Investigation of the cytochrome P450 3A4 induction potential of the compound SPM 8272 in cryopreserved human hepatocytes (BA 535-02)(December 2002). SPM 8272 did not cause a detectable induction of CYP3A4 activity or an increase in CYP 3A4 mRNA levels in cryopreserved human hepatocytes at a concentration of 9.5 nM (therapeutic plasma concentration).

Determination of the cytochrome P450 induction potential of fesoterodine in human hepatocytes (Study no. 692, SPM 907)(December 2004). The cytochrome P450 induction potential of fesoterodine (20 and 200 uM) was investigated in cryopreserved human hepatocytes (72 hour incubation). The cutoff for a positive induction was a more than 200% change in enzymatic activity of treated versus non-treated hepatocytes (control). Down regulation was considered significant when the enzymatic activity of the treated hepatocytes was below 50% of that obtained for the non-treated hepatocytes. No notable effects on enzyme activities associated with CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4 were observed:

	Donor	Substrate (concentration)	Control inducer		Fesoterodine % of control	
			Compound (concentration)	% of control	20 nM	200 nM
CYP1A2	417	7-ethoxyresorufin	Omeprazole	462	102	117
	FEP	(5 µM)	(50 µM)	826	98.6	103
CYP2B6	417	(S)-mephenytoin	Phenobarbital	604	121	129
	FEP	(100 µM)	(200 µM)	610	117	84.8
CYP2C9	417	(S)-warfarin	Rifampicin	435	103	97.6
	FEP	(10 µM)	(20 µM)	359	109	102
CYP2C19	417	(S)-mephenytoin	Rifampicin	595	114	119
	FEP	(100 µM)	(20 µM)	n.t.	n.t.	n.t.
CYP3A4	417	Testosterone	Rifampicin	1276	131	124
	421	(250 µM)	(20 µM)	372	116	79.8

n.t. no metabolic turnover

SPM 8272: Effect on cytochrome P450 and related parameters in male and female CD-1 mice following oral administration at dose levels of 0, 5, 25, and 75 mg/kg/day (increased to 100 mg/kg/day in males and 125 mg/kg/day in females from week 16) for 6 months (Study no. 0798/029)(July 2002). 7-Ethoxyresorufin O-deethylase was used as a marker for CYP1A, testosterone 6β- and 2β-hydroxylase for CYP3A, testosterone 16β-hydroxylase for CYP2B, testosterone 16α- and 2α-hydroxylase for CYP2C and lauric acid 11- and 12-hydroxylase for CYP2E and CYP4A. No notable effects on the concentrations of hepatic microsomal protein or cytochrome P450 activities were observed. A decrease in testosterone 16β-hydroxylase and 6β-hydroxylase (to ca 34% of the corresponding control value, relative to microsomal protein), was observed at the lowest dose level in male mice.

SPM 8272: Effect on cytochrome P450 and related parameters in male and female Beagle dogs following oral administration at dose levels of 0, 0.5, 2.5 and 12.5 mg/kg/day for 9 months (Study no. 0798/030)(July 2002). There were no notable effects on the concentrations of hepatic microsomal protein and cytochrome P450 or on

the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A and CYP4A in the beagle dog.

Interaction of the compounds SPM 8272, SPM 7605, SPM 5509, SPM 6923, and SPM 9078 with the cytochrome P450 isoenzymes 1A2, 2C9, 2C19, 2D6, and 3A4 (Study no. BA 474-02)(November 2001). Specific CYP-substrates were metabolized to fluorogenic molecules in the presence of test compounds (competitors) or specific control inhibitors in an automated microtiter plate-based competitive assay:

	$LogIC_{50}$	IC_{50} [µM]	K_i [µM]
CYP3A4:			
SPM 8272:	3.638 ± 0.120	4.3	2.8
SPM 7605:	4.685 ± 0.071	48.5	30.9
SPM 5509:	5.191 ± 0.538	155.2	99.1
SPM 6923:	no interaction detectable		
SPM 9078:	4.012 ± 0.040	10.3	6.4
Ketoconazole:	1.273 ± 0.046	0.019	0.012
	1.318 ± 0.085	0.021	0.013
	1.212 ± 0.032	0.016	0.010
CYP2D6:			
SPM 8272:	4.193 ± 0.043	15.6	7.8
SPM 7605:	4.001 ± 0.040	10.0	5.0
SPM 5509:	4.342 ± 0.062	22.0	10.9
SPM 6923:	no interaction detectable		
SPM 9078:	3.526 ± 0.023	3.4	1.7
Quinidine:	1.187 ± 0.057	0.015	0.008
	1.548 ± 0.025	0.035	0.018
	1.251 ± 0.041	0.018	0.009
CYP1A2:			
SPM 8272:	no interaction detectable, calculation not reasonable		
SPM 7605:	no interaction detectable, calculation not reasonable		
SPM 5509:	no interaction detectable, calculation not reasonable		
SPM 6923:	no interaction detectable, calculation not reasonable		
SPM 9078:	no interaction detectable, calculation not reasonable		
Furafylline:	2.994 ± 0.058	0.99	0.41
	3.062 ± 0.042	1.15	0.48
	3.033 ± 0.047	1.08	0.45
CYP2C9:			
SPM 8272:	5.680 ± 0.512	478.35	246.28
SPM 7605:	low interaction detectable, calculation not reasonable		
SPM 5509:	5.464 ± 0.211	291.32	149.99
SPM 6923:	low interaction detectable, calculation not reasonable		
SPM 9078:	5.293 ± 0.151	196.49	101.17
Sulfaphenazole:	2.537 ± 0.025	0.34	0.18
	2.545 ± 0.031	0.35	0.18
	2.538 ± 0.059	0.34	0.18

CYP2C19:			
SPM 8272:	no interaction detectable, calculation not reasonable		
SPM 7605:	no interaction detectable, calculation not reasonable		
SPM 6509:	no interaction detectable, calculation not reasonable		
SPM 6923:	no interaction detectable, calculation not reasonable		
SPM 9078:	5.073 ± 0.099	118.40	64.18
Omeprazole:	3.457 ± 0.037	2.87	1.55
	3.458 ± 0.033	2.87	1.56
	3.456 ± 0.031	2.86	1.55

No relevant (lower µM range) IC_{50}/K_i-values of the test compounds for CYP1A2, CYP2C9 and CYP2C19 interactions were detectable.

2.6.4.6 Excretion

Excretion following single doses of [^{14}C]-fesoterodine (animals) or fesoterodine (human) (majority of dose recovered within 24 hours)(sponsor's summary table)

Species	Dose (mg/kg)	Route	% Administered dose					
			Urine [a]		Feces		Total [b]	
			Male	Female	Male	Female	Male	Female
Mouse	5	oral	42 ± 7	37 ± 1	52 ± 9	54 ± 4	93 ± 4	92 ± 3
	2.5	intravenous	47 ± 15	31 ± 2	45 ± 19	59 ± 8	91 ± 1	90 ± 6
Rat	5	oral	11 ± 4	11 ± 4	76 ± 3	76 ± 7	88 ± 2	87 ± 5
	2.5	intravenous	18 ± 2	16 ± 1	78 ± 1	79 ± 1	96 ± 1	96 ± 2
Dog	0.5	oral	60 ± 14	67 ± 2	26 ± 6	25 ± 2	86 ± 9	91 ± 0
	0.25	intravenous	57 ± 1	63 ± 5	36 ± 6	24 ± 3	93 ± 5	88 ± 4
Human	8 mg	oral	69.7		6.84		76.5	
	4 mg	intravenous	82.3		2.41		84.7	

Excretion of total radioactivity was determined over 168 hours after dosing (animal studies DHGY1005, DHGY1007, DHGY1006). In trial SP567, SPM 7605 and the 3 secondary metabolites were determined in urine and feces samples by LC-MS/MS. Values are means ± SD (n=3 animals/sex) or means (n=11 male human subjects).
a - includes radioactivity in cage wash in animal studies
b - includes radioactivity in carcass and GI tract in mice and rats

2.6.4.7 Pharmacokinetic drug interactions

No drug interaction studies were performed in animals. Studies *in vitro* of drug metabolizing mechanisms are included under Metabolism above.

2.6.4.8 Other Pharmacokinetic Studies NA

2.6.4.9 Discussion and Conclusions

Absorption, distribution, metabolism and excretion of fesoterodine were studied in mice (CD-1, C57BL), rats (Sprague-Dawley, Lister Hooded) and dogs (Beagle). Mice were most similar to human in terms of metabolic profile, and dogs were most similar in terms

of routes of excretion (primarily in urine). Mice and dogs were chosen as the primary toxicity species. Pigmented tissues were investigated in male mice and rats. Elimination of drug-related materials from the eyes of pigmented rats was evident after 168 hours, but no drug accumulation or drug related ocular toxicity was observed in toxicology studies. Placental transfer was observed to occur in pregnant mice and rats. Fesoterodine and its major human metabolites were also monitored in toxicity studies in mice (CD-1), rats (Sprague-Dawley, CD), rabbits (Himalayan) and dogs (Beagle). Fesoterodine (dog only) and/or SPM 7605 (active entity / hydroxy metabolite), and carboxy (SPM 5509), carboxy-N-desisopropyl (SPM 7790) and N-desisopropyl metabolites (SPM 7789)(none pharmacologically active), as measured by LC-MS/MS, were adequately represented in toxicity studies. Parent drug was studied at about 30 times the expected clinical exposure via AUC in mice and at about 20 times in dogs. Metabolite profiles were similar among species. No inversion at the chiral centre of fesoterodine has been observed. The parameters for the method validations included accuracy, precision, selectivity, sensitivity, linearity, reproducibility, recovery, and stability. The analytes and matrix were the same as in clinical trials.

2.6.4.10 Tables and figures to include comparative TK summary

Human pharmacokinetic summary:

Parameter	CYP2D6	8 mg QD			
		SPM7605	SPM5509	SPM7789	SPM7790
C_{max} (ng/ml)	EM	4.0±1.1	14.8±4.3	0.25±0.15	7.47±2.59
	PM	6.9±2.7	7.53±1.0	0.64±0.22	4.27±1.25
	Worst case*	7.21±1.73[e]	17.5±4.3[b]	0.9±0.1[c]	23±9.1[d]
AUC0-tz (ng/ml*h)	EM	45.3±14.5	209±55	1.23±1.33	115±35
	PM	88.7±31.9	117±14.2	6.82±3.14	76.0±26
	Worst case*	132±25[e]	376±123[a]	10.2±1.9[c]	313±73[d]

* If severe renal impairment and strong CYP3A4 inhibitors are limited to 4 mg dose
[a] severe renal impairment + 4 mg fesoterodine
[b] keto + 8 mg in EM subjects
[c] rifampicin + 8 mg in PM subjects
[d] rifampicin + 8 mg in EM subjects, severe renal impaired + 4 mg also yielded similar exposures
[e] moderate hepatic impairment + 8 mg

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Absorption after a single dose in mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

Species	Mouse, CD-1	Mouse, CD-1	Mouse, CD-1	Mouse, CD-1
Gender (M/F)/Number of animals	30 M [a]	30 F [a]	30 M [a]	30 F [a]
Feeding condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	Water/Solution	Water/Solution	Saline/Solution	Saline/Solution
Method of administration	Oral (gavage)	Oral (gavage)	Intravenous bolus	Intravenous bolus
Dose (mg/kg)	5	5	2.5	2.5
Sample	Plasma [b]	Plasma [b]	Plasma [c]	Plasma [c]
Analyte	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C
Assay	LSC	LSC	LSC	LSC
PK parameters:				
C_0 (ng equiv/g)	NA	NA	1294 ± 215	1306 ± 209
C_{max} (ng equiv/g)	1394 ± 488	1522 ± 574	1304 ± 209	1391 ± 165
T_{max} (h)	0.5	0.25	0.25	0
AUC_{last} (h ng equiv/g)	2505 ± 247	2198 ± 397	2225 ± 97.4	2170 ± 230
F (%)	56.3	50.4	NA	NA

Additional information:
Mean ± SD pharmacokinetic parameters are tabulated except for T_{max} (median) and F (derived from means)
TRA denotes total radioactivity, LSC denotes liquid scintillation counting
NA denotes not applicable
a - Three animal/sample per time point were tabulated
b - Plasma samples were obtained at 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24 and 48 hours
c - Plasma samples were obtained at 5 minutes, 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 hours

Absorption after a single dose in rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Species	Rat, Sprague Dawley	Rat, Sprague Dawley	Rat, Sprague Dawley	Rat, Sprague Dawley
Gender (M/F)/Number of animals	3 M	3 F	3 M	3 F
Feeding condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	Water/Solution	Water/Solution	Saline/Solution	Saline/Solution
Method of administration	Oral (gavage)	Oral (gavage)	Intravenous (bolus)	Intravenous (bolus)
Dose (mg/kg)	5	5	2.5	2.5
Sample	Plasma [a]	Plasma [a]	Plasma [b]	Plasma [b]
Analyte	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C
Assay	LSC	LSC	LSC	LSC
PK parameters:				
C_0 (ng equiv/g)	NA	NA	13553 ± 16563	14482 ± NA
C_{max} (ng equiv/g)	246 ± 20.5	204 ± 36.3	13553 ± 16563	14482 ± NA
T_{max} (h)	4	0.5	0	0
AUC_{last} (h ng equiv/g)	3293 ± 221	4933 ± 382	6734 ± 4158	16092 ± NA
$T_{1/2}$ (h)	23.3 ± 3.38	25.8 ± 2.62	43.9 ± 4.11	NA
F (%)	24.5	14.4	NA	NA

Additional information:
Mean ± SD pharmacokinetic parameters are tabulated except for T_{max} (median) and F (derived from means)
TRA denotes total radioactivity, LSC denotes liquid scintillation counting
NA denotes not applicable
a - Plasma obtained at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours (pre3) and at 0.75 hours (pre1)
b - Plasma obtained at 5 minutes, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours

Absorption after a single dose in rabbit

Test Article: Fesoterodine
Location in CTD: 4.2.2.2.3
Study no.: [redacted]-4902/01

Species	Rabbit, Himalayan	Rabbit, Himalayan	Rabbit, Himalayan	Rabbit, Himalayan
Gender (M/F)/Number of animals	3 F	3 F	3 F	3 F
Feeding condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	Water/Solution	Water/Solution	Water/Solution	Water/Solution
Method of administration	Oral (gavage)	Oral (gavage)	Oral (gavage)	Subcutaneous bolus
Dose (mg/kg)	3	6	3	3
Sample	Plasma [a]	Plasma [a]	Plasma [b]	Plasma [b]
Analyte	SP64 7605	SP64 7605	SP64 7605	SP64 7605
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK parameters:				
	Day 1 (Treatment 1)	Day 1 (Treatment 1)	Day 1 (Treatment 1)	Day 1 (Treatment 1)
C_{max} (ng/mL)	4.21 (3.58-5.63)	7.83 (2.39-11.5)	9.20 (7.36-72.8)	724 (643-831)
T_{max} (min)	20 (20-20)	40 (10-130)	20 (20-20)	40 (40-60)
AUC_{inf} (h ng/mL)	9.24 (8.88-13.1)	22.7 (13.4-30.0)	35.0 (27.4-150)	3256 (2195-2892)
$T_{1/2}$ (h)	1.92 (1.88-2.57)	2.18 (1.93-2.42)	2.17 (1.89-2.88)	1.45 (1.39-1.84)
F_{rel} (%)	1.34 (1.18-1.76)	1.51 (1.02-2.00)	1.46 (1.21-6.83)	NA

Additional information:
Medians (ranges) are tabulated.
F_{rel} denotes bioavailability after oral dose as compared to subcutaneous dose
a - Plasma samples were obtained at 20, 40 minutes, and 1, 3 and 6 (prior to 2nd dosing) hours
b - Plasma samples were obtained at 20, 40 minutes, and 1, 2, 4 and 8 hours
NA denotes not applicable

b(4)

Absorption after a single dose in dog

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.4
Study no.: DHGY1006

Species	Dog, Beagle	Dog, Beagle	Dog, Beagle	Dog, Beagle
Gender (M/F)/Number of animals	3 M	3 F	3 M	3 F
Feeding condition	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation	Water/Solution	Water/Solution	Saline/Solution	Saline/Solution
Method of administration	Oral (gavage)	Oral (gavage)	Intravenous bolus	Intravenous bolus
Dose (mg/kg)	0.5	0.5	0.25	0.25
Sample	Plasma[a]	Plasma[a]	Plasma[b]	Plasma[b]
Analyte	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C	TRA, ^{14}C
Assay	LSC	LSC	LSC	LSC
PK parameters:				
C_0 (ng equiv/g)	NA	NA	219 ± 24.6	222 ± 29.7
C_{max} (ng equiv/g)	346 ± 32.7	338 ± 40.1	207 ± 32.4	202 ± 33.2
T_{max} (h)	1	1	5	5
AUC_{inf} (h ng equiv/g)	2736 ± 235	2384 ± 253	1399 ± 69.3	1223 ± 190
$T_{1/2}$ (h)	1.47 ± 0.15	1.44 ± 0.43	NC	NC
F (%)	98.7 ± 10.2	98.1 ± 8.49	NA	NA

Additional information:
Mean ± SD pharmacokinetic parameters are tabulated except for T_{max} (median)
TRA denotes total radioactivity; LSC denotes liquid scintillation counting
NA denotes not applicable
NC not calculated
a - Plasma samples obtained at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours
b - Plasma samples obtained at 5, 10, 30 minutes, and 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours

Test Article: Fesoterodine
Location in CTD: 4.2.2.2.5
Study no.: 12893/99

Species	Dog, Beagle	Dog, Beagle	Dog, Beagle	Dog, Beagle
Gender (M/F)/Number of animals	3 M	3 M	3 M	3 M
Feeding condition	Fasted	Fasted	Fasted	Fasted
Vehicle/Formulation	NA	NA	Saline/Solution	Saline/Solution
Method of administration	Oral (capsule)	Oral (capsule)	Intravenous bolus	Intravenous bolus
Dose (mg/kg)	0.2	0.2	0.2	0.2
Sample	Plasma[a]	Plasma[b]	Plasma[b]	Plasma[b]
Analyte	Fesoterodine	SPM 7605	Fesoterodine	SPM 7605
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK parameters:				
C_{max} (ng/mL)	0.52 ± 0.56	1.45 ± 1.46	108 ± 26.5	9.51 ± 2.3
T_{max} (min)	40 (20-60)	60 (40-120)	5 (5-5)	20 (10-20)
$AUC_{0-\infty}$ (h ng/mL)	1.05 ± 0.51	4.8 ± 5.5	35.8 ± 5.1	17.5 ± 5.6
$T_{1/2}$ (min) or (h)	NC	NC	36 ± 3 min	1.90 ± 0.33 h
F (%)	2.75 ± 0.84	NA	NA	NA
Ratio Metabolite:Parent	NA	6.3 ± 4.9	NA	0.75 ± 0.11

Additional information:
Mean ± SD pharmacokinetic parameters are tabulated except for T_{max} (median (range))
NA denotes not applicable, NC denotes not calculated
a - Plasma samples were obtained at 0, 20, 40 min, and 1, 2, 3, 4, 6 and 8 hours
b - Plasma samples were obtained at 0, 5, 10, 20, 40 min, and 1, 2, 3, 4, 6, and 8 hours

Ratio Metabolite : Parent = $\frac{(\text{Molecular weight of parent}) \times (\text{AUC of metabolite})}{(\text{Molecular weight of metabolite}) \times (\text{AUC of parent})}$

b(4)

Test Article: Fesoterodine and SPM 7605
Location in CTD: 4.2.2.2.6
Study no.: 14841/01

Species	Dog, Beagle	Dog, Beagle	Dog, Beagle	Dog, Beagle	Dog, Beagle
Gender (M/F)/Number of animals	5 F	5 F	5 F	5 F	5 F
Feeding condition	Fasted	Fasted	Fasted	Fasted	Fasted
Test article	Fesoterodine	Fesoterodine	Fesoterodine	Fesoterodine	SPM 7605
Vehicle/Formulation	NA	NA	Water for injection	Water for injection	Ready-to-use solution
Method of administration	Oral (SR tablet)	Oral (SR tablet)	Oral (gavage)	Oral (gavage)	24-hour infusion
Dose (mg/kg)	3.8-4.2	3.8-4.2	2	2	1
Sample	Plasma[a]	Plasma[a]	Plasma[c]	Plasma[c]	Plasma[b]
Analyte	Fesoterodine	SPM 7605	Fesoterodine	SPM 7605	SPM 7605
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK parameters:			Day 1 (Treatment 1)	Day 1 (Treatment 1)	
C_{max} (ng/mL)	4.33 ± 4.91	6.44 ± 1.93	4.23 ± 2.59	4.87 ± 2.07	9.43 ± 2.81
T_{max} (h)	6 (6-8)	4 (2-8)	1 (0.17-1)	1 (0.5-4)	8 (8-24)
AUC_{0-t} or AUC_{0-ss} (h ng/mL)	43.0 ± 49.1 [d]	71.9 ± 58.1 [d]	7.69 ± 3.66 [e]	19.7 ± 2.87 [e]	176 ± 39.6 [e]
AUC_{inf} (h ng/mL)	43.7 ± 48.7	73.4 ± 59.5	NC	21.6 ± 3.03	186 ± 36.7
$T_{1/2}$ (h)	NC	NC	NC	NC	1.01 ± 0.15
Ratio Metabolite:Parent	NA	8.1 ± 10.5	NA	4.9 ± 1.9	NA

Additional information:
Mean ± SD pharmacokinetic parameters are tabulated except for T_{max} (median (range)); NA denotes not applicable; NC denotes not calculated;
a - Plasma samples obtained at 0, 1, 2, 3, 4, 6, 8, 12, 24 and 30 hours; b - Plasma samples obtained at 0, 1, 4, 8, 24, 24.5, 25 and 28 hours;
c - Plasma samples obtained at 0, 0.17 (10 minutes), 0.5, 1, 2, 4, 6, 8 and 12 hours; d - AUC_{0-24h}; e - AUC_{0-ss}

Ratio Metabolite : Parent = $\frac{(\text{Molecular weight of parent}) \times (\text{AUC of metabolite})}{(\text{Molecular weight of metabolite}) \times (\text{AUC of parent})}$

b(4)

Absorption after repeated doses in rabbit

Test Article: Fesoterodine
Location in CTD: 4.2.2.2.5
Study no.: 19902/01

b(4)

Species	Rabbit, Himalayan	Rabbit, Himalayan	Rabbit, Himalayan	Rabbit, Himalayan
Gender (M/F)/Number of animals	3 ♀	3 ♀	3 ♀	3 ♀
Feeding condition	Fed	Fed	Fed	Fed
Vehicle/Formulation	Water/Solution	Water/Solution	Water/Solution	Water/Solution
Method of administration	Oral (gavage)	Oral (gavage)	Oral (gavage)	Subcutaneous bolus
Dose (mg/kg/day)	9 (3 x 3)	18 (3 x 6)	27 (3 x 9)	9
Sample	Plasma[a]	Plasma[a]	Plasma[a]	Plasma[b]
Analyte	SPM 7605	SPM 7605	SPM 7605	SPM 7605
Assay	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
PK parameters:				
	Day 4 (Treatment 10)	Day 4 (Treatment 10)	Day 4 (Treatment 10)	Day 4 (Treatment 4)
C_{max} (ng/mL)	3.26 (3.14-5.91)	9.27 (3.31-13.5)	28.7 (21.8-68.8)	805 (777-882)
T_{max} (min)	20 (20-40)	20 (20-40)	20 (20-40)	60 (60-60)
AUC_{tau} (h·ng/mL)	9.83 (9.27-11.7)	33.0 (33.4-42.5)	78.4 (56.6-316)	2547 (2514-3012)
$T_{1/2}$ (h)	1.23 (0.84-1.37)	1.54 (1.20-2.87)	1.54 (1.28-2.17)	1.53 (1.44-1.53)
F_{rel} (%)[c]	1.16 (1.09-1.38)	1.94 (0.95-2.56)	1.12 (2.34-4.55)	NA
R (Accumulation factor)	0.59 (0.59-1.11)	1.21 (1.00-1.46)	1.59 (0.53-3.32)	1.13 (1.04-1.13)

Additional information:
Medians (ranges) are tabulated
a - Plasma samples were obtained at predose (prior to 10th dosing), 20, 40 minutes, and 1, 3, 6 hours (prior to 11th dosing)
b - Plasma samples were obtained at predose (prior to 9th dosing), 20, 40 minutes, and 1, 2, 4, 8 and 12 hours
c - F_{rel} denotes bioavailability after oral dose as compared to subcutaneous dose
NA denotes not applicable

Absorption after repeated doses in dog

Test Article: Fesoterodine
Location in CTD: 4.2.2.2.3
Study no.: 14841/01

b(4)

Species	Dog, Beagle	Dog, Beagle
Gender (M/F)/Number of animals	3 ♀	3 ♀
Feeding condition	Fed	Fed
Vehicle/Formulation	Water/Solution	Water/Solution
Method of administration	Oral (gavage)	Oral (gavage)
Dose (mg/kg/12hours)	2[a]	2[a]
Sample	Plasma	Plasma
Analyte	Fesoterodine	SPM 7605
Assay	LC-MS/MS	LC-MS/MS
PK parameters:		
	Day 7 (Treatment 13)	Day 7 (Treatment 13)
C_{max} (ng/mL)	17.38 ± 10.23	23.21 ± 17.00
T_{max} (h)	0.5 (0.17-2)	0.5 (0.17 - 2)
AUC_{0-tau} (h·ng/mL)	24.56 ± 14.50	39.11 ± 21.95
AUC_{inf} (h·ng/mL)	NC	51.30 ± 29.09
$T_{1/2}$ (h)	NC	2.43 ± 1.28
Ratio Metabolite:Parent	NA	6.1 ± 2.8
R (Accumulation factor)	3.48 ± 1.53	3.90 ± 1.53

Additional information:
Mean ± SD pharmacokinetic parameters tabulated except for T_{max} (median (range)); Plasma samples were obtained at 0, 0.17 (10 minutes), 0.5, 1, 2, 4, 6, 8 and 12 hours post-dose; NA denotes not applicable; NC denotes not calculated;
a - 2 mg/kg twice daily every 12 hours

$$\text{Ratio Metabolite : Parent} = \frac{(\text{Molecular weight of parent}) \times (\text{AUC of metabolite})}{(\text{Molecular weight of metabolite}) \times (\text{AUC of parent})}$$

Organ distribution in male mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

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Species:	Mouse, CD-1
Gender (M/F)/Number of animals:	6 M (1 animal per time point)
Feeding condition:	Fed
Vehicle/Formulation:	Water/Solution
Method of administration:	Oral (gavage)
Dose (mg/kg):	5
Radionuclide:	^{14}C
Assay:	QWBA (quantitative whole body autoradiography)
Sampling time:	0.5, 1, 4, 8, 24 and 72 hours

Tissue/organ:	Concentrations (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	24 hours	72 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv·h/g)
LOQ									
Adrenal							1048	0.5	1944
Bile							NC	NC	NC
Bone marrow							438	0.5	781
Bone							NC	NC	NC
Brain							81.3	0.5	164
Brown fat							559	0.5	972
Caecum contents							NC	NC	NC
Cardiac blood							845	0.5	1529
Cardiac muscle							419	0.5	788
Epididymis							477	0.5	839
Harderian gland							691	0.5	478

