redacted](UK)	DM14	
	Dog	po	5 mg/kg	[redacted](UK)	DM40	
	Monkey	po	50 mg/kg	[redacted](UK)	DM37	
	Human	po	300 mg	[redacted](UK)	DM43	
	Human	po	300 mg	[redacted](UK)	DM25	
(2) Metabolites in Excreta	Mouse	po	20 mg/kg	[redacted](UK)	DM15	
	Mouse (CD1)	po	200 mg/kg	[redacted](UK)	DM38	
	Mouse (TgrasH2)	po	200 mg/kg	[redacted](UK)	DM39	
	Rat	po	10 mg/kg	[redacted](UK)	DM13	
	Rat	po	100 mg/kg	[redacted](UK)	DM36	
	Rabbit	po	30 mg/kg	[redacted](UK)	DM41	
	Dog	po	10 mg/kg	[redacted](UK)	DM14	
	Dog	po	5 mg/kg	[redacted](UK)	DM40	
	Monkey	po	50 mg/kg	[redacted](UK)	DM37	
	Human	po	300 mg	[redacted](UK)	DM43	
	Human	po	300 mg	[redacted](UK)	DM25	
	Human	po	30 mg	[redacted](UK)	DM29	

2.6.5.1. Pharmacokinetics: overview (continued) Overview (3/5) Test Article: UK-427,857

Type of Study	Test System	Method of Administration	Dose/Spiked Concentration	Testing Facility	Study Number	Location
(3) Metabolites in Bile	Rat	iv	3 mg/kg	[redacted](UK)	DM17	
	Rat	IPRL	1 mg	[redacted](UK)	DM8	
(4) *In vitro* metabolism	Hepatic microsomes, recombinant CYP450 (Human)	*In vitro*	1 µmol/L	[redacted](UK)	DM5	
	Hepatic microsomes (Human)	*In vitro*	1 – 1000 µmol/L	[redacted](UK)	DM35	
	Hepatocytes, microsomes (Human)	*In vitro*	10 µmol/L	[redacted](UK)	DM42	
	Hepatic microsomes, Supermix®, recombinant CYPs (Human)	*In vitro*	1 µmol/L	[redacted](UK)	DM24	
	Hepatocytes (Dog, Monkey, Human)	*In vitro*	5 µmol/L	[redacted](France)	DM19	
(4) Inhibition of cytochrome P450	Recombinant CYP450s (Baculosomes™)	*In vitro*	Up to 100 µmol/L	[redacted](UK)	DM7	
	Hepatic microsomes (Human)	*In vitro*	0.03 –30 µmol/L	[redacted](UK)	DM22	

2.6.5.1. Pharmacokinetics: overview (continued) Overview (4/5) Test Article: UK-427,857

Type of Study	Test System	Method of Administration	Dose/Spiked Concentration	Testing Facility	Study Number	Location
(4) Inhibition of cytochrome P450 (continued)	Hepatic microsomes (Human)	*In vitro*	0.03 –30 µmol/L	[redacted](UK)	DM33	
(5) Enzyme Induction	Not applicable					
2.6.4.6 Excretion						
(1) Excretion into urine and faeces	Mouse	po	20 mg/kg	[redacted](UK)	DM9	
	Mouse	po	200 mg/kg	[redacted](UK)	DM27	
	Mouse (TgrasH2)	po	200 mg/kg	[redacted](UK)	DM34	
	Rat	po	10 mg/kg	[redacted](UK)	DM10	
	Rat	po	100 mg/kg	[redacted](UK)	DM26	
	Rabbit	po	30 mg/kg	[redacted](UK)	DM31	
	Dog	po	10 mg/kg	[redacted](UK)	DM11	
	Dog	po	5 mg/kg	[redacted](UK)	DM30	
	Monkey	po	50 mg/kg	[redacted](UK)	DM28	
	Human	po	300 mg	[redacted](UK)	DM25	
(2) Biliary excretion	Rat	iv	3 mg/kg	[redacted](UK)	DM17	
(3) Excretion in milk	Rat	po	100mg/kg	[redacted](UK)	DM45	
2.6.4.7 Pharmacokinetic Drug Interactions						
Permeability P-GP/CACO-2	Human	*In vitro*		[redacted](UK)	DM44	

2.6.5.2 Analytical Methods and Validation Reports

Test Article: UK-427,857

Location in CTD:

Assay performance (1/3)

Species	Mouse	Mouse	Mouse	Mouse	Rat	Rat	Rat	Rat
Study No.	DM2	DM27	DM27	DM34	DM1	DM26	DM26	DM26
Analyte	UK-427,857	UK-427,857	UK-463,977	UK-427,857	UK-427,857	UK-427,857	UK-463,977	UK-463,977
Sample	Plasma	Plasma	Urine	Plasma	Plasma	Plasma	Plasma	Urine
Method	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS
Internal Standard	UK-377,461	UK-462,015	CP-728,903	UK-462,015	UK-377,461	UK-462,015	CP-728,903	CP-728,903
Range of determination	10-2000 ng/mL	10-200 ng/mL	10-1000 ng/mL	10-200 ng/mL	10-2000 ng/mL	10-200ng/mL	0.5-5 ng/mL	10-1000 ng/mL
LOQ	10 ng/ml	10 ng/mL	10 ng/mL	10 ng/mL	10 ng/ml	10 ng/mL	0.5 ng/mL	10 ng/mL
Inaccuracy		+0.4%		+0.4%		-10.1%	+8.0%	-1.9%
Low (conc.)	+19.5% (20 ng/ml)	(10 ng/mL) -4.4% (16 ng/mL)	-3.3% (10 ng/ml)	(10 ng/mL) -4.4% (16 ng/mL)	+4.5% (20 ng/ml)	(10 ng/mL) -3.3% (16 ng/mL)	(0.5 ng/ml) -1.0% (1 ng/ml)	(10 ng/ml) -0.5% (20 ng/ml)
Medium (conc.)	+5.0% (200 ng/ml)	-0.3% (20 ng/mL) -7.3% (80 ng/mL)	+5.0% (100 ng/ml)	-0.3% (20 ng/mL) -7.3% (80 ng/mL)	-1.0% (200 ng/ml)	-6.1% (100 ng/mL) -5.3% (128 ng/mL)	+3.8% (5 ng/ml)	-4.3% (100 ng/ml)
High (conc.)	+1.0% (2000 ng/ml)	-14.3% (180 ng/mL)	+2.1% (1000 ng/ml)	-14.3% (180 ng/mL)	+0.5% (2000 ng/ml)	-7.4% (180 ng/mL)	+4.6% (50 ng/ml)	-6.8% (1000 ng/ml)
Imprecision		1.3%		1.3%		1.4%	7.0%	12.8%
Low (conc.)	17.0% (20 ng/ml)	(10 ng/mL) 1.6% (16 ng/mL)	7.3% (10 ng/ml)	(10 ng/mL) 1.6% (16 ng/mL)	15.0% (20 ng/ml)	(10 ng/mL) 5.0% (16 ng/mL)	(0.5 ng/ml) 7.2% (1 ng/ml)	(10 ng/ml) 3.1% (20 ng/ml)
Medium (conc.)	9.2% (200 ng/ml)	1.3% (20 ng/mL) 1.2% (80 ng/mL)	2.6% (100 ng/ml)	1.3% (20 ng/mL) 1.2% (80 ng/mL)	1.3% (200 ng/ml)	0.6% (100 ng/mL) 0.3% (128 ng/mL)	4.0% (5 ng/ml)	1.1% (100 ng/ml)
High (conc.)	1.8% (2000 ng/ml)	0.9% (180 ng/mL)	3.9% (1000 ng/ml)	0.9% (180 ng/mL)	2.3% (2000 ng/ml)	1.6% (180 ng/mL)	4.2% (50 ng/ml)	4.2% (1000 ng/ml)
n	6	6	8	6	6	6	6	8

Additional Information:

2.6.5.2 Analytical Methods and Validation Reports (continued)

Test Article: UK-427,857

Location in CTD:

Assay performance (2/3)

Species	Rabbit	Dog	Dog	Dog	Dog	Dog
Study No.	DM31	DM4	DM11	DM30	DM30	DM30
Analyte	UK-427,857	UK-427,857	UK-427,857	UK-427,857	UK-463,977	UK-463,977
Sample	Plasma	Plasma	Plasma	Plasma	Plasma	Urine
Method	LC-MS-MS	LC-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS
Internal Standard	UK-462,015	UK-377,461	UK-462,015	UK-462,015	CP-728,903	CP-728,903
Range of determination	10-200 ng/mL	2.5-1000 ng/mL [b]	1.25-250 ng/mL	4-200 ng/mL	0.2-20 ng/mL	10-1000 ng/mL
LOQ	10 ng/mL	25 ng/mL [b]	1.25 ng/mL	4 ng/mL	0.2 ng/mL	10 ng/mL
Inaccuracy	-6.9%		[a]	-2.5%		+5.0%
Low (conc.)	(10 ng/mL)	+2.0%		(4 ng/mL)	-15.0%	(10 ng/mL)
	-9.4%	(25 ng/mL)	[a]	-10.7%	(0.2 ng/mL)	+5.3%
	(16 ng/mL)			(10 ng/mL)		(20 ng/mL)
			[a]	-9.4%		
Medium (conc.)	-5.5%	-6.0%		(16 ng/mL)	-5.5%	+1.9%
	(80 ng/mL)	(250 ng/mL)	[a]	-9.2%	(2 ng/mL)	(100 ng/mL)
				(100 ng/mL)		
High (conc.)	-5.0%	-10.4%	[a]	-9.4%	-4.0%	+1.0%
	(180 ng/mL)	(500 ng/mL)	[a]	(180 ng/mL)	(20 ng/mL)	(1000 ng/mL)
Imprecision	4.1%		12.0% (2.5 ng/mL)	2.0%		14.4%
Low (conc.)	(10 ng/mL)	8.0%		(4 ng/mL)	6.0%	(10 ng/mL)
	3.0%	(25 ng/mL)	2.0% (5 ng/mL)	0.7%	(0.2 ng/mL)	7.2%
	(16 ng/mL)			(10 ng/mL)		(20 ng/mL)
			-1.8% (25 ng/mL)	1.2%		
Medium (conc.)	2.6%	2.8%		(16 ng/mL)	1.3%	6.2%
	(80 ng/mL)	(250 ng/mL)	-2.6% (50 ng/mL)	1.5%	(2 ng/mL)	(100 ng/mL)
				(100 ng/mL)		
High (conc.)	1.2%	2.3%	-3.3% (75 ng/mL)	1.0%	1.8%	2.8%
	(180 ng/mL)	(500 ng/mL)	-15.2% (125 ng/ml)	(180 ng/mL)	(20 ng/mL)	(1000 ng/mL)
n	6	7	single QC samples	6	6	7

Additional Information: [a] A full validation was not conducted; single point QC data for assay run only. [b] calibration range 2.5-100 ng/mL, validation range 25-500ng/mL

2.6.5.2 Analytical Methods and Validation Reports (continued)

Assay performance (3/3)

Test Article: UK-427,857

Location in CTD:

Species	Monkey	Monkey	Monkey	Human	Human	Human
Study No.	DM28	DM28	DM28	DM25	DM25	DM29
Analyte	UK-427,857	UK-463,977	UK-463,977	UK-463,977	UK-463,977	UK-408,027
Sample	Plasma	Plasma	Urine	Plasma	Urine	Urine
Method	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS
Internal Standard	UK-462,015	CP-728,903	CP-728,903	CP-728,903	CP-728,903	UK-418,659
Range of determination	10-200 ng/mL	0.5-50 ng/mL	40-4000 ng/mL	0.1-5 ng/mL	10-1000 ng/mL	5-1000 ng/mL
LOQ	10 ng/mL	0.5 ng/mL	40 ng/mL	0.1 ng/mL	10 ng/mL	5 ng/mL
Inaccuracy	-0.2%	+6.0%				-0.5%
Low (conc.)	(10 ng/mL)	(0.5 ng/mL)	-1.3%	-1.5%	+14.0%	(5 ng/mL)
	+0.9%	+2.0%	(40 ng/mL)	(0.1 ng/mL)	(10 ng/mL)	-1.8%
	(16 ng/mL)	(1 ng/mL)				(10 ng/mL)
	-7.3%					+2.6%
Medium (conc.)	(20 ng/mL)	-1.2%	+2.8%	+1.6%	+7.4%	(50 ng/mL)
	-2.6%	(5 ng/mL)	(400 ng/mL)	(0.5 ng/mL)	(100 ng/mL)	+5.0%
	(100 ng/mL)					(500 ng/mL)
High (conc.)	-2.2%	-9.4%	+3.2%	+5.0%	+4.5%	-2.5%
	(180 ng/mL)	(50 ng/mL)	(4000 ng/mL)	(5 ng/mL)	(1000 ng/mL)	(1000 ng/mL)
Imprecision	2.2%	5.9%				13.2%
Low (conc.)	(10 ng/mL)	(0.5 ng/mL)	5.9%	11.3%	2.0%	(5 ng/mL)
	0.9%	5.3%	(40 ng/mL)	(0.1 ng/mL)	(10 ng/mL)	6.6%
	(20 ng/mL)	(1 ng/mL)				(10 ng/mL)
	0.7%					3.3%
Medium (conc.)	(20 ng/mL)	2.8%	2.0%	7.6%	4.2%	(50 ng/mL)
	1.1%	(5 ng/mL)	(400 ng/mL)	(0.5 ng/mL)	(100 ng/mL)	3.3%
	(100 ng/mL)					(100 ng/mL)
High (conc.)	0.9%	3.2%	5.1%	2.2%	1.4%	3.5%
	(180 ng/mL)	(50 ng/mL)	(4000 ng/mL)	(5 ng/mL)	(1000 ng/mL)	(1000 ng/mL)
n	6	6	8	6	8	8

Additional Information:

2.6.5.2 Analytical Methods and Validation Reports (continued) **Test Article: UK-463,977**

Stability **Location in CTD:**

UK-408,027						
Species	**Sample**	**Condition**	**Conc. tested**	**Change (%)**	**n**	**Study No.**
Human	Urine	Room temp 24hr	10 ng/mL	+0.8	3	DM29
	Urine	Room temp 24hr	1000 ng/mL	-2.4	3	DM29
Human	Urine	4°C for 24hr	10 ng/mL	+2.9	3	DM29
	Urine	4°C for 24hr	1000 ng/mL	-2.5	3	DM29
Human	Urine	-20°C for 24h	10 ng/mL	+14.3	3	DM29
	Urine	-20°C for 24h	1000 ng/mL	+0.2	3	DM29
UK-463,977						
Species	**Sample**	**Freeze –thaw cycle**	**Conc. tested**	**Change (%)**	**n**	**Study No.**
Human	Urine	3	10 ng/mL	-5.1	3	DM25
	Urine	3	1000 ng/mL	-4.3	3	DM25
Species	**Sample**	**Freeze –thaw cycle**	**Conc. tested**	**Change (%)**	**n**	**Study No.**
UK-408,027						
Species	**Sample**	**Freeze –thaw cycle**	**Conc. tested**	**Change (%)**	**n**	**Study No.**
Human	Urine	3	10 ng/mL	+6.1	3	DM29
	Urine	3	1000 ng/mL	-2.3	3	DM29

Additional Information: -

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD:

Species:	Mouse (mdr1a/1b ko)	Mouse (fvb wild type)	Mouse (CD1)
Gender (M/F)/	Male / n=2 per time	Male / n=2 per time	Male / n=2 per time
Number of Animals:	point	point	point
Study No.	DM2	DM2	DM27
Feeding Condition	Fed	Fed	Fed
Vehicle/Formulation	5% DMSO/94.5% water/0.5% 1M HCl	5% DMSO/94.5% water/0.5% 1M HCl	0.2M lactate buffer pH3
Method of Administration	Oral	Oral	Oral
Dose (mg/kg)	16	16	200
Sample	Plasma	Plasma	Plasma
Analyte	UK-427,857	UK-427,857	UK-427,857
Assay	LC-MS-MS	LC-MS-MS	LC-MS-MS
PK Parameters:			
Elimination half-life (h)	1	0.7	NA
Clearance (ml/min/kg)	NA	NA	NA
Volume of Distribution (L/kg)	NA	NA	NA
Cmax (ng/ml)	1119	536	4230
Tmax (h)	0.5	0.5	1
$AUC_{(0\text{-}inf)}$ (ng.h/ml)	1247	440	17700 [a)]
Oral Bioavailability (%)	NC	NC	NC

Additional Information
[a)] AUC_t. NA; Not applicable. NC; Not calculable.

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD:

Species:	Rat	Rat	Rat
Gender (M/F)/ Number of Animals:	Male / n=2 per time point [a)]	Male / n=2 per time point [a)]	Male / n=2 per time point [a)]
Study No.	DM1	DM1	DM1
Feeding Condition	Fed	Fed	Fed
Vehicle/Formulation	5% DMSO/94.5% saline/0.5% 1M HCl	5% DMSO/94.5% water/0.5% 1M HCl	5% DMSO/94.5% water/0.5% 1M HCl
Method of Administration	Intravenous	Oral	Oral
Dose (mg/kg)	1	3	10
Sample	Plasma	Plasma	Plasma
Analyte	UK-427,857	UK-427,857	UK-427,857
Assay	LC-MS-MS	LC-MS-MS	LC-MS-MS
PK Parameters:			
Elimination half-life (h)	0.9	NA	NA
Clearance (ml/min/kg)	74	NA	NA
Volume of Distribution (L/kg)	6.5	NA	NA
Cmax (ng/ml)	369	Portal: 38.3 Systemic: BLQ	Portal: 433 Systemic: 54.8
Tmax (h)	0.1	Portal: 3 Systemic: NC	Portal: 2 Systemic: 2
$AUC_{(0\text{-}inf)}$ (ng.h/ml)	227	Portal: 120 Systemic: NC	Portal: 669 Systemic: 124
Oral Bioavailability (%)	NA	NC	5

Additional Information:
[a)] Serial blood samples were collected from two jugular vein cannulated animals. NA; Not applicable. NC; Not calculable. BLQ; below limit of quantification (<10 ng/ml).

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD

Species:	Rat	Rat	Rat	Rat
Gender (M/F)/ Number of Animals:	Male / n=1 per time point	Male / n=1 per time point	Female / n=1 per time point	Female / n=1 per time point
Study No.	DM26	DM26	DM26	DM26
Feeding Condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	0.2M lactate buffer pH3	0.2M lactate buffer pH3	0.2M lactate buffer pH3	0.2M lactate buffer pH3
Method of Administration	Oral	Oral	Oral	Oral
Dose (mg/kg)	100	100	100	100
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	UK-427,857	UK-463,977	UK-427,857	UK-463,977
Assay	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS
PK Parameters:				
Elimination half-life (h)	NA	NA	NA	NA
Clearance (ml/min/kg)	NA	NA	NA	NA
Volume of Distribution (L/kg)	NA	NA	NA	NA
Cmax (ng/ml)	429	2.08	607	2.87
Tmax (h)	3	1	1	3
$AUC_{(0\text{-}inf)}$ (ng.h/ml) [a)]	1764	10.4	3663	13.2
Oral Bioavailability (%)	NC	NC	NC	NC

Additional Information:
[a)] AUC_t. NA; Not applicable. NC; Not calculable.

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD:

Species:	Rabbit
Gender (M/F)/	Female / n=3 per time
Number of Animals:	point [b)]
Study No.	DM31
Feeding Condition	Fed
Vehicle/Formulation	0.2M lactate buffer pH3
Method of Administration	Oral
Dose (mg/kg)	30
Sample	Plasma
Analyte	UK-427,857
Assay	LC-MS-MS
PK Parameters:	
Elimination half-life (h)	NA
Clearance (ml/min/kg)	NA
Volume of Distribution (L/kg)	NA
Cmax (ng/ml)	367
Tmax (h)	1
$AUC_{(0\text{-}inf)}$ (ng.h/ml) [a)]	835.3
Oral Bioavailability (%)	NC

Additional Information:
[a)] AUC_t. [b)] Serial blood samples were collected from the ear vein of 3 animals. NA; Not applicable. NC; Not calculable.

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD:

Species:	Dog	Dog	Dog	Dog
Gender (M/F)/ Number of Animals:	Male, female / n=2 per sex per time point [a)]	Male, female / n=1 per sex per time point [b)]	Male, female / n=1 per sex per time point [b)]	Male, female / n=1 per sex per time point [b)]
Study No.	DM4	DM4	DM4	DM11
Feeding Condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	5% DMSO/94.5% saline/0.5% 1M HCl	0.2M lactate buffer pH3.85	0.2M lactate buffer pH3.86	0.2M lactate buffer pH3.8
Method of Administration	Intravenous	Oral	Oral	Oral
Dose (mg/kg)	0.5	1	2	10
Sample	Plasma	Plasma	Plasma	Plasma
Analyte	UK-427,857	UK-427,857	UK-427,857	UK-427,857
Assay	LC-MS	LC-MS	LC-MS	LC-MS
PK Parameters:				
Elimination half-life (h)	2.3	2.3	1.8	NA
Clearance (ml/min/kg)	21.4	NA	NA	NA
Volume of Distribution (L/kg)	4.3	NA	NA	NA
Cmax (ng/ml)	586	82	256	1155
Tmax (h)	EOI	1.5	0.75	0.75
$AUC_{(0\text{-}inf)}$ (ng.h/ml)	396	335	583	3178 [c)]
Oral Bioavailability (%)	NA	42	40	NC

Additional Information:
[a)] No sex difference observed so data are mean of four animals. [b)] No sex difference observed so data are average of two animals. [c)] AUC_t. NA; Not applicable. NC; Not calculable. EOI End of 15min infusion.

2.6.5.3. Pharmacokinetics: Absorption after a Single Dose

Test Article: UK-427,857
Location in CTD:

Species:	Dog	Dog
Gender (M/F)/ Number of Animals:	Male, female / n=1 per sex per time point [a)]	Male, female / n=1 per sex per time point [a)]
Study No.	DM30	DM30
Feeding Condition	Fed	Fed
Vehicle/Formulation	0.2M lactate buffer pH3	0.2M lactate buffer pH3
Method of Administration	Oral	Oral
Dose (mg/kg)	5	5
Sample	Plasma	Plasma
Analyte	UK-427,857	UK-463,977
Assay	LC-MS-MS	LC-MS-MS
PK Parameters:		
Elimination half-life (h)	NA	NA
Clearance (ml/min/kg)	NA	NA
Volume of Distribution (L/kg)	NA	NA
Cmax (ng/ml)	273	10.8
Tmax (h)	0.5 (M), 2 (F)	0.5 (M), 2 (F)
$AUC_{(0\text{-}inf)}$ (ng.h/ml)	896 [b)]	41.9 [b)]
Oral Bioavailability (%)	NC	NC

Additional Information:
[a)] No sex difference observed so data are mean of two animals. [b)] AUC_t

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: UK-427,857
Location in CTD:
Report Number: DM6

Species: Rat (Lister hooded)
Gender (M/F)/Number of Animals: 6 males
Feeding Condition: Fed
Vehicle/Formulation: 5% DMSO/0.5% 0.1M HCl/94.5 saline
Method of Administration: Intravenous
Dose (mg/kg): 3
Radionuclide: [^{3}H]
Specific Activity: 1.15 GBq/mg (31.07mCi/mg)

Tissues/Organs	Concentration (µg equivalents/g)					
	Male (0.1h)	Male (1h)	Male (6h)	Male (24h)	Male (48h)	Male (96h)
Adipose tissue	0.40	0.20	0.02	0.01	BLQ	BLQ
Adrenal gland	2.8	0.62	0.04	BLQ	BLQ	BLQ
Bladder	38.3	7.0	0.05	0.05	0.01	BLQ
Blood	1.2	0.09	0.01	0.001	BLQ	BLQ
Brain	0.06	0.03	0.01	0.002	BLQ	0.01
Eyes	1.0	0.59	0.47	0.50	0.39	0.38
Harderian gland	3.5	0.52	0.13	BLQ	BLQ	BLQ
Heart	2.9	0.24	0.01	BLQ	BLQ	BLQ
Kidney	10.2	1.28	0.08	0.02	0.01	0.01
L. intestine contents	0.91	3.3	66.1	0.57	0.03	0.02
Large intestine	1.5	0.75	4.0	0.10	0.01	BLQ
Liver	8.1	1.0	0.20	0.02	0.01	BLQ
Lungs	3.9	1.0	0.07	0.01	0.01	BLQ
Muscle	2.4	0.38	0.02	BLQ	BLQ	BLQ
Pancreas	2.4	0.37	0.04	0.01	0.003	0.002
Pituitary gland	NS	2.1	0.62	0.19	0.04	BLQ
Prostate gland	21.6	1.7	0.04	0.01	BLQ	BLQ

2.6.5.5 Pharmacokinetics: Organ Distribution

Test Article: UK-427,857
Location in CTD:
Report Number: DM6 (continued)

Tissues/Organs	Concentration (µg equivalents/g)					
	Male (0.1h)	Male (1h)	Male (6h)	Male (24h)	Male (48h)	Male (96h)
S. intestine contents	8.7	82.3	3.3	0.07	0.01	BLQ
Salivary gland	4.3	0.77	0.04	BLQ	BLQ	BLQ
Seminal vesicle	7.8	3.1	0.06	0.01	0.01	BLQ
Skin (non pigmented)	1.2	0.26	0.02	0.003	BLQ	BLQ
Skin (pigmented)	1.7	0.35	0.03	0.01	0.01	0.004
Small intestine	11.8	11.5	0.39	0.02	0.01	BLQ
Spleen	2.6	1.0	0.09	0.01	0.01	0.01
Stomach	1.3	0.28	0.03	BLQ	BLQ	BLQ
Stomach contents	0.09	0.53	0.13	BLQ	BLQ	0.01
Testes	0.53	0.41	0.23	0.23	0.11	0.07
Thymus	1.2	0.40	0.04	0.03	0.08	0.27

Additional Information:
NS= No sample
BLQ=Below limit of quantification

2.6.5.6. Pharmacokinetics: Plasma Protein Binding

Test Article: UK-427,857
Location in CTD:
Report Number: DM12

Study System: *In vitro*

Target Entity, Test System and Method: UK-427,857 in plasma by equilibrium dialysis

Species	n	Sex	Conc Tested	% Bound
Mouse	5	Male	1 ng/mL	68.2 ± 1.9
Mouse	5	Male	30 ng/mL	64.7 ± 2.2
Mouse	5	Male	1000 ng/mL	66.0 ± 5.7
Rat	5	Male	1 ng/mL	48.4 ± 1.6
Rat	5	Male	30 ng/mL	45.3 ± 1.9
Rat	5	Male	1000 ng/mL	44.5 ± 2.1
Rabbit	5	Female	1 ng/mL	50.8 ± 1.5
Rabbit	5	Female	30 ng/mL	52.7 ± 4.9
Rabbit	5	Female	1000 ng/mL	47.4 ± 2.3
Dog	5	Male	1 ng/mL	50.9 ± 4.5
Dog	5	Male	30 ng/mL	54.3 ± 3.2
Dog	5	Male	1000 ng/mL	51.2 ± 1.8
Human	5	Male	1 ng/mL	78.5 ± 2.7
Human	5	Male	30 ng/mL	78.9 ± 1.4
Human	5	Male	1000 ng/mL	77.6 ± 3.3

Additional Information:
Plasma protein binding measured in control plasma from each species. Addition of [^{3}H]-UK-427,857 allowed analysis of total radioactivity by liquid scintillation counting.

2.6.5.6. Pharmacokinetics: Plasma Protein Binding

Test Article: UK-427,857
Location in CTD:
Report Number: DM23

Study System: *Ex vivo*

Target Entity, Test System and Method: UK-427,857 in plasma by equilibrium dialysis

Species	n	Sex	Conc Tested	% Bound
Mouse	4	Male/Female	4.0 - 9.96 ng/mL	59.1 ± 5.8
Mouse	4	Male/Female	11.51 - 19.73 ng/mL	56.6 ± 4.3
Mouse	4	Male/Female	8.52 – 25.09 ng/mL	58.3 ± 3.3
Rat	3	Male	1.06 – 1.42 ng/mL	50.6 ± 1.9
Rat	3	Male	3.16 – 6.79 ng/mL	50.3 ± 2.6
Rat	3	Male	5.86 – 8.82 ng/mL	52.2 ± 2.2
Rabbit	10	Female	1.68 – 2.21 ng/mL	66.0 ± 4.4
Rabbit	10	Female	5.05 – 7.39 ng/mL	65.9 ± 2.3
Dog	18	Male/Female	0.47 – 1.27 ng/mL	64.4 ± 5.7
Dog	18	Male/Female	1.7 – 15.49 ng/mL	64.8 ± 9.3
Dog	18	Male/Female	4.72 – 18.65 ng/mL	62.0 ± 6.6
Monkey	8	Male/Female	0.2 – 1.81 ng/mL	51.5 ± 3.7
Monkey	8	Male/Female	0.24 – 2.74 ng/mL	48.7 ± 3.1
Monkey	8	Male/Female	2.58 – 10.88 ng/mL	45.0 ± 6.1
Human	27	Male	121 -307 ng/mL	73.1 ± 4.1
Human	27	Male	821 – 1720 ng/mL	78.0 ± 2.8

Additional Information:
Plasma protein binding measured in plasma samples obtained during toxicology studies in mouse, rat, rabbit, dog and monkey, and a multiple dose clinical study in human. Addition of a small amount of [^{14}C]-UK-427,857 (<10% of total drug measured) allowed analysis of total radioactivity by liquid scintillation counting. Where both sexes were studied, n numbers were equal and there was no apparent difference in binding.