Kidney cortex	9480	0.5	21309
Kidney medulla	5297	0.5	19676
Large intestine contents	NC	NC	NC
Liver	3989	0.5	21699
Lung	659	1	2916
Nasal mucosa	415	0.5	720
Pancreas	1506	0.5	3911
Pituitary gland[a]	717	0.5	466
Preputial gland	1218	8	3692
Seminal vesicle[a]	66.0	0.5	46.3
Skeletal muscle	345	0.5	393
Small intestine contents	NC	NC	NC
Spinal cord[a]	63.6	0.5	42.3
Spleen	601	0.5	3189
Stomach contents	NC	NC	NC
Submaxillary salivary gland	675	0.5	921
Testes	169	0.5	217
Thymus	306	0.5	495
Thyroid gland[a]	377	0.5	239
Testes	169	0.5	217
Thymus	306	0.5	495
Thyroid gland[a]	377	0.5	239
Urinary bladder wall	92734	4	290479
Urine	NC	NC	NC
White fat	132	0.5	232
Whole eye[a]	43.3	1	28.7

Additional information:
a - data calculated from two consecutive values; NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in female mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.3.2.1
Study no.: DHGY1005

Species: Mouse, CD-1
Gender (M/F)/Number of animals: 6 F (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 24 and 72 hours

Tissue/organ:	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	24 hours	72 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ									
Adrenal							839	0.5	743
Bile							360291	1	681382
Bone marrow[a]							489	0.5	323
Bone							NC	NC	NC
Brain							60.5	0.5	NC
Bronchi							932	0.5	756
Caecum contents							NC	NC	NC
Cardiac blood							1094	0.5	1031
Cardiac muscle							713	0.5	677
Harderian gland							1733	0.5	1764
Kidney cortex							3334	0.5	4983
Kidney medulla							3481	0.5	4422
Large intestine contents							NC	NC	NC
Liver							5487	0.5	20123
Lung							1392	0.5	1736
Nasal mucosa[a]							526	0.5	447
Ovary[a]							859	0.5	537
Pancreas							792	0.5	609
Pineal body[a]							295	0.5	161
Pituitary gland[a]							583	0.5	302
Skeletal muscle[a]							232	0.5	172
Small intestine contents							NC	NC	NC
Spinal cord							64.4	0.5	NC
Spleen							669	0.5	844
Stomach contents							NC	NC	NC
Submaxillary salivary gland							1051	0.5	936
Thymus[a]							310	0.5	184
Thyroid gland[a]							1284	0.5	708
Urinary bladder wall[a]							227829	1	531014
Urine							NC	NC	NC
Uterus							NC	NC	NC
White fat							230	0.5	132
Whole eye							20.6	0.5	12.7

Additional information:
a - data calculated from two consecutive values; NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in pregnant female mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

Species: Mouse, CD-1 (pregnant)
Gender (M/F)/Number of animals: 8 F (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 24 and 72 hours

Tissues/organs	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	24 hours	72 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ									
Adrenal							1277	1	2869
Bile							316372	0.5	200061
Bone marrow							NC	0.5	NC
Bone							NC	0.5	NC
Brain							28.0	1	NC
Brown fat							364	0.5	429
Caecum contents							NC	NC	NC
Cardiac blood							472	0.5	1223
Cardiac muscle							378	0.5	378
Chorioallantoic placenta							NC	NC	NC
Faeces							156	4	438
Harderian gland							849	0.5	1932
Kidney cortex							1523	0.5	10293
Kidney medulla							1877	0.5	6472
Large intestine contents							NC	NC	NC
Liver							3856	0.5	22172
Lung							778	0.5	2356
Nasal mucosa							1020	8	2586
Ovary							505	0.5	816
Pancreas							644	1	1809
Pineal body							NC	NC	NC
Pituitary gland							489	0.5	617
Placenta							670	0.5	1163
Preputial gland							NC	NC	NC
Skeletal muscle[a]							275	0.5	563
Skin/fur							NC	NC	NC
Small intestine contents							NC	NC	NC
Spinal cord							NC	NC	NC
Spleen							266	0.5	907
Stomach contents							NC	NC	NC
Submaxillary salivary gland							861	0.5	1475
Thymus							351	0.5	1246
Thyroid gland							116191	1	337134
Urinary bladder wall[a]							163561	1	372643
Urine							393	4	1055
Uterus							394	4	1036
White fat							140	0.5	445
Whole eye							34.4	1	25.7

Additional information:
a - data calculated from two consecutive values; NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in male pigmented mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

Species: Mouse, C57BL (pigmented)
Gender (M/F)/Number of animals: 7 M (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 24, 72 and 168 hours

Tissues/organs	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	24 hours	72 hours	168 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ										
Adrenal								979	0.5	1910
Bile								303294	4	1502323
Bone marrow[a]								320	0.5	228
Bone								220	0.5	115
Brain								35.6	0.5	113
Brown fat[a]								735	0.5	478
Caecum contents								NC	NC	NC
Cardiac blood								979	0.5	1828
Cardiac muscle								671	0.5	1057
Epididymis[a]								1005	1	702
Harderian gland								1408	0.5	7598
Kidney cortex								3423	0.5	3902

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Kidney medulla	3631	0.5	7724
Large intestine contents	240260	8	2322648
Liver	8280	0.5	15035
Lung	1664	0.5	1923
Nasal mucosa[a]	382	0.5	467
Pancreas	589	0.5	3193
Pigmented eye	3472	0.5	149348
Pituitary gland	944	0.5	1466
Preputial gland	639	0.5	1123
Seminal vesicle[a]	262	0.5	149
Skeletal muscle	249	0.5	348
Skin	783	0.5	13906
Small intestine contents	191420	1	678433
Spinal cord[a]	64.8	0.5	40.1
Spleen	1709	0.5	1677
Stomach contents	254697	0.5	330949
Submaxillary salivary gland	816	0.5	1385
Testes	133	0.5	166
Thymus[a]	439	0.5	270
Thyroid gland[a]	3489	0.5	1796
Urinary bladder wall	NC	NC	NC
Urine	76570	1	442502
White fat	257	0.5	273
Whole eye	64.8	8	1002

Additional information:
a - data calculated from two consecutive values; NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in male rat

Test Article: [^{14}C]-Perzabrodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Species: Rat, Sprague Dawley
Gender (M/F)/Number of animals: 6 M (3 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 12 and 24 hours

Tissue/organ	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	12 hours	24 hours	Pharmacokinetic parameters: C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ									
Adrenal cortex							NC	NC	NC
Adrenal medulla							NC	NC	NC
Bone marrow							NC	NC	NC
Bone							NC	NC	NC
Brain							33.5	1	34.7
Brown fat							ND	ND	ND
Caecum contents							ND	ND	ND
Caecum wall							NC	NC	NC
Cardiac blood							127	0.5	309
Cardiac muscle							84.1	0.5	182
Epididymis							NC	NC	NC
Harderian gland							NC	NC	NC
Kidney cortex							724	8	11498
Kidney medulla							2548	12	43935
Large intestine contents							NC	NC	NC
Liver							3186	0.5	40907
Lung							145	0.5	593
Nasal mucosa							NC	NC	NC
Pancreas							842	4	4471
Pituitary gland							NC	NC	NC
Preputial gland							NC	NC	NC
Seminal vesicle							NC	NC	NC
Skeletal muscle							36.3	12	72.5
Small intestine contents							NC	NC	NC
Small intestine wall							NC	NC	NC
Spinal cord							NC	NC	NC
Spleen							108	4	1057
Stomach contents							NC	NC	NC
Stomach wall							NC	NC	NC
Submaxillary							93.3	0.5	95.0
Testes							NC	NC	NC
Thymus							NC	NC	NC
Thyroid gland							49.4	1	123
Urine							NC	NC	NC
White fat							26.7	4	147
Whole eye							NC	NC	NC
Whole blood							130	0.5	1282

Additional information:
NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in female rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Species: Rat, Sprague Dawley
Gender (M/F)/Number of animals: 5 F (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 12 and 24 hours

Tissue/organ	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	12 hours	24 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ									
Adrenal cortex							NC	NC	NC
Adrenal medulla							NC	NC	NC
Bone marrow							NC	NC	NC
Bone							NC	NC	NC
Brain							54.1	4	110
Brown fat							NC	NC	NC
Caecum contents							NC	NC	NC
Cardiac blood							84.8	4	360
Cardiac muscle							70.6	4	182
Harderian gland							NC	NC	NC
Kidney cortex							136	4	9061
Kidney medulla							2674	8	49542
Large intestine contents							NC	NC	NC
Liver							3072	8	78630
Lung							174	4	1263
Nasal mucosa							NC	NC	NC
Ovary							144	4	371
Pancreas							NC	NC	NC
Pineal body							NC	NC	NC
Pituitary gland							NC	NC	NC
Skeletal muscle							30.6	8	206
Small intestine contents							NC	NC	NC
Spinal cord							NC	NC	NC
Spleen							NC	NC	NC
Stomach contents							NC	NC	NC
Stomach wall							NC	NC	NC
Submaxillary							142	4	344
Thymus							NC	NC	NC
Thyroid gland							94.9	4	237
Urine							NC	NC	NC
Uterus							NC	NC	NC
White fat							34.7	1	13.7
Whole eye							NC	NC	NC
Whole blood							107	1	1623

Additional information:
NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

b(4)

Organ distribution in pregnant female rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Species: Rat, Sprague Dawley (pregnant)
Gender (M/F)/Number of animals: 5 F (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 0.5, 1, 4, 8, 12 and 24 hours

Tissue/organ	Concentration (ng equiv/g) 0.5 hours	1 hour	4 hours	8 hours	12 hours	24 hours	Pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{last} (ng equiv h/g)
LOQ									
Adrenal cortex							NC	NC	NC
Adrenal medulla							NC	NC	NC
Bone marrow							NC	NC	NC
Bone							NC	NC	NC
Brain							31.2	4	203
Brown fat							NC	NC	NC
Caecum contents							NC	NC	NC
Caecum wall							NC	NC	NC
Cardiac blood							86.7	4	1218
Cardiac muscle							86.6	8.5	439
Chorioallantoic placenta							184	4	3797
Foetus							96.5	4	797

b(4)

Harderian gland	NC	NC	NC
Kidney cortex	461	1	6512
Kidney medulla	1729	12	33173
Large intestine contents	NC	NC	NC
Liver	3158	12	94918
Lung	138	1	1764
Nasal mucosa	NC	NC	NC
Ovary	69.3	12	1204
Pancreas	NC	NC	NC
Pineal body	NC	NC	NC
Pituitary gland	NC	NC	NC
Placenta	53.8	4	1236
Preputial gland	NC	NC	NC
Skeletal muscle	40.9	1	270
Small intestine contents	NC	NC	NC
Spinal cord	NC	NC	NC
Spleen	NC	NC	NC
Stomach contents	NC	NC	NC
Submaxillary salivary gland	102	1	371
Thymus	NC	NC	NC
Thyroid gland	114	1	856
Urine	NC	NC	NC
Uterus	NC	NC	NC
White fat	33.5	0.5	112
Whole eye	NC	NC	NC
Whole blood	118	0.5	1926

b(4)

Additional information:
NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

Organ distribution in male pigmented rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.3.2.2
Study no.: DHGY1007

Species: Rat, Lister Hooded (pigmented)
Gender (M/F)/Number of animals: 6 F (1 animal per time point)
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: QWBA (quantitative whole body autoradiography)
Sampling time: 1, 4, 12, 24, 72 and 168 hours

Tissues/organs	Concentration (µg equiv/g) 1 hour	4 hour	12 hours	24 hours	72 hours	168 hours	Pharmacokinetic parameters C_{max} (µg equiv/g)	T_{max} (h)	AUC_{last} (µg equiv h/g)
LOQ									
Adrenal cortex							NC	NC	NC
Adrenal medulla							NC	NC	NC
Bone marrow							NC	NC	NC
Bone							NC	NC	NC
Brain							16.6	4	184
Brown fat							NC	NC	NC
Caecum contents							NC	NC	NC
Caecum wall							NC	NC	NC
Cardiac blood							113	1	373
Cardiac muscle							76.1	4	216
Epididymis							NC	NC	NC
Harderian gland							NC	NC	NC
Kidney cortex							330	4	23299
Kidney medulla							3151	4	136080
Large intestine contents							NC	NC	NC
Liver							6040	1	76965
Lung							201	4	533
Nasal mucosa							NC	NC	NC
Pancreas							NC	NC	NC
Pigmented eye							479	168	53258
Pituitary gland							NC	NC	NC
Preputial gland							NC	NC	NC
Seminal vesicle							NC	NC	NC
Skeletal muscle							31.5	1	292
Small intestine contents							NC	NC	NC
Spinal cord							NC	NC	NC
Spleen							NC	NC	NC
Stomach contents							NC	NC	NC
Stomach wall							NC	NC	NC
Submaxillary							97.3	4	273
Testes							NC	NC	NC
Thymus							NC	NC	NC
Thyroid gland							165	1	478
Urine							NC	NC	NC
White fat							17.3	1	8.68
Whole eye							NC	NC	NC
Whole blood							174	1	3939

b(4)

Additional information:
NC denotes not calculated; ND denotes sample cannot be distinguished from surrounding tissue on the image; BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

Organ distribution in dog

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.3.2.4
Study no.: DHGY1006

Species:	Dog, Beagle
Gender (M/F)/Number of animals:	3 M, 3 F (1 animal per time point)
Feeding condition:	Fasted
Vehicle/Formulation:	Water/Solution
Method of administration:	Oral (gavage)
Dose (mg/kg):	0.5
Radionuclide:	^{14}C
Assay:	LSC (Liquid scintillation counting) of homogenates
Sampling time:	1, 4, 8, 24, 48 and 96 hours post-dose

Tissue/organ	Concentration (ng equiv/g) 1 hour M	4 hours F	8 hours M	24 hours F	48 hours M	96 hours F	Plasma pharmacokinetic parameters C_{max} (ng equiv/g)	T_{max} (h)	AUC_{inf} (ng equiv h/g)
Adrenal							337	24	19215
Bone marrow							193	2	2014
Bone mineral							30.6	8	1643
Brain							39.1	1	317
Eye							54.3	4	1782
Fat							26.8	1	780
Heart							225	1	2543
Kidney							1114	1	8765
Large intestine wall							5310	4	44659
Large intestine contents							NA	NA	NA
Liver							4936	1	33094
Lung							442	2	3958
Muscle							189	2	2188
Ovary							136	4	4940
Parotid gland							191	1	2448
Prostate							431	1	9158
Skin							198	1	2086
Small intestine wall							1504	1	10361
Small intestine contents							NA	1	NA
Spleen							378	1	2658
Stomach wall							147	4	2371
Stomach contents							NA	NA	NA
Testes							128	1	2396
Thyroid							256	1	4805
Uterus							149	4	3092
Plasma							336	1	2324
Whole blood							NA	NA	NA
Remaining carcass							NA	NA	NA

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Additional information:
Total recovery expressed as % of administered dose accounted for 82.7% (1 hour), 62.0% (4 hours), 60.3% (8 hours), 8.01% (24 hours), 2.27% (48 hours) and 1.46 % (96 hours).
NA denotes not applicable; BLQ denotes below the limit of quantification; a - sample includes large intestine wall and contents

Plasma protein binding (interspecies)

Test Article: [^{14}C]-Fesoterodine and [^{14}C]-5-PM 7605

Study system: In vitro

Target entity, test system and method: Mouse, rat, rabbit, dog, monkey and human plasma, equilibrium dialysis, LSC for quantification of total radioactivity

Species	Fesoterodine concentration (ng/mL)	5-PM 7605 concentration (ng/mL)	% Bound (mean ± SD, n = 3) Fesoterodine	5-PM 7605	Study No.	Location
Mouse	200	118	34 ± 2	25 ± 2	BA 456-02	4.2.2.3.1
Rat	200	118	29 ± 2	32 ± 1	BA 456-02	4.2.2.3.1
Rabbit	200	118	21 ± 2	21 ± 2	BA 456-02	4.2.2.3.1
Dog	200	118	36 ± 6	30 ± 4	BA 456-02	4.2.2.3.1
Monkey	200	118	37 ± 4	37 ± 3	BA 456-02	4.2.2.3.1
Human	200	118	31 ± 4	33 ± 2	BA 456-02	4.2.2.3.1

Additional information:
In Phase 1 Trial SP568 blood samples were drawn at 6 hours post-dose to determine the in vivo protein binding of 5-PM 7605 by equilibrium dialysis (3.3.5.3.2, SP568).
Trial design: single oral administration of 4 mg fesoterodine/subject, male and female patients with renal impairment, n=8/group, 18 to 75 years, Group 1: CL_{cr} ≥ 80 mL/min (healthy control), Group 2: 80 mL/min > CL_{cr} ≥ 50 mL/min (mild renal impairment), Group 3: 50 mL/min > CL_{cr} ≥ 30 mL/min (moderate renal impairment), Group 4: CL_{cr} < 30 mL/min (severe renal impairment). Results (n=8/group):

Parameter	Unit	Group 1 (healthy controls)	Group 2 (mildly impaired)	Group 3 (moderately impaired)	Group 4 (severely impaired)
Conc. of 5-PM 7605 at 6 hours post-dose (range)	ng/mL	0.19 - 2.94	1.24 - 3.66	1.37 - 3.89	2.03 - 5.77
f_u 5-PM 7605 (geometric mean (CV%))		0.54 (8.4)	0.45 (11.4)	0.43 (9.0)	0.43 (15.6)

CL_{cr} - creatinine clearance
f_u - unbound fraction
overall binding of 5-PM 7605 (n=32): 53.5 ± 6.8% (mean ± SD), 39.4 - 65.2% (range)

Plasma protein binding (human plasma proteins)

Test Article: [^{14}C]-Fesoterodine and [^{14}C]-5-PM 7605

Study system: In vitro

Target entity, test system and method: Human serum albumin and alpha 1 acid glycoprotein, equilibrium dialysis, LSC for quantification of total radioactivity

Species	Concentration tested (ng/mL)	Pooled plasma	% Bound HSA c = 45 mg/mL	AGP c = 1 mg/mL	HSA (45 mg/mL) + AGP (1 mg/mL)	Study no.	Location
	Fesoterodine						
Human	62.5	48	31	60	80	BA 456-02	4.2.2.3.1
	250	49	31	76	92		
	500	34	28	73	84		
	750	32	30	74	94		
	1000	32	32	76	93		
	Mean ± SD*	31 ± 2	30 ± 2	72 ± 7	91 ± 6		
	5-PM 7605						
Human	74	33	14	13	35	BA 456-02	4.2.2.3.1
	295	33	12	19	40		
	591	33	17	20	40		
	886	33	11	18	40		
	1182	31	14	9	38		
	Mean ± SD*	33 ± 1	14 ± 3	16 ± 5	39 ± 1		

Additional information:
Recovery was 90 to 95% of nominal concentration due to adsorption to the surface vial
HSA = human serum albumin
AGP = alpha-1-acid glycoprotein
a - mean of overall dose range

Placental transfer in the mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

Placental transfer	
Species:	Mouse, CD-1 (pregnant)
Gestation day/Number of animals:	Day 15 of gestation at dosing/3 F (1 animal per time point)
Feeding condition:	Fed
Vehicle/Formulation:	Water/Solution
Method of administration:	Oral (gavage)
Dose (mg/kg):	5
Radionuclide:	^{14}C
Assay:	QWBA (Quantitative whole body autoradiography)
Sampling time:	0.5, 1, 4, 8, 24 and 72 hours

Concentration (ng equiv/g)

Time (hour):	0.5 hours	1 hour	4 hours	8 hours	24 hours	72 hours
LOQ						
Maternal cardiac blood						
Chorioallantoic placenta						
Foetus						
Maternal liver						
Maternal ovary						
Placenta						
Uterus						

b(4)

Additional information:
BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

Placental transfer in the rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Placental transfer	
Species:	Rat, Sprague Dawley (pregnant)
Gestation day/Number of animals:	Day 15 of gestation at dosing/3 F (1 animal per time point)
Feeding condition:	Fed
Vehicle/Formulation:	Water/Solution
Method of administration:	Oral (gavage)
Dose (mg/kg):	5
Radionuclide:	^{14}C
Assay:	QWBA (Quantitative whole body autoradiography)
Sampling time:	0.5, 1, 4, 8, 12 and 24 hours

Concentration (ng equiv/g)

Time (hour):	0.5 hours	1 hour	4 hours	8 hours	12 hours	24 hours
LOQ						
Maternal cardiac blood						
Chorioallantoic placenta						
Foetus						
Maternal liver						
Maternal ovary						
Placenta						
Uterus						

b(4)

Additional information:
BLQ denotes below the limit of quantification; LOQ denotes limit of quantification

Metabolism in mouse plasma

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.1
Study no.: 634

Species:	Mouse, CD-1								Mouse, CD-1							
Gender(M/F)/Number of animals:	12 M, 12 F								18 M, 18 F							
Feeding condition:	Fed								Fed							
Test article:	Fesoterodine								Fesoterodine							
Vehicle/Formulation:	Water/Solution								Water/Solution							
Method of administration:	Oral (gavage)								Oral (gavage)							
Dose (mg/kg/day):	5								5							
Duration of administration:	26 weeks								26 weeks							
Sample:	Plasma, pooled								Plasma, pooled							
Assay:	LC-MS/MS								LC-MS/MS							
Plasma samples derived from study:	13348/00								13399/00							
Analytes:	SPM 7603		SF		SPM 7789		SPM 7790		SPM 1503		SF		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PK-Parameters:																
C_{max} (nmol/L)	41.0	43.0	49.7	73.7	3.62	3.78	57.3	58.8	38.4	29.3	85.5	89.8	3.05	1.72	44.6	45.6
T_{max} (h)	0.5	0.5	0.5	0.5	0.5	2	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
AUC_{inf} (h nmol/L)	52.2	54.6	166	271	10.3	6.13	139	177	43.8	62.0	162	325	4.53	3.89	72.2	77.4
Ratio C_{max}	1	1	1.70	1.76	0.09	0.09	1.40	1.37	1	1	2.29	3.07	0.08	0.04	1.16	1.49
Ratio AUC_{inf}	1	1	3.18	5.13	0.20	0.11	2.67	3.24	1	1	3.71	2.02	0.10	0.04	1.65	1.25

b(4)

Additional information:
Pooled plasma samples (n=3 animals/time point) were obtained at 0.5, 2, 6 and 24 hours (LPT 13348/00) or at 0.5, 1, 2, 4, 6 and 12 hours (LPT 13399/00)
SPM 7603 = hydroxy metabolite, SPM 1503 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

Species:	Mouse, CD-1								Mouse, CD-1					
Gender(M/F)/Number of animals:	12 M, 12 F								12 M, 12 F					
Dose (mg/kg/day):	15								25					
Duration of administration:	26 weeks								26 weeks					
Plasma samples derived from study:	13398/00								13348/00					
Analytes:	SPM 7605	SPM 5309		SPM 7789		SPM 7790		SPM 7605	SPM 5309		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PK-Parameters:														
C_{max} (nmol/L)	135	366	163	276	23.7	52.5	127	312	422	755	245	390	60.8	122	235	533
T_{max} (h)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
AUC_{last} (h nmol/L)	253	397	459	504	69.8	91.9	402	687	947	1402	636	913	184	278	928	1528
Ratio C_{max}	1	1	1.20	0.75	0.18	0.14	0.94	0.85	1	1	0.58	0.52	0.14	0.16	0.56	0.71
Ratio AUC_{last}	1	1	1.59	1.27	0.25	0.23	1.42	1.68	1	1	0.71	0.65	0.22	0.20	1.10	1.09

Species:	Mouse, CD-1								Mouse, CD-1					
Gender(M/F)/Number of animals:	12 M, 12 F								12 M, 12 F					
Dose (mg/kg/day):	45								100 (M) / 125 (F)					
Duration of administration:	weeks								weeks					
Plasma samples derived from study:	13398/00								13348/00					
Analytes:	SPM 7605	SPM 5309		SPM 7789		SPM 7790		SPM 7605	SPM 5309		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PK-Parameters:														
C_{max} (nmol/L)	1484	2764	589	473	304	466	719	934	4890	8697	565	571	817	1137	1158	1806
T_{max} (h)	0.5	0.5	0.5	1	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	2
AUC_{last} (h nmol/L)	2661	3104	1382	1412	600	750	1812	3149	11344	24178	1683	3099	2832	3248	6218	13622
Ratio C_{max}	1	1	0.40	0.17	0.22	0.17	0.51	0.34	1	1	0.12	0.07	0.17	0.13	0.24	0.18
Ratio AUC_{last}	1	1	0.52	0.45	0.23	0.24	0.68	1.01	1	1	0.15	0.13	0.25	0.23	0.56	0.56

Additional information:
Pooled plasma samples (n=3 animals/sex/time) were obtained at 0.5, 2, 6 and 24 hours (LPT 13348/00) or at 0.5, 1, 2, 4, 6 and 12 hours (LPT 13398/00)
SPM 7605 = hydroxy metabolite, SPM 5309 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Metabolism in rat plasma

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.2
Study no.: 667

Species:	Rat, CD					Rat, CD		
Gender(M/F)/Number of animals:	3 M					3 F		
Feeding condition:	Fed					Fed		
Test article:	Fesoterodine					Fesoterodine		
Vehicle/Formulation:	Water/Solution					Water/Solution		
Method of administration:	Oral (gavage)					Oral (gavage)		
Dose (mg/kg/day):	15					15		
Duration of administration:	13 weeks					13 weeks		
Sample:	Plasma					Plasma		
Assay:	MS/MS					MS/MS		
Plasma samples derived from study:	13684/00					13684/00		
Analytes:	SPM 7605	SPM 5309	SPM 7789	SPM 7790	SPM 7605	SPM 5309	SPM 7789	SPM 7790
	M	M	M	M	F	F	F	F
PK-Parameters:								
C_{max} (nmol/L)	40.7	25.3	11.1	32.0	63.8	48.1	1.23	20.2
T_{max} (h)	1	1	1	1	0.5	0.75	0.75	0.75
AUC_{last} (h nmol/L)	363	228	26.8	558	141	263	0.31	57.4
Ratio C_{max}	1	0.62	0.27	2.01	1	1.09	0.03	0.33
Ratio AUC_{last}	1	0.62	0.07	1.55	1	1.99	0.002	0.43

Additional information:
Individual data (males) and medians (females, n=2) are presented
Plasma samples were obtained at 0.5, 1, 3, 6, 12 and 24 hours by staggered sampling, each rat had to be bled two to three times per day
SPM 7605 = hydroxy metabolite, SPM 5309 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Species:	Rat, CD					Rat, CD		
Gender(M/F)/Number of animals:	3 M					3 F		
Feeding condition:	Fed					Fed		
Test article:	Fesoterodine					Fesoterodine		
Vehicle/Formulation:	Water/Solution					Water/Solution		
Method of administration:	Oral (gavage)					Oral (gavage)		
Dose (mg/kg/day):	45					45		
Duration of administration:	13 weeks					13 weeks		
Sample:	Plasma					Plasma		
Assay:	MS/MS					MS/MS		
Plasma samples derived from study:	13684/00					13684/00		
Analytes:	SPM 7605	SPM 5309	SPM 7789	SPM 7790	SPM 7605	SPM 5309	SPM 7789	SPM 7790
	M	M	M	M	F	F	F	F
PK-Parameters:								
C_{max} (nmol/L)	254	95.0	475	709	120	114	21.4	464
T_{max} (h)	0.5	0.5	0.5	0.5	0.75	0.75	1	1
AUC_{last} (h nmol/L)	1025	370	1241	3565	665	734	304	447
Ratio C_{max}	1	0.38	1.87	2.75	1	0.92	0.20	0.38
Ratio AUC_{last}	1	0.36	1.21	3.48	1	1.09	0.30	0.68

Additional information:
Individual data (males) and medians (females, n=2) are presented
Plasma samples were obtained at 0.5, 1, 3, 6, 12 and 24 hours by staggered sampling, each rat had to be bled two to three times per day
SPM 7605 = hydroxy metabolite, SPM 5309 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Species:	Rat, CD						Rat, CD					
Gender(M/F)/Number of animals:	9 M, 9 F						9 M, 9 F					
Dose (mg/kg/day):	5						15					
Duration of administration:	26 weeks						26 weeks					
Plasma samples derived from study:	[redacted] 13400/00						[redacted] 13400/00					
Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790		SPM 7605		SPM 5509	
	M	F	M	F	M	F	M	F	M	F	M	F
PK-Parameters:												
C_{max} (nmol/L)	28.0	11.7	28.5	45.1	1.86	1.36	61.6	19.2	41.6	26.2	87.8	98.6
T_{max} (h)	12	1	3	0.5	0.75	0.5	1	0.5	0.5	0.5	0.5	0.5
AUC_{last} (h nmol/L)	211	93.0	145	111	0.47	0.34	295	37.2	266	128	752	484
Ratio C_{max}	1	1	1.03	2.76	0.06	0.12	2.70	1.63	1	1	3.04	3.86
Ratio AUC_{last}	1	1	0.69	1.13	0.006	0.01	1.40	0.49	1	1	3.35	2.95

SPM 7789		SPM 7790	
M	F	M	F
0.5	0.5	0.5	0.5
NA	1*	3	1.5
0	2.48	1273	3288
NA	0.89*	28	49
NA	0.29*	90	326

b(4)

Species:	Rat, CD
Gender(M/F)/Number of animals:	9 M, 9 F
Dose (mg/kg/day):	45
Duration of administration:	26 weeks
Plasma samples derived from study:	[redacted] 13400/00

Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F
PK-Parameters:								
C_{max} (nmol/L)	209	149	324	373	363	28.0	4033	348
T_{max} (h)	0.5	1	0.5	0.5	0.5	1	0.5	0.5
AUC_{last} (h nmol/L)	904	758	2207	1577	972	110	11169	738
Ratio C_{max}	1	1	2.62	1.31	1.77	0.20	14.1	0.76
Ratio AUC_{last}	1	1	1.96	2.18	1.29	0.15	12.4	1.43

Additional information:
Median data (n=3) are presented
Plasma samples were obtained at 0.5, 1, 3, 6, 12 and 24 hours by staggered sampling, each rat had to be bled two to three times per day
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

Metabolism in rabbit plasma

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.3
Study no.: 628

Species:	Rabbit, Himalayan					Rabbit, Himalayan		
Gender(M/F)/Number of animals:	3 F					3 F		
Feeding condition:	Fed					Fed		
Test article:	Fesoterodine					Fesoterodine		
Vehicle/Formulation:	Water/Solution					Water/Solution		
Method of administration:	Oral (gavage)					Oral (gavage)		
Dose (mg/kg/day):	9 (3 x 3)					18 (3 x 6)		
Duration of administration:	4 days					4 days		
Sample:	Plasma					Plasma		
Assay:	LC-MS/MS					LC-MS/MS		
Plasma samples derived from study:	[redacted] 14902/01					[redacted] 14902/01		
Analytes:	SPM 7605	SPM 5509	SPM 7789	SPM 7790	SPM 7605	SPM 5509	SPM 7789	SPM 7790
PK-Parameters:								
C_{max} (nmol/L)	57.2	157	16.4	758	27.1	318	13.6	1359
T_{max} (h)	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33
AUC_{last} (h nmol/L)	23.7	207	9.49	1270	73.8	490	26.1	2164
Ratio C_{max}	1	9.2	1.0	44	1	11	0.5	52
Ratio AUC_{last}	1	8.7	0.4	54	1	9.3	0.4	29

Additional information:
Plasma samples were obtained at predose (prior to 10th dosing), 20, 40 minutes, and 1, 3, 6, 7 and 12 hours. Median data of Day 4 are reported.
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

Species:	Rabbit, Himalayan					Rabbit, Himalayan		
Gender(M/F)/Number of animals:	3 F					3 F		
Feeding condition:	Fed					Fed		
Test article:	Fesoterodine					Fesoterodine		
Vehicle/Formulation:	Water/Solution					Water/Solution		
Method of administration:	Oral (gavage)					Subcutaneous (bolus)		
Dose (mg/kg):	27 (3 x 9)					9		
Duration of administration:	4 days					4 days		
Sample:	Plasma					Plasma		
Assay:	LC-MS/MS					LC-MS/MS		
Plasma samples derived from study:	[redacted] 14902/02					[redacted] 14902/01		
Analytes:	SPM 7605	SPM 5509	SPM 7789	SPM 7790	SPM 7605	SPM 5509	SPM 7789	SPM 7790
PK-Parameters:								
C_{max} (nmol/L)	54.0	746	26.4	2868	2357	266	0	659
T_{max} (h)	0.33	0.33	0.33	0.33	1	2	NA	2
AUC_{last} (h nmol/L)	201	1608	49.3	4345	7417	1169	0	2911
Ratio C_{max}	1	6.3	0.3	26	1	0.10	NA	0.28
Ratio AUC_{last}	1	4.1	0.3	18	1	0.14	NA	0.35

Additional information:
Plasma samples were obtained at predose (prior to 10th dosing), 20, 40 minutes, and 1, 3, 6, 7 and 12 hours after oral administration and at predose (prior to 4th dosing), 20, 40 minutes and 1, 2, 4, 8 and 12 hours after subcutaneous administration. Median data of Day 4 are reported.
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
NA denotes not applicable

Metabolism in dog plasma

Test Article: Fesoterodine or SPM 7605
Location in CTD: 4.2.2.4.4
Study no.: 669

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	2 M, 2 F
Feeding condition:	Fed
Test article:	Fesoterodine
Vehicle/Formulation:	NA/Solid
Method of administration:	Oral (capsule)
Dose (mg/kg/day):	0.5
Duration of administration:	9 months
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted] 13349/00

Analytes:	Fesoterodine		SPM 7605		SPM 5509		SPM 7789		SPM 7790	
PK-Parameters:	M	F	M	F	M	F	M	F	M	F
C_{max} (nmol/L)	2.38	0.89	8.35	6.59	154	304	0	2.21	145	180
T_{max} (h)	1.5	4.5	1.5	1.5	2	1.5	NA	1*	3	1.5
AUC_{last} (h nmol/L)	2.94	1.40	14.6	9.73	1017	1357	0	2.48	1273	3288
Ratio C_{max}	0.40	0.28	1	1	25	84	NA	0.89*	28	49
Ratio AUC_{last}	0.21	0.23	1	1	70	286	NA	0.29*	90	326

Additional information:
Plasma samples were obtained at 1, 2, 4, 8 and 24 hours after administration. Median data (n = 2) are reported.
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
NA denotes not applicable
a - individual data

b(4)

Species:	Dog, Beagle									
Gender(M/F)/Number of animals:	2 M, 2 F									
Method of administration:	Oral (capsule)									
Dose (mg/kg/day):	2.5									
Duration of administration:	9 months									
Plasma samples derived from study:	[redacted] 13349/00									
Analytes:	Fesoterodine		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	7.06	41.0	195	80.8	503	706	21.5	19.9	264	305
T_{max} (h)	1.5	3	1.5	3	3	4	2.5	3	3	4
AUC_{last} (h nmol/L)	11.3	58.5	457	475	1555	6555	142	182	2469	3381
Ratio C_{max}	0.03	0.44	1	1	6.2	12.1	0.17	0.29	2.6	6.2
Ratio AUC_{last}	0.03	0.25	1	1	13.7	21.8	0.35	0.5	6.9	12.9
Species:	Dog, Beagle									
Gender(M/F)/Number of animals:	2 M, 2 F									
Dose (mg/kg/kg):	12.5									
Duration of administration:	9 months									
Plasma samples derived from study:	LPT 13349/00									
Analytes:	Fesoterodine		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	90.9	656	2177	2907	3040	3489	382	527	1072	1202
T_{max} (h)	2.5	1	3	1.5	6	3	6	3	6	3
AUC_{last} (h nmol/L)	223	925	10728	10653	34205	51402	3181	2218	13960	13381
Ratio C_{max}	0.03	0.18	1	1	1.4	2.1	0.15	0.23	0.49	0.89
Ratio AUC_{last}	0.02	0.07	1	1	3.2	5.4	0.29	0.26	1.3	1.5

Additional information:
Plasma samples were obtained at 1, 2, 4, 8 and 24 hours after administration. Median data (n = 2) are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Species:	Dog, Beagle					Dog, Beagle				
Gender(M/F)/Number of animals:	2 F					2 F				
Feeding condition:	Fed					Fed				
Test article:	Fesoterodine					Fesoterodine				
Vehicle/Formulation:	NA					Water/Solution				
Method of administration:	Oral (SR tablet)					Oral (gavage)				
Dose (mg/kg):	4					4 (2 x 2)				
Duration of administration:	Single dose					7 days				
Sample:	Plasma					Plasma				
Assay:	LC-MS/MS					LC-MS/MS				
Plasma samples derived from study:	[redacted] 14841/01					[redacted] 14841/01				
Analytes:	Feso-terodine	SPM 7605	SPM 3509	SPM 7789	SPM 7790	Feso-terodine	SPM 7605	SPM 3509	SPM 7789	SPM 7790
PK-Parameters:										
C_{max} (nmol/L)	14.0	16.4	436	4.03	445	28.8	42.3	450	9.03	232
T_{max} (h)	7	8	6	8	6	1.1	1.3	3	2	3
AUC_{last} (h nmol/L)	98.2	222	6525	55.4	6530	50.8	199	2872	52.9	1733
Ratio C_{max}	0.79	1	34	0.30	30	0.78	1	11	0.23	5.7
Ratio AUC_{last}	0.42	1	31	0.25	30	0.26	1	15	0.27	8.8

Additional information:
Plasma samples were obtained at predose, 1, 2, 3, 4, 6, 8, 12, 24 and 30 hours after administration of SR tablet and at predose, 10 minutes, and 0.5, 1, 2, 4, 6, 8 and 12 hours after administration by gavage. Median data (n = 2) are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Species:	Dog, Beagle									
Gender(M/F)/Number of animals:	2 M, 2 F									
Feeding condition:	Fed									
Test article:	Fesoterodine									
Vehicle/Formulation:	NA									
Method of administration:	Oral (SR tablet)									
Dose (mg/kg/day):	8									
Duration of administration:	14 days									
Sample:	Plasma									
Assay:	LC-MS/MS									
Plasma samples derived from study:	[redacted] 15408/02									
Analytes:	Fesoterodine		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	323	169	1358	677	2087	1422	173	99.1	671	473
T_{max} (h)	2.5	2.5	3	2.5	4	8	3	8	4	8
AUC_{last} (h nmol/L)	1119	840	7225	6835	19260	18483	1366	1223	7886	6730
Ratio C_{max}	0.24	0.25	1	1	1.5	2.2	0.13	0.15	0.49	0.71
Ratio AUC_{last}	0.16	0.13	1	1	2.7	2.8	0.21	0.19	1.1	0.99

Additional information:
Plasma samples were obtained at 1, 2, 4, 8, 12 and 24 hours after administration. Median data (n = 2) are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite.

b(4)

Species:	Dog, Beagle									
Gender(M/F)/Number of animals:	2 M, 2 F									
Feeding condition:	Fed									
Test article:	Fesoterodine									
Vehicle/Formulation:	NA									
Method of administration:	Oral (SR tablet)									
Dose (mg/kg/day):	32									
Duration of administration:	14 days									
Sample:	Plasma									
Assay:	LC-MS/MS									
Plasma samples derived from study:	[redacted] 15408/03									
Analytes:	Fesoterodine		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	171	98.1	2297	1574	4278	3545	414	285	2049	1339
T_{max} (h)	2/1	4/1	4/24	8/1	8/24	8/2	4/24	8/8	8/24	24/8
AUC_{last} (h nmol/L)	2128	968	33211	21613	71253	55012	6422	4258	35902	24796
Ratio C_{max}	0.08	0.08	1	1	1.9	2.4	0.18	0.18	0.90	0.85
Ratio AUC_{last}	0.07	0.05	1	1	2.2	2.9	0.20	0.20	1.1	1.2

Additional information:
Plasma samples were obtained at 1, 2, 4, 8, 12 and 24 hours after administration. Median data (n = 2) are reported for C_{max}, AUC_{last} and respective ratios, individual data are reported for T_{max} because of high variation.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

b(4)

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	1 M, 1 F
Feeding condition:	Fed[a]
Test article:	Fosaprepitant
Vehicle/Formulation:	Saline/Solution
Method of administration:	Intravenous (4-hour infusion)
Duration of administration:	3 days
Dose (mg/kg/4 hours):	1
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]15340/03

Analytes:	Fosaprepitant		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	189	193	43.3	35.1	319	347	1.95	2.50	200	282
T_{max} (h)	3	3	4	4	4	4	4	4	4.5	4
AUC_{last} (h nmol/L)	512	488	295	199	1225	1357	5.93	7.16	781	1148
Ratio C_{max}	3.0	3.5	1	1	3.0	6.3	0.03	0.05	3.2	5.1
Ratio AUC_{last}	2.1	2.4	1	1	5.0	6.8	0.02	0.04	3.2	5.8

Additional information:
Plasma samples were obtained at predose, 3, 4, 4.5, 5 and 6 hours after start of infusion. Individual data are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
a - food was offered for two hours after administration or after blood sampling

b(4)

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	1 M, 1 F
Feeding condition:	Fed[a]
Test article:	Fosaprepitant
Vehicle/Formulation:	Saline/Solution
Method of administration:	Intravenous (4-hour infusion)
Duration of administration:	3 days
Dose (mg/kg/4 hours):	5
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]15340/02

Analytes:	Fosaprepitant		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	514	1075	791	822	1684	1833	32.5	44.8	442	731
T_{max} (h)	3	4	4.5	4	4.5	4	4	4	4.5	4.5
AUC_{last} (h nmol/L)	1432	3142	2637	2760	6053	7048	118.3	159	1838	3230
Ratio C_{max}	0.65	1.3	1	1	2.1	2.2	0.04	0.05	0.56	0.91
Ratio AUC_{last}	0.55	1.1	1	1	2.3	2.6	0.04	0.06	0.70	1.2

Additional information:
Plasma samples were obtained at predose, 3, 4, 4.5, 5 and 6 hours after start of infusion. Individual data are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
a - food was offered for two hours after administration or after blood sampling

b(4)

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	1 M, 1 F
Feeding condition:	Fed[a]
Test article:	Fosaprepitant
Vehicle/Formulation:	Saline/Solution
Method of administration:	Intravenous (4-hour infusion)
Duration of administration:	3 days
Dose (mg/kg/4 hours):	10
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]15340/02

Analytes:	Fosaprepitant		SPM 7605		SPM 3509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F
PK-Parameters:										
C_{max} (nmol/L)	1369	1478	2490	1953	3072	2864	161	124	637	768
T_{max} (h)	5	4	4.5	4.5	5	4.5	4	4.5	5	5
AUC_{last} (h nmol/L)	4791	4443	8391	7212	11368	11091	603	455	2570	2975
Ratio C_{max}	0.63	0.76	1	1	1.2	1.5	0.06	0.06	0.26	0.39
Ratio AUC_{last}	0.52	0.62	1	1	1.3	1.5	0.07	0.06	0.29	0.41

Additional information:
Plasma samples were obtained at predose, 3, 4, 4.5, 5 and 6 hours after start of infusion. Individual data are reported.
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
a - food was offered for two hours after administration or after blood sampling

b(4)

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	2 F
Feeding condition:	Fed
Test article:	SPM 7605
Vehicle/Formulation:	Ready to use solution
Method of administration:	Intravenous (continuous infusion)
Dose (mg/kg):	1
Duration of administration:	24 hours
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]14941/01

Analytes:	SPM 7605	SPM 3509	SPM 7789	SPM 7790
	F	F	F	F
PK-Parameters:				
C_{max} (nmol/L)	29.8	118	0	64.3
T_{max} (h)	24-24	8-24	NA/NA	24-24
AUC_{last} (h nmol/L)	361	2403	0	1402
Ratio C_{max}	1	3.9	NA	2.3
Ratio AUC_{last}	1	4.3	NA	2.3

Additional information:
Plasma samples were obtained at predose, 1, 4, 8, 24, 24.5, 25 and 26 hours after start of infusion. Median data are reported for C_{max}, AUC_{last} and respective ratios, individual data are reported for T_{max}
SPM 7605 = hydroxy metabolite, SPM 3509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite
NA denotes not applicable

b(

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	2 M, 2 F
Feeding condition:	Fed
Test article:	SPM 7605
Vehicle/Formulation:	Ready to use solution
Method of administration:	Intravenous (continuous infusion)
Dose (mg/kg/day):	1.5
Duration of administration:	14 days
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]15409102

Analytes:	SPM 7605		SPM 5569		SPM 7589		SPM 7590	
	M	F	M	F	M	F	M	F
PK-Parameters:								
C_{max} (nmol/L)	204	141	219	264	3.02	1.26	63.6	103
T_{max} (h)	4/4	4/4	24/4	4/24	8/24	4/NA	24/4	24/24
AUC_{last} (h·nmol/L)	1975	2491	4358	5732	53.1	28.5	1257	2351
Ratio C_{max}	1	1	2.2	1.9	0.05	0.01	0.61	0.76
Ratio AUC_{last}	1	1	2.3	2.3	0.04	0.01	0.64	0.95

b(4)

Additional information:
Plasma samples were obtained at predose, 4, 8, 12 and 24 hours after start of infusion. Median data are reported for C_{max}, AUC_{last} and respective ratios, individual data are reported for T_{max}.
SPM 7605 = hydroxy metabolite, SPM 5569 = carboxy metabolite, SPM 7589 = N-desisopropyl metabolite, SPM 7590 = carboxy-N-desisopropyl metabolite
NA denotes not applicable

Species:	Dog, Beagle
Gender(M/F)/Number of animals:	2 M, 2 F
Feeding condition:	Fed
Test article:	SPM 7605
Vehicle/Formulation:	Ready to use solution
Method of administration:	Intravenous (24-hour infusion)
Dose (mg/kg):	6
Duration of administration:	14 days
Sample:	Plasma
Assay:	LC-MS/MS
Plasma samples derived from study:	[redacted]15408502

Analytes:	SPM 7605		SPM 5569		SPM 7589		SPM 7590	
	M	F	M	F	M	F	M	F
PK-Parameters:								
C_{max} (nmol/L)	580	1029	913	1167	26.0	50.0	269	291
T_{max} (h)	4/4	4/4	4/4	4/24	4/8	4/24	4/24	4/8
AUC_{last} (h·nmol/L)	11251	20368	19495	24628	328	1045	5397	6408
Ratio C_{max}	1	1	3.6	1.1	0.05	0.05	0.46	0.29
Ratio AUC_{last}	1	1	1.7	1.2	0.03	0.05	0.51	0.31

b(4)

Additional information:
Plasma samples were obtained at predose, 4, 8, 12 and 24 hours after start of infusion. Median data are reported for C_{max}, AUC_{last} and respective ratios, individual data are reported for T_{max}.
SPM 7605 = hydroxy metabolite, SPM 5569 = carboxy metabolite, SPM 7589 = N-desisopropyl metabolite, SPM 7590 = carboxy-N-desisopropyl metabolite

Metabolism in mouse urine and feces

Test Article:	[^{14}C]-Fesoterodine
Location in CTD:	4.2.2.4.5
Study no.:	DHGY1008

Species:	Mouse, CD-1
Gender(M/F)/Number of animals:	M, F/pools from 3 animals per sex
Feeding condition:	Fed
Vehicle/Formulation:	Water/Solution
Method of administration:	Oral (gavage)
Dose (mg/kg):	5
Radionuclide:	^{14}C
Assay:	HPLC with radio- and UV detection

Gender	Sample	Sampling period	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5569	SPM 7589	SPM 7590	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	25.8±4.91	2.54 [0.7]	41.6 [10.7]	25.5 [6.6]	17.3 [4.5]	-	8.85 [2.3]	7
		6 – 24 hours	9.45±1.17	1.39 [0.1]	28.7 [2.7]	-	6.81 [0.6]	-	69.2 [6.5]	7
	Feces	0 – 24 hours	48.2±6.88	-	23.6 [12.3]	73.6 [34.5]	2.84 [1.4]	-	-	3
		24 – 48 hours	2.74±2.41	-	30.7 [0.4]	62.1 [1.7]	-	-	7.28 [0.2]	3
Female	Urine	0 – 6 hours	37.3±3.95	1.73 [0.3]	55.6 [9.6]	-	15.3 [2.7]	-	27.4 [4.7]	3
		6 – 24 hours	7.72±NA	-	21.3 [1.6]	-	1.59 [0.1]	61.6 [4.8]	15.5 [1.2]	3
	Feces	0 – 24 hours	50.2±1.59	-	27.7 [13.9]	68.0 [34.1]	4.27 [2.1]	-	-	3
		24 – 48 hours	3.36±2.82	-	20.3 [0.8]	71.9 [2.8]	7.80 [0.3]	-	-	3

Species:	Mouse, CD-1
Gender(M/F)/Number of animals:	M, F/pools from 3 animals per sex
Feeding condition:	Fed
Vehicle/Formulation:	Saline/Solution
Method of administration:	Intravenous bolus
Dose (mg/kg):	2.5
Radionuclide:	^{14}C
Assay:	HPLC with radio- and UV detection

Gender	Sample	Sampling interval	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5569	SPM 7589	SPM 7590	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	40.1±NA	IS	IS	IS	IS	IS	IS	IS
		6 – 24 hours	15.3±8.67	-	32.3 [8.0]	39.0 [6.0]	4.79 [0.7]	-	4.09 [0.6]	5
	Feces	0 – 24 hours	43.0±14.6	-	1.87 [0.8]	92.1 [40]	2.36 [1.0]	2.72 [1.2]	0.86 [0.4]	5
		24 – 48 hours	1.28±0.45	IS	IS	IS	IS	IS	IS	IS
Female	Urine	0 – 6 hours	4.0±NA	2.69 [0.3]	78.5 [9.2]	-	2.07 [0.3]	-	16.5 [0.7]	3
		6 – 24 hours	21.8±1.57	1.54 [0.3]	78.1 [17]	-	2.79 [0.6]	-	17.6 [3.8]	3
	Feces	0 – 24 hours	56.2±3.72	-	2.09 [1.2]	91.2 [53]	5.41 [3.9]	-	-	4
		24 – 48 hours	2.44±2.24	IS	IS	IS	IS	IS	IS	IS

Additional information:
Urine and feces samples were obtained from study DGHY1005 following intravenous administration.
SPM 7605 = hydroxy metabolite, SPM 5569 = carboxy metabolite, SPM 7589 = N-desisopropyl metabolite, SPM 7590 = carboxy-N-desisopropyl metabolite.
NA denotes not applicable, IS denotes insufficient sample to allow analysis; - denotes not determined.

Metabolism in rat urine and feces

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.5
Study no.: DHGY1008

Species: Rat, Sprague-Dawley
Gender(M/F)/Number of animals: M, F/pools from 5 animals per sex
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 5
Radionuclide: ^{14}C
Assay: HPLC with radio- and UV detection

Gender	Sample	Sampling interval	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5580	SPM 7789	SPM 7790	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	3.24±3.80	-	12.1 [0.4]	-	51.3 [1.7]	-	36.6 [1.2]	5
		6 – 24 hours	5.40±2.79	-	11.0 [0.5]	-	70.2 [3.8]	-	18.8 [1.0]	5
	Feces	0 – 24 hours	47.74±22.9	-	4.94 [2.4]	-	7.36 [3.4]	8.47 [4.0]	79.3 [38]	7
		24 – 48 hours	23.9±16.9	-	-	-	10.5 [2.5]	30.6 [7.3]	58.8 [14]	3
Female	Urine	0 – 6 hours	3.6±2.87	-	30.7 [0.8]	16.4 [0.6]	32.7 [1.2]	4.0 [0.1]	14.2 [0.5]	8
		6 – 24 hours	3.66±1.89	-	21.0 [0.8]	36.5 [0.6]	42.9 [1.5]	-	19.6 [0.7]	4
	Feces	0 – 24 hours	35.6±24.3	-	33.0 [18.3]	-	8.45 [4.7]	-	58.6 [33]	7
		24 – 48 hours	3.76±2.70	-	-	-	11.4 [0.8]	-	88.6 [7.1]	6

Species: Rat, Sprague-Dawley
Gender(M/F)/Number of animals: M, F/pools from 3 animals per sex
Feeding condition: Fed
Vehicle/Formulation: Saline/Solution
Method of administration: Intravenous bolus
Dose (mg/kg): 2.5
Radionuclide: ^{14}C
Assay: HPLC with radio- and UV detection

Gender	Sample	Sampling interval	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5580	SPM 7789	SPM 7790	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	10.3±4.10	-	80.3 [5.3]	2.16 [0.2]	14.2 [1.5]	-	3.32 [0.3]	5
		6 – 24 hours	2.56±2.03	-	-	-	18.2 [1.9]	8.14 [0.4]	73.6 [4.1]	4
	Feces	0 – 24 hours	74.2±1.65	-	0.84 [0.6]	10.7 [8.0]	15.3 [11.4]	-	73.2 [54]	6
		24 – 48 hours	2.26±3.64	-	-	-	-	-	100 [2.2]	2
Female	Urine	0 – 6 hours	9.26±1.82	-	7.66 [0.7]	4.84 [0.4]	27.0 [2.5]	59.3 [5.5]	1.22 [0.1]	5
		6 – 24 hours	5.26±3.82	-	21.6 [1.0]	-	12.3 [0.6]	-	66.1 [3.4]	3
	Feces	0 – 24 hours	74.3±0.64	-	18.3 [14]	9.96 [7.4]	2.18 [1.6]	-	69.7 [51]	5
		24 – 48 hours	2.26±0.23	-	-	-	-	-	100 [2.2]	1

Additional information:
Urine and feces samples were obtained from study DGHY1007 following intravenous administration.
SPM 7605 = hydroxy metabolite, SPM 5569 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite.
- denotes not determined.