2.6.5.6. Pharmacokinetics: Plasma Protein Binding

Test Article: UK-427,857
Location in CTD:
Report Number: DM18

Study System: *In vitro*

Target Entity, Test System and Method: UK-427,857 human albumen and AAG by equilibrium dialysis

Species	n	Conc Tested	% Bound
Human Albumen	5	1 ng/mL	55.0 ± 2.3
Human Albumen	5	30 ng/mL	55.6 ± 2.3
Human Albumen	5	1000 ng/mL	56.2 ± 1.1
Human AAG	5	1 ng/mL	73.8 ± 1.2
Human AAG	5	30 ng/mL	69.6 ± 2.6
Human AAG	5	1000 ng/mL	63.8 ± 6.4

Additional Information:
AAG = α-1-acid glycoprotein. Physiological concentrations of human albumen and AAG were used.

2.6.5.7. Pharmacokinetics: Study in Pregnant or Nursing Animals

Test Article: UK-427,857
Location in CTD:
Report Number: DM45

Excretion Into Milk
Species: Rat
Parturition Day/Number of Animals: Day 12 / n=3 per time point
Feeding Condition: Fed
Vehicle/Formulation: 0.2M lactate buffer pH3
Method of Administration: Oral
Dose (mg/kg): 100
Analyte: Total radioactivity
Assay: Radioactivity [^{14}C] Scintillation Counting

Time (hours)	1	4	12	24
Concentration (μg equiv/g)				
Milk:	2.73 ± 0.19	2.07 ± 0.25	0.16 ± 0.04	BLQ
Plasma:	1.13 ± 0.25	0.80 ± 0.16	0.06 ± 0.02	BLQ
Milk/Plasma:	2.5 ± 0.6	2.6 ± 0.2	2.7 ± 0.2	BLQ

Additional Information:
BLQ = Below Limit of Quantification.. The profile of radioactivity in plasma and milk was also investigated. UK-427,857 was the major component accounting for 75% and 86% of radioactivity in plasma and milk, respectively. The secondary amine UK-408,027 was also identified as a minor (<5%) metabolite in both plasma and milk, and the alcohol UK-453,465 was identified as a minor (<5%) metabolite in plasma.

2.6.5.8. Pharmacokinetics: Other Distribution Study

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM16, DM32

***In vitro* blood : plasma concentration ratio**

Study System: ***In vitro***
Target Entity, Test System and Method: UK-427,857 in whole blood by measurement of radioactivity

Radionuclide: [^{3}H] (DM16) [^{14}C] (DM32)
Specific Activity: 1.15 GBq/mg (31.07 μCi/mg) (DM16), 1.22 MBq/mg (33 μCi/mg) (DM32)

Species	n	Sex	Conc Tested	Blood to Plasma ratio	Report Number
Rat	3	M	100 ng/mL	1.08	DM16
Dog	3	M	100 ng/mL	0.89	DM16
Human	3	M	100 ng/mL	0.66	DM16
Human	6	M/F	100 ng/mL	0.59 ± 0.09	DM32

Additional Information:
Addition of [^{3}H]-UK-427,857 or [^{14}C]-UK-427,857 allowed analysis of total radioactivity.

2.6.5.8. Pharmacokinetics: Other Distribution Study

Test Article: UK-427,857
Location in CTD:
Report Number: DM3

Brain Penetration
Number of animals: 4 (male)
Feeding condition: Fed
Vehicle / Formulation: 5% DMSO/95% saline
Method of Administration: Intravenous
Dose (mg/kg): 1.3 mg/kg (loading dose) followed by 0.03mg/min/kg (infusion, 1.25h)
Analyte: UK-427,857
Assay: LC-MS-MS

Species	n	Plasma (ng/mL)	Cerebrospinal Fluid (CSF) (ng/mL)	Ratio CSF:Plasma
Rat	4	196 ± 34	9.6 ± 5.2	0.052 ± 0.031

Additional Information:
The CSF:Plasma ratio is for total drug.

2.6.5.8. Pharmacokinetics: Other Distribution Study

Test Article: UK-427,857
Location in CTD:
Report Number: DM21

***In vitro* Affinity of UK-427,857 for Recombinant Human P-glycoprotein**

Study System: ***In vitro***
Target Entity, Test System and Method: UK-427,857, human P-glycoprotein membrane (human MDR1 gene in cultured sf9 insect cells via baculovirus vector), P-glycoprotein-ATPase assay.

Concentration tested: 5-500 μM

Analyte	n	Km (μM)	Vmax (nmol/mg.min)
UK-427,857	5	37 ± 6.4	55 ± 3.4

Additional Information:

2.6.5.8. Pharmacokinetics: Other Distribution Study

Test Article: UK-427,857
Location in CTD:
Report Number: DM20

***In vitro* Permeability in Caco-2 cells and effect of P-glycoprotein and MRP inhibitors**

Study System: ***In vitro***
Target Entity, Test System and Method: UK-427,857, caco-2 cells cultured in MEM supplemented with 20% fetal calf serum, 1% non-essential amino acids, 2nM L-glutamine and 2mM sodium pyruvate. Cells used were at passage 34 (verapamil and CP-100,356 inhibition) and at passage 41 (inhibition with MK-571).

Concentration tested: 25 µM

Inhibitor	Inhibitor Concentration (µM)	n	Papp A-B ($x10^{-6}$ cm/s)	Papp B-A ($x10^{-6}$ cm/s) (range)
P-glycoprotein				
None	NA	3	<1	12 (11-14)
Verapamil	100	3	1	6 (6-7)
CP-100,356	10	3	2	7 (6-7)
MRP-2				
None	NA	2	<1	24 (23 & 24)
MK-571	50	2	<1	12 (12 &13)

Additional Information:
NA = not applicable

2.6.5.8. Pharmacokinetics: Other Distribution Study

Test Article: UK-427,857
Location in CTD:
Report Number: DM44

***In vitro* permeability in caco-2 cells in the presence of P-glycoprotein inhibitors**

Study System: ***In vitro***
Target Entity, Test System and Method: UK-427,857, caco-2 cells cultured in MEM supplemented with 20% fetal calf serum, 1% non-essential amino acids, 2nM L-glutamine and 2mM sodium pyruvate. Cells used were at passage 26 (indinavir), 27 (saquinavir), 28 (nelfinavir) and 29 (ritonavir and ketoconazole).

Concentration tested: 5 µM

Inhibitor	Inhibitor Concentration range (µM)	IC50 (µM)
Nelfinavir	0.1 - 30	14.02 ± 1.67
Saquinavir	0.1 - 30	>30
Indinavir	0.1 -100	>100
Ritonavir	0.1 -30	7.63 ± 0.76
Ketoconazole	1 -100	2.25 ± 0.19

Additional Information:

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM15

Species:	Mouse
Gender (M/F)/Number of Animals:	Male / n=3 (excreta), n=2 per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3.8
Method of Administration:	Oral
Dose (mg/kg):	20
Radionuclide:	[^{3}H]
Specific Activity:	1.15 GBq/mg (31.07 mCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]				
				Parent (M5)	M1	M2	M3	M4
Male mouse	Plasma	1h & 4h	NA	67	17	ND	ND	ND
	Urine	0-24h	4	4	ND	ND	ND	ND
	Faeces	0-24h	93	81	ND	1	1	10

Additional Information:
NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
M1 = Glucuronide conjugate of a product of mono-hydroxylation **M2, M3**= mono-oxidation in the difluorocyclohexyl ring **M4** = UK-437,719 **M5** = UK-427,857

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM38

Species:	Mouse
Gender (M/F)/Number of Animals:	Male / n=3 (excreta), n=2 per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	200
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]										
				Parent (M22)	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**
Male mouse	Plasma	0-7h	NA	58	1	6	6	ND	2	ND	ND	ND	ND	ND
	Urine	0-24h	8	3	1	<1	3	<1	1	ND	ND	ND	ND	ND
	Faeces	0-24h	75	36	ND	ND	4	ND	ND	<1	<1	1	1	1
(Continued)				**M11**	**M12**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**
Male mouse	Plasma	0-7h	NA	ND	1	1	1	2	ND	3	ND	5	8	ND
	Urine	0-24h	8	ND	<1	<1	<1	<1	ND	<1	ND	<1	<1	<1
	Faeces	0-24h	75	2	8	<1	2	3	<1	3	1	4	8	1

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
M1, M2 = analogues of UK-408,027 involving oxidation of the triazole ring; **M3** = UK-408,027; **M4** = oxidation in triazole ring with oxidation and glucuronidation in the phenyl ring; **M5** = mono-oxidation and glucuronidation in phenyl ring; **M6, M9, M10, M11, M13, M16, &M21** = oxidation in both triazole moiety and difluorocyclohexane ring; **M7** = mono-oxidation on the phenyl, triazole and difluorocyclohexane moieties; **M8** = mono-oxidation on triazole and phenyl rings; **M12** = UK-437,719; **M14, M15, M17 &M18** = mono-oxidation in the difluorocyclohexane ring; **M19&M20** = mono-oxidation in triazole ring

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM39

Species:	Mouse (TgrasH2 WT)
Gender (M/F)/Number of Animals:	Male / n=3 (excreta), n=2 per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	200
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (M22)	M1	M2	M3	M12	M14	M15	M17	M18	M19
Male mouse	Plasma	0-7h	NA	74	5	5	8	ND	<1	2	ND	ND	2
	Urine	0-24h	11	6	1	<1	4	ND	<1	<1	<1	ND	<1
	Faeces	0-24h	79	59	ND	ND	5	<1	1	2	2	1	<1

(Continued)

				M19A	M20	M21
Male mouse	Plasma	0-7h	NA	ND	3	ND
	Urine	0-24h	11	ND	<1	<1
	Faeces	0-24h	79	3	5	1

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
M1, **M2** = analogues of UK-408,027 involving oxidation of the triazole ring; **M3** = UK-408,027; **M12** = UK-437,719; **M14**, **M15**, **M17 &M18** = mono-oxidation in the difluorocyclohexane ring; **M19&M20** = mono-oxidation in triazole ring; **M21& M19A** = oxidation in both triazole moiety and diflurocyclohexane ring

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM13

Species:	Rat
Gender (M/F)/Number of Animals:	Male, Female / n=2 per sex (excreta), n=2 per sex per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3.8
Method of Administration:	Oral
Dose (mg/kg):	10
Radionuclide:	[^{3}H]
Specific Activity:	1.15 GBq/mg (31.07 mCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]
				Parent
Male rat	Plasma	1h	NA	91
	Urine	0-24h	- [b)]	- [b)]
	Faeces	0-24h	95	95
Female rat	Plasma	1h	NA	62
	Urine	0-24h	- [b)]	- [b)]
	Faeces	0-24h	92	92

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity. b) Urine contained 2% of the dose and was not profiled for metabolites.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM36

Species:	Rat
Gender (M/F)/Number of Animals:	Male / n=2 (excreta), n=1 per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	100
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (R14)	R1	R2	R3	R4	R5	R6	R7	R8	R9
Male rat	Plasma	0-7h	NA	54	34	ND	12	ND	ND	ND	ND	ND	ND
	Urine	0-24h	4	3	<1	<1	1	ND	ND	ND	ND	ND	ND
	Faeces	0-48h	86	77	ND	ND	4	<1	3	<1	<1	1	<1

(Continued)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]			
				R10	R11	R12	R13
Male rat	Plasma	0-7h	NA	ND	ND	ND	ND
	Urine	0-24h	7	ND	ND	ND	ND
	Faeces	0-48h	83	<1	<1	<1	1

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
R1 = Unknown; **R2** =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **R3** = UK-408,027; **R4** = mono-oxidation on both diflurocyclohexane and phenyl rings; **R5** = UK-437,719; **R6, R7, R8 & R10** = mono-oxidation in diflurocyclohexane ring; **R9, R12** & **R13** = mono-oxidation in triazole moiety; **R11** = mono-oxidation in both triazole and diflurocyclohexane rings.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM36

Species:	Rat
Gender (M/F)/Number of Animals:	Female / n=2 (excreta), n=1 per time point (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	100
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (R14)	R1	R2	R3	R4	R5	R6	R7	R8	R9
Female rat	Plasma	0-24h	NA	79	11	ND	5	ND	ND	ND	ND	ND	ND
	Urine	0-24h	7	6	<1	ND	1	ND	ND	ND	ND	ND	ND
	Faeces	0-48h	83	71	ND	ND	3	<1	6	<1	<1	2	ND

(Continued)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]			
				R10	R11	R12	R13
Female rat	Plasma	0-24h	NA	ND	ND	ND	ND
	Urine	0-24h	7	ND	ND	ND	ND
	Faeces	0-48h	83	<1	ND	<1	1

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
R1 = Unknown; **R2** =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **R3** = UK-408,027; **R4** = mono-oxidation on both diflurocyclohexane and phenyl rings; **R5** = UK-437,719; **R6, R7, R8 & R10** = mono-oxidation in diflurocyclohexane ring; **R9, R12 & R13** = mono-oxidation in triazole moiety; **R11** = mono-oxidation in both triazole and diflurocyclohexane rings.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM41