Metabolism in dog urine and feces

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.5
Study no.: DHGY1008

Species: Dog, Beagle
Gender(M/F)/Number of animals: 3 M, 3 F
Feeding condition: Fed
Vehicle/Formulation: Water/Solution
Method of administration: Oral (gavage)
Dose (mg/kg): 0.5
Radionuclide: ^{14}C
Assay: HPLC with radio- and UV detection

Gender	Sample	Sampling interval	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5569	SPM 7789	SPM 7790	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	24.0±7.66	0.36 [0.1]	34.2 [8.7]	15.3 [3.8]	3.32 [1.3]	33.3 [8.05]	8.71 [2.1]	7
		6 – 24 hours	26.8±11.9	-	61.3 [16]	21.8 [5.8]	3.04 [1.4]	-	11.9 [3.2]	6
	Feces	0 – 24 hours	14.6±12.6	-	44.4 [6.5]	-	55.2 [8.1]	-	-	3
		24 – 48 hours	9.7±7.40	-	46.2 [4.5]	-	53.5 [5.2]	-	-	2
Female	Urine	0 – 6 hours	36.5±3.91	-	39.7 [15]	-	1.34 [0.5]	56.2 [21]	2.82 [1.0]	4
		6 – 24 hours	25.0±3.37	-	60.5 [15]	28.6 [7.4]	4.28 [1.1]	-	6.32 [1.6]	6
	Feces	0 – 24 hours	18.2±3.35	-	42.4 [7.8]	-	57.2 [10]	-	-	3
		24 – 48 hours	4.95±1.54	-	45.3 [2.3]	-	54.7 [2.7]	-	-	3

Species: Dog, Beagle
Gender(M/F)/Number of animals: 3 M, 3 F
Feeding condition: Fed
Vehicle/Formulation: Saline/Solution
Method of administration: Intravenous bolus
Dose (mg/kg): 0.25
Radionuclide: ^{14}C
Assay: HPLC with radio- and UV detection

Gender	Sample	Sampling interval	% of Dose in sample	Relative peak area in chromatogram (%) [% of Dose] Fesoterodine	SPM 7605	SPM 5569	SPM 7789	SPM 7790	Unknown	Number of peaks reported
Male	Urine	0 – 6 hours	23.8±6.46	-	68.1 [11]	4.75 [1.2]	1.78 [0.4]	58.3 [9.0]	5.26 [1.3]	8
		6 – 24 hours	37.7±8.65	-	47.4 [18]	41.9 [12]	1.63 [0.5]	-	9.04 [2.5]	6
	Feces	0 – 24 hours	28.1±4.23	-	60.2 [17]	-	37.5 [11]	-	2.35 [0.7]	3
		24 – 48 hours	3.32±1.44	-	38.4 [1.3]	-	61.6 [2.1]	-	-	2
Female	Urine	0 – 6 hours	32.9±13.9	-	2.37 [0.8]	33.2 [11]	1.34 [0.4]	-	63.0 [21]	5
		6 – 24 hours	23.9±12.9	-	59.8 [16]	31.5 [8.3]	2.46 [0.6]	-	6.44 [1.7]	6
	Feces	0 – 24 hours	19.6±3.28	-	54.7 [11]	-	41.8 [8.2]	-	3.42 [0.7]	3
		24 – 48 hours	3.13±0.88	-	47.3 [1.5]	-	47.3 [1.5]	-	5.15 [0.2]	3

Additional information:
Urine and feces samples were obtained from study DGHY1006 following intravenous administration.
SPM 7605 = hydroxy metabolite, SPM 5569 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite.
- denotes not determined.

Metabolism in Caco-2 cells *in vitro*

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.6
Study no.: 010.01.0200 (step 2)

Test system: Caco-2 cell monolayer cultivated for 7 days.
Method: Supernatant, rinsing solution and cell homogenates were analyzed for fesoterodine and SPM 7605 by a validated HPLC-method to determine the metabolism of fesoterodine in Caco-2 cells.

Incubation time (hours)	Amount (mean ± SD) in µg					
	Supernatant		Rinsing solution		Cell homogenate	
	Fesoterodine	SPM 7605	Fesoterodine	SPM 7605	Fesoterodine	SPM 7605
0	208.7 ± 1.73	0 ± 0	0 ± 0		0 ± 0	0 ± 0
1	104.6 ± 4.60	52.3 ± 8.16	3.41 ± 0.97	2.34 ± 0.79	0 ± 0	4.34 ± 0.22
2	55.3 ± 1.26	94.1 ± 1.04	1.81 ± 0.61	0.66 ± 0	0 ± 0	5.63 ± 0.21
4	19.9 ± 2.95	124.2 ± 5.39	1.45 ± 0.45	0 ± 0	0 ± 0	5.61 ± 0.21

Additional information:
The total mass balance of fesoterodine and SPM 7605 shows a recovery of 83%. At the end of the study the cells were detached of the flask by a cell scraper. After washing and centrifugation steps, the prepared cell extracts were investigated by HPLC. In the cell homogenate only SPM 7605 but no fesoterodine has been found.

Metabolism in mouse liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.7
Study no.: DHGY1009

Test system: Mouse liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	0.1			0.5			1		
Concentration (%)									
Time (minutes)	5	15	30	5	15	30	5	15	30
Compounds (retention time: in minutes)									
Fesoterodine (16)	40.0	12.4	2.61	2.23	0.770	0.497	1.81	ND	ND
SPM 7605 (6)	57.1	82.0	89.1	88.8	74.1	40.2	85.3	59.1	44.5
SPM 5589 (11)	2.90	3.32	5.39	6.95	18.6	53.0	8.53	37.2	50.7
SPM 7789 (4)	ND	2.22	2.92	2.69	3.38	3.58	5.04	3.74	4.71
SPM 7790 (8)	ND	ND	ND	ND	3.14	2.48	1.32	7.11	14.5
Unknown 1 (2)	ND	ND	ND	ND	ND	ND	ND	0.793	1.30
Unknown 2 (3)	ND	ND	ND	ND	ND	ND	ND	ND	1.04

Additional information:
Data are means of 3 replicates. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
ND = not detected; SPM 7605 = hydroxy metabolite; SPM 5589 = carboxy metabolite; SPM 7789 = N-desisopropyl metabolite;
SPM 7790 = carboxy-N-desisopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found:
30.6% Fesoterodine, 67.4% SPM 7605 and 2.02% SPM 5589 (5 minutes incubation time) or
97.1% SPM 7605, 2.39% SPM 5589 and 0.533% SPM 7790 were found (30 minutes incubation time).

Metabolism in rat liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.7
Study no.: DHGY1009

Test system: Rat liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	0.1			0.5			1		
Concentration (%)									
Time (minutes)	5	15	30	5	15	30	5	15	30
Compounds (retention time: in minutes)									
Fesoterodine (16)	53.8	45.7	42.5	39.7	30.5	19.8	53.6	22.8	13.4
SPM 7605 (6)	8.37	14.7	22.8	14.7	12.7	6.12	10.4	6.44	4.61
SPM 5589 (11)	0.453	0.498	0.313	ND	ND	ND	ND	ND	ND
SPM 7789 (4)	1.61	3.31	13.7	12.8	33.1	45.1	14.6	33.4	19.5
SPM 7790 (7)	ND	1.47	3.37	2.72	7.46	11.7	3.80	9.62	8.55
Unknown 1 (1.5)	ND	ND	ND	ND	0.933	5.00	ND	3.79	12.3
Unknown 2 (2.2)	ND	ND	ND	ND	0.983	2.97	ND	2.67	17.2
Unknown 3 (4.2)	ND	ND	ND	ND	ND	ND	ND	ND	11.9
Unknown 5 (14)	2.25	3.60	7.92	6.80	8.85	4.12	10.2	8.51	ND
Unknown 6 (17)	1.38	2.70	2.87	3.35	3.38	6.21	5.17	7.55	9.14

Additional information:
Data are means of 3 replicates. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5589 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite,
SPM 7790 = carboxy-N-desisopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found:
66.5% Fesoterodine, 30.8% SPM 7605, 1.52% SPM 5589, and 1.12% unknown 6 (5 minutes incubation time) or
13.3% Fesoterodine, 80.1% SPM 7605, 2.03% SPM 5589, 2.73% Unknown 1, and 1.79% Unknown 6 (30 minutes incubation time).

Metabolism in hamster liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.8
Study no.: DHGY1030

Test system: Hamster liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	0.1				0.5				1			
Concentration (%)												
Time (minutes)	5	15	30	60	5	15	30	60	5	15	30	60
Compounds (retention time: in minutes)												
Fesoterodine (20)	53.8	30.7	4.52[a]	2.67	19.2	14.3	5.93	2.25	17.6	3.84	2.56	2.93
SPM 7605 (7)	38.3	53.6	73.0	68.5	55.6	34.8	29.0	6.52	54.6	39.1	6.91	5.99
SPM 5589 (15)	3.45	6.97	3.61	4.55	5.77	37.6	21.6	49.8	8.85	22.8	57.8	60.7
SPM 7833 (4)	ND	ND	5.38	3.99	2.01	2.22[b]	3.11	ND	2.52	4.61	1.50	1.63
SPM 7790 (9)	ND	ND	ND	5.50	1.59	5.38[b]	32.7	22.1	1.03	6.78	12.4	12.0
Unknown M1 (1.5)	ND	ND	ND	ND	ND	ND	2.05	3.45	ND	1.45	6.28	8.65
Unknown M2 (3)	ND	ND	ND	ND	ND	ND	2.08	2.26	ND	1.85	1.52	ND
Unknown M5 (6.5)	ND	ND	ND	ND	ND	ND	2.55	ND	ND	0.933	ND	ND
Unknown M8 (12)	ND	ND	ND	ND	ND	5.59	6.89	9.53	1.83	4.87	7.78	5.32
Unknown M10 (15.5)	ND	ND	11.1	14.2	9.79	ND	13.9	ND	8.18	10.3	ND	ND
Unknown M11 (19)	1.57	3.32	2.04[b]	ND	3.38	1.78[b]	ND	ND	3.36	1.29	ND	ND
Unknown M13 (21)	2.95	3.41	1.16[b]	2.33	2.71	4.39	2.66	2.11	2.24	2.43	3.23	2.82

Additional information:
Data are means of 3 replicates except for a and b. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
a = data from two replicates, b = individual data, ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5589 = carboxy metabolite,
SPM 7833 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found:
7.42% Fesoterodine, 88.0% SPM 7605, 1.53% SPM 5589, 0.442 SPM 7833, 0.623% Unknown M2, and 1.74% Unknown M13 (5 minutes incubation time) or
1.21% Fesoterodine, 94.8% SPM 7605, 2.35% SPM 5589, and 2.35%* Unknown M11 (60 minutes incubation time).

Metabolism in rabbit liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.8
Study no.: DHGY3030

Test system: Rabbit liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	Concentration (%) 0.1				0.5				1			
Time (minutes)	5	15	30	60	5	15	30	60	5	15	30	60
Compounds (retention times in minutes)												
Fesoterodine (20)	2.68	1.94[a]	ND	ND	ND	2.38[a]	ND	ND	ND	ND	ND	ND
SPM 7605 (7)	92.2	91.9	86.4	83.6	85.7	74.4	69.5	56.2	88.1	69.7	49.9	17.1
SPM 5509 (15)	3.50	4.36	6.09	4.36	6.49	10.2	9.50	10.6	3.93	7.88	12.8	11.6
SPM 7833 (4)	1.81	3.23	5.65	7.15	3.93	5.94	7.90	13.5	3.95	6.39	7.09	11.3
SPM 7790 (9)	ND	ND	1.35	4.85	5.89	9.57	13.3	20.8	1.69	12.7	31.1	45.9
Unknown M1 (1.5)	ND	ND	ND	ND	ND	ND	ND	2.34	ND	ND	1.94	3.94[a]
Unknown M2 (3)	ND	ND	ND	ND	ND	1.11	2.76	5.29	ND	1.53	4.75	7.74
Unknown M4 (4.9)	ND	ND	ND	ND	ND	ND	ND	3.22	ND	ND	1.39	5.73
Unknown M5 (6.5)	ND	ND	ND	ND	ND	ND	ND	1.27	ND	ND	ND	ND
Unknown M10 (15.5)	ND	ND	ND	ND	ND	ND	ND	ND	2.32	2.05	ND	ND

Additional information:
Data are means of 3 replicates except for a. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
a = individual data, ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7833 = N-dealkopropyl metabolite, SPM 7790 = carboxy-N-dealkopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found: 0.350%[a] Fesoterodine, 97.1% SPM 7605, and 2.79% SPM 5509 (5 minutes incubation time) or 97.6% SPM 7605, and 2.41% SPM 5509 (60 minutes incubation time).

Metabolism in dog liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.7
Study no.: DHGY1609

Test system: Dog liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	Concentration (%) 0.2			1			2		
Time (minutes)	5	15	30	5	15	30	5	15	30
Compounds (retention times in min)									
Fesoterodine (16)	37.3	28.6	15.2	14.3	1.88	1.26	6.35	ND	ND
SPM 7605 (6)	34.9	63.9	74.9	78.7	83.1	78.7	85.0	77.1	68.9
SPM 5509 (15)	1.89	3.24	4.48	3.96	8.72	11.3	5.32	13.1	16.5
SPM 7789 (4)	ND	1.93	2.58	1.24	3.63	3.42	2.08	3.05	6.35
SPM 7790 (7)	ND	ND	ND	ND	2.54	4.34	ND	4.78	6.09
Unknown 5 (14)	1.67	2.34	2.71	1.73	ND	ND	0.890	ND	ND
Unknown 6 (17)	ND	ND	0.395	ND	ND	0.923	0.356	ND	ND

Additional information:
Data are means of 3 replicates. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-dealkopropyl metabolite, SPM 7790 = carboxy-N-dealkopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (2 mg/mL) the following compounds were found: 30.9% Fesoterodine, 66.5% SPM 7605 and 2.21% SPM 5509 (5 minutes incubation time) or 97.1% SPM 7605 and 2.63% SPM 5509 (30 minutes incubation time).

Metabolism in primate liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.8
Study no.: DHGY3060

Test system: Primate liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

Microsomal protein (mg/mL)	Concentration (%) 0.1				0.5				1			
Time (minutes)	5	15	30	60	5	15	30	60	5	15	30	60
Compounds (retention times in min)												
Fesoterodine (20)	53.7	45.9	30.9	2.49	15.4	14.5	2.85	1.49	6.21	0.947	1.16	1.84
SPM 7605 (7)	40.4	55.0	65.7	86.7	84.7	57.1	49.7	54.4	79.1	70.4	53.3	6.98
SPM 5509 (15)	1.39	ND	4.84	6.14	4.58	6.25	7.43	26.1	0.903	6.56	27.8	40.1
SPM 7833 (4)	2.21	ND	11.6	13.1	7.39	8.29	9.63	5.29	5.71	7.97	5.28	3.58
SPM 7790 (9)	ND	ND	5.26	5.84	2.35	3.58	13.6	19.1	1.51	6.03	20.6	33.6
Unknown M1 (1.5)	ND	ND	ND	ND	ND	ND	1.20[a]	2.26	ND	ND	2.22	3.44
Unknown M2 (3)	ND	ND	1.25	1.46	ND	ND	2.30	2.17	ND	0.605	2.11	2.75
Unknown M4 (4.9)	ND	ND	ND	1.74	ND	ND	4.30	6.83	ND	ND	5.40	7.04
Unknown M5 (6.5)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.359[a]	ND
Unknown M10 (15.5)	ND	ND	ND	ND	ND	ND	6.82	ND	3.45	5.49	ND	ND
Unknown M11 (19)	2.07	ND	ND	ND	1.65	4.09	ND	ND	0.647	ND	ND	ND
Unknown M13 (21)	ND	ND	2.49	2.32	4.08	6.45	3.18	3.98	2.48	2.27	1.96	3.65

Additional information:
Data are means of 3 replicates except for a. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
a = individual data, ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7833 = N-dealkopropyl metabolite, SPM 7790 = carboxy-N-dealkopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found: 4.02% Fesoterodine, 90.3% SPM 7605, 2.05% SPM 5509, 0.820% SPM 7833, 0.703% Unknown M2, and 1.93% Unknown M13 (5 minutes incubation time) or 85.7% SPM 7605, 2.50% SPM 5509, and 3.03%[a] Unknown M15 (60 minutes incubation time).

Metabolism in human liver microsomes *in vitro*

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.7
Study no.: DHGY1029

Test system: Human liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

	Concentration (%)											
Microsomal protein (mg/mL)	0.1				0.5				1			
Time (minutes)	5	15	30	60	5	15	30	60	5	15	30	60
Compounds (retention times in min)												
Fesoterodine (16)	ND	0.909	ND	0.955	ND	ND	ND	ND	ND	ND	ND	ND
SPM 7605 (6)	98.2	96.9	94.4	92.2	95.8	92.7	85.5	77.0	93.7	83.5	77.4	61.4
SPM 5509 (13)	2.43	2.23	3.23	3.87	3.59	3.99	4.86	6.67	4.35	5.43	6.31	7.27
SPM 7789 (4)	ND	ND	1.86	2.93	0.576	3.27	5.59	9.43	1.96	5.57	9.52	14.4
SPM 7790 (7)	ND	ND	ND	ND	ND	ND	2.91	6.93	ND	5.52	6.77	12.8
Unknown 4 (10.5)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	4.17

Additional information:
Data are means of 3 replicates. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite,
SPM 7790 = carboxy-N-desisopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found:
0.950% Fesoterodine, 98.2% SPM 7605 and 0.813% SPM 5509 (5 minutes incubation time) or
100% SPM 7605 (60 minutes incubation time).

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.4.8
Study no.: DHGY1039

Test system: Human liver microsomes
Method: 10 µM [^{14}C]-fesoterodine, NADPH-regenerating system present, HPLC using radiochemical and UV-detection with reference standards

	Concentration (%)											
Microsomal protein (mg/mL)	0.1				0.5				1			
Time (minutes)	5	15	30	60	5	15	30	60	5	15	30	60
Compounds (retention times in min)												
Fesoterodine (20)	17.0	6.41	ND	ND	9.16	5.52[a]	2.39[b]	ND	1.13	ND	ND	ND
SPM 7605 (7)	79.3	82.3	96.4	96.0	87.5	92.0	92.5	90.8	95.7	94.9	89.7	87.1
SPM 5509 (15)	3.77	3.30	3.62	3.97	3.32	4.29	5.20	7.95	2.99	5.61	7.48	9.89
SPM 7833 (4)	ND	ND	ND	ND	ND	ND	1.57	1.29	0.440	1.33	2.05	2.19
SPM 7790 (9)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.16[b]	1.35[a]
Unknown XIII (21)	ND	ND	ND	ND	ND	ND	ND	ND	0.565	ND	ND	ND

Additional information:
Data are means of 3 replicates except for a and b. Concentration denotes percentage of total eluted radioactivity in each chromatogram.
a = data from two replicates, b = individual data. ND = not detected, SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite,
SPM 7833 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite.
In the absence of NADPH-regenerating system at the highest microsomal protein concentration (1 mg/mL) the following compounds were found:
8.59% Fesoterodine, 96.9% SPM 7605, and 2.47% SPM 5509 (5 minutes incubation time) or
97.3% SPM 7605, and 2.71% SPM 5509 (60 minutes incubation time).

Enzyme mapping *in vitro*

Test Article: [^{14}C]-SPM 8311
Location in CTD: 4.2.2.4.9
Study no.: DHGY1029

Test system: Pool of human liver microsomes
Method: 0.3 to 300 µM[^{14}C]-SPM 8311, 1 mg microsomal protein per mL, incubation time 60 minutes. NADPH regenerating system present, analysis by HPLC with radiochemical detection

b(4)

Tabulated results:	Peak	K_m (µM)	V_{max} (pmol/min/mg protein/min)	Hill coefficient
	1[a]	(161.6)	(23.3)	1.336)
	2[b]	(4.57)	(4.04)	NC
	2[c]	(51.2)	(13.5)	NC

Additional information:
Standard deviation is given in brackets, NC denotes not calculated. a - peak 1, co-eluting with reference compound SPM 7833; b - high affinity enzyme, peak 2 co-eluting with reference compound SPM 5509; c - low affinity enzyme, peak 2 co-eluting with reference compound SPM 5509

Test system: Pool of human liver microsomes
Method: 0.3 µM [^{14}C]-SPM 8311, 1 mg/mL microsomal protein, incubation time 60 minutes, NADPH regenerating system present, analysis by HPLC with radiochemical detection

Tabulated results:		Inhibition (% of vehicle control activity)	
	Chemical inhibitors (enzyme marker)	Peak 1	Peak 2
	Furafylline (10 µM)	19.5	No inhibition measured
	Methoxsalen (2.5 µM)	35.3	4.75
	Quercetin (10 µM)	23.8	No inhibition measured
	Sulphaphenazole (10 µM)	5.00	No inhibition measured
	Tranylcypromine (50 µM)	19.0	34.3
	Quinidine (1 µM)	No inhibition measured	82.3
	DDC (50 µM)	22.9	35.4
	Ketoconazole (1 µM)	45.9	39.5

Additional information:
Results are means ± standard deviation of n = 3 replicates

Test system: Baculovirally expressed human CYP isoforms (Supersomes™)
Method: 0.7 µM [^{14}C]-SPM 8311, 25 pmoles of CYP per 0.5 mL, incubation time 60 minutes, analysis by HPLC with radiochemical detection

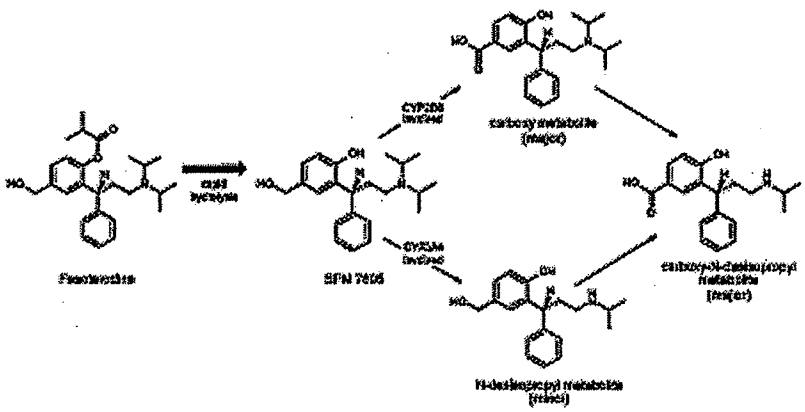
b(4)

Tabulated results:	Supersomes expressing CYP cDNAs	Peak 1 (pmol/min/pmol CYP)	Peak 2 (pmol/min/pmol CYP)
	Control (without transfected CYP enzyme)	ND	0.00198 ± 0.000250
	CYP1A1	ND	0.00267 ± 0.000691
	CYP1A2		
	CYP2A6		
	CYP2B6	[redacted]	0.00222 ± 0.000199
	CYP2C8	0.000781/0.000116[b]	0.00203 ± 0.000364
	CYP2C9	0.000426/0.000607[b]	0.00202 ± 0.000304
	CYP2C19.rg	ND	0.00190 ± 0.000340
	CYP2D6	0.00813/0.00303[b]	0.362 ± 0.00388
	CYP2E1	0.000543[b]	0.00194 ± 0.000274
	CYP3A4	0.00142[b]	0.00231 ± 0.000271
	CYP3A5	0.000333/0.00138[b]	0.00265 ± 0.000496
	CYP4A11	ND	0.00185 ± 0.000150

Additional information:
Results are means ± standard deviation of n = 3
a - individual data (n = 1)
b - n = 2
ND denotes not detected

Possible metabolic pathways

Test Article: Fesoterodine, [^{14}C]-fesoterodine, [^{14}C]-SPM 8311[a] and SPM 7605



Additional information:
The known metabolites of fesoterodine were identified in vitro (mouse, rat, hamster, rabbit, dog, primate and human liver microsomes (Table 2.6.3.10B to Table 2.6.3.10I, DHGY1009 and DHGY1030)) and in vivo in plasma and/or in excreta (mouse, rat, rabbit, dog (Table 2.6.3.9A to 2.6.3.9G, 634, 667, 828, 869, DHGY1008) and man (Phase 1 Trial, 5.3.1.1.2, SP567)). The enzymes involved in the metabolism of SPM 7605 were identified in human and recombinant microsomes (Table 2.6.3.10I, DHGY1029).
SPM 7605 = hydroxy metabolite; Carboxy metabolite = SPM 5509; Carboxy-N-desisopropyl metabolite = SPM 7790 (racemate) or SPM 6923 (R-enantiomer); N-desisopropyl metabolite = SPM 7789 (racemate) or SPM 7833 (R-enantiomer).
2 - Hydrogen fumarate of SPM 7605

Induction/inhibition of drug-metabolizing enzymes

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.10
Study no.: BA 535-02

Test system: Cryopreserved human hepatocytes
Method: Positive controls: dexamethasone and rifampicin, solvent controls: DMSO and acetonitrile.
A) Determination of CYP3A4 activity by measurement of 6-β-hydroxytestosterone concentration by HPLC
B) Determination of mRNA levels of cyp 1A2, 2D6, 2C9, 2C19, 3A4 and GAPDH (control for unspecific induction) by using a commercially available kit with fluorescence detection

Tabulated results:

Sequence	Donor	Induction factor for CYP3A4				
		Solvent control	Dexamethasone (50 µM)	Rifampicin (20 µM)	Fesoterodine (9.5 nM)	Fesoterodine (95 nM)
1	1	1.0	1.2	3.2	1.0	0.8
	2	1.0	1.3	3.8	0.8	1.2
	3	1.0	1.4	3.4	0.9	0.8
2	1	1.0	1.2	4.5	1.0	1.5
	2	1.0	1.7	2.5	1.1	1.0
	3	1.0	3.2	13.5	1.4	2.7

Additional information:
The induction factor (IF) was calculated as $IF = \frac{\text{metabolite concentration in sample or control medium}}{\text{metabolite concentration in solvent control}}$
Sequence 1: 1% DMSO, sequence 2: 1% acetonitrile.
The 6-β-hydroxytestosterone concentrations were determined in duplicate.

Tabulated results:

mRNA level	Sequence	Induction factor on mRNA level				
		Solvent control	Dexamethasone (50 µM) (range)	Rifampicin (20 µM) (range)	Fesoterodine (9.5 nM) (range)	Fesoterodine (95 nM) (range)
cyp1A2	1	1.0	0.9 - 1.2	0.7 - 1.1 [b]	0.6 - 1.2	0.6 - 1.1
	2	1.0	0.3 - 1.2	0.3 - 1.3	0.3 - 1.7	0.3 - 2.0
cyp2C9	1	1.0 [a]	0.7 [a]	1.3 - 1.4 [a]	0.9 - 1.0 [a]	NC
	2	NC	NC	NC	NC	NC
cyp2C19	1	1.0	0.6 - 1.1	0.7- 1.6	0.5 - 1.1	0.5 - 1.3
	2	1.0	0.7 - 1.1	0.8 - 1.1	0.6 - 1.1	1.3 [b]
cyp2D6	1	1.0	0.6 - 1.2	0.5 - 1.2	0.5 - 1.3	0.4 - 1.4
	2	1.0	0.5 - 1.1	0.5 - 1.1	0.5 - 1.2	0.3 - 1.6
cyp3A4	1	1.0	1.1 - 1.5	2.2 - 2.9	0.7 - 0.9	0.7 - 1.1
	2	1.0	1.1 - 2.5	2.5 - 7.5	0.8 - 1.1	0.8 - 1.4
GAPDH	1	1.0	0.9 - 1.1	0.9 - 1.1	0.8 - 1.1	NC
	2	1.0	0.9 - 1.0	1.0 - 1.1	0.9 - 1.0	0.9 - 1.0

Additional information:
The results are ranges of 1 to 3 donors. Sequence 1: 1% DMSO, sequence 2: 1% acetonitrile
The induction factor (IF) was calculated as $IF = \frac{\text{concentration in sample or control medium}}{\text{concentration in solvent control}}$
GAPDH = glyceraldehyde-phosphate dehydrogenase (control for unspecific induction)
a - n=2
b - n=1
NC denotes not calculated

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.11
Study no.: 692

Test system: Cryopreserved human hepatocytes from male and female donors
Method: Incubation with fesoterodine at 20 or 200 nM for 72 hours, analysis by fluorimetry or by HPLC with UV or radio detection
Tabulated results:

CYP isoform	Donor	Substrate (nM)	Control inducer	Control induction	Fesoterodine 20 nM	Fesoterodine 200 nM
			Compound (nM)	% of control	% of control	% of control
CYP1A2	417	7-ethoxyresorufin (5)	Omeprazole (30)	462	105	117
	FEP			428	98.8	103
CYP2B6	417	(S)-mephenytoin (100)	Phenobarbital (200)	604	121	129
	FEP			610	117	84.8
CYP2C9	417	(S)-warfarin (10)	Rifampicin (20)	455	105	97.6
	FEP			359	109	102
CYP2C19	417	(S)-mephenytoin (100)	Rifampicin (20)	595	114	119
	FEP			n.d.	n.d.	n.d.
CYP3A4	417	Testosterone (250)	Rifampicin (20)	1276	151	124
	421			372	118	79.8

Additional information:
n.d. denotes no metabolic turnover observed
Induction was considered positive at more than 200% and negative at less than 10% of enzymatic activities of control
Gender of donors: 417 male, FEP and 421 female

Induction/inhibition of drug-metabolizing enzymes in the mouse

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.12
Study no.: 0789-029; 0789-029-a1

Test system: Mouse liver microsomes obtained from study [redacted]13345/00 after oral (gavage) administration of fesoterodine for 26 weeks
Method: Markers for enzyme activities: 7-ethoxyresorufin O-dealkylase (CYP1), 11-hydroxylauric acid (CYP2E), 12-hydroxylauric acid (CYP4A), 6β-hydroxytestosterone (CYP3A), 16β-hydroxytestosterone (CYP2B), and 16α-hydroxytestosterone (CYP2C). Fluorimetry and HPLC analysis with UV detection using reference standards.

b(4)

Group:	Protein concentration (mg/g liver)	Cytochrome P450 (nanomoles/mg protein)	Resorufin	Production of 11-hydroxy lauric acid	12-hydroxy lauric acid	6β-hydroxy testosterone	16β-hydroxy testosterone	6α-hydroxy testosterone
				(pmoles/min/mg protein)				
Male								
Control	22.67 (100%)	0.33 (100%)	72 (100%)	341 (100%)	516 (100%)	1361 (100%)	100 (100%)	232 (100%)
5 mg/kg/day	20.86 (92%)	0.63 (119%)	42 (58%)	357 (66%)	229 (79%)	447 (33%)	34 (34%)	112 (48%)
25 mg/kg/day	21.32 (95%)	0.76 (147%)	66 (119%)	321 (95%)	357 (103%)	1165 (85%)	82 (82%)	209 (90%)
100 mg/kg/day	20.47 (90%)	0.72 (138%)	83 (115%)	1074 (126%)	500 (151%)	1720 (107%)	109 (109%)	274 (118%)
Female								
Control	23.77 (100%)	0.46 (100%)	65 (100%)	1053 (100%)	328 (100%)	934 (100%)	50 (100%)	33 (100%)
5 mg/kg/day	20.86 (88%)	0.51 (111%)	62 (94%)	934 (88%)	306 (93%)	849 (91%)	38 (76%)	45 (82%)
25 mg/kg/day	21.14 (89%)	0.48 (104%)	76 (115%)	1122 (107%)	323 (98%)	1033 (111%)	60 (120%)	81 (147%)
125 mg/kg/day	20.83 (88%)	0.62 (135%)	95 (146%)	1358 (129%)	561 (171%)	1163 (125%)	63 (126%)	48 (87%)

Additional information:
Results are expressed as mean of 2 pools, data in brackets are expressed as percentage of the corresponding control group mean.

Induction/inhibition of drug-metabolizing enzymes in the dog

Test Article: Fesoterodine
Location in CTD: 4.2.2.4.13
Study no.: 0789-030; 0789-030-a1

Test system: Dog liver microsomes were obtained from study [redacted]13349/00 after oral administration of fesoterodine for 9 months
Study system: Markers for enzyme activities: 7-ethoxyresorufin O-dealkylase (CYP1A), 11-hydroxylauric acid (CYP2E1), 12-hydroxylauric acid (CYP4A), 6β- and 2β-hydroxytestosterone (CYP3A4), 16β-hydroxytestosterone (CYP2B11 and CYP2C1), 16α-hydroxytestosterone (CYP2C), 6α-hydroxytestosterone, 17β-hydroxytestosterone. Fluorimetry and HPLC with UV detection using reference standards.

b(4)

	Protein concentration (mg/g liver)	Cytochrome P450 (nanomoles/mg protein)	Resorufin	Production of 11-hydroxy lauric acid (pmoles/min/mg protein)	12-hydroxy lauric acid	6β-hydroxy testosterone
Male						
Control	18.70 (100%)	0.356 (100%)	164 (100%)	473 (100%)	2263 (100%)	475 (100%)
0.5 mg/kg/day	17.71 (95%)	0.377 (106%)	238 (145%)	513 (108%)	2701 (119%)	454 (96%)
2.5 mg/kg/day	19.49 (104%)	0.312 (88%)	158 (96%)	450 (95%)	2337 (104%)	373 (79%)
12.5 mg/kg/day	19.56 (105%)	0.248 (70%)	156 (120%)	336 (71%)	1974 (87%)	369 (64%)
Female						
Control	21.16 (100%)	0.328 (100%)	134 (100%)	468 (100%)	2430 (100%)	474 (100%)
0.5 mg/kg/day	21.88 (103%)	0.300 (91%)	201 (129%)	467 (100%)	2245 (92%)	439 (93%)
2.5 mg/kg/day	22.10 (104%)	0.307 (94%)	126 (81%)	413 (89%)	2164 (89%)	432 (91%)
12.5 mg/kg/day	20.02 (95%)	0.283 (86%)	136 (100%)	422 (90%)	2426 (84%)	358 (75%)

Additional information:
Results are expressed as mean of 4 livers, data in brackets are expressed as percentage of the corresponding control group mean.

	16β-hydroxytestosterone	16α-hydroxytestosterone	2β-hydroxytestosterone (pmoles/min/mg protein)	6α-hydroxytestosterone	Androstenedion
Male					
Control	46 (100%)	155 (100%)	79 (100%)	23 (100%)	105 (100%)
0.5 mg/kg/day	37 (80%)	200 (129%)	77 (97%)	23 (100%)	126 (120%)
2.5 mg/kg/day	32 (70%)	182 (117%)	57 (72%)	20 (87%)	119 (113%)
12.5 mg/kg/day	30 (65%)	152 (98%)	55 (70%)	18 (78%)	101 (96%)
Female					
Control	52 (100%)	169 (100%)	93 (100%)	24 (100%)	118 (100%)
0.5 mg/kg/day	45 (87%)	197 (117%)	78 (85%)	19 (79%)	127 (108%)
2.5 mg/kg/day	42 (81%)	193 (114%)	67 (73%)	24 (100%)	134 (114%)
12.5 mg/kg/day	29 (56%)	192 (114%)	60 (65%)	17 (71%)	109 (92%)

Additional information:
Results are expressed as mean of 4 livers, data in brackets are expressed as percentage of the corresponding control group mean.

Induction/inhibition of drug-metabolizing enzymes *in vitro*

Test Article: Fesoterodine, SPM 7605, SPM 6925, SPM 9078 and SPM 5509
Location in CTD: 4.2.2.4.14
Study no.: BA 474-02; BA 474-02-a1

Test system: Enzymologically expressed human CYP isoforms
Method: Concentration ranges of test articles: 200 - 0.09 µM (CYP1A2, CYP2C9, CYP2C19) or 100 - 0.05 µM (CYP2D6, CYP3A4).
Control inhibitors: furafylline (CYP1A2), sulfaphenazole (CYP2C9), omeprazole (CYP2C19), quinidine (CYP2D6), ketoconazole (CYP3A4). Substrates: CEC (4.9 µM, CYP 1A2), MFC (3.3 µM, CYP2C9), CEC (24.3 µM, CYP 2C19), AMMC (7.4 µM, CYP2D6), BFC (50 µM, CYP3A4). Fully automated microtiter plate-based competitive endpoint assay with fluorescence detection.

Tabulated results:

CYP isoform	Fesoterodine		SPM 7605		Compound SPM 5509		SPM 6925		SPM 9078	
	IC_{50}	Ki	IC_{50}	Ki	IC_{50}	Ki	IC_{50}	Ki	IC_{50}	Ki
CYP 1A2[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
CYP 2C9[b]	478	246	LD	LD	291	150	LD	LD	196	101
CYP 2C19[c]	ND	ND	ND	ND	ND	ND	ND	ND	118	64
CYP 2D6[d]	13.6	7.3	10.0	5.00	22.0	10.9	ND	ND	3.4	1.7
CYP 3A4[e]	4.3	2.3	48.5	30.9	155	99.1	ND	ND	10.3	6.4

Additional information:
a - Furafylline: IC_{50}=0.59-1.35, K_i=0.43-0.45; b - Sulfaphenazole: IC_{50}=0.34-0.55, K_i=0.18; c - Omeprazole=IC_{50}: 2.86-2.87, K_i=1.55-1.36;
d - Ketoconazole IC_{50}=0.016-0.029, K_i=0.010-0.12; e - Quinidine: IC_{50}=0.015-0.35, K_i=0.004-0.015
ND denotes no interaction detected
LD denotes low interaction detected, calculation not reasonable
CEC=3-cyano-7-ethoxycoumarin; MFC=7-methoxy-4-trifluoromethylcoumarin; AMMC=3-[2-(N,N-diethyl-N-methylamino)ethyl]-7-methoxy-4-methylcoumarin; BFC=7-hydroxy-4-trifluoromethylcoumarin

Excretion in the mouse

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.1
Study no.: DHGY1005

Species:	Mouse, CD-1				Mouse, CD-1			
Gender (M/F)/Number of animals:	3 M				3 F			
Feeding condition:	Fed				Fed			
Vehicle/Formulation:	Water/Solution				Water/Solution			
Method of administration:	Oral (gavage)				Oral (gavage)			
Dose (mg/kg):	3				3			
Analyte:	TRA, ^{14}C				TRA, ^{14}C			
Assay:	LSC				LSC			
Tabulated results:	% Administered dose							
Excretion route:	Urine	Feces	Cagewash	Total	Urine	Feces	Cagewash	Total
Time								
0 - 8 hours	25.8 ± 8.91	NS	NS	NC	17.5 ± 3.59	NS	NS	NC
0 - 24 hours	35.2 ± 7.73	48.2 ± 6.48	4.11 ± 1.03	87.5 ± 5.90	22.4 ± 2.17	60.2 ± 1.39	8.46 ± 4.85	91.3 ± 4.63
0 - 48 hours	35.7 ± 7.75	50.9 ± 8.24	3.87 ± 1.29	91.5 ± 5.33	25.5 ± 4.88	54.0 ± 2.30	10.7 ± 6.20	90.3 ± 3.77
0 - 72 hours	36.1 ± 7.39	51.3 ± 9.07	3.23 ± 1.35	92.7 ± 4.82	25.9 ± 4.82	54.5 ± 2.17	10.8 ± 6.21	91.0 ± 3.58
0 - 96 hours	36.2 ± 7.54	51.4 ± 9.04	3.28 ± 1.36	92.8 ± 4.56	25.9 ± 4.83	54.4 ± 2.21	10.8 ± 6.26	91.2 ± 3.65
0 - 120 hours	36.2 ± NA	51.3 ± NA	3.34 ± 1.36	93.0 ± 4.85	25.9 ± 4.78	54.5 ± 2.17	11.4 ± 3.72	91.9 ± 3.10
0 - 144 hours	36.2 ± NA	51.5 ± NA	3.34 ± 1.36	93.0 ± 4.86	26.0 ± 4.83	54.6 ± 2.22	11.4 ± 3.72	92.0 ± 3.12
0 - 168 hours	36.2 ± NA	51.5 ± NA	3.34 ± 1.36	93.1 ± 4.82	26.0 ± 4.83	54.6 ± 2.23	11.4 ± 3.72	92.1 ± 3.13

Additional information:
Mean data ± standard deviation parameters tabulated (n=3). Total contains expired air, gastrointestinal tract and carcass. Cumulative excretion in expired air, carcass and gastrointestinal tract accounts for less than 0.05% of the administered dose.
TRA = total radioactivity, LSC = liquid scintillation counting, NS = no samples collected, NC = not calculated

Species:	Mouse, CD-1				Mouse, CD-1			
Gender (M/F)/Number of animals:	3 M				3 F			
Feeding condition:	Fed				Fed			
Vehicle/Formulation:	Saline/Solution				Saline/Solution			
Method of administration:	Intravenous bolus				Intravenous bolus			
Dose (mg/kg):	2.3				2.3			
Analyte:	^{14}C				^{14}C			
Assay:	TRA, LSC				TRA, LSC			
Tabulated results:	% Administered dose							
Excretion route:	Urine	Feces	Cagewash	Total	Urine	Feces	Cagewash	Total
Time								
0 - 8 hours	40.8 ± NC	NS	NS	NC	4.04* ± NA	NS	NS	NC
0 - 24 hours	42.5 ± 15.4	43.0 ± 14.6	2.70 ± 1.57	88.2 ± 1.32	23.3 ± 2.37	56.2 ± 5.72	6.23 ± 4.73	85.7 ± 4.15
0 - 48 hours	42.9 ± 15.6	44.3 ± 13.0	2.90 ± 1.62	90.1 ± 1.06	23.8 ± 2.65	58.6 ± 7.09	6.81 ± 4.72	89.3 ± 5.03
0 - 72 hours	43.1 ± 15.6	44.7 ± 14.9	2.98 ± 1.69	90.7 ± 0.67	24.1 ± 2.75	58.9 ± 7.33	6.87 ± 4.67	89.9 ± 5.19
0 - 96 hours	43.1 ± 15.6	44.7 ± 14.8	3.12 ± 1.70	90.7 ± 1.01	24.2 ± 2.70	58.9 ± 7.37	6.95 ± 4.65	90.0 ± 5.23
0 - 120 hours	43.2 ± 15.6	44.9 ± 14.8	3.17 ± 1.73	91.2 ± 0.52	24.2 ± 2.73	58.9 ± 7.37	6.95 ± 4.65	90.1 ± 5.28
0 - 144 hours	43.2 ± 15.6	44.8 ± 14.8	3.17 ± 1.73	91.2 ± 0.52	24.2 ± 2.70	58.9 ± 7.12	6.93 ± 4.63	90.1 ± 5.30
0 - 168 hours	43.2 ± 15.6	44.9 ± 14.8	3.17 ± 1.73	91.3 ± 0.49	24.2 ± 2.70	58.9 ± 7.12	6.93 ± 4.63	90.1 ± 5.30

Additional information:
Mean data ± standard deviation parameters tabulated (n=3). Total contains expired air, gastrointestinal tract and carcass. Cumulative excretion in expired air, carcass and gastrointestinal tract accounts for less than 0.10% of the administered dose.
TRA = total radioactivity, LSC = liquid scintillation counting, NS = no samples collected, NC = not calculated

Excretion in the rat

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.2
Study no.: DHGY1007

Species:	Rat, Sprague Dawley				Rat, Sprague Dawley			
Gender (M/F)/Number of animals:	3 M				3 F			
Feeding condition:	Fed				Fed			
Vehicle/Formulation:	Water/Solution				Water/Solution			
Method of administration:	Oral (gavage)				Oral (gavage)			
Dose (mg/kg):	3				3			
Analyte:	TRA, ^{14}C				TRA, ^{14}C			
Assay:	LSC				LSC			
Tabulated results:	% Administered dose							
Excretion route:	Urine	Feces	Cagewash	Total	Urine	Feces	Cagewash	Total
Time								
0 - 8 hours	3.51 ± 0.60	NS	NS	NC	5.63 ± 0.61	NS	NS	NC
0 - 24 hours	8.68 ± 2.24	68.7 ± 21.0	0.80 ± 0.25	78.3 ± 20.8	7.22 ± 2.26	55.4 ± 24.3	2.09 ± 1.67	64.6 ± 23.9
0 - 48 hours	9.43 ± 2.38	72.6 ± 6.43	1.23 ± 0.38	83.4 ± 3.83	8.21 ± 3.20	61.1 ± 24.6	2.44 ± 1.32	71.8 ± 22.3
0 - 72 hours	9.59 ± 2.40	75.2 ± 5.56	1.41 ± 0.76	86.2 ± 2.33	8.46 ± 3.35	74.4 ± 8.28	2.77 ± 0.98	85.6 ± 5.72
0 - 96 hours	9.64 ± 2.64	76.8 ± 2.56	1.49 ± 0.86	88.0 ± 0.67	8.49 ± 3.33	7.30 ± 7.59	2.82 ± 0.97	86.3 ± 5.56
0 - 120 hours	9.65 ± 2.64	77.0 ± 2.81	1.52 ± 0.91	88.2 ± 0.77	8.51 ± 3.33	75.2 ± 7.80	2.88 ± 1.04	86.6 ± 5.28
0 - 144 hours	9.67 ± 2.65	77.0 ± 2.77	1.57 ± 0.92	88.3 ± 0.82	8.54 ± 3.33	75.3 ± 7.80	2.90 ± 1.03	86.8 ± 5.24
0 - 168 hours	9.69 ± 2.65	77.1 ± 2.79	1.59 ± 0.95	88.3 ± 0.86	8.55 ± 3.34	75.6 ± 7.46	2.96 ± 1.10	87.3 ± 4.77

Additional information:
Mean data ± standard deviation are tabulated (n=3). Total contains expired air, gastrointestinal tract and carcass. Expired air, gastrointestinal tract and carcass contained less than 0.05% of the administered dose.
TRA = total radioactivity, LSC = liquid scintillation counting, NS = no samples collected, NC = not calculated.

Species:	Rat, Sprague Dawley				Rat, Sprague Dawley			
Gender (M/F)/Number of animals:	3 M				3 F			
Feeding condition:	Fed				Fed			
Vehicle/Formulation:	Saline/Solution				Saline/Solution			
Method of administration:	Intravenous bolus				Intravenous bolus			
Dose (mg/kg):	2.5				2.5			
Analyte:	TRA, ^{14}C				TRA, ^{14}C			
Assay:	LSC				LSC			
Tabulated results:	% Administered dose							
Excretion route:	Urine	Feces	Cagewash	Total[a]	Urine	Feces	Cagewash	Total
Time								
0 - 6 hours	10.3 ± 4.10	NS	NS	NC	9.15 ± 1.53	NS	NS	NC
0 - 24 hours	15.8 ± 3.07	74.2 ± 2.79	0.79 ± 0.51	90.9 ± 2.50	14.4 ± 1.32	78.4 ± 0.60	0.68 ± 0.56	93.4 ± 0.90
0 - 48 hours	16.2 ± 2.66	76.5 ± 3.30	0.91 ± 0.59	93.6 ± 1.70	14.9 ± 1.16	76.6 ± 0.80	0.89 ± 0.61	92.3 ± 0.90
0 - 72 hours	16.3 ± 2.63	77.0 ± 3.34	0.98 ± 0.62	94.3 ± 1.47	15.0 ± 1.13	77.8 ± 0.94	1.07 ± 0.70	93.9 ± 3.35
0 - 96 hours	16.4 ± 2.63	77.1 ± 3.46	1.00 ± 0.65	94.5 ± 1.51	15.1 ± 1.13	78.1 ± 1.07	1.12 ± 0.71	94.3 ± 2.51
0 - 120 hours	16.4 ± 2.63	77.3 ± 3.33	1.02 ± 0.65	94.9 ± 1.27	15.1 ± 1.14	78.4 ± 1.27	1.15 ± 0.70	94.6 ± 1.76
0 - 144 hours	16.4 ± 2.63	77.6 ± 3.30	1.02 ± 0.64	95.1 ± 1.24	15.1 ± 1.14	78.5 ± 1.33	1.16 ± 0.70	94.8 ± 1.75
0 - 168 hours	16.4 ± 2.63	77.7 ± 3.29	1.26 ± 0.75	96.2 ± 0.99	15.2 ± 1.13	78.6 ± 1.30	1.25 ± 0.70	95.6 ± 3.60

Additional information:
Mean data ± standard deviation are tabulated (n=3). Total excretion expired air, gastrointestinal tract and carcass
confirmed less than 0.07% of the administered dose.
TRA = total radioactivity, LSC = liquid scintillation counting, NS = no samples collected, NC = not calculated.

Excretion in the dog

Test Article: [^{14}C]-Fesoterodine
Location in CTD: 4.2.2.2.4
Study no.: DHGY1006

Species:	Dog, Beagle			Dog, Beagle			Dog, Beagle			Dog, Beagle		
Gender (M/F)/Number of animals:	3 M			3 F			3 M			3 F		
Feeding condition:	Fasted			Fasted			Fasted			Fasted		
Vehicle/Formulation:	Water/Solution			Water/Solution			Saline/Solution			Saline/Solution		
Method of administration:	Oral (gavage)			Oral (gavage)			Intravenous bolus			Intravenous bolus		
Dose (mg/kg):	0.5			0.5			0.25			0.25		
Analyte:	TRA, ^{14}C			TRA, ^{14}C			TRA, ^{14}C			TRA, ^{14}C		
Assay:	LSC			LSC			LSC			LSC		
Tabulated results:	% Administered dose											
Excretion route:	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Time												
0 - 6 hours	34.0	NS	NC	54.5	NS	NC	22.8	NS	NC	32.9	NS	NC
0 - 24 hours	50.3	14.6	67.8	82.4	13.2	92.3	50.3	28.1	81.2	58.8	19.6	80.1
0 - 48 hours	54.3	24.3	81.3	85.8	23.2	88.8	52.0	31.4	86.8	60.2	22.8	83.1
0 - 72 hours	54.9	25.5	83.5	86.1	24.2	90.8	52.3	33.2	88.2	60.5	23.9	86.5
0 - 96 hours	55.0	26.1	84.3	86.2	24.3	90.7	52.5	33.9	91.5	60.6	24.1	87.0
0 - 120 hours	55.4	26.2	85.2	86.5	24.6	90.9	52.6	33.2	92.2	60.7	24.3	87.4
0 - 144 hours	55.4	26.2	85.4	86.5	24.6	91.1	52.7	33.4	92.6	60.7	24.3	87.5
0 - 168 hours	55.5	26.3	85.8	86.5	24.6	91.3	52.7	33.5	92.9	60.8	24.4	87.6

Additional information:
Mean data are tabulated (n=3). Total contains cagewash. Cumulative excretion in cagewash (mean ± standard deviation) after 168 hours accounted for 4.03 ± 1.68% (M, oral), 2.32 ± 1.21% (F, oral), 4.36 ± 0.95% (M, iv) and 2.45 ± 1.05% (F, iv).
TRA = total radioactivity, LSC = liquid scintillation counting, NS = no samples collected, NC = not calculated.

Excretion in human

Test Article: Fesoterodine and SPM 7605
Location in CTD: 5.3.1.1.2
Study no.: SP567

Trial design	Non-blind, randomized, three-way crossover Healthy male subjects, 28 to 45 years Treatment D: single oral administration of 8 mg fesoterodine in a fasted state Treatment E: single intravenous infusion of 4 mg fesoterodine over 4 hours Treatment F: single intravenous infusion of 2.6 mg SPM 7605 over 4 hours
Analysis	Collection of urine and feces samples over 4 days post-dose, determination of SPM 7605 and the three secondary metabolites by LC-MS/MS

Tabulated results: Cumulative recovery in 0 - 96 hours interval, % administered dose

	Treatment D: 8 mg fesoterodine, oral			Treatment E: 4 mg fesoterodine, 4-hour iv infusion			Treatment F: 2.6 mg SPM 7605, 4-hour iv infusion		
Excretion route:	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
SPM 7605	18.2 ± 4.25	4.41 ± 3.75	20.6 ± 4.58	27.3 ± 5.01	0.04 ± 0.14	27.3 ± 5.04	33.6 ± 6.68	0 ± 0	33.3 ± 6.68
SPM 5589	33.7 ± 10.3	1.44 ± 1.01	35.2 ± 10.9	36.3 ± 8.56	1.47 ± 1.03	37.8 ± 8.88	36.5 ± 6.22	1.08 ± 0.83	37.6 ± 6.68
SPM 7789	1.27 ± 0.75	0.22 ± 0.21	1.45 ± 0.85	0.75 ± 0.50	0.14 ± 0.27	0.89 ± 0.77	0.77 ± 0.44	0 ± 0	0.77 ± 0.44
SPM 7790	18.3 ± 7.25	0.77 ± 0.50	19.3 ± 7.23	17.9 ± 9.22	0.76 ± 0.86	18.7 ± 9.25	23.6 ± 6.99	0.42 ± 0.49	24.0 ± 6.56
Total[a]	69.7	6.84	76.6	82.2	2.41	84.7	84.8	1.50	86.3

Additional information:
Mean data ± standard deviation are tabulated (n=11)
a - calculated from sum of means

Absorption *in vitro*

Test Article: Fesoterodine
Location in CTD: 4.2.2.7.1
Study no.: 010.01.0200 (step 3)

Test system:	Caco-2-cell monolayers[a] cultivated in DMEM at pH 7.4, serum on Transwell filter inserts for 19 days			
Analytes:	Fesoterodine, SPM 7605, SPM 9078			
Assay:	HPLC			
Tabulated results:		Fesoterodine	SPM 7605	SPM 9078
	C_0 (µg/mL)	16.3	14.4	15.7
	P_{app} (cm/s)[b]	NC	2.5×10^{-6}	1.0×10^{-6}

Additional information:
Integrity of Caco-2-cell monolayers was assessed by comparison of permeation coefficients of fluorescein, atenolol and propranolol
a - TEER (trans epithelial electric resistance) value at day 19 determined as 359.3 ± 18.3 [Ohm*cm²]
P_{app} = apparent permeability coefficient
DMEM = Dulbecco's modified Eagle's medium
ND: dioxane not determined due to partial decontamination of fesoterodine

Stability in gastric and intestinal fluid

Test Article: Fexofenadine
Location in CTD: 4.2.2.7.2
Study no.: BA 378-02

Test system: Simulated gastric and intestinal fluid
Method: 4.9 mg fexofenadine in 200 mL simulated gastric fluid (pepsin activity 1763 U/mL) or intestinal fluid (pancreatin concentration 10 mg/mL) or the respective controls were incubated at approximately 37°C for up to 4 or 18 hours, determination of fexofenadine by HPLC with UV detection

Tabulated results:

Time (hours)	Recovery of fexofenadine (mean ± SD of 3 replicates)			
	Simulated gastric fluid	Control gastric fluid [a]	Simulated intestinal fluid	Control intestinal fluid [b]
0	103 ± 3%	86 ± 7%	94 ± 3%	83 ± 6%
0.5	NS	NS	77 ± 3%	NS
1	107 ± 8%	90 ± 9%	57 ± 2%	80 ± 7%
1.5	NS	NS	49 ± 2%	NS
2	102 ± 3%	83 ± 9%	36 ± 2%	78 ± 12%
3	NS	NS	23 ± 1%	NS
4	99 ± 4%	81 ± 9%	16 ± 1%	82 ± 4%
4-rep [c]	96 ± 4%	77 ± 5%	NA	NA
8	NS	NS	4 ± 0%	72 ± 5%
18	NS	NS	0 ± 0%	78 ± 6%

Additional information:
SD denotes standard deviation
NS denotes no samples collected
NA denotes not applicable
a - without pepsin
b - without pancreatin
c - repeated with 4.6-fold higher pepsin activity of 8046 U/mL

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Exaggerated pharmacological effects (including mydriasis and increased heart rate) were the primary limiting toxicity for both mice and dogs. No treatment related histopathological changes were observed after treatment for 6 months in mice or 9 months in dogs.