Species: Rabbit
Gender (M/F)/Number of Animals: Female / n = 3
Feeding Condition: Fed
Vehicle/Formulation: 0.2M lactate buffer pH2.99
Method of Administration: Oral
Dose (mg/kg): 30
Radionuclide: [^{14}C]
Specific Activity: 1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a]									
				Parent (Rb16)	Rb1	Rb2	Rb3	Rb4	Rb5	Rb6	Rb7	Rb8	Rb9
Female rabbit	Plasma	0-8h	NA	40	38	ND	12	2	ND	1	ND	<1	1
	Urine	0-72h	4	2	1	<1	1	<1	ND	<1	<1	<1	<1
	Faeces	0-96h	90	76	ND	ND	5	ND	<1	2	1	<1	1

(Continued)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a]					
				Rb10	Rb11	Rb12	Rb13	Rb14	Rb15
Female rabbit	Plasma	0-8h	NA	ND	1	ND	ND	ND	ND
	Urine	0-72h	4	ND	<1	ND	ND	ND	<1
	Faeces	0-96h	90	<1	1	<1	1	1	2

Additional Information: NA = not applicable; ND = not detected; [a] For plasma this is percentage of circulating radioactivity.
Rb1 = Unknown; **Rb2** =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **Rb3** = UK-408,027 **Rb4** = mono-oxidation and glucuronidation; **Rb5** = oxidation in both triazole moiety and diflurocyclohexane ring; **Rb6** = UK-437,719; **Rb7, Rb10 & Rb13** = mono-oxidation in the tropane ring; **Rb8, Rb9, Rb11** & **Rb12** = mono-oxidation in the diflurocyclohexane ring; **Rb14 & Rb15** = mono-oxidation in the triazole group.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM14

Species: Dog
Gender (M/F)/Number of Animals: Male, Female / n = 1 per sex
Feeding Condition: Fed
Vehicle/Formulation: 0.2M lactate buffer pH3.8
Method of Administration: Oral
Dose (mg/kg): 10
Radionuclide: [^{3}H]
Specific Activity: 1.15 GBq/mg (31.07 mCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]							
				Parent (D8)	D1	D2	D3	D4	D5	D6	D7
Male dog	Plasma	0-168h	NA	97	ND	ND	ND	ND	ND	ND	ND
	Urine	0-24h	10	10	ND	ND	ND	ND	ND	ND	ND
	Faeces	0-96h	46	18	10	4	4	2	2	2	4
Female dog	Plasma	0-168h	NA	94	ND	ND	ND	ND	ND	ND	ND
	Urine	0-24h	13	13	ND	ND	ND	ND	ND	ND	ND
	Faeces	0-96h	55	27	11	3	3	2	2	3	4

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
D1, D2 & D5 = mono-oxidation in the difluorocyclohexyl ring; **D3** = UK-437,719; **D4, D6 & D7** = mono-oxidation in the triazole moiety.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM40

Species:	Dog
Gender (M/F)/Number of Animals:	Male / n=1
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	5
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (D15)	D1	D2	D3	D4	D5	D6	D7	D8	D9
Male dog	Plasma	0-8h	NA	63	≤4	13	ND	ND	ND	≤2	1	2	ND
	Urine	0-48h	5	3	<1	2	ND	ND	ND	<1	<1	<1	ND
	Faeces	0-48h	77	59	ND	2	≤1	≤1	≤1	3	1	3	<1

(Continued)

				D10	D11	D12	D13	D14
Male dog	Plasma	0-8h	NA	<1	1	<1	2	2
	Urine	0-48h	5	<1	<1	<1	<1	<1
	Faeces	0-48h	77	1	1	1	2	4

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity
D1 =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **D2** = UK-408,027; **D3, D4, D5 & D9** = mono-oxidation in both triazole and diflurocyclohexane rings; **D6** = UK-437,719; **D7, D8, D10 & D12** = mono-oxidation in diflurocyclohexane ring; **D11, D13 & D14** = mono-oxidation in triazole ring.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM40

Species:	Dog
Gender (M/F)/Number of Animals:	Female / n=1
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH3
Method of Administration:	Oral
Dose (mg/kg):	5
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (D15)	D1	D2	D3	D4	D5	D6	D7	D8	D9
Female dog	Plasma	0-8h	NA	53	≤5	17	ND	ND	ND	≤1	1	2	ND
	Urine	0-48h	14	9	<1	4	ND	ND	ND	<1	<1	<1	ND
	Faeces	0-96h	58	19	ND	1	≤2	≤2	≤1	4	1	11	<1

(Continued)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]				
				D10	D11	D12	D13	D14
Female dog	Plasma	0-8h	NA	1	<1	1	2	5
	Urine	0-48h	14	<1	<1	<1	<1	1
	Faeces	0-96h	58	4	2	2	3	11

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity
D1 =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **D2** = UK-408,027; **D3, D4, D5** & **D9** = mono-oxidation in both triazole and diflurocyclohexane rings; **D6** = UK-437,719; **D7, D8, D10 & D12** = mono-oxidation in diflurocyclohexane ring; **D11, D13** & **D14** = mono-oxidation in triazole ring.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM37

Species:	Monkey
Gender (M/F)/Number of Animals:	Male / n=2 (excreta), n=1 per timepoint (plasma)
Feeding Condition:	Fed
Vehicle/Formulation:	0.2M lactate buffer pH2.99
Method of Administration:	Oral
Dose (mg/kg):	50
Radionuclide:	[^{14}C]
Specific Activity:	1.22 MBq/mg (33 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (Mk15)	Mk1	Mk2	Mk3	Mk4	Mk5	Mk6	Mk7	Mk8	Mk9
Male monkey	Plasma	1h	NA	56	3	6	12	ND	ND	ND	ND	3	<1
	Plasma	4h	NA	59	5	ND	32	ND	ND	ND	ND	ND	ND
	Urine	0-48h	3	2	<1	ND	1	ND	ND	ND	ND	<1	<1
	Faeces	0-72h	73	56	ND	ND	2	1	<1	<1	<1	10	1
(Continued)				**Mk10**	**Mk11**	**Mk12**	**Mk13**	**Mk14**					
Male monkey	Plasma	1h	NA	1	ND	ND	ND	ND					
	Plasma	4h	NA		ND	ND	ND	ND					
	Urine	0-48h	3	<1	ND	ND	ND	<1					
	Faeces	0-72h	73	1	1	<1	<1	1					

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
Mk1 =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **Mk2** = N-dealkylation and oxidation in the triazole group; **Mk3** =UK-408,027; **Mk4, Mk6, Mk7** & **Mk13** = mono-oxidation in both triazole and diflurocyclohexane rings; **Mk5** = UK-437,719; **Mk8, Mk9, Mk10** & **Mk11** = products of mono-oxidation in diflurocyclohexane ring; **Mk12** & **Mk14** = mono-oxidation in triazole moiety.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM25, DM43

Species:	Human
Gender (M/F)/Number of Animals:	Male / n=3
Feeding Condition:	Fed
Vehicle/Formulation:	0.01M HCl
Method of Administration:	Oral
Dose (mg):	300
Radionuclide:	[^{14}C]
Specific Activity:	0.34 MBq/mg (9.3 µCi/mg)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]									
				Parent (H14)	H1	H2	H3	H4	H5	H6	H7	H8	H9
Male human	Plasma	0-18h	NA	42	11	22	1	2	2	ND	2	2	1
	Urine	0-36h	16	8	2	5	<1	<1	<1	ND	<1	<1	<1
	Faeces	0-120h	71	25	<1	2	1	1	2	<1	8	7	1

(Continued)

Species	Sample	Sample Time or Period	% of Dose in Sample	% of Compound in Sample [a)]			
				H10	H11	H12	H13
Male human	Plasma	0-18h	NA	1	ND	ND	3
	Urine	0-36h	16	<1	ND	ND	1
	Faeces	0-120h	71	9	5	1	9

Additional Information: NA = not applicable; ND = not detected; [a)] For plasma this is percentage of circulating radioactivity.
H1 =N-dealkylation adjacent to tropane moiety and oxidation of methyl group in triazole ring; **H2** = UK-408,027; **H3, H4, H5** & **H9** = mono-oxidation in both triazole and diflurocyclohexane rings; **H6** = UK-437,719; **H7, H8, H10** &**H11**= mono-oxidation in diflurocyclohexane ring, position confirmed by NMR (DM43); **H12** = products of mono-oxidation in triazole ring; **H13** = hydroxymethyl product resulting from oxidation of the triazole ring.

2.6.5.9. Pharmacokinetics: Metabolism *in vivo*

Test Article: UK-427,857
Location in CTD:
Report Number: DM29

Species: Human
Gender (M/F)/Number of Animals: Male / n=8
Feeding Condition: Fed
Vehicle/Formulation: Solution
Method of Administration: Intravenous infusion
Dose (mg): 3, 10, 30 (UK-427,857)
Analyte: UK-408,027
Assay: LC-MS-MS

Subject	Dose (mg)	Sample	Sample Period	% of Dose
1 (200493)	3	Urine	0-24 hr	3.7
1 (200493)	10	Urine	0-24 hr	3.5
1 (200493)	30	Urine	0-24 hr	4.3
2 (203732)	30	Urine	0-24 hr	2.1
3 (200201)	30	Urine	0-24 hr	3.6
4 (200550)	30	Urine	0-24 hr	3.9
5 (203804)	30	Urine	0-24 hr	4.8
6 (200184)	30	Urine	0-24 hr	4.0
7 (200585)	30	Urine	0-24 hr	3.9
8 (204043)	30	Urine	0-24 hr	2.5
Mean	**30**	**Urine**	**0-24 hr**	**3.6**

Additional Information:
Samples from Clinical Study A4001009

2.6.5.10. Pharmacokinetics: Metabolism in vitro

Test Article: UK-427,857
Location in CTD:
Report Number: DM5

In vitro metabolism of UK-427,857

Study System: Species:	Hepatic microsomes Human			
Liver ID	UK-427,857 half-life (min)	CYP2C9 activity (pmol/mg/min)	CYP2D6 activity (pmol/mg/min)	CYP3A4 activity (pmol/mg/min)
HM/9-2	>120	1282.0	14.5	17.3
HM/28	>120	1093.6	10.8	272.8
HM/29	80 ± 5	2720.1	38.7	219.7

Additional Information:
In microsomes from baculovirus cells expressing individual P450 enzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) it was only possible to detect metabolism in incubations with CYP3A4 and CYP2D6.

2.6.5.10. Pharmacokinetics: Metabolism *in vitro*

Test Article: UK-427,857
Location in CTD:
Report Number: DM24

In vitro metabolism of UK-427,857: Identification of CYP enzymes involved in metabolism

Study System:	Hepatic microsomes, Supermix, Recombinanat enzymes
Species:	Human

Study System	Disappearance Half-life (min)
Inhibitor (CYP) [a]	(n=4)
None	13.1 ± 0.7
10μM Sulphaphenazole (CYP2C9)	13.3 ± 1.4
1μM Quinidine (CYP2D6)	13.3 ± 2.1
1μM Ketoconazole (CYP3A4)	79 ± 17.4
Supermix [b]	(n=4)
Control Supermix	8.2 ± 2.7
CYP2D6PM Supermix	7.4 ± 1.2
CYP2C19PM Supermix	8.1 ± 1.8
Recombinant CYPs [c]	(n=3)
CYP1A2	>120
CYP2B6	>120
CYP2C8	>120
CYP2C9	>120
CYP2C19	>120
CYP2D6	>120
CYP3A4	4.2 ± 0.7
CYP3A5	99 ± 22

Additional Information:
a) CYP2C9 and CYP2D6 inhibitors do not influence rate of UK-427,857 metabolism, CYP3A4 contributes approx. 83.3% to UK-427,857 metabolism; b) Metabolism of UK-427,857 in Supermix lacking CYP2D6 and CYP2C9 (CYP2D6PM and CYP2C9, respectively) is unchanged; c) In recombinant enzyme systems UK-427,857 was only metabolised by CYP3A4 and its orthologue CYP3A5.

2.6.5.10. Pharmacokinetics: Metabolism *in vitro*

Test Article: UK-427,857
Location in CTD:
Report Number: DM35

In vitro metabolism of UK-427,857: Enzymology of UK-408,027 formation

Study System	Km (μM)	Vmax (pmol/mg/min)
Human liver microsomes	23	154
Recombinant CYP3A4	13	3 [a)]

Additional Information:
Studies with specific inhibitors of CYP1A2 (furafylline; 3&30 μM), CYP2C9 (sulphaphenazole; 1&10 μM), CYP2C19 (benzylnirvanol; 1&10 μM), CYP2D6 (quinidine; 0.1&1 μM), CYP3A4 (ketaconazole; 0.1&1 μM) showed that UK-408,027 formation was only inhibited (.50%) by ketaconazole indicating an important role for CYP3A4.
a) Units are pmol/pmol/min.