Although a clearly defined effect on QT prolongation was not observed in dogs administered oral fesoterodine, effects were observed in dogs exposed intravenously to greater than 10 times the expected clinical exposure (see Safety Pharmacology section.).

Genetic toxicology: Fesoterodine was negative for genotoxicity and/or mutagenicity in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity: Two-year bioassays were conducted in rats and mice up to a maximally tolerated dose of fesoterodine. There was adequate exposure to each of the major human metabolites. No treatment related increases in the type or incidence of neoplastic and/or hyperplastic lesions were observed.

Reproductive toxicology:

In a mouse fertility study (oral), at 45 mg/kg/day, no effect on male fertility or the male reproductive system was observed. In females, numbers of corpora lutea, implantation sites, live fetuses, and uterine weight were decreased at this dose. At 15 mg/kg/day (about equal to the expected clinical exposure), no effects on female fertility, the female reproductive system, or early embryonic development were observed.

In a mouse embryo/fetal study (oral), at 75 mg/kg/day (about 6-30 times the expected clinical exposure of an 8 mg dose via AUC), one dam died, and body weight, gravid uterine weight, and the number of live fetuses were decreased. Resorptions were increased. At 45 mg/kg/day (about 3 times) one dam died, but no effect on body weight was observed. The number of live fetuses appeared to be decreased, but did not reach statistical significance. Lack of significance for resorptions in the mid dose group may have been due to the decrease in implantation sites seen in this group. At the lowest dose of 15 mg/kg/day (about equal to the expected clinical exposure), the number of resorptions was increased and the number of live fetuses was decreased. In addition, 1 fetus with cleft palate was observed in each of the treated groups, but not in the control group. As any of these effects may be considered a symptom of maternal stress, it should be considered that no NoAEL was observed for maternal or fetal effects in the study.

In a rabbit embryo/fetal study (oral), at 27 mg/kg/day (about 4-12 times the expected clinical exposure of an 8 mg dose via AUC), one dam died following dosing. Resorptions were increased at this dose and the total number of live fetuses was decreased. No

malformations were observed, but the number of fetuses with incompletely ossified sternebrae were increased. At 9 mg/kg/day (about 0.2-0.3 times the expected clinical exposure), one dam aborted and was sacrificed. Although, the number of fetuses with incompletely ossified sternebrae appeared to be increased, statistical significance was not reached. A no effect level for maternal and fetal toxicity was not clearly identified in the study.

In a rabbit embryo/fetal study (subcutaneous), at 4.5 mg/kg/day by subcutaneous administration (about 10-12 times the expected clinical exposure of an 8 mg dose via AUC of the active entity SPM 7605), mortality was observed in dams in conjunction with clonic convulsions, dyspnea, miosis, and a decrease in body weight and food consumption. No effects on number of corpora lutea, implantation sites, resorptions, placental and fetal weights, or number of live fetuses were observed. No external or skeletal malformations were observed. No treatment related external or skeletal variations were observed. No treatment related skeletal retardations were observed except incomplete ossification of the sternebra(e). At 1.5 mg/kg/day (about 3-4 times), no maternal or fetal effects were observed except for a decrease in maternal food consumption. At 0.5 mg/kg/day, no maternal or fetal effects were observed.

In a mouse developmental study, at 60 mg/kg/day (estimated to be about 5-24 times the expected exposure of an 8 mg clinical dose via AUC), one dam was found dead during the lactation period and decreased maternal body weight and food consumption were observed. Decreased litter weight and developmental delay (time to ear opening) were observed in the F1 generation. At 30 mg/kg/day (about 2-12 times), decreased maternal body weight was observed. A decrease in litter weight did not reach statistical significance at this dose, but developmental delay (time to ear opening) and increased activity level (not significant, but present at 60 mg/kg/day) were observed in the F1 generation. At 10 mg/kg/day, no effects on dams or the F1 generation were observed. No effects on reproductive performance of the F1 generation were observed nor any effects on the F2 generation, at any dose.

There was adequate exposure to each of the major human metabolites in reproductive studies.

Special toxicology: Fesoterodine exhibited no phototoxicity in *in vitro* and *in vivo* assays.

2.6.6.2 Single-dose toxicity

—12351/99. Three NMRI mice per sex and group were treated with 100, 215 and 464 mg/kg fesoterodine (oral). The no-observed-effect-level (NOEL) was 100 mg/kg and an approximate LD_{50} was 316 mg/kg. At 215 mg/kg, slight clinical signs (reduced motility, ataxia, dyspnea and reduced muscle tone) were observed. Between 20 and 30 minutes following administration of 464 mg/kg, all mice died after showing abdominal position and moderate mydriasis. No substance related histopathology (liver and kidney) was observed.

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— 12352/99. Fesoterodine was administered to 3 NMRI mice/ sex /group at doses of 4.64, 10.0, 21.5 and 46.4 mg/kg (iv). The NOEL was 10.0 mg/kg and an approximate LD_{50} was 31.6 mg/kg. At 21.5 mg/kg slightly reduced motility, slight ataxia, slight dyspnea and slightly reduced muscle tone were observed. At 46.4 mg/kg, all animals died within 2 minutes after administration after showing abdominal position and moderate mydriasis. No substance related histopathology (liver and kidney) was observed. b(4)

—12353/99. Single doses of 100, 215, 464 and 1000 mg/kg fesoterodine (oral) were administered to 3 Sprague-Dawley rats /sex/group.. The NOEL was 100 mg/kg and an approximate LD_{50} was 681 mg/kg for male rats and 454 mg/kg for female rats, 24 hours after administration. After 14 days the LD_{50} was 681 mg/kg for the males and 316 mg/kg for the females. Starting at 215 mg/kg, slightly reduced motility, slight ataxia, slight dyspnea and slightly reduced muscle tone were observed. Abdominal position was observed at 1000 mg/kg. All female rats treated with 464 mg/kg and all male animals dosed with 1000 mg/kg died between 10 and 120 minutes after administration. No substance related histopathology (liver and kidney) was observed. b(4)

—12354/99. Fesoterodine was administered to Sprague-Dawley rats (3/sex/group, iv) at doses of 4.64, 10.0, 21.5 and 46.4 mg/kg. The NOEL was 10.0 mg/kg and the approximate LD_{50} was 31.6 mg/kg. At 21.5 mg/kg, slightly to severely reduced motility, slight to severe ataxia, slight to moderate dyspnea and moderately to severely reduced muscle tone were observed. All animals at 46.4 mg/kg died about 2 minutes post-dose after showing abdominal position and moderate mydriasis. No substance related histopathology (liver and kidney) was observed. b(4)

2.6.6.3 Repeat-dose toxicity

Studies in mice:

—12834/99. In a 1-week dose-range finding study in NMRI mice (5/sex/group), doses were 0, 30, 100 and 200 mg/kg fesoterodine (oral). The NOEL in this study was 100 mg/kg. No mortality was observed. A dose of 200 mg/kg caused a slight but statistically significant reduction of body weight (males: -15%, females: -8%), a moderate decrease in reticulocyte counts in the female mice (-60%), slight to moderate increased blood urea levels in both sexes (males: +12%, females: +30%; statistically not significant) and a significantly decreased total cholesterol level in male mice (-28%). No substance related histopathology was observed. b(4)

—15538/02. In a 3-day study in CD-1 mice, three male animals per group were dosed with 5, 10 or 20 mg/kg fesoterodine (iv) in 0.9% NaCl solution for 4 hours per day. An additional 3 males per group were used for toxicokinetics. No animal died prematurely. No local or systemic toxicity was observed. Food consumption of all mice was reduced by -60% at study termination and body weights were reduced by up to -25% in all groups, including the control. b(4)

15539/02. In a 2-week study in CD-1 mice (10/sex/group plus 3 male controls and 18/sex/group for tk and 5 control and 5 HD for 2-week recovery), doses were 0, 2, 6 and 18 mg/kg fesoterodine (iv, 4 hour infusion) in 0.9% NaCl solution. The NOEL was 6 mg/kg, the NOAEL was 18 mg/kg. None of the animals died prematurely. Treatment with 18 mg/kg fesoterodine led to slightly to moderately reduced motility of the male mice from day 3 onwards. Neither local intolerance reactions nor any influence on body weight, food consumption, clinical biochemistry or hematology were seen in any dose group. No treatment related histopathology was observed.

Study title: 13-Week Subchronic Toxicity Study of SPM 8272 by Oral Administration to CD-1 Mice with an Interim Dissection after 2 Test Weeks

Study no: 12940/00 and 13683/00 (supplemental study)
Conducting laboratory and location: b(4)

Date of study initiation: 26 January 2000
GLP compliance: yes
QA report: yes (x) no ( )
Drug: batch # AC 8288, WE No. SPM 10964, 96.94% pure and batch # RD 7891/1, WE No. SPM 11013 (supplemental study)
Formulation/vehicle: aqua ad injectibilia
Dosing:

Species/strain: CD-1 / CD®-1(ICR)BR mice
#/sex/group or time point (main study): 15 and 10 (supplemental study) b(4)
Satellite groups used for toxicokinetics or recovery: 5/sex/group for interim dissection (2 weeks), 5/sex/group for recovery (4 weeks), and 18/sex/group for toxicokinetics
Age: 37 days (males) and 53 days (females)
Weight: 25.0-30.8 g (males) and 24.7-30.4 g (females)
Doses in administered units: 0, 5, 25, 75, and 125 mg/kg/day
Route, form, volume, and infusion rate: oral gavage, 10 ml/kg

Results:

Mortality:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	5	25	75	125	0	5	25	75	125
Premature death				2 (days 41 & 86)	2 (days 41 and 27) + 1 recovery group mouse (day 53)		1 (day 86)			1 (day 55)

13 week suppl.	Males (mg/kg/day)			Females (mg/kg/day)		
	0	15	45	0	15	45
Premature death	--	--	--	--	--	3 satellite

Clinical signs:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	5	25	75	125	0	5	25	75	125
Piloerection										
__slight				All (week 7+)					All (week 7 +)	
__slight to moderate					All (week 3 +)					All (week 3 +)

Body weights:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	5	25	75	125	0	5	25	75	125
Body weight (%)	--	-3.6	-2.2	-9.8	-12.9	--	+1.4	+0.3	-2.7	-5.8
Body weight change (%)	--	-12.9	-26.9	-43.6	-56.4	--	+26.3	+15.8	-31.6	-84.2

Food consumption: No treatment related effects were observed.
Ophthalmoscopy: No treatment related effects were observed.
Hematology: No treatment related effects were observed.
Clinical chemistry: No treatment related effects were observed.
Organ weights: No treatment related effects were observed.
Gross pathology: No treatment related effects were observed.
Histopathology: No treatment related effects were observed.

Toxicokinetics:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	5	25	75	125	0	5	25	75	125
Cmax (ng/ml)										
__day 1	--	24.7	39.0	370	1290	--	3.87	47.4	571	776
__day 14	--	14.0	69.2	1070	2360	--	17.0	211	820	2010
__day 90	--	11.0	176	631	2000	--	13.1	374	1440	1880
AUC0-24hr (ng·hr/ml)										
__day 1	--	17.8	156	1162	3254	--	4.7	178	1669	2922
__day 14	--	20.4	237	2771	5707	--	23.1	377	3081	8310
__day 90	--	103.4	696	1960	4037	--	53.4	627	3641	7741

13 week suppl.	Males (mg/kg/day)		Females (mg/kg/day)	
	15	45	15	45
Cmax (ng/ml)	52.7	422.5	58.6	408.0
$AUC_{0\text{-}24hr}$ (ng·hr/ml)	137	945	152	1111

Study title: 6-Month chronic toxicity study of SPM 8272 by oral administration to CD-1 mice
Study no: 13348/00
Conducting laboratory and location: b(4)
Date of study initiation: 14 August 2000
GLP compliance: yes
QA report: yes (x) no ( )
Drug: lot # AC 8340/1 WE No. SPM 11386, 96.45% pure
Formulation/vehicle: aqua ad injectabilia b(4)
Dosing:
Species/strain: CD-1 / CD®-1 (ICR)BR mice

#/sex/group: 25/sex per group + 5/sex/group for a 4-week recovery period + 12/sex/group for toxicokinetics
Age: 35 days (male) and 53 days (female)
Weight: 25.3-33.0 g (male) and 24.0-30.8 (female)
Doses in administered units: 0, 5, 25, and 75/100/125 mg/kg/day (males administered 75 mg/kg through test week 15 and 100 mg/kg every day thereafter, and females administered 75 mg/kg through test week 15 & 125 mg/kg thereafter)
Route, form, volume, and infusion rate: oral gavage, 10 ml/kg b.w.

Results:

Mortality:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	25	75/100	0	5	25	75/125
Premature death	0	0	1 (lymphoblastic lymphoma, sacrificed wk 22)	1 (wk 25)	0	0	0	2 (wks 18 & 25)(1 with lymphoblastic lymphoma died wk 25)

Clinical signs: High dose animals exhibited piloerection from week 11 onwards. No other treatment related effects were observed.

Body weights: Body weight was not influenced by treatment with 5 mg/kg/day in males or females or by 25 mg/kg/day in males. A marginal decrease in body weight was observed in females at 25 mg/kg/day in weeks 11, 15-19, and 25-26 ($p \leq 0.01$). A transient decrease in body weight was observed in high dose males in test weeks 11, 12, and 16-18 ($p<0.01$) (- 5-6%). A transient decrease in body weight was also observed in high dose females in test weeks 17, 18, and 26 ($p<0.01$) (- 8%).

Food consumption: No treatment related effects were observed.

Ophthalmological and auditory examination: No treatment related effects were observed.

Hematology:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	25	75/100	0	5	25	75/125
Platelets (10^9/l)								
__week 13	1363	1164	1284	1073**	1211	1180	1108	1090
__week 26	1581	1327	1416	1208**	1375	1255	1248	1094**
__week 30	1509	1561	1488	1402	1367	1373	1290	1147

Clinical chemistry:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	25	75/100	0	5	25	75/125
Triglycerides (mmol/l)								
__week 13	1.013	0.847	0.742	0.591**	0.659	0.706	0.708	0.582
__week 26	0.962	0.828	0.660	0.519**	0.693	0.587	0.522	0.438
__week 30	0.648	0.752	0.660	0.672	0.890	0.694	0.626	0.696
Glucose (mmol/l)								
__week 13	6.570	6.167	6.709	6.200	5.322	5.126	5.842	6.254
__week 26	4.875	5.225	5.017	5.414	4.434	4.363	4.690	5.579**
__week 30	4.404	5.000	4.828	4.714	4.222	4.676	4.430	3.474
Urea (mmol/l)								
__week 13	7.392	8.748	9.276	11.496**	7.341	7.719	7.180	8.462
__week 26	7.640	8.969	8.778	10.033**	7.584	7.198	7.311	7.735
__week 30	7.322	6.770	9.218	8.660	6.646	6.784	7.256	6.776

Alkaline phosphatase (U/l)								
__week 13	157.6	146.9	180.9	192.4	188.4	217.5	210.0	245.4
__week 26	141.5	142.0	164.3	190.9	201.7	239.1	228.2	229.9
__week 30	158.0	221.4	134.2	189.0	173.6	191.2	179.4	234.2

Organ weights: No treatment related effects were observed.
Gross pathology: No treatment related effects were observed.

Histopathology: No treatment related changes were observed. Lymphoblastic lymphoma was observed in one male control animal, one male in the mid dose group, and one female in the high dose group. A thymoma was observed in one female of the high dose group.

Toxicokinetics:

	Males (mg/kg/day)			Females (mg/kg/day)		
	5	25	75/100	5	25	75/125
Cmax (ng/ml)						
__day 1	11.4	106	753	18.6	266	1370
__week 13	7.01	178	1150	10.1	143	1260
__week 26	14.0	144	1670	14.7	258	2970
AUD (0-24)(ng·hr/ml)						
__day 1	24	399	2321	28	690	3950
__week 13	16	400	3149	17	429	3897
__week 26	28	379	3806	29	575	8325
Tmax (hr)	0.5	0.5	0.5	0.5	0.5	0.5

Summary: Effects in the high dose group consisted primarily of mortality and piloerection. One male in the mid dose group also died. Multiples of human clinical exposure were greater than 5 (C_{max}, AUC) in the mid dose group and greater than 30 in the high dose group.

Studies in rats:

— 12355/99. In a 1-week rat study (3/sex/group plus 3/sex/group for tk), doses were 0, 10, 30 or 100 mg/kg fesoterodine (oral). Animals of the low dose group were treated for an additional 7 days with 200 mg/kg fesoterodine. The NOEL was 10 mg/kg in female rats and 30 mg/kg in male rats. At 30 mg/kg, females showed increased ALAT, ASAT, cholesterol, triglycerides and bilirubin. At 100 mg/kg, females had slightly reduced body weight (-13%) and food intake (-36%), elevated erythrocyte (+12%) and platelet (+48%) counts, decreased reticulocyte count (-48%) and an increased urine volume (+106.7%) and increased relative liver weights. Male rats at 100 mg/kg had an elevated cholesterol value (+37%) and an increased ASAT activity (+40%). At 200 mg/kg, male toxicity was similar to females, but with elevated lactate dehydrogenase (LDH) levels (+90%) (no histopathological findings or changes in organ weights). At 200 mg/kg, regurgitation movements, intake of bedding material and reduced motility were observed in males and females. All females treated with 200 mg/kg died following the 5th or 7th administration. Although no treatment related histopathology of the liver or kidney was observed, a mild to marked bile duct proliferation with focal moderate necrosis of hepatocytes, a lympho-

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histiocytic inflammatory reaction, a moderate diffuse fatty infiltration of hepatocytes, and mild fatty infiltrations of the tubular epithelial cells in the kidney were observed.

Study title: 13-week MTD study of SPM 8272 by oral administration to Sprague-Dawley rats

Study no: 12941/00 b(4)
Conducting laboratory and location: [redacted]

Date of study initiation: 8 March 2000
GLP compliance: yes
QA report: yes (x) no ( )
Drug: batch # AC 8288, WE No. SPM 10964, 96.94% pure
Formulation/vehicle: aqua ad injectibilia
Dosing:
Species/strain: rat, Sprague-Dawley/CD®BR b(4)
#/sex/group or time point (main study): 10
Satellite groups used for toxicokinetics or recovery: 4/sex/group for toxicokinetics
Doses in administered units: 0, 5, 25, and 75 mg/kg/day
Route, form, volume, and infusion rate: oral gavage, in 5 ml/kg
Results:
Mortality: No premature mortality was observed.
Clinical signs: No clinical signs were observed.
Body weights:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	25	75	0	5	25	75
Body weight (%)	--	+4.4	-3.6	-9.5	--	+2.1	-1.7	-4.1
Body weight change (%)	--	+4.9	-4.8	-13.5	--	+1.8	-0.8	-10.0

13 week suppl.	Males (mg/kg/day)			Females (mg/kg/day)		
	0	15	45	0	15	45
Body weight change (%)	--		-8	--		+0.5

Food consumption: Food consumption was transiently decreased in both sexes with females being more affected than males.

Hematology: Mean corpuscular volume and the mean corpuscular hemoglobin were decreased in high dose females and platelet counts were increased by 9% in males and 19% in females at 75 mg/kg.

Clinical chemistry: ALAT, ASAT, triglycerides and total bilirubin were increased at 25 mg/kg and above. Cholesterol and alkaline phosphatase were also increased, with a greater effect in females than in males.

Urinalysis: Urinalysis showed significantly increased pH values in both sexes at 75 mg/kg and increased urine volume and decreased specific gravity in females.

Organ weights: In females, relative liver weights were increased at 25 mg/kg and absolute liver weights were increased by 38% at 75 mg/kg.

Histopathology: Substance-related morphological lesions (pericholangitis with mild bile duct proliferation) was observed in the liver of all females at 75 mg/kg.

Toxicokinetics:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	25	75	0	5	25	75
Cmax (ng/ml)								
day 1	--	10.35	23.19	41.26	--	5.47	36.16	37.64
day 30	--	4.13	22.10	77.99	--	2.71	24.22	58.62
day 90	--	5.38	29.66	103.28	--	3.06	24.03	89.60
$AUC_{0\text{-}24hr}$ (ng·hr/ml)								
day 1	--	62.98	97.43	318.98	--	17.60	182.80	301.04
day 30	--	33.78	172.38	592.02	--	16.32	115.05	410.88
day 90	--	19.57	106.87	627.35	--	13.93	112.61	392.78

In a supplemental toxicokinetic study, male rats (N=10) dosed with 45 mg/kg had a significantly reduced body weight from test week 5 onwards (-8%). Both sexes showed increased absolute (significant in female rats only) and relative liver weights. However, neither macroscopical nor histopathological changes were found in the liver.

13 week suppl.	Males (mg/kg/day)		Females (mg/kg/day)	
	15	45	15	45
Cmax (ng/ml)	53.5	86.7	8.31	32.0
AUC0-24hr (ng·hr/ml)	153	350	65.8	241

Studies in dogs:

12357/99. Escalating doses of 1, 3, 10 and 30 mg/kg fesoterodine were administered to 1 beagle dog per sex (oral wafer capsules for 3 days each dose, separated by a 3-day wash-out phase). One dog per sex was given 18 mg/kg daily for 1 week. The NOEL was 3 mg/kg during the MTD phase; 30 mg/kg was within the lethal range. At 10 mg/kg fesoterodine, hematological and chemical changes were observed. At 30 mg/kg, slight ataxia, reduced motility, severe conjunctivitis and a pale gingiva were observed in the male dog (sacrificed after the 3rd administration). No substance related pathology was observed. Body weight and food consumption of both dogs were decreased at 30 mg/kg. The male dog showed increased erythrocytes, leucocytes, hemoglobin, hematocrit, platelets, bilirubin, triglycerides, inorganic phosphate, ALAT and LDH; reticulocytes were decreased after the 3-day treatment with 30 mg/kg. Changes observed in the female dog at 30 mg/kg included increased triglyceride and inorganic phosphate values and reduced reticulocyte counts. After 7 days with 18 mg/kg, the body weights and food intake (female) were slightly decreased.

b(4)

15409/02. Beagle dogs (2/ sex) were treated for 14 days with 0, 8, or 32 mg/kg fesoterodine (sustained release tablets/gelatin capsules). Mydriasis and conjunctivitis were observed at 5 days. Food consumption was reduced in males at 8 mg/kg and in females at 32 mg/kg. Body weights were reduced in both treated groups on days 8 and 15 (up to 8% and 18% at 8 and 32 mg/kg, respectively). SPM 7605 was administered at 1.5 or 6 mg/kg/day (in 0.9% NaCl, 24 hour infusion) for 14 days. Mydriasis, conjunctivitis, decreased food consumption and body weight were observed in both groups. b(4)

15540/02. In a 3 day study in Beagle dogs (iv, 4 hour infusion, 1/sex/dose) 1, 5 and 10 mg/kg fesoterodine were administered. The NOEL was 1 mg/kg. No signs of local intolerance or mortality were observed. At 5 mg/kg, reduced motility, mydriasis, increased leucocytes and platelets were observed. At 10 mg/kg, reduced food consumption and body weight (up to 15%) were observed. b(4)

15541/02. In a 2 week study in Beagle dogs (iv, 4 hour administration, 2/sex/group) doses of 0, 0.6, 2 and 6 mg/kg fesoterodine were administered. An additional 2 animals per sex for the control and high dose groups were assigned to a 2-week recovery period. The NOAEL was 2 mg/kg. No signs of local intolerance or mortality were observed. Mydriasis, slight conjunctivitis and slight salivation were observed in the high dose group. No signs were observed at the end of the recovery period. At 6 mg/kg body weight was slightly reduced and food consumption was reduced up to 47%. Heart rate was increased in all dose groups on test days 1, 2 and 13 at 15 minutes after dosing but subsided after 24 hours. ECG and blood pressure were not affected. Severe mydriasis was observed in all treated animals b(4)

Study title: 9-Month chronic toxicity study of SPM 8272 by oral administration to Beagle dogs

Study no: 13349/000 and SPT 19381/05 (supplemental histopathological examination of the retina of the left eye of all animals)
Conducting laboratory and location: b(4)

Date of study initiation: 15 August 2000
GLP compliance: yes
QA report: yes (x) no ( )
Drug: batch # AC 8340/1, WE No. SPM 11386, % pure
Formulation/vehicle: gelatin capsule
Dosing:
- Species/strain: Beagle dog
- #/sex/group: 5 + 2 /sex/group for 4 week recovery period
- Age: 8-9 months
- Weight: 5.7-8.2 (males) and 4.8-6.6 (females)
- Doses in administered units: 0, 0.5, 2.5, 12.5 mg/kg/day
- Route: oral capsule

Results:
- Mortality: No premature deaths occurred

Clinical signs: Conjunctivitis, occasionally accompanied by adhesions of the eyelid, was observed in all high dose animals (see Opthalmology).

Body weights: Body weights were significantly lower in high dose males weeks 31-39.

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Day 274/275 (at end of treatment autopsy)(kg)	8.20	7.72	7.26	6.34	6.16	6.58	6.04	5.84
Day 302 (following recovery)	7.90	8.10	8.40	8.40	6.70	6.50	6.15	5.55

Food consumption: A transient decrease in food consumption in high dose animals was noted during weeks 1-4.

Ophthalmoscopy: Conjunctivitis, occasionally accompanied by adhesions of the eyelid, was observed in all high dose animals. This was considered to be due to a pharmacologically induced decrease in lacrimal secretion and was eliminated by daily treatment with artificial lacrimal fluid. A supplemental histopathological examination of the retina of the left eye of all animals was performed. No treatment related changes were observed in any of the layers of the retina (retinal pigment epithelium, photoreceptors, outer nuclear layer, inner nuclear layer, inner plexiform layer, and ganglion cell layer) examined in 8 H.&E.-stained paraffin sections per animal.

Electrocardiography:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Heart rate (beats/min.)								
__Day 1, 0 hours	108.4	103.1	91.0	92.6	97.1	100.9	82.9	82.6
__Day 1, 4 hours	108.1	109.3	108.6	162.4	86.9	111.7	148.4*	176.9*
Heart rate (beats/min.)								
__Week 13, 0 hours	88.1	86.3	89.4	97.1	84.0	91.0	89.3	102.7*
__Week 13, 4 hours	87.7	85.4	117.4	119.4*	83.0	86.6	105.9*	134.1*
Heart rate (beats/min.)								
__Week 26, 0 hours	89.7	94.7	95.3	90.7	81.4	83.3	84.9	98.0
__Week 26, 4 hours	82.7	87.3	157.0*	125.7*	81.0	89.7	115.1	131.1*
Heart rate (beats/min.)								
__Week 39, 0 hours	92.0	75.7	82.1	99.3	77.0	89.1	91.9	112.0*
__Week 39, 4 hours	98.4	88.1	84.6	110.4	75.4	91.6	101.1	128.7*
QT interval (msec)								
__Day 1, 0 hours	248.0	251.7	248.6	230.9	243.1	236.0	235.7	224.9
__Day 1, 4 hours	237.1	244.9	240.3	228.6	236.0	241.1	222.9	209.4
QT interval (msec)								
__Week 13, 0 hours	230.9	236.3	242.0	248.0	224.3	232.6	231.4	254.0
__Week 13, 4 hours	253.1	237.7	236.3	240.0	241.7	242.6	218.9	220.0
QT interval (msec)								
__Week 26, 0 hours	232.9	233.1	244.6	247.4	228.0	230.9	232.0	215.1
__Week 26, 4 hours	238.9	243.1	218.9	220.3	231.4	237.7	220.0	212.9
QT interval (msec)								
__Week 39, 0 hours	223.4	228.9	249.1	212.0	231.1	234.3	233.4	217.4
__Week 39, 4 hours	236.9	237.7	236.0	232.3	230.6	234.3	216.9	216.0
QTc value (Fred. formula)(msec)								
__Day 1, 0 hours	300.3	300.1	283.9	266.2	283.6	280.0	261.4	249.7
__Day 1, 4 hours	287.9	296.6	292.0	312.9	266.8	291.9	301.7	299.9

QTc value (Fred. formula)(msec)								
__Week 13, 0 hours	262.1	266.3	275.8	289.4	251.0	266.2	264.1	301.7
__Week 13, 4 hours	286.2	266.9	293.8	301.2	269.3	271.8	263.7	287.4
QTc value (Fred. formula)(msec)								
__Week 26, 0 hours	265.5	270.5	284.7	282.3	251.0	255.0	259.6	252.8
__Week 26, 4 hours	265.8	274.4	300.2	280.9	254.7	269.7	270.6	275.5
QTc value (Fred. formula)(msec)								
__Week 39, 0 hours	255.0	245.0	276.1	249.2	250.9	265.9	268.3	267.2
__Week 39, 4 hours	278.2	268.6	263.2	285.0	249.1	268.7	256.2	278.3
QTc value (van de Water)(msec)								
__Day 1, 0 hours	285.1	286.6	276.3	259.6	273.3	269.5	257.8	247.8
__Day 1, 4 hours	273.3	281.2	277.9	280.3	262.5	276.4	274.0	266.6
QTc value (van de Water)(msec)								
__Week 13, 0 hours	256.9	262.1	270.0	277.7	248.8	260.6	259.8	289.7
__Week 13, 4 hours	278.5	262.8	276.1	282.1	265.2	266.8	255.6	267.5
QTc value (van de Water)(msec)								
__Week 26, 0 hours	261.1	263.9	273.0	274.7	248.2	252.0	256.3	247.0
__Week 26, 4 hours	261.4	268.3	271.4	264.4	252.2	261.9	259.5	263.5
QTc value (van de Water)(msec)								
__Week 39, 0 hours	251.5	241.4	271.7	244.3	247.2	259.2	261.3	256.9
__Week 39, 4 hours	269.7	259.5	257.9	271.6	246.7	262.4	149.0	262.1
Peripheral arterial systolic BP (mmHg)								
__Day 1, 0 hours	140.3	141.1	160.4*	149.0	141.9	137.1	134.6	118.9*
__Day 1, 4 hours	126.6	130.9	135.6	125.7	118.9	100.3	111.6	71.4*
Peripheral arterial systolic BP (mmHg)								
__Week 13, 0 hours	134.0	138.0	146.6	152.6	156.9	147.3	140.9	148.9
__Week 13, 4 hours	127.1	145.6	162.3*	166.0*	143.9	160.0	146.4	143.0
Peripheral arterial systolic BP (mmHg)								
__Week 26, 0 hours	130.4	134.1	141.0	149.3	126.0	124.3	144.9	148.9
__Week 26, 4 hours	116.9	120.4	119.3	134.6	116.0	123.3	131.0	124.6
Peripheral arterial systolic BP (mmHg)								
__Week 39, 0 hours	132.4	135.0	144.0	162.0	152.3	163.7	163.9	156.0
__Week 39, 4 hours	162.4	173.6	174.0	180.0*	157.6	163.0	159.0	160.0

Hematology:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Platelets (x10^9/l blood)								
__week 39	300.1	350.0	285.3	407.4	336.0	357.1	362.0	367.6
__week 43	285.5	295.5	341.0	344.0	337.5	370.5	335.5	346.0

Clinical chemistry:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Urea								
__week 13	3.76	3.60	3.99	5.59*	4.75	4.77	4.77	5.19
__week 26	4.04	4.08	4.49	4.68	4.00	4.42	4.35	5.35
__week 39	4.33	4.52	4.39	5.32	4.67	5.21	4.98	5.52
__week 43	3.10	2.82	3.68	2.87	4.00	4.77	4.34	4.39
Bile acids (µmol/l serum)								
__week 13	5.73	5.71	5.77	7.30	5.90	5.83	5.76	11.30
__week 26	9.33	11.47	14.77	10.11	9.47	10.51	9.30	11.49
__week 39	6.29	7.01	6.59	10.37	6.46	6.97	5.96	10.69
__week 43	2.10	1.20	2.85	1.95	3.50	2.30	2.20	3.75

Glucose (mmol/l serum)								
__week 13	5.54	5.48	5.53	5.71	5.71	5.43	5.66	5.24
__week 26	5.20	5.20	5.25	5.10	5.06	4.97	4.99	4.75
__week 39	5.39	5.06	5.50	4.77	5.00	5.20	4.81	4.80
__week 43	6.33	6.26	6.16	5.48	6.13	6.16	5.83	5.09
Creatinine (µmol/l serum)								
__week 13	50.9	52.4	50.3	46.0	54.1	54.4	50.9	45.7*
__week 26	55.1	56.0	53.3	47.7*	54.9	61.0	51.0	45.4*
__week 39	53.6	54.3	53.6	45.6	53.1	57.9	51.6	46.4
__week 43	42.5	41.5	47.0	49.5	43.5	52.0	42.0	46.0
Chloride (mmol/l serum)								
__week 13	107.3	107.4	107.1	106.0	108.1	107.4	108.0	109.0
__week 26	109.0	109.1	108.4	106.9	108.9	108.7	107.9	107.3
__week 39	110.7	110.3	110.3	108.3*	109.7	109.6	109.4	109.4
__week 43	109.0	109.0	109.0	110.0	109.0	109.0	108.5	109.0
Alkaline phosphatase (U/l plasma)								
__week 13	195.0	186.1	155.9	141.4	161.3	197.1	160.9	146.0
__week 26	150.6	144.9	127.7	116.9	146.7	170.3	139.7	129.7
__week 39	128.4	135.4	115.0	103.1	123.0	165.6	129.3	121.7
__week 43	137.5	147.0	161.0	210.0	143.5	203.5	192.5	130.0
Albumin/globulin ratio								
__week 13	1.1	1.2	1.3*	1.3*	1.3	1.3	1.3	1.3
__week 26	1.2	1.2	1.3	1.2	1.3	1.3	1.4	1.2
__week 39	1.4	1.3	1.4	1.1	1.3	1.4	1.5	1.3
__week 43	1.3	1.0	1.2	1.0	1.1	1.4	1.3	1.1
α2-globulin, week 39 (g/l serum)	5.2	5.4	5.4	6.6*	4.7	4.9	4.8	5.1
γ-globulin, week 39 (g/l serum)	5.5	5.7	5.5	7.5	5.6	5.6	4.2	5.3

Urinalysis: No treatment related changes were observed.

Organ weights: No treatment related changes were observed.

Gross pathology:

N=7	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Conjunctivae, reddened w/swelling	0	0	0	2	0	0	0	2
Gall bladder, tightly filled	0	0	1	1	0	0	1	5

Histopathology: No treatment related changes were observed.

Toxicokinetics: (9 months)

SPM 8272	Males (mg/kg/day)			Females (mg/kg/day)		
	0.5	2.5	12.5	0.5	2.5	12.5
C_{max} (ng/ml)	1.24	3.27	90.5	0.67	4.96	184
C_{max} range	0.37-2.35	1.26-4.59	7.53-508	0.27-1.39	2.73-38.8	26.0-695
T_{max} (hr)	1	1	1	1	1	1
$AUC_{0\text{-}24hr}$ (ng·hr/ml)	1.69	5.73	226	0.96	23.3	604
AUC range	0.37-3.01	1.71-9.40	37.4-1012	0.27-6.70	6.65-80.9	51.2-851

SPM 7605	Males (mg/kg/day)			Females (mg/kg/day)		
	0.5	2.5	12.5	0.5	2.5	12.5

C_{max} (ng/ml)	2.65	54.2	763	1.79	36.0	674
C_{max} range	1.59-3.27	24.9-108	558-876	0.72-3.78	9.25-105	246-1739
T_{max} (hr)	1	1	2	1	2	1
$AUC_{0\text{-}24hr}$ (ng·hr/ml)	5.43	114	3484	3.05	92.9	2679
AUC range	4.15-6.78	107-237	1907-4118	1.60-6.42	75.0-267	2040-5386

Summary of individual study findings:

In the mid and high dose group, pharmacological toxicity was observed. Effects included decreases in gall bladder contractility and increases in heart rate. Mydriasis was observed in the high dose group.

Effects on QT interval: While C_{max} occurred at 1-2 hours following dosing, cardiac parameters were measured at 0 and 4 hours following dosing. A wide variability in blood levels of the SPM 7605 metabolite was observed at these time points, and while statistically significant differences in adjusted QT interval were not calculated, some trends toward an increase in adjusted QT interval were observed. In a safety pharmacology study, following iv dosing, increases in QT interval and adjusted QT interval were observed at lower measured blood levels than in this study.

No treatment related histopathological changes were observed at any dose.

Doses in this study, using either C_{max} or AUC of SPM 7605 as a basis for comparison, are at least double the highest expected clinical exposure in the mid dose group and 20 times in the high dose group. Dogs, unlike humans, also exhibit measurable blood levels of the parent compound SPM 8272. A clinical QT study was conducted.

Toxicology summary/conclusions: Exaggerated pharmacological effects were the primary limiting toxicity for both mice and dogs. No treatment related histopathological changes were observed after 6 months in mice or after 9 months of treatment in dogs.

Although a clearly defined effect on QT prolongation was not observed in dogs administered oral fesoterodine, effects were observed in dogs exposed intravenously to greater than 10 times the expected clinical exposure (see Safety Pharmacology section.).

Study title: 13-week subchronic toxicity study of SPM 8272 by oral administration to Beagle dogs (two week interim dissection and a 4 week recovery period)

Key study findings: A NOEL of 0.5 mg/kg/day and a NOAEL of 2.5 mg/kg/day were determined (dose ranging study).

Study no.: 12358/99
Conducting laboratory and location: [redacted]
GLP compliance: yes
QA report: yes (x) no ( )

b(4)

Methods

Doses: 0, 0.5, 2.5 or 10 mg/kg/day
Species/strain: Beagle dog
Number/sex/group or time point (main study): 5/sex/group
Route, formulation, volume, and infusion rate: oral, gelatin capsules
Satellite groups used for toxicokinetics or recovery: 2/sex/group for recovery and 2/sex/group for an interim dissection

Results

Mortality/ Clinical signs: No mortality and no clinical signs were observed at any dose.

EKG: Heart rate was increased at 2.5 and 10 mg/kg on test day 1 and in test weeks 2 and 6, for at least 6 hours post-dose. At 13 weeks, the effect was reversed (females in the high dose group still showed a significant effect 2 hours post-dose). No substance-related effects on the EKG were observed.

Hematology: Transient increases in platelet counts (up to 63%) in males at 2.5 and 10 mg/kg and leukocytes (36%) in both sexes at 10 mg/kg were observed.

Clinical chemistry: ALAT, ASAT and LDH were transiently increased in week 2 in the high dose group males. Urea levels were slightly increased in both sexes throughout the main study (up to 38%, not significant).

Histopathology: No treatment related effects were observed.

Study title: 13-week subchronic toxicity study of SPM 7605 by 24-hr continuous i.v. infusion to Beagle dogs

Key study findings: In high dose animals following 13 week of continuous iv administration, at approximately 21-30 times the expected clinical exposure via AUC and approximately 12-19 times via Cmax, bladder hemorrhage was observed in 1/6 females and 3/6 males, accompanied by signs of inflammation. No histopathology was observed

after oral exposures reaching 39 times the average clinical AUC or nearly 100 times the clinical Cmax for 9 months.

Study no.: 16842/1/03
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 02 February 2004
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: 0.005% SPM 7605: 20311019 (from 09 Feb to 27 Mar 2004) 20311020 (from 28 Mar to 10 May 2004), 0.015% SPM 7605: 20311033 (from 09 Feb to 06 Apr 2004) 20311034 (from 07 Apr to 10 May 2004), 0.045% SPM 7605: 20311041 (from 09 Feb to 11 Mar 2004) 20311042 (from 12 Mar to 09 Apr 2004) 20312007 (from 10 Apr to 08 May 2004) 20312006 (from 09 May to 10 May 2004), 99.81-99.91 % pure

Methods

Doses: 0, 0.005, 0.015 and 0.045% solutions of SPM 7605 (0, 0.5, 1.5, and 4.5 mg/kg/day), based on the results of a 2-week dog i.v. study which showed reduced food consumption, body weight, and lacrimation at 1.5 and 6 mg/kg/day after 14 days administration.

Species/strain: Beagle dog

Number/sex/group or time point: 4 + 2 for recovery in groups 1 and 4

Route, formulation, volume, and infusion rate: continuous i.v. (24 hours per day), via the vena cava caudalis, in 10 ml/kg b.w./24 hours

Age: 7 months

Weight: 6.3-8.5 kg (males) and 5.7-7.6 kg (females)

Unique study design or methodology: The active hydrolysis product of SPM 8272 was instilled directly to insure adequate exposure.

Results

Mortality: None was observed. All dogs exhibited injection site erythema and edema.

Clinical signs: No drug related effects were observed.

Body weights: A marginal reduction in body weight was observed in male dogs from test week 4 onwards. Slightly decreased body weight (up to 20 %) was observed in mid and high dose females. Decreases in body weight gain were reversed during recovery for both males and females.

Food consumption: No treatment related effects were observed.

Ophthalmoscopy: Fluorescein staining was observed in all treated animals; mydriasis and negative pupillary reflex were observed in all high dose dogs. One female dog in the high dose had a slight clouding of the corneal epithelium. All changes reversed during recovery.

EKG: Changes in heart rate, observed during the treatment period, were reversed during recovery.

Time point	Increase in the heart rate compared with the controls [%]					
	0.5 mg/kg		1.5 mg/kg		4.5 mg/kg	
	males	females	males	females	males	females
TD 1 (3 h p.a.)	none	+34	+30	+40**	+48**	+71**
TD 1 (6 h p.a.)	none	+27	+13	+46**	+26**	+56**
TD 1 (22 h 20 h p.a.)	none	+29	+21	+40**	+37**	+52**

** = statistically significant at $p \leq 0.01$

Increased peripheral arterial systolic (up to 17%) and diastolic (up to 26%) blood pressure were observed in female animals at 4.5 mg/kg/day but reversed during recovery.

Hematology: No treatment related effects were observed.
Clinical chemistry: No treatment related effects were observed.
Urinalysis: No treatment related effects were observed.
Gross pathology: No treatment related effects were observed.
Organ weights: No treatment related effects were observed.

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes ( ), no (x)

	Males (mg/kg/day				Females (mg/kg/day)			
	0	0.5	1.5	4.5	0	0.5	1.5	4.5
Urinary bladder								
__cystitis, lymphocytic						1/4	1/4	
__cystic calculi				1/6				
__lympho-histiocytic infiltration				1/6				
__supperative cystitis				2/6				
__epithelial hyperplasia				1/6		1/4	1/4	
__subepithelial edema			3/4	1/6				
__hemorrhage				3/6				1/6

Toxicokinetics:

Group	Day	Sex	Dose [mg/kg/day]	C_{max} [ng/mL]	C_{av} [ng/mL]	AUC_{24h} [h ng/mL]
2	8	Male	0.5	5.3 ± 0.3	3.9 ± 0.6	93.0 ± 13.8
		Female		4.9 ± 0.3	4.3 ± 0.4	102 ± 9.3
	78	Male		8.2 ± 1.4	6.4 ± 0.7	155 ± 15.8
		Female		8.7 ± 1.2	6.3 ± 1.0	151 ± 23.5
3	8	Male	1.5	20.0 ± 1.5	16.7 ± 1.2	402 ± 28.1
		Female		23.8 ± 3.9	19.4 ± 3.2	466 ± 76.9
	78	Male		34.7 ± 8.1	28.2 ± 4.9	677 ± 117
		Female		30.9 ± 7.9	26.8 ± 7.1	643 ± 171
4	8	Male	4.5	115 ± 54.6	79.2 ± 34.3	1900 ± 824
		Female		88.2 ± 15.3	78.1 ± 15.8	1875 ± 379
	78	Male		121 ± 15.3	105 ± 13.6	2520 ± 328
		Female		130 ± 58.6	110 ± 53.2	2642 ± 1278

Histopathology inventory (optional)

Study	13349	13348	13400	13399
Species	Dog	Mouse	Rat	Mouse
Adrenals	X	X	X	X
Aorta	X	X	X	X
Bone Marrow smear	X	X	X	X
Bone (femur)	X	X	X	X
Brain	X	X	X	X
Cecum	X	X	X	X
Cervix	X	X	X	X
Colon	X	X	X	X
Duodenum	X	X	X	X
Epididymis	X	X	X	X
Esophagus	X		X	X
Eye	X	X	X	X
Fallopian tube	X		X	X
Gall bladder	X	X		X
Gross lesions	X	X	X	X
Harderian gland		X	X	X
Heart	X	X	X	X
Ileum	X	X	X	X
Jejunum	X	X	X	X
Kidneys	X	X	X	X
Lachrymal gland	X		X	X
Larynx	X	X	X	X
Liver	X	X	X	X
Lungs	X	X	X	X
Lymph nodes, cervical	X	X	X	X
Lymph nodes mandibular	X			
Lymph nodes, mesenteric	X	X	X	X
Mammary Gland	X	X	X	X
Optic nerves	X	X	X	X
Ovaries	X	X	X	X
Pancreas	X	X	X	X
Parathyroid	X	X	X	X
Peripheral nerve	X	X	X	X
Pharynx	X	X	X	X
Pituitary	X	X	X	X
Prostate	X	X	X	X
Rectum	X	X	X	X
Salivary gland	X	X	X	X
Sciatic nerve	X	X	X	X
Seminal vesicles	X	X	X	X
Skeletal muscle	X	X	X	X
Skin	X	X	X	X
Spinal cord	X	X	X	X
Spleen	X	X	X	X
Sternum		X	X	X
Stomach	X	X	X	X
Testes	X	X	X	X
Thymus	X	X	X	X
Thyroid	X	X	X	X
Tongue	X	X	X	X
Trachea	X	X	X	X
Urinary bladder	X	X	X	X
Uterus	X	X	X	X
Vagina	X	X	X	X
Zymbal gland		X	X	X

2.6.6.4 Genetic toxicology

Study title: Mutagenicity Study of SPM 8272 in the *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay (*in Vitro*)

Key study findings: SPM 8272 was judged to be negative for mutagenicity under the conditions of this assay.

Study no: 12359/99
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 23 November, 1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #AC-8282, 95.78% pure

Methods:

Cell line: TA 98, TA 100, TA 102, TA 1535, TA 1537, WP2 *uvr*A
Basis of dose selection: Concentrations up to 5000 µg/plate were tested. In both tests, 3160 µg/plate was found to be toxic in all strains with or without metabolic activation. 1000 µg/plate was found to be toxic in WP2 *uvr*A without metabolic activation.
Metabolic activation system: Aroclor 1254-iduced rat liver
Controls:
Vehicle: aqua ad injectabilia
Negative controls: aqua ad injectabilia
Positive controls: without metabolic activation: sodium azide in H_2O (10 µg/plate, TA 1535 and TA 100), 2-nitrofluorene in DMSO (10 µg/plate, TA 98), 9-amino-acridine in ethanol (100 µg/plate, TA 1537), methyl methane sulfonate in DMSO (1300 µg/plate, TA 102 and WP2 *uvr* A) and with metabolic activation: 2-anthracene amide in DMSO (2 µg/plate)
Doses used in definitive study: 31.6, 100, 316, 1000, and 3160 µg/plate
Study design: one plate incorporation and one preincubation assay
Analysis:
No. of replicates: 3 replicates of each concentration per experiment

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected.
Study outcome: No increase in the number of revertants was observed at any concentration of test material, and SPM 8272 was judged to be negative for mutagenicity under the conditions of this assay.

Study title: Mutagenicity study of SPM 8272 in the *Salmonella typhimurium* reverse mutation assay (*in vitro*)-employing mouse S9 mix

Key findings: SPM 8272 was judged to be negative for mutagenicity under the conditions of this assay.

Study no.: 15411/02

Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 16 July 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch no. WE 11809 (RD 7778-1), 96.01% pure

Methods

Strains/species/cell line: TA 98, TA 100, TA 102, TA 1535, TA 1537
Doses used in definitive study: 31.6, 100, 316, 1000, and 3160 µg/plate in the presence of Aroclor 1254-iduced mouse liver S9
Basis of dose selection: The concentrations used were the same as for study 12359/99 (3160 µg/plate was found to be toxic in all strains with or without metabolic activation.)
Negative controls: aqua ad injectabilia
Positive controls: 2-anthracene amide in DMSO (2 µg/plate)(TA 98, TA 102, TA 1537) and cyclophosphamide (1500 µg/plate)(TA 100, TA 1535)
Incubation and sampling times: 48 hours

Results

Study validity: One plate incorporation and one preincubation assay were performed using 3 replicates of each concentration per experiment. Positive and negative controls responded as expected.

Study outcome: No increase in the number of revertants was observed at any concentration of test material, and SPM 8272 was judged to be negative for mutagenicity under the conditions of this assay.

Study title: *In vitro* assessment of the clastogenic activity of SPM 8272 in cultured human peripheral lymphocytes-employing mouse S9 mix

Key findings: SPM 8272 was considered not to be genotoxic under the conditions of this assay.

Study no.: 15412/02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 16 July 2002
GLP compliance: yes

QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch no. WE no. 11809 (RD 7778-1), 94.75% pure by HPLC

Methods

Strains/species/cell line: cultured human peripheral lymphocytes
Doses used in definitive study: 0, 125, 250, 500, 1000, and 2000 µg/ml (2 replicates per concentration, 2 experiments, 100 metaphases examined per culture) for 4 hour treatments in the presence of Aroclor -1254 induced mouse liver S9
Basis of dose selection: The same concentrations were used as in study 12361/99. Toxicity was complete at 2000 µg/ml and slight at 1000 µg/ml.
Negative controls: aqua ad injectibilia
Positive controls: cyclophosphamide (10 and 20 µg/ml)
Incubation and sampling times: 48 hours

Results

Study validity: Positive and negative controls responded as expected.
Study outcome: The mean incidence of chromosomal aberrations (excluding gaps) of the cells treated with SPM 8272 (125 to 500 µg/ml in the 1st experiment, 125 to 1000 µg/ml medium in the 2nd experiment) in the presence of metabolic activation ranged from 0.5% to 3.0% (within the normal range of the negative control where a mean incidence of chromosomal aberrations (excluding gaps) of 1.5% or 0.5% was observed. SPM 8272 was considered not to be genotoxic under the conditions of this assay.

Study title: *In Vitro* Assessment of the Clastogenic Activity of SPM 8272 in V79 Cells

Key study findings: It was concluded that SPM 8282 was not genotoxic under the conditions of this study.

Study no: 12360/99
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 24 January, 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #AC-8282, 95.22% pure

Methods:
Strains/species/cell line: V79 Chinese hamster lung fibroblasts
Dose selection criteria:
Basis of dose selection: In range finding studies, cytotoxicity was observed at 1000 ug/ml in the absence of metabolic activation (20 hour exposure) and at 5000 ug/ml in the presence of metabolic activation (4 hour exposure).

Metabolic activation system: Aroclor -1254 induced rat liver S9
Controls:
Vehicle: DMEM-FCS
Negative controls: DMEM-FCS
Positive controls: Mitomycin C, cyclophosphamide
Exposure conditions:
Incubation and sampling times: 4 hour (+ S9) and 20 hour (- S9) exposures with 20 hour sampling times
Doses used in definitive study: 0, 156.25, 312.5, 625, 1250, 2500 µg/ml for 4hours and 0, 31.25, 62.5, 125, 250, 500 µg/ml for 20 hours

Analysis:
No. of replicates: duplicates for each condition in two separate assays, 200 metaphases counted except where conditions were profoundly cytotoxic

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected.
Study outcome: The mean incidence of chromosomal aberrations (excluding gaps) was not elevated in cells treated with SPM 8272 over the incidence in control cells except in cultures treated with profoundly toxic 250 µg/ml (20 hours)(mitotic index 0.19). SPM 8272 was therefore considered not to be genotoxic under the conditions of this study.

Study title: In Vitro Assessment of the Clastogenic Activity of SPM 8272 in Cultured Human Peripheral Lymphocytes

Key study findings: It was concluded that SPM 8282 was not genotoxic under the conditions of this study.

Study no: 12361/99
Conducting laboratory and location: [redacted] b(4)
Date of study initiation: 24 January 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #AC-8282, WE no.SPM 10948, 95.22 % pure
Methods:
Strains/species/cell line: human lymphocyte cultures
Dose selection criteria:
Basis of dose selection: Cytotoxicity was observed at 2500 ug/ml and above in the absence or presence of metabolic activation (4 hour exposure)
Metabolic activation system: aroclor 1254-induced rat liver S9
Controls:
Vehicle: treatment medium
Negative controls: treatment medium
Positive controls: mitomycin C in the absence of metabolic activation and cyclophosphamide in the presence of metabolic activation

Exposure conditions:
Incubation and sampling times: 4 hour treatment with 24 hour sampling time and continuous 24 hour treatment with 24 hour sampling time
Doses used in definitive study: 0, 125, 250, 500, 1000, and 2000 ug/ml for 4 hour and 24 hour treatments
Study design: 4 hour treatments were in the absence and presence of S9; 24 hour treatments were in the absence of S9 only
Analysis:
No. of replicates: duplicate cultures, 100 metaphases per culture where possible

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected.
Study outcome: After 24 hours of exposure, moderate cytotoxicity was observed at 500 ug/ml and complete cytotoxicity was observed at 1000 ug/ml. No increase in chromosomal aberrations were observed following the 24 hour treatment. For the 4 hour treatments in the absence and presence of metabolic activation, cytotoxicity was observed at 1000 ug/ml. At the pronounced cytotoxic concentration of 1000 ug/ml (mitotic index 0.43, 77 evaluable metaphases) in the presence of metabolic activation, the number of chromosomal aberrations was increased to 12.7% (from 2% in controls). SPM 8272 was considered not to be genotoxic under the conditions of this assay.

Study title: Micronucleus Test of SPM 8272 in Bone Marrow Cells of the NMRI Mouse by Oral Administration

Key study findings: It was concluded that SPM 8282 was not genotoxic under the conditions of this study.

Study no: 12362/99
Submission # 001, volume # 34, and page #204
Conducting laboratory and location: b(4)

Date of study initiation: 1 December 1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #AC 8282, 95.78 % pure

Formulation/vehicle: oral aqua ad injectabilia b(4)

Methods:
Strains/species/cell line: NMRI BR mouse
Dose selection criteria:
Basis of dose selection: toxicity (reduced motility, ataxia, dyspnea, and reduced muscle tone) at 215 mg/kg and lethality at 464 mg/kg in earlier study
Controls:

Vehicle: oral aqua ad injectabilia
Positive controls: cyclophosphamide, 27 mg/kg i.p.
Exposure conditions:
Incubation and sampling times: 24 and 48 hour sampling times
Doses used in definitive study: 0, 62.5, 125, and 250 mg/kg, oral
Analysis:
No. of replicates: 5 males and 5 females, 2000 erythrocytes per animal
Summary of individual study findings:
Study validity: Positive and negative controls responded as expected.
Study outcome: No increase in micronucleated polychromatic erythrocytes was observed at any dose. No effect on the ratio of polychromatic to normochromatic erythrocytes was observed. It was concluded that SPM 8282 was not genotoxic under the conditions of this study.