2.6.5.10. Pharmacokinetics: Metabolism *in vitro*

Test Article: UK-427,857
Location in CTD:
Report Number: DM19

In vitro metabolism of [^{3}H]-UK-427,857: Characterisation of metabolites

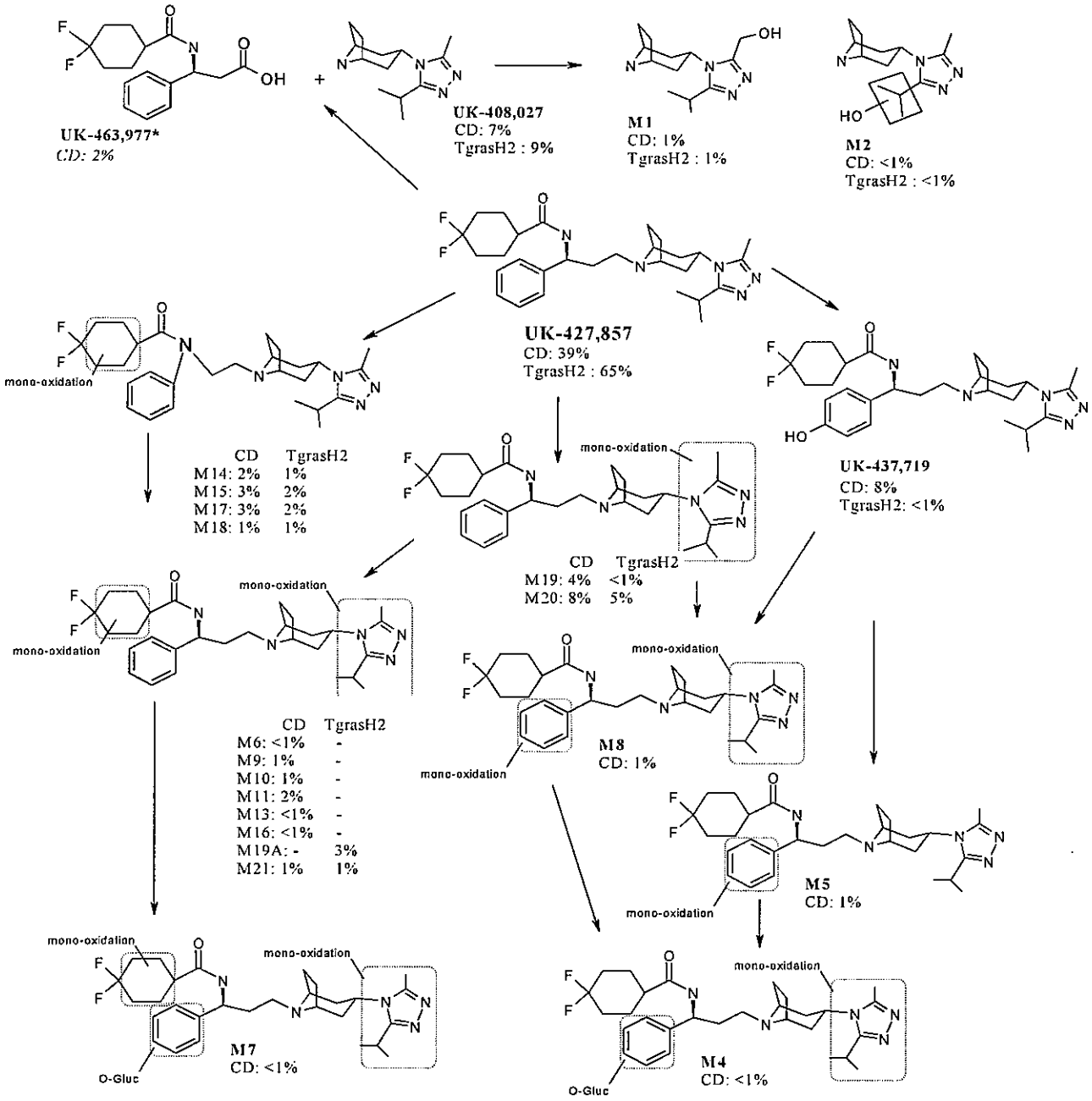
Study System:	Hepatocytes		
Species:	Dog	Monkey	Human
Metabolite			
M1	✓	✓	✓
M2	✓	✓	✓
M3	✓	ND	ND
M4	✓	✓	✓
M5	✓	✓	✓
M6	✓	ND	ND
UK-427,857 (M7)	✓	✓	✓
M8	✓	✓	✓

Additional Information: ND = not detected; ✓ = detected.
M1, M2, M3, M4, M5, M6, M8 = mono-hydroxylated metabolites of UK-427,857 (m/z 530). Unchanged UK-427,857 was the major component in all species. Metabolites accounted for 6.6% of radioactivity in monkey and <1% in dog and human.
[Click here to type footnotes]

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Mouse Excreta

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM27, DM38, DM39

Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to male CD and TgrasH2 mouse.

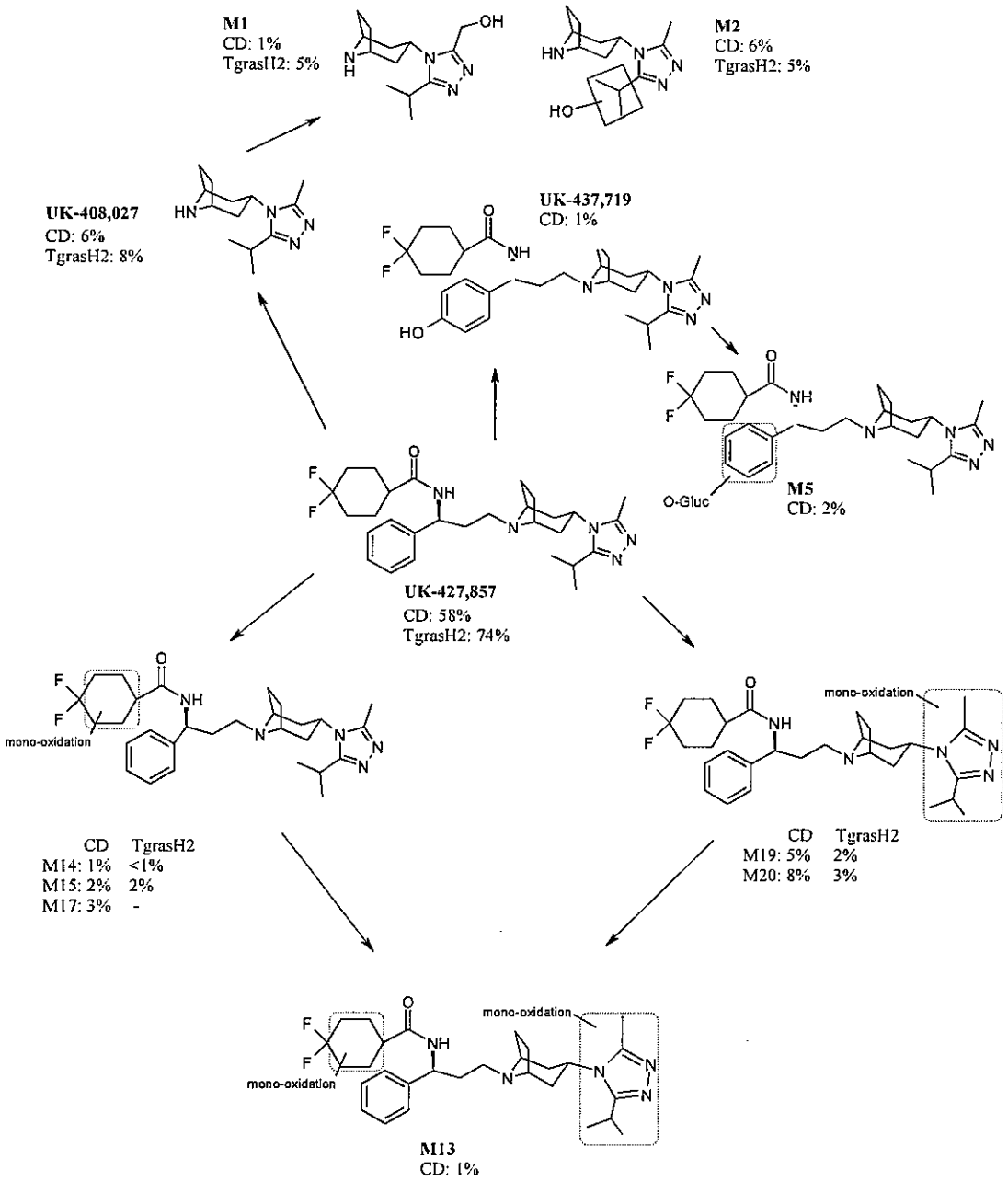


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Mouse Plasma

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM38, DM39

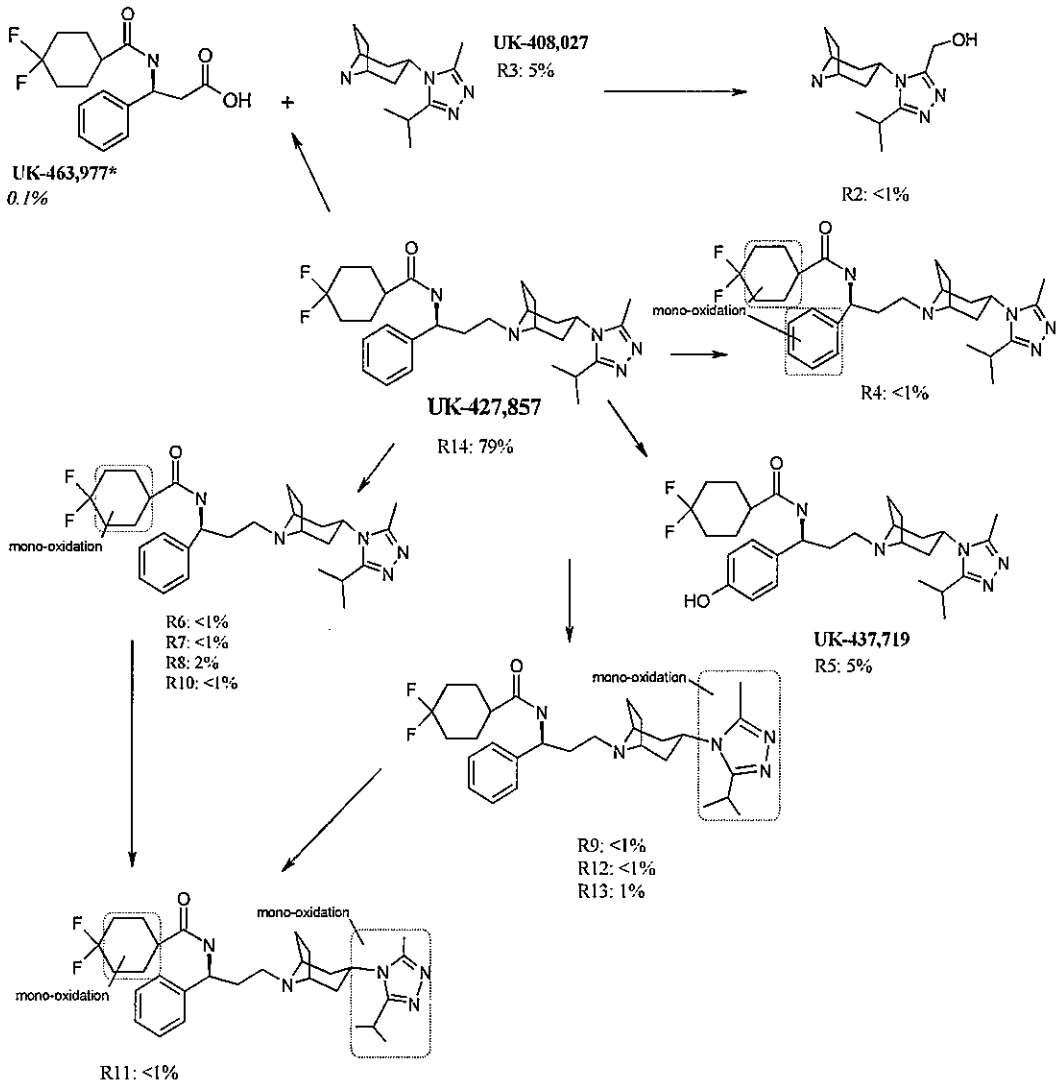
Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to male CD and TgrasH2 mouse.



2.6.5.11 Pharmacokinetics: Metabolic Pathways in Rat Excreta

Test Article: UK-427,857
Location in CTD:
Report Number: DM26, DM36

Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to male and female rat. Results shown are mean of both sexes.

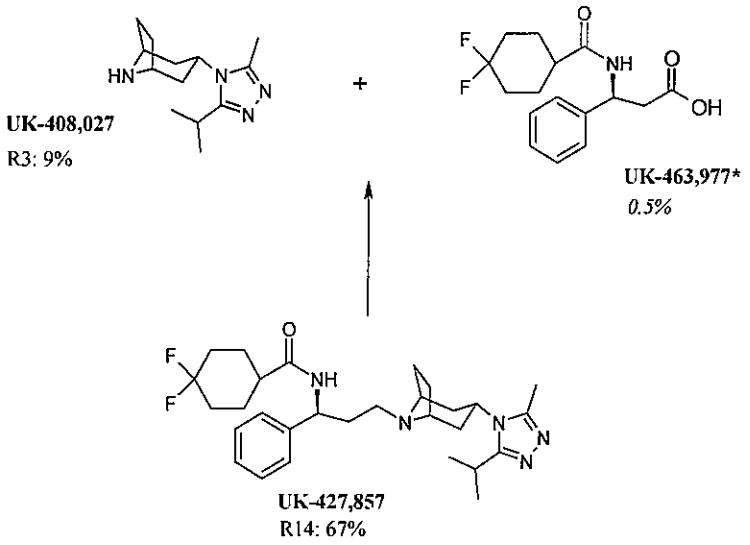


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Rat Plasma

Test Article: UK-427,857
Location in CTD:
Report Number: DM26, DM36

Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to male and female rat. Results shown are mean of both sexes.

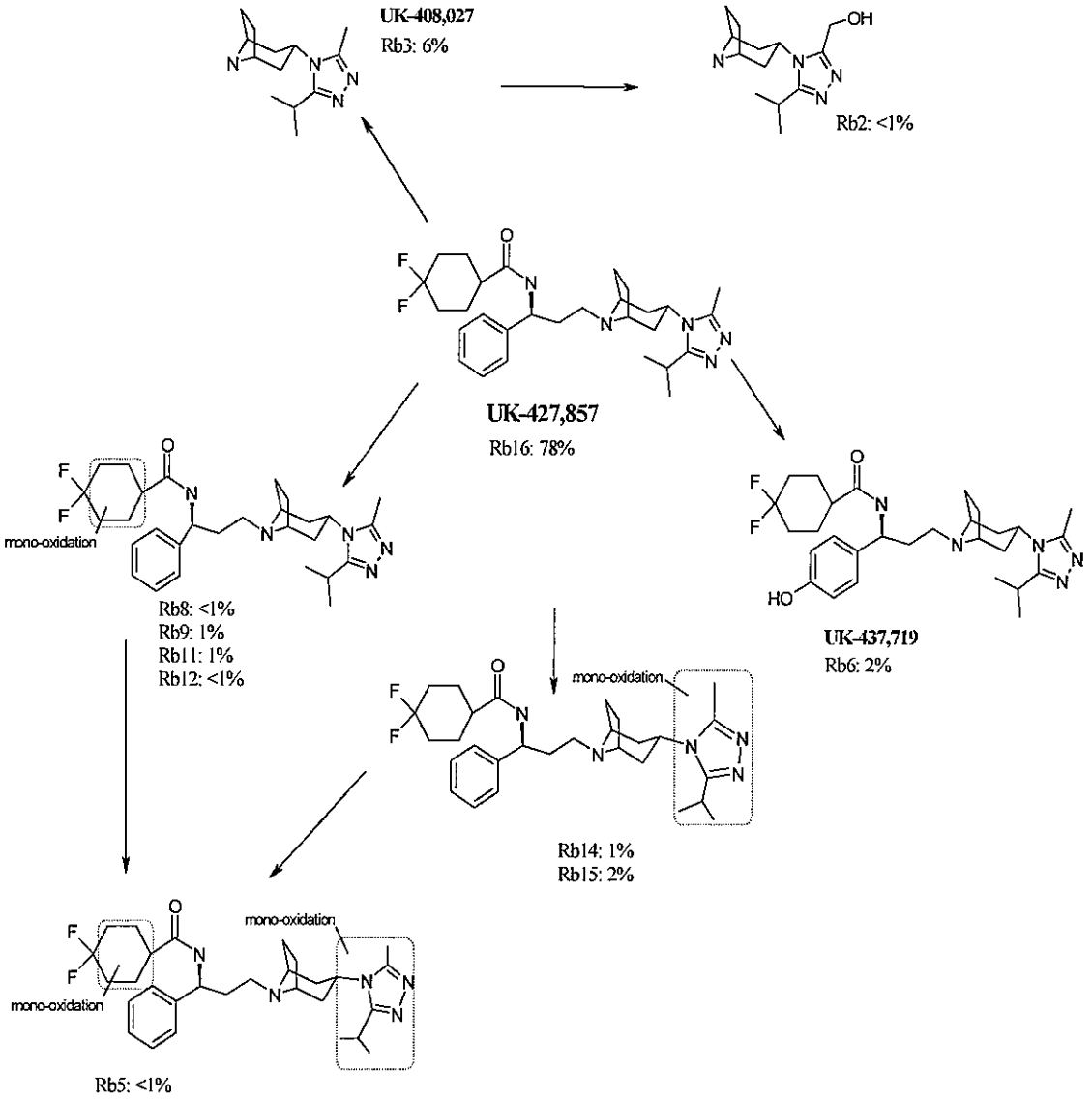


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in plasma. All other metabolites contained the radiolabelled centre. The concentration of UK-463,977 at Cmax was corrected for the MW difference compared with maraviroc, and converted to a % of circulating drug-related material.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Rabbit Excreta

Test Article: UK-427,857
Location in CTD:
Report Number: DM41

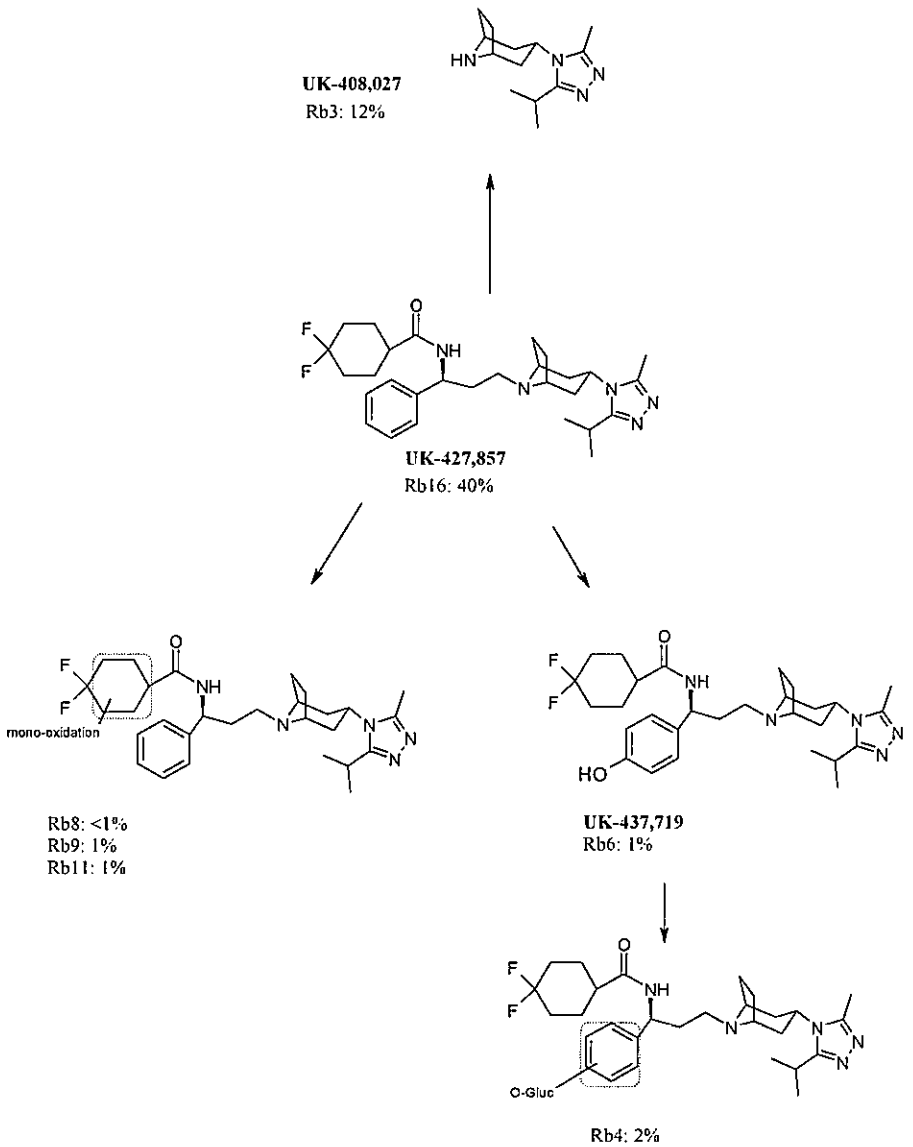
Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to female rabbit.



2.6.5.11 Pharmacokinetics: Metabolic Pathways in Rabbit Plasma

Test Article: UK-427,857
Location in CTD:
Report Number: DM41

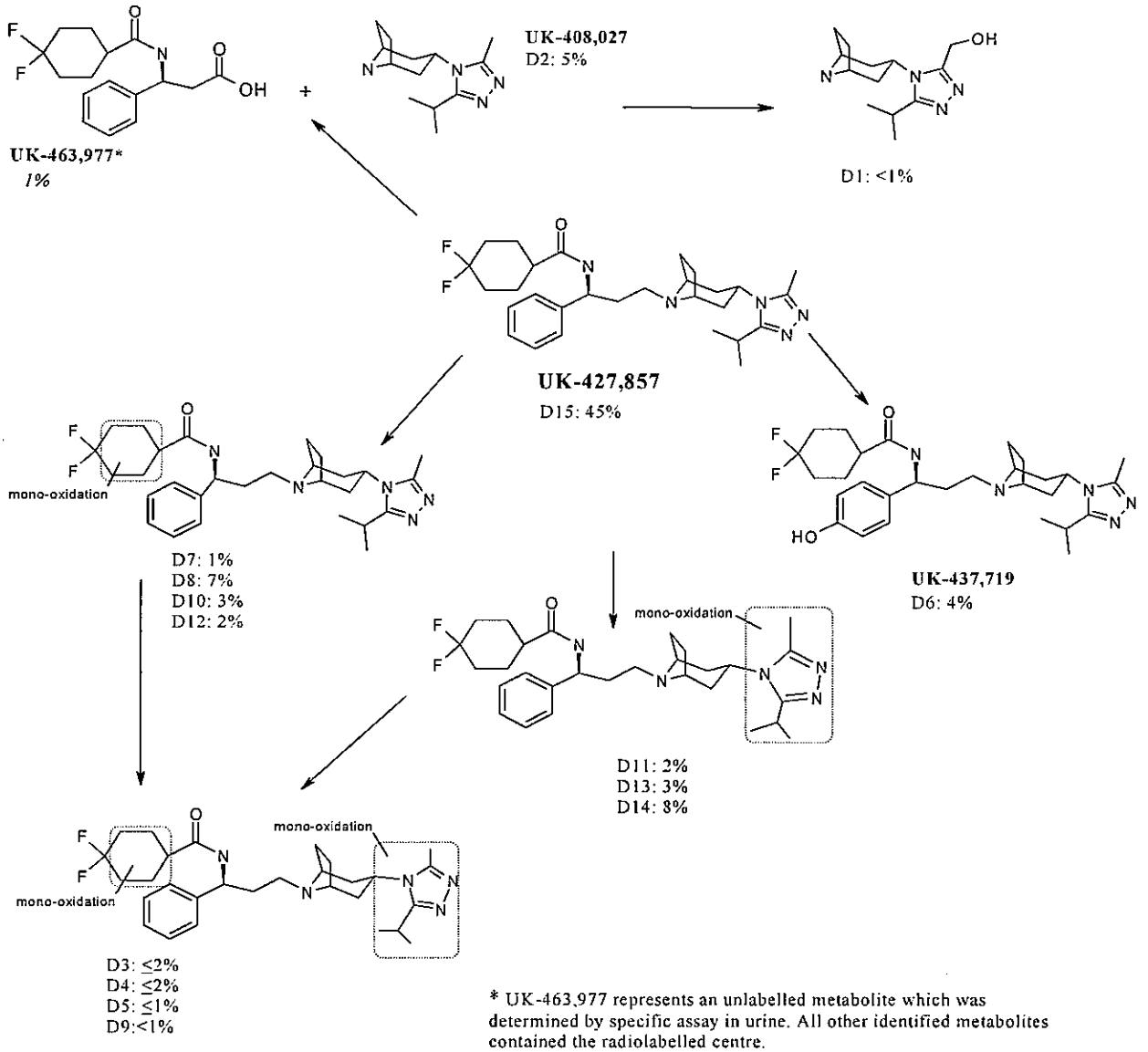
Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to female rabbit.



2.6.5.11 Pharmacokinetics: Metabolic Pathways in Dog Excreta

Test Article: UK-427,857
Location in CTD:
Report Number: DM30, DM40

Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to male and female dog. Results shown are mean of both sexes.

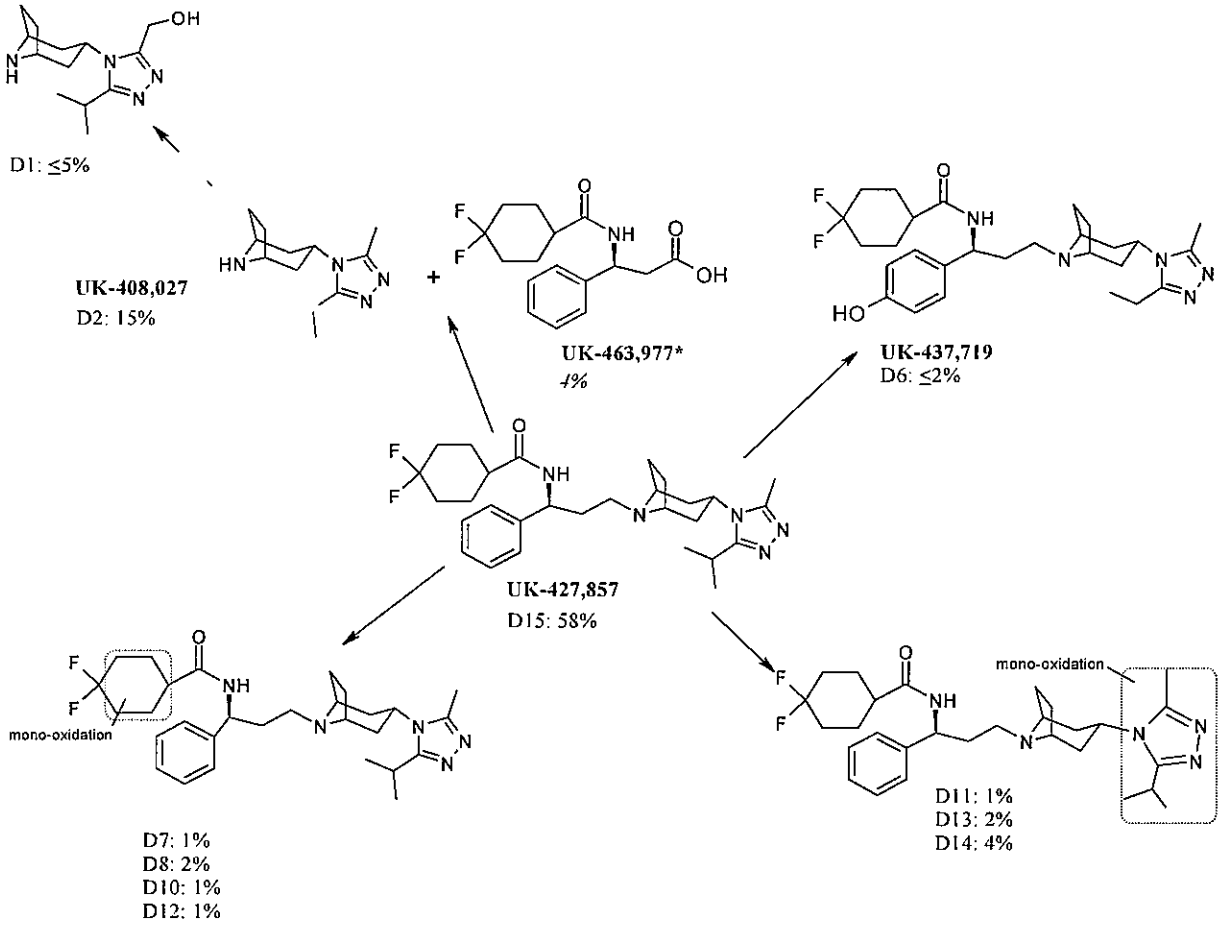


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Dog Plasma

Test Article: UK-427,857
Location in CTD:
Report Number: DM30, DM40

Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to male and female dog. Results shown are mean of both sexes.

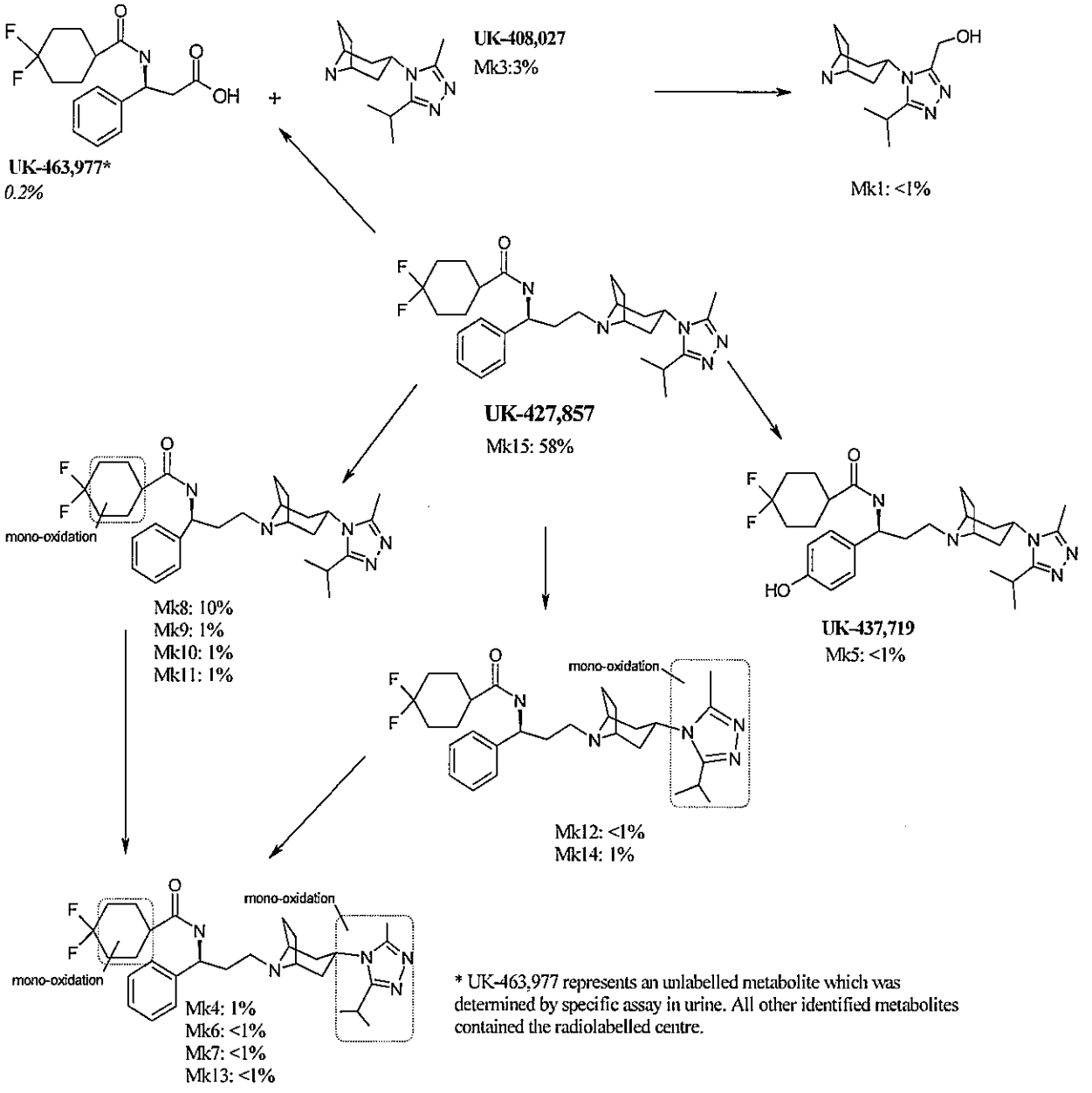


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in plasma. All other metabolites contained the radiolabelled centre. The concentration of UK-463,977 at C_{max} was corrected for the MW difference compared with maraviroc, and converted to a % of circulating drug-related material.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Monkey Excreta

Test Article: UK-427,857
Location in CTD:
Report Number: DM28, DM37

Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to male monkey.

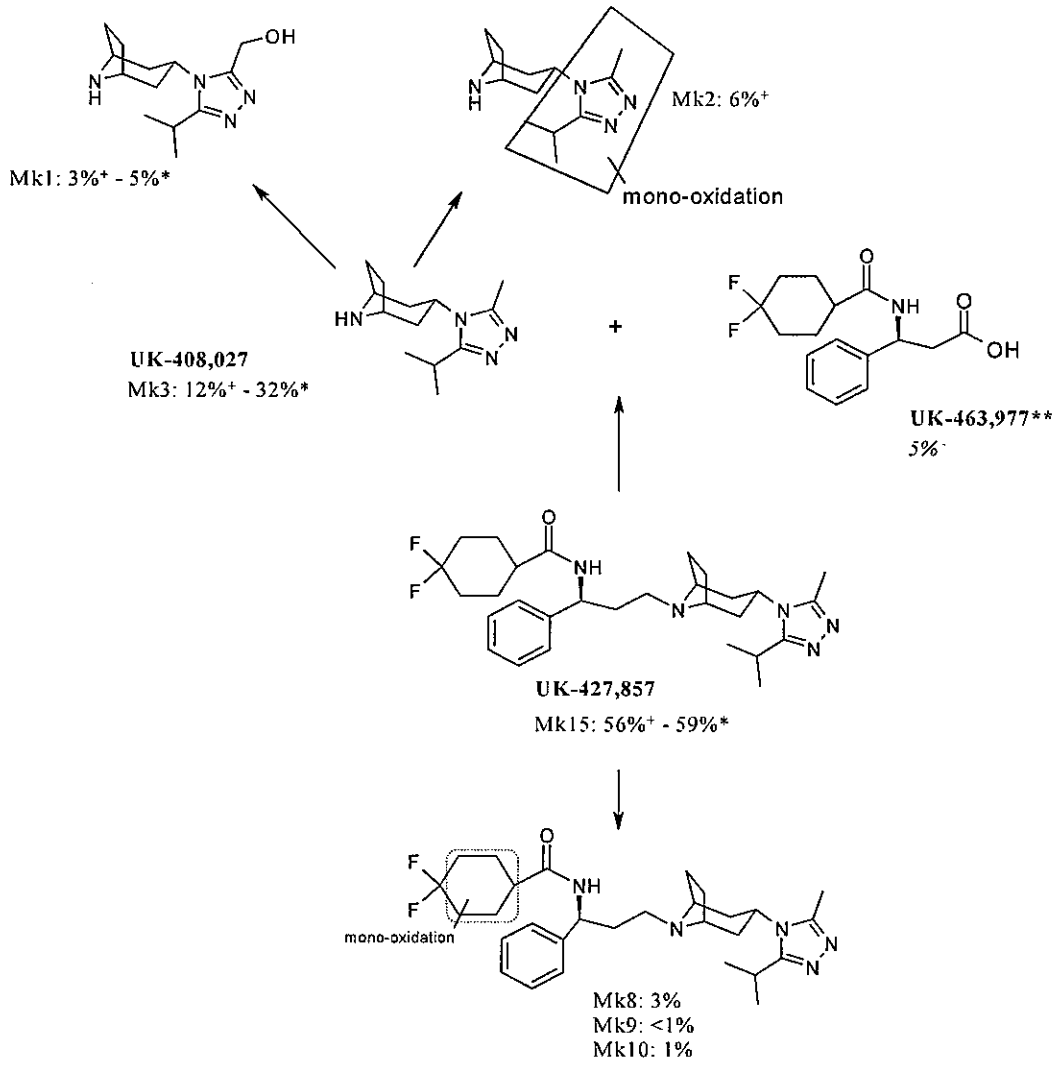


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Monkey Plasma

Test Article: UK-427,857
Location in CTD:
Report Number: DM28, DM37

Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to male monkey.

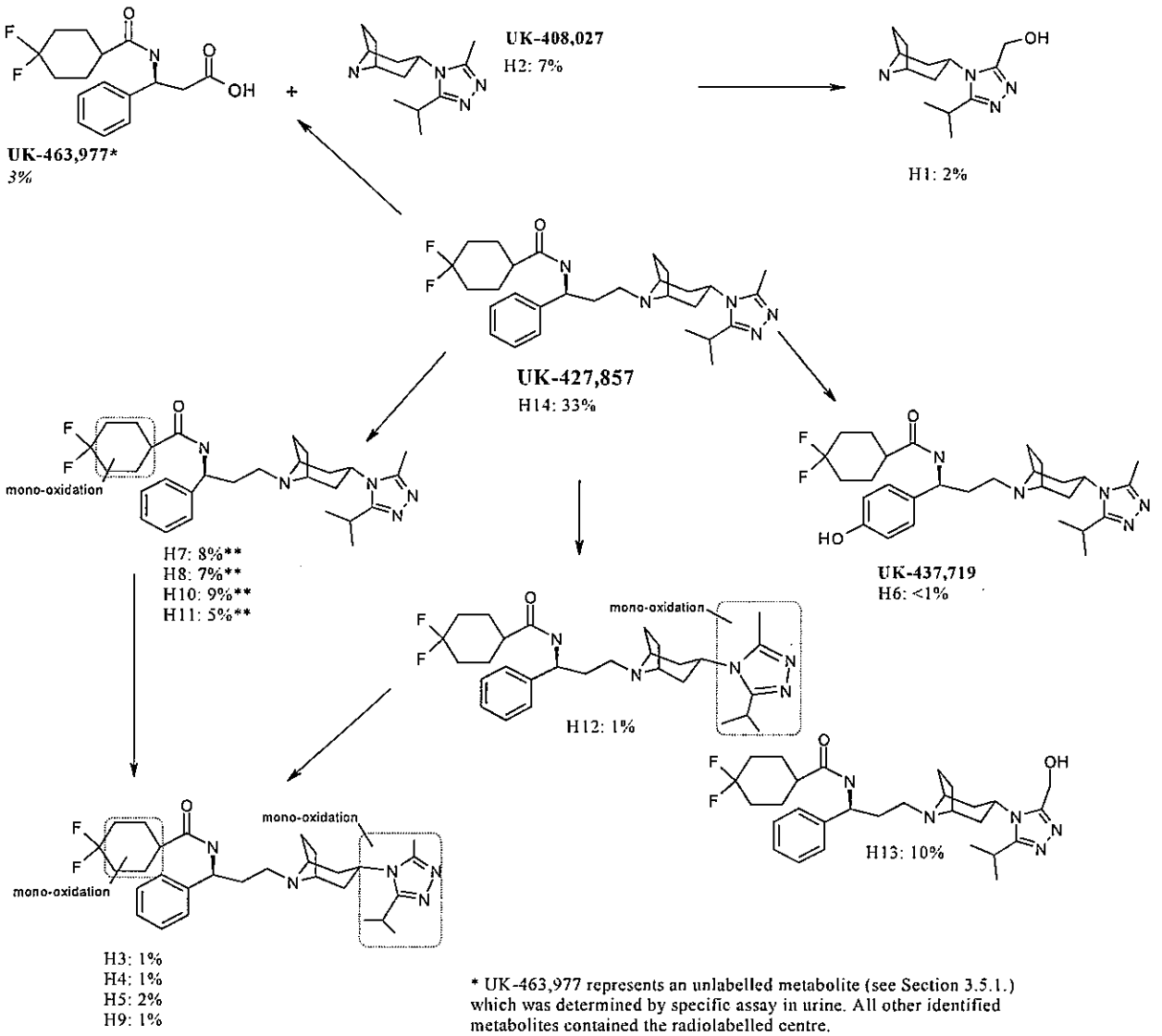


+ % at 1 hour post-dose
* % at 4 hour post-dose
** UK-463,977 represents an unlabelled metabolite which was determined by specific assay in plasma. All other metabolites contained the radiolabelled centre. The concentration of UK-463,977 at C_{max} was corrected for the MW difference compared with maraviroc, and converted to a % of circulating drug-related material.

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Human Excreta

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM25, DM43

Excreted metabolites of UK-427,857 (as % of the dose) following administration of [^{14}C]-UK-427,857 to male human volunteers.

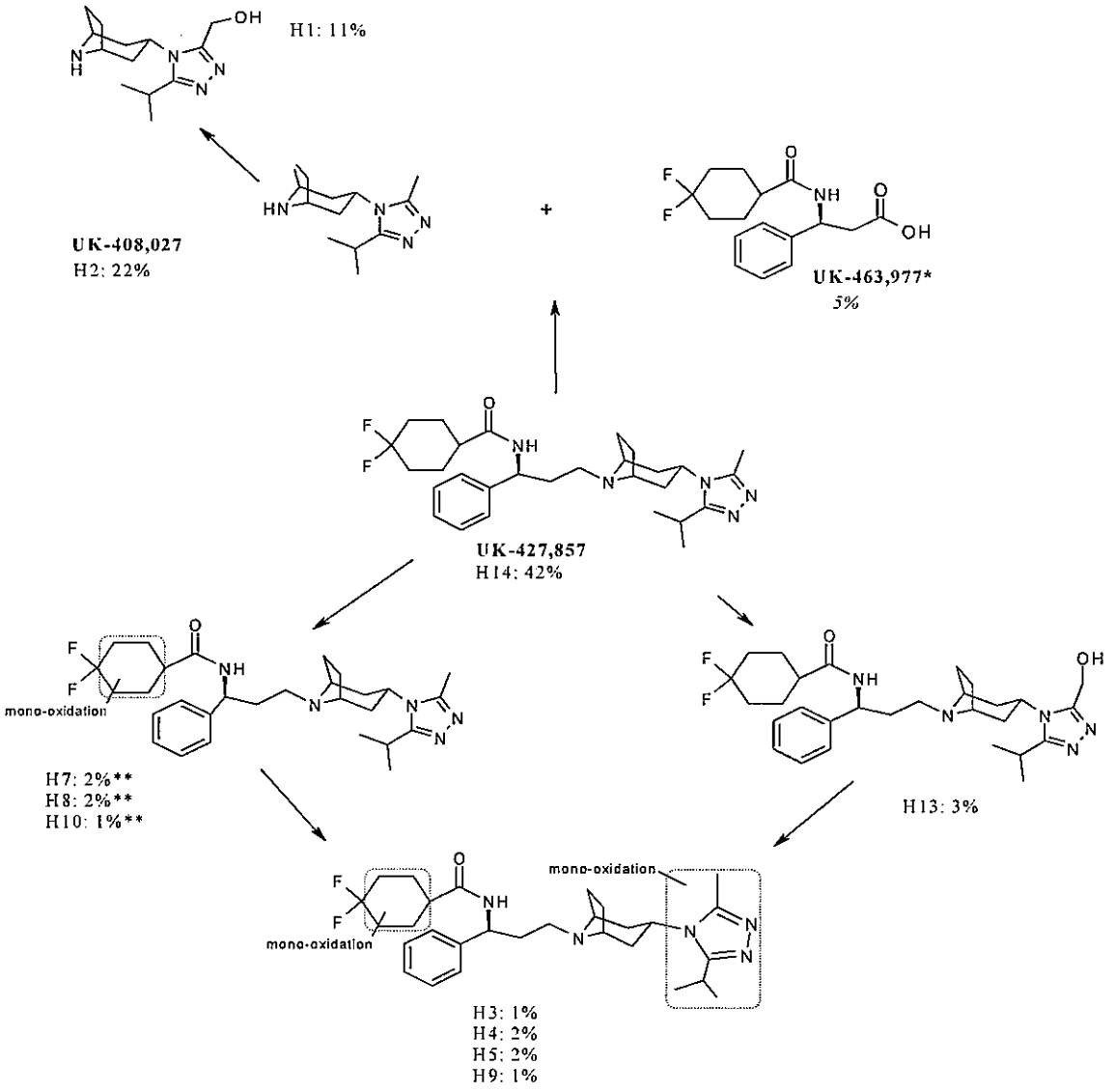


* UK-463,977 represents an unlabelled metabolite (see Section 3.5.1.) which was determined by specific assay in urine. All other identified metabolites contained the radiolabelled centre.
** The position of oxidation for metabolites H7, H8, H10 and H11 has been elucidated using NMR (see Study Report DM43).

2.6.5.11 Pharmacokinetics: Metabolic Pathways in Human Plasma

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM25 & DM43

Circulating metabolites of UK-427,857 following administration of [^{14}C]-UK-427,857 to male human volunteers.

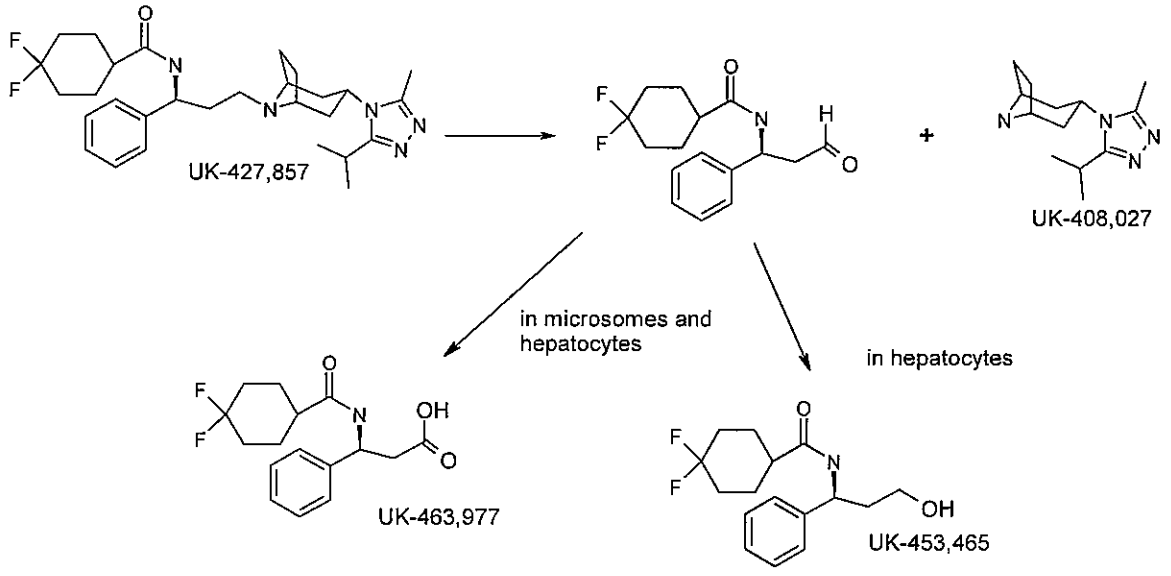


* UK-463,977 represents an unlabelled metabolite which was determined by specific assay in plasma. All other metabolites contained the radiolabelled centre. The concentration of UK-463,977 at C_{max} was corrected for the MW difference compared with maraviroc, and converted to a % of circulating drug-related material.
** The position of oxidation for metabolites H7, H8 and H10 has been elucidated using NMR (see Study Report DM43).

2.6.5.11 Pharmacokinetics: Metabolic Pathways In Vitro

Test Article: UK-427,857
Location in CTD:
Report Number: DM42

Study System:	Hepatic microsomes, hepatocytes
Species:	Human
Radionuclide	[^{14}C] (dual label)
Specific activity	1.26 MBq/mg (34 μCi/mg)



Additional Information:
Dual labeled [^{14}C]-UK-427,857 was used to identify major metabolites arising from N-dealkylation.

2.6.5.12. Pharmacokinetics: Inhibition of Drug-metabolizing Enzymes

Test Article: UK-427,857
Location in CTD:
Report Number: DM7

In vitro metabolism of UK-427,857: Recombinant Cytochrome P450 Inhibition

Study System: Recombinant CYP450 Species: Human		Inhibition	
P450 Enzyme	**Substrate**	**No pre-incubation IC_{50} (μM)**	**Plus pre-incubation IC_{50} (μM)**
CYP1A2	CEC	>100	>100
CYP2C9	7-MFC	>100	>100
CYP2C19	CEC	>100	>100
CYP2D6	AMMC	87 ± 2	50 ± 5
CYP3A4	DBF	>100	>100
CYP3A4	7-BFC	>100	>100
CYP3A4	7-BQ	>100	>100

Additional Information:
CEC = 3-cyano-7-ethoxycoumarin; 7-MFC = 7-methoxy-4-trifluoromethylcoumarin; AMMC = 3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin; DBF = dibenzylfuorescein; 7-BFC = 7-benzyloxy-4-(trifluoromethyl)-coumarin; 7-BQ = 7-benzyloxyquinoline.

2.6.5.12. Pharmacokinetics: Inhibition of Drug-metabolizing Enzymes

Test Article: UK-427,857
Location in CTD:
Report Number: DM22 & DM33

In vitro metabolism of UK-427,857: Cytochrome P450 Inhibition

Study System: Hepatic microsomes
Species: Human

		Inhibition		
P450 Enzyme	Substrate	No pre-incubation IC_{50} (μM)	Plus preincubation IC_{50} (μM)	Report Number
CYP1A2	Phenacetin	>30	>30	DM22
CYP2C9	Diclofenac	>30	>30	DM22
CYP2C19	S-Mephenytoin	>30	>30	DM22
CYP2D6	Dextromethorphan	>30	>30	DM22
CYP3A4	Midazolam	>30	>30	DM22
CYP3A4	Testosterone	>30	>30	DM22
CYP3A4	Felodipine	>30	>30	DM22
CYP2B6	Bupropion	>30	>30	DM33
CYP2C8	Rosigltazone	>30	>30	DM33

Additional Information:

2.6.5.13. Pharmacokinetics: Excretion in Mouse

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM9, DM27 & DM34

Species / Strain:	Mouse / CD			Mouse / CD			Mouse / TgrasH2 WT		
Gender (M/F)/Number of Animals:	Male / n=3			Male / n=3			Male / n=3		
Feeding Condition:	Fed			Fed			Fed		
Vehicle/Formulation:	0.2M lactate buffer pH 3.8			0.2M lactate buffer pH 3			0.2M lactate buffer pH 3		
Method of Administration:	Oral			Oral			Oral		
Dose (mg/kg):	20			200			200		
Analyte:	Radioactivity [^{3}H]			Radioactivity [^{14}C]			Radioactivity [^{14}C]		
Assay:	Scintillation Counting			Scintillation Counting			Scintillation Counting		
Excretion Route:	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total
Time									
0 - 24 hr	3.9	101.3	105.2	8.5	85.5	94	10.4	87.1	97.5
0 - 96 hr	5.0	103.1	108.5	10.0	86.9	97.5	11.6	88.9	100.5

Additional Information:
Total (0-96hr) includes cage wash and carcass

2.6.5.13. Pharmacokinetics: Excretion in Rat

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM10 & DM26

Species:	Rat			Rat			Rat			Rat		
Gender (M/F)/Number of Animals:	Male / n=2			Female / n=2			Male / n=2			Female / n=2		
Feeding Condition:	Fed			Fed			Fed			Fed		
Vehicle/Formulation:	0.2M lactate buffer pH 3.8			0.2M lactate buffer pH 3.8			0.2M lactate buffer pH 3			0.2M lactate buffer pH 3		
Method of Administration:	Oral			Oral			Oral			Oral		
Dose (mg/kg):	10			10			100			100		
Analyte:	Radioactivity [^{3}H]			Radioactivity [^{3}H]			Radioactivity [^{14}C]			Radioactivity [^{14}C]		
Assay:	Scintillation Counting			Scintillation Counting			Scintillation Counting			Scintillation Counting		
Excretion Route:	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total
Time												
0 - 24 hr	1.2	103.6	104.8	1.6	91.8	93.4	4.3	88.9	93.2	7.1	86.4	93.5
0 - 96 hr	1.5	106.1	108.3	1.9	96.6	99.1	4.5	93.7	98.3	7.5	88.4	95.9

Additional Information:
Total (0-96hr) includes cage wash and carcass

2.6.5.13. Pharmacokinetics: Excretion in Rabbit

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM31

Species:	Rabbit		
Gender (M/F)/Number of Animals:	Female / n=3		
Feeding Condition:	Fed		
Vehicle/Formulation:	0.2M lactate buffer pH 2.99		
Method of Administration:	Oral		
Dose (mg/kg):	30		
Analyte:	Radioactivity [^{14}C]		
Assay:	Scintillation Counting		
Excretion Route:	Urine	Faeces	Total
Time			
0 - 24 hr	3.0	35.5	38.5
24-48 hr	1.3	36.0	37.3
0 - 120 hr	4.6	94.6	104.9

Additional Information:
Total (0-120hr) includes cage wash and carcass

2.6.5.13. Pharmacokinetics: Excretion in Dog

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM11 & DM30

Species:	Dog			Dog			Dog			Dog		
Gender (M/F)/Number of Animals:	Male / n=1			Female / n=1			Male / n=1			Female / n=1		
Feeding Condition:	Fed			Fed			Fed			Fed		
Vehicle/Formulation:	0.2M lactate buffer pH 3.8			0.2M lactate buffer pH 3.8			0.2M lactate buffer pH 3			0.2M lactate buffer pH 3		
Method of Administration:	Oral			Oral			Oral			Oral		
Dose (mg/kg):	10			10			5			5		
Analyte:	Radioactivity [^{3}H]			Radioactivity [^{3}H]			Radioactivity [^{14}C]			Radioactivity [^{14}C]		
Assay:	Scintillation Counting			Scintillation Counting			Scintillation Counting			Scintillation Counting		
Excretion Route:	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total
Time												
0 – 24 hr	9.3	8.0	17.3	12.6	NS	12.6	2.7	1.7	4.4	14.0	33.3	47.3
0 - 48 hr	9.6	57.2	66.8	13.3	47.0	60.3	5.9	84.0	89.9	15.7	33.3	49.0
0- 168 hr	NA	NA	NA	NA	NA	NA	6.8*	86.0	93.2	16.5*	72.0	89.3
0 - 192 hr	10.1*	63.2	99.6	14.0*	77.2	91.6	NA	NA	NA	NA	NA	NA

Additional Information: NA = not applicable; * urine was collected until 96h post-dose.
Total (0-192hr) includes cage wash and vomit from male dog at 0.5-1 h post dose (26%)
Total (0-168 hr) includes cage wash

2.6.5.13. Pharmacokinetics: Excretion in Monkey

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM28

Species:	Monkey		
Gender (M/F)/Number of Animals:	Male / n=2		
Feeding Condition:	Fed		
Vehicle/Formulation:	0.2M lactate buffer pH 2.99		
Method of Administration:	Oral		
Dose (mg/kg):	50		
Analyte:	Radioactivity [^{14}C]		
Assay:	Scintillation Counting		
Excretion Route:	Urine	Faeces	Total
Time			
0 - 24 hr	3.1	40.0	43.1
0 - 120 hr	4.0	78.9	92.1

Additional Information:
Total (0 –120 hr) includes cage wash and debris

2.6.5.13. Pharmacokinetics: Excretion in Human

Test Article: UK-427,857
Location in CTD:
Report Numbers: DM25

Species:	Human		
Gender (M/F)/Number of Animals:	Male / n=3		
Feeding Condition:	Fed		
Vehicle/Formulation:	0.01M Hydrochloric acid		
Method of Administration:	Oral		
Dose (mg/kg):	300 mg once		
Analyte:	Radioactivity [^{14}C]		
Assay:	Scintillation Counting		
Excretion Route:	Urine	Faeces	Total
Time			
0 - 24 hr	17.1	2.5	19.6
0 – 48 hr	18.6	38.4	57.0
0 - 168 hr	19.6	76.4	96.0
Additional Information:			

2.6.5.14 Pharmacokinetics: Excretion into Bile

Test Article: UK-427,857
Location in CTD:
Report Number: DM17

Bile Duct Cannulated Rat

Species	Rat
Gender (M/F) / Number of animals	Male / n=2
Dose (mg/kg)	3
Vehicle / Formulation	5% DMSO/94.5% saline/0.5% 1M HCl
Radionuclide	[^{3}H]
Specific Activity	1.15 GBq/mg (31.07 mCi/mg)
Analyte	Radioactivity
Assay	Scintillation Counting

Recoveries of total radioactivity in Bile, Urine, Liver, GI Tract and GI Tract contents

Sampling time (hr)	Recovery (% of dose)				
	Bile	Urine	Liver	GI Tract	GI Tract contents
0 - 0.25	14.5				
0.25 - 0.5	13.9				
0.5 - 1	17.6				
1 - 2	11.5				
2 - 4	5.6				
4 - 6	1.5				
Total (0 –6)	64.4	12.8	1.2	3.5	11.5

Additional Information: Urine, Liver, GI Tract & contents collected at the end of the study

2.6.5.14 Pharmacokinetics: Excretion into Bile

Test Article: UK-427,857
Location in CTD:
Report Number: DM8

Isolated Perfused Rat Liver

Species	Rat
Gender (M/F) / Number of animals	Male / n=1
Dose (mg)	1
Vehicle / Formulation	5% DMSO / 95% saline
Analyte	UK-427,857
Assay	LC-MS-MS (perfusate, bile)

UK-427,857 in perfusate (µg/mL)			UK-427,857 in bile		
Sampling time (h)	**Pre-liver**	**Post-liver**	**Time (min)**	**Concentration (µg)**	**% dose**
0.03	4.96	2.27	0-15	27	2.7
0.08	4.31	1.96	15-30	162*	16.2*
0.16	3.52	1.73	30-45	65	6.5
0.25	2.87	3.69	45-60	54	5.4
0.33	2.50	2.38	60-75	20	2.0
0.5	1.75	1.45	75-90	15	1.5
0.75	1.31	0.93	Total	343	34
1.0	0.84	0.74			
1.25	0.64	0.54			
1.5	0.38	0.40			
Half-life (hr)		0.5			
Clearance (mL/min)		6			
Vol of distribution (mL)		239			
Extraction ratio		0.4			

Additional Information: * = Value obtained from concentration above the calibration limit.