2.6.6.5 Carcinogenicity

Study title: 104-week carcinogenicity study of SPM 8272 by oral administration to CD®-rats

Key study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: A two-year bioassay was conducted in the CD® / CD® rat up to a maximally tolerated dose (FDA concurrence was given to an interim analysis of body weight and mortality after week 53) under GLP conditions. Rats were demonstrated to be exposed to an accurate concentration of the prodrug SPM 8272 and to adequate concentrations of the active drug SPM 7605 and its major human metabolites SPM 5509 and SPM7790. An adequate number of animals survived to perform histopathological examinations and statistical analysis. b(4)

Evaluation of tumor findings: No treatment related increases in the type or incidence of neoplastic and/or hyperplastic lesions were observed.

Study no.: 13400/00 b(4)
Conducting laboratory and location:

Date of study initiation: 21 May 2001
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 8272 (fumarate salt), batch # RD 7778/1,
CAC concurrence:

Methods

Doses: 0, 5 15, and 45/60 mg/kg/day (Doses in the high dose groups were increased from 45 to 60 mg/kg/day at week 28 due to any lack of observable toxicity and were maintained at 60 mg/kg/day for the remaining 76 weeks.)

Basis of dose selection: maximally tolerated dose

Species/strain: rat / CD® / CD®

b(4)

Number/sex/group (main study): 50/sex/group

Route, formulation, volume: oral gavage, in 5 ml/kg water

Frequency of dosing: once daily

Satellite groups used for toxicokinetics or special groups: 10/sex/group

Age: 6 weeks

Weight: 178.1-257.0 g (males) and 141.3 – 192.5 g (females)

Animal housing: individual

Restriction paradigm for dietary restriction studies: NA

Drug stability/homogeneity: Stability tested on 31 March 2004 and found to be 96.02 to 97.23 % (by HPLC, 100% method)

Purity

Water content	**0.27 %**	**2003-PHA-1075**
Chromatographic Purity HPLC Detection wavelength 220 nm	**97.23 %** SPM 7605: 1.34 % SPM 7675: 0.70 %	**2003-PHA-1076**
Optical Purity CCE Detection wavelength 200 nm	**≥ 99.6 %**	**2003-PHA-1009**
Content (C_{51}) HPLC Detection wavelength 220 nm	**95.8 %**	**2003-PHA-1074**

Dual controls employed: no

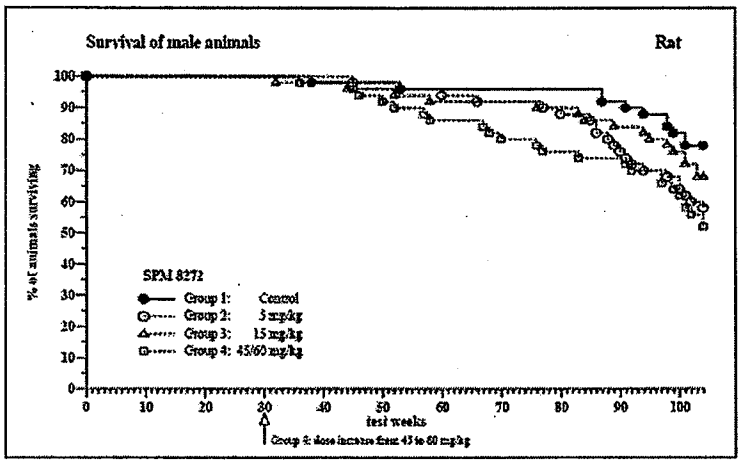
Interim sacrifices: no

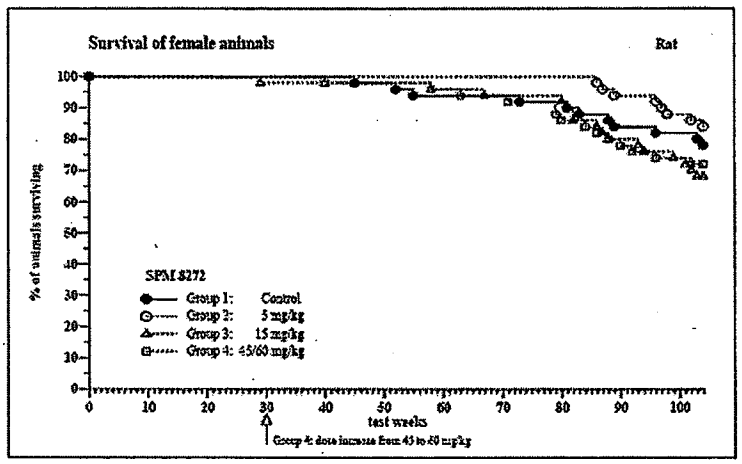
Results

Mortality:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Survival rate at termination (%)	78	58**	68	52**	78	84	68	72
Mean survival time (test weeks)								
Prematurely deceased or sacrificed	86.1	85.1	82.0	78.0	79.0	94.9*	83.3	79.1
All animals	100.8	96.6	97.6	92.1*	99.3	103.4	98.0	97.8

** Significantly different from the control at $p \leq 0.01$ (Fisher test)

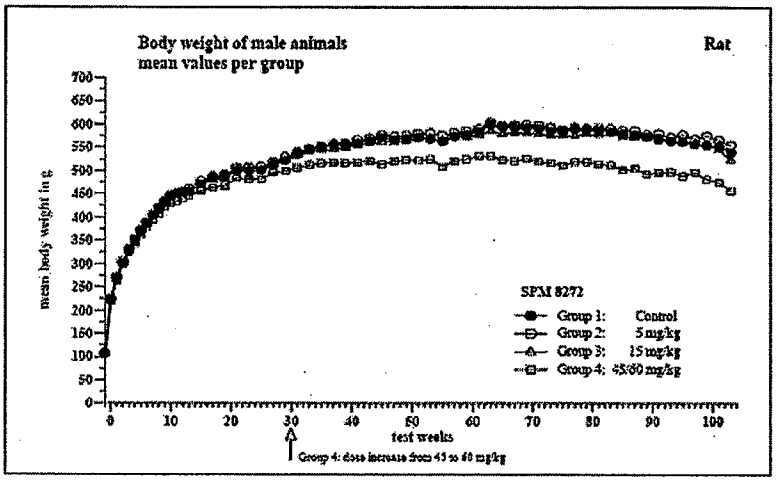


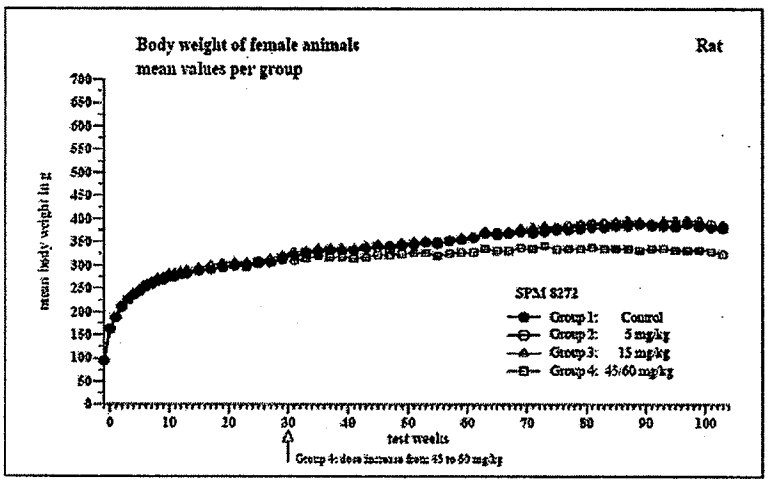


Clinical signs: No treatment related clinical signs were observed.

Body weights: Reduced body weight and body weight gain were observed in the high dose group. Statistical significance was reached in males starting week 17 for males and week 57 for females. Body weight was reduced by 15.4% for males and by 14.3% for females in test week 103.

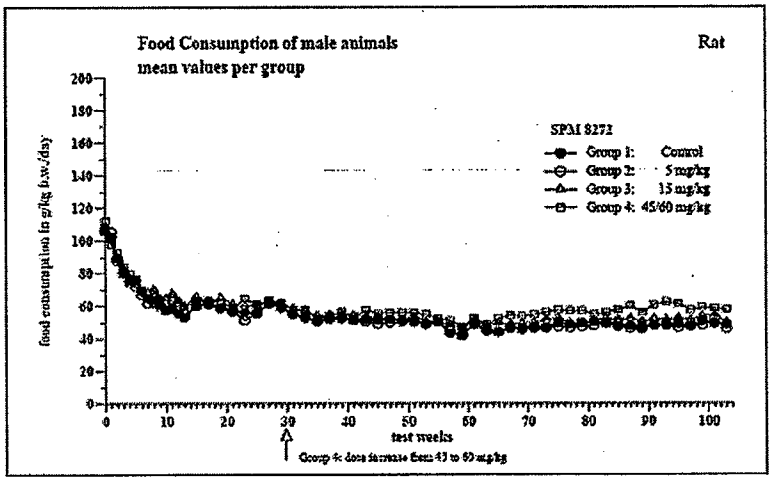
	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Mean body weight (g)								
week 0	222.9	224.8	221.7	220.5	163.7	162.5	164.3	160.9
week 103	540.7	555.9	523.9	457.5	378.7	382.8	386.2	324.4
Body weight (% difference from control at week 103	--	2.8	-3.1	-15.4	--	1.1	2.0	-14.3
Body weight gain (% difference from control)	--	4.2	-4.9	-25.4	--	2.5	3.2	-24.0

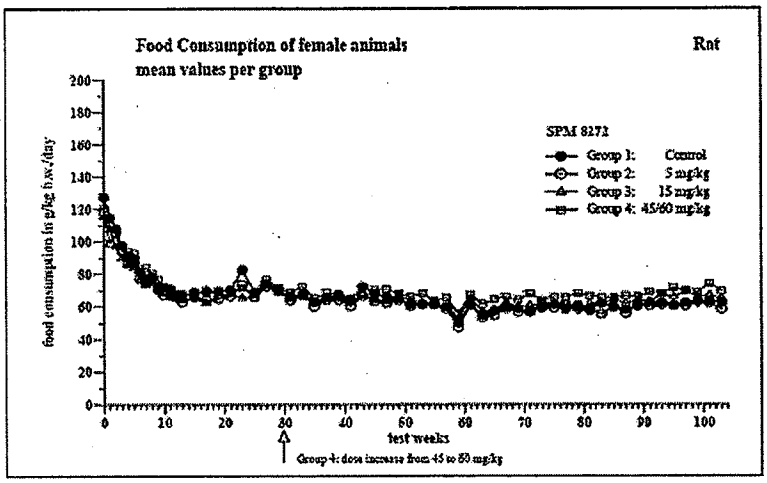




Food consumption:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Mean weekly food consumption (g/kg)	55.92	55.32	59.01	61.44	69.08	66.69	68.01	72.13





Changes in haematological parameters compared to the control group

Parameter	Difference to the control in [%]			
	Group 4: 45/60 mg/kg			
	Test week 52		Test week 104	
	Males	Females	Males	Females
Platelets	+25**	+33**	+25	+57**
MCH	-7	-6	-7**	none

** = statistically significant at $p \leq 0.01$

Changes in biochemical parameters compared to the control group

Parameter	Difference to the control in [%]							
	Group 3: 15 mg/kg				Group 4: 45/60 mg/kg			
	Test week 52		Test week 104		Test week 52		Test week 104	
	males	females	males	females	males	females	males	females
Cholesterol	+15	+93**	+50	+49	+47	+179**	+106**	+120
Triglycerides	+35	+148	+88	+223	+80	+267**	+141	+323
ALAT	+236**	+82	+88	none	+250**	+47	+129**	+21
aP	+17	+18	+31	none	+68**	+51	+54	+29
ASAT	+215**	+21	+110	none	+184	none	+65	none

** = statistically significant at $p \leq 0.01$

Urinalysis: A slight increase in urine volume was observed in female rats at 15 mg/kg/day and increased urine volume ($p \leq 0.01$) and increased urine pH ($p \leq 0.01$) were observed in female rats at 45/60 mg/kg/day

Gross pathology: No treatment related effects were observed.

Organ	Difference to the control [%]							
	Group 3: 15 mg/kg				Group 4: 45/60 mg/kg			
	males		females		males		females	
	rel.	abs.	rel.	abs.	rel.	abs.	rel.	abs.
Liver	+11	+8	+13	+20**	+36**	+17**	+44**	+26**
Spleen	none	-5	none	none	-11	-25**	-19	-30**
Prostate	none	-11	-	-	none	-33**	-	-

** = statistically significant at $p \leq 0.01$

Histopathology: Peer review: yes (x), no ( )

Neoplastic: No treatment related effects were observed (see statistical review by Steve Thomson).

Non-neoplastic:

All fates	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
N	50	50	50	50	50	50	50	50
Adrenals								
__Vacuolization, cortex	16	12	17	14	0	2	7	4
__Hyperplasia, cortex, unilat.	9	6	2	7	2	3	8	3
__Hyperplasia, cortex, bilat.	3	4	2	3	0	1	0	0
Mammary glands								
__glandular hyperplasia	0	0	1	2	1	1	1	3
__hyperplasia of mammary gland	1	0	3	1	3	1	4	3
__total	1	0	4	3	4	2	5	6
Pancreas								
__islet cell hyperplasia	3	8	9	7	11	6	8	4
__less secretion	5	8	7	8	9	10	11	13

Lungs								
__interstit.macroph.w/brownish pigmnt	1	2	4	18	4	5	9	20
__alveolar emphysema	0	0	2	5	0	0	1	1
Liver								
__necrosis	2	3	9	2	1	4	10	12
__vacuolization, hepatocytes	2	0	1	0	0	2	4	2
Nasal cavity, purulent rhinitis	3	3	3	9	4	1	4	1
Urinary bladder, not emptied	1	12	10	8	0	2	4	5
Salivary glands, reduced secretory act	5	9	6	10	5	7	16	14
Lacrimal glands								
__reduced secretory activity	10	12	13	17	9	16	27	23
__karyorrhexis	1	1	2	1	1	1	4	5
Heart								
__Fibrosis/Myocard.degen.	10	14	12	16	8	15	13	10
__Vasculitis	0	0	0	1				
__Periarteritis	0	0	0	2				
Epididymides								
__aspermia, unilat.	2	3	3	4				
__aspermia, bilat.	2	3	2	4				
__vacuol., epith. Cells	4	5	1	9				
__basophilic inclusions	0	0	0	4				
Testicle								
__atrophied tubuli, bilat.	6	9	8	13				
__mineralization	0	2	3	2				
__atrophied tubuli, unilat.	3	6	5	2				
__atrophied testis, bilat.	2	1	5	5				
__atrophy of testis, unilat.	0	0	0	4				
__hyperplasia, Leydig cells, unilat.	1	4	5	6				
__hyperplasia, Leydig cells, bilat.	3	1	3	5				
Kidneys								
__chron.progressive nephropathy					26	30	41	35
__hydronephrosis	0	0	0	2	0	0	3	0
Zymbal's gland								
__glandular ecstasia	0	4	0	2	0	1	0	0
__cystic duct ecstasia	0	9	4	3	1	5	6	0
Harderian glands								
__Mixed cell infiltration	0	0	0	3				
__Lympho-histioc.infiltration	9	8	11	15	13	13	15	22

The myeloid / erythroid ratio was not influenced by treatment with 45/60 mg/kg/day.

Toxicokinetics:

Group	Week	Dose of SPM 8272 [mg/kg/day]	Males			Females		
			C_{max} [ng/mL]	t_{max} [h]	AUC_{last} [h ng/mL]	C_{max} [ng/mL]	t_{max} [h]	AUC_{last} [h ng/mL]
2	26	5	6.73	3	68.9	10.32	1	29.5
	52		5.28	1	26.4	4.08	1	17.4
	104		2.26	0.5#	16.8	5.12	0.5#	19.9
3	26	15	14.79	0.5#	77.0	9.61	0.5#	51.8
	52		21.40	1	107.2	11.57	0.5#	66.3
	104		11.06	0.5#	85.9	23.71	1	90.2
4	26	45	74.79	0.5#	326.7	50.27	1	258.5
	52	60	200.90	0.5#	733.0	116.80	0.5#	486.7
	104		340.68	0.5#	1406.3	286.40	0.5#	740.7

#: first time point

Species:	Rat, CD								Rat, CD					
Gender (M/F)/Number of animals:	9 M, 9 F								9 M, 9 F					
Dose (mg/kg/day):	3								15					
Duration of administration:	26 weeks								26 weeks					
Plasma samples derived from study:	LPT 13400/00								LPT 13400/00					
Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790		SPM 7605		SPM 5509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
PK-Parameters:																
C_{max} (nmol/L)	28.0	11.7	28.8	45.1	1.86	1.36	61.6	19.2	41.6	26.2	87.9	98.6	33.6	4.28	340	34.0
T_{max} (h)	42	1	3	0.5	0.75	0.5	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	1
AUC_{last} (h nmol/L)	221	93.0	145	111	0.47	0.34	293	372	206	128	752	484	45.4	8.22	2855	143
Ratio C_{max}	1	1	1.03	2.76	0.06	0.12	2.20	1.65	1	1	3.04	3.86	0.38	0.16	12.6	1.18
Ratio AUC_{last}	1	1	0.69	1.11	0.006	0.01	1.40	0.99	1	1	3.55	2.95	0.22	0.06	10.4	1.01

Species:	Rat, CD							
Gender (M/F)/Number of animals:	9 M, 9 F							
Dose (mg/kg/day):	45							
Duration of administration:	26 weeks							
Plasma samples derived from study:	LPT 13400/00							
Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M	F
PK-Parameters:								
C_{max} (nmol/L)	209	149	524	372	363	28.0	4073	548
T_{max} (h)	0.5	1	0.5	0.5	0.5	1	0.5	0.5
AUC_{last} (h nmol/L)	904	758	2207	1577	973	110	11169	738
Ratio C_{max}	1	1	2.62	1.51	1.77	0.20	14.5	0.76
Ratio AUC_{last}	1	1	1.96	0.18	1.29	0.15	12.4	1.41

Additional information:
Median shm (n=3) are presented
Plasma samples were obtained at 0.5, 1, 3, 6, 12 and 24 hours by staggered sampling, each rat had to be bled two to three times per day
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

Study title: 104-week carcinogenicity study of SPM 8272 by oral administration to CD-1 mice

Key study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: A two-year bioassay in CD-1 ↘ . CD®-1(ICR)BR mice up to a maximally tolerated dose under GLP conditions. FDA concurrence was given to dose reduction in high dose males from 60 to 45 mg/kg/day in week 42 and from 45 to 30 mg/kg/day in week 66. Dosing was reduced to 0 mg/kg/day in week 84, as per CAC instructions, as tabulated in table below. The administration of test item was terminated in the high dose males, in agreement with CAC, and in high dose females and in low dose males after a mortality rate of 60% was reached. Mice were demonstrated to be exposed to an accurate concentration of the prodrug SPM 8272 and to adequate concentrations of the active drug SPM 7605 and its major human metabolites SPM 5509 and SPM7790. An adequate number of animals survived to perform histopathological examinations and statistical analysis.

b(4)

Evaluation of tumor findings: No treatment related increases in the type or incidence of neoplastic and/or hyperplastic lesions were observed.

Study no.: 13399/00
Volume #1, and page #1
Conducting laboratory and location: J [redacted] b(4)

Date of study initiation: 6 June 2001
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: SPM 8272 (fumarate salt), batch # RD 7778/1, 95.8 to 97.23% by HPLC

Purity

Water content	0.27 %	2003-PHA-1075
Chromatographic Purity HPLC [redacted] Detection wavelength 220 nm	97.23 % SPM 7605: 1.54 % SPM 7675: 0.70 %	2003-PHA-1076
Optical Purity CCE [redacted] Detection wavelength 200 nm	≥ 99.6 %ee	2003-PHA-1009
Content (G_{30}) HPLC [redacted] Detection wavelength 220 nm	95.8 %	2003-PHA-1074

CAC concurrence: yes

Methods

Doses: 0, 5, 15, and 45/60 mg/kg/day:

From test week 28 onwards the dose level of the high dose group was increased from 45 to 60 mg/kg/day as the initial high dose of 45 mg/kg/day appeared not to result in a sufficient degree of toxicity (based on body weight?). Due to an increased mortality rate the dose level of the high dose males was reduced gradually to 30 mg/kg/day starting in test week 47. The administration of test item was terminated in the high dose males (in agreement with CAC) and in high dose females and in low dose males after a mortality rate of 60% was reached.

Treatment schedule II (groups with early terminated administration)

Group / sex	SPM 8272 dose in mg/kg b.w./day, p.o.	Time interval of treatment (MS)#
2 m	5	TD 1 - TD 708 (TW 102)
	0	from TD 709 (TW 102) onwards
3 m	15	TD 1 - TD 702 (TW 101)
	0	from TD 703 (TW 101) onwards
4 m	45	TD 1 - TD 189 (TW 27)
	60	TD 190 (TW 28) - TD 327 (TW 47)
	45	TD 328 (TW 47) - TD 475 (TW 68)
	30	TD 476 (TW 68) - TD 584 (TW 84)
	0	from TD 585 (TW 84) onwards
4 f	45	TD 1 - TD 189 (TW 27)
	60	TD 190 (TW28) - TD 721 (TW 103)
	0	from TD 722 (TW 104) onwards

MS: main study
0: no administration
#: due to organisational reasons the satellite animals of the respective dose groups were dosed 1 to 3 further days after termination of treatment in order to conduct blood sampling for toxicokinetics

Basis of dose selection: maximally tolerated dose b(4)
Species/strain: mouse, CD-1 — CD®-1(ICR)BR
Number/sex/group (main study): 50/sex/dose
Route, formulation, volume: oral gavage, 10 ml/kg bw in water
Frequency of dosing: daily
Satellite groups used for toxicokinetics or special groups: 18/sex/dose
Age: 6 weeks
Weight: 22.9-36.0 g (males) and 17.9-27.4 g (females)
Animal housing: individual
Restriction paradigm for dietary restriction studies: NA
Drug stability/homogeneity: 31 March 2004
Purity (HPLC, 100% method): 96.02 %
Assay (HPLC, external standard method):
Dual controls employed: NA
Interim sacrifices: NA
Deviations from original study protocol: see dose schedule above, CAC minutes and amendments in Appendix

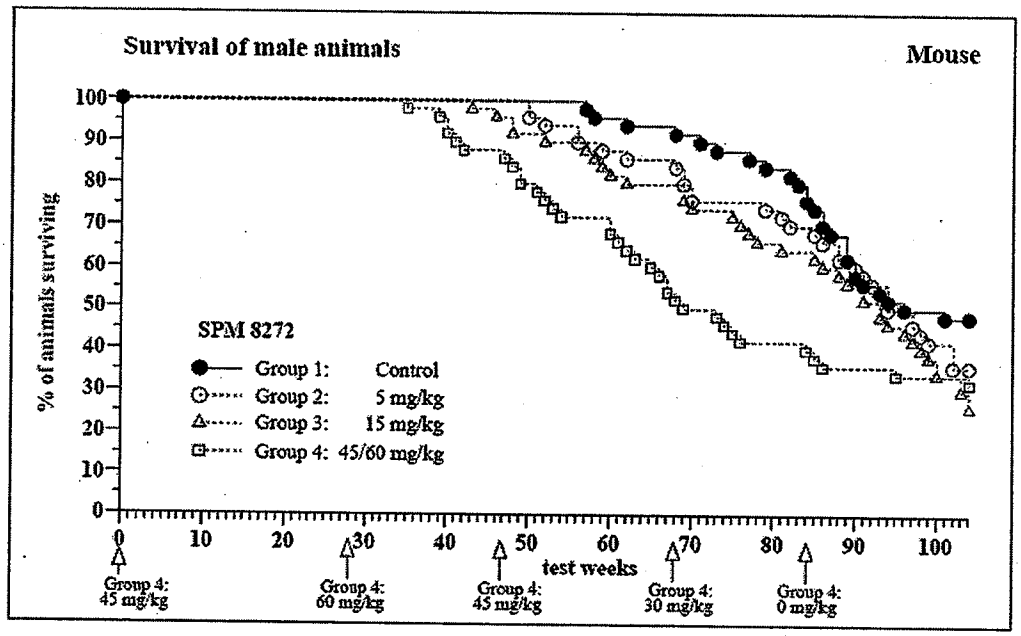
Results

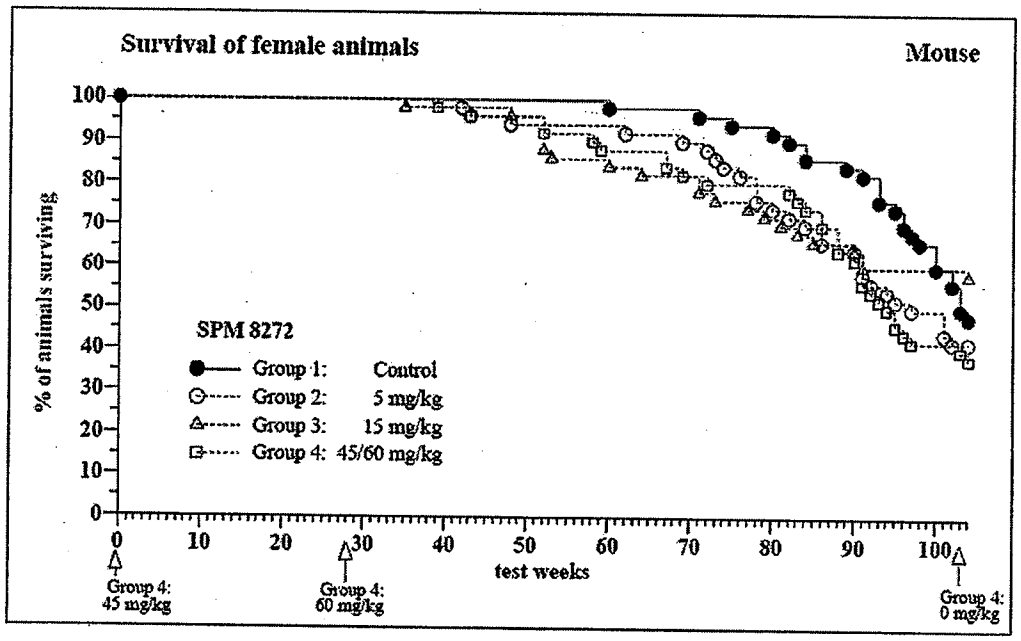
Mortality:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0				0			
Survival # at study termination	24	18	13	16	24	21	29	19
Survival % at study termination	48	36	26**	32**	48	42	58	38
Mean survival time (weeks)								
__all animals	93.3	89.2	86.1	75.6**	98.3	91.2	90.2	89.8
__prematurely deceased animals	82.5	80.4	79.5	61.8**	92.1	81.3	69.7**	80.5

b(4)

Mean study survival (weeks)		background survival data (range, in weeks)	
		N=2 studies, 2003-2004	
males	females	males	females
75.6-93.3	89.8-98.3	76.8-93.7	78.6-91.9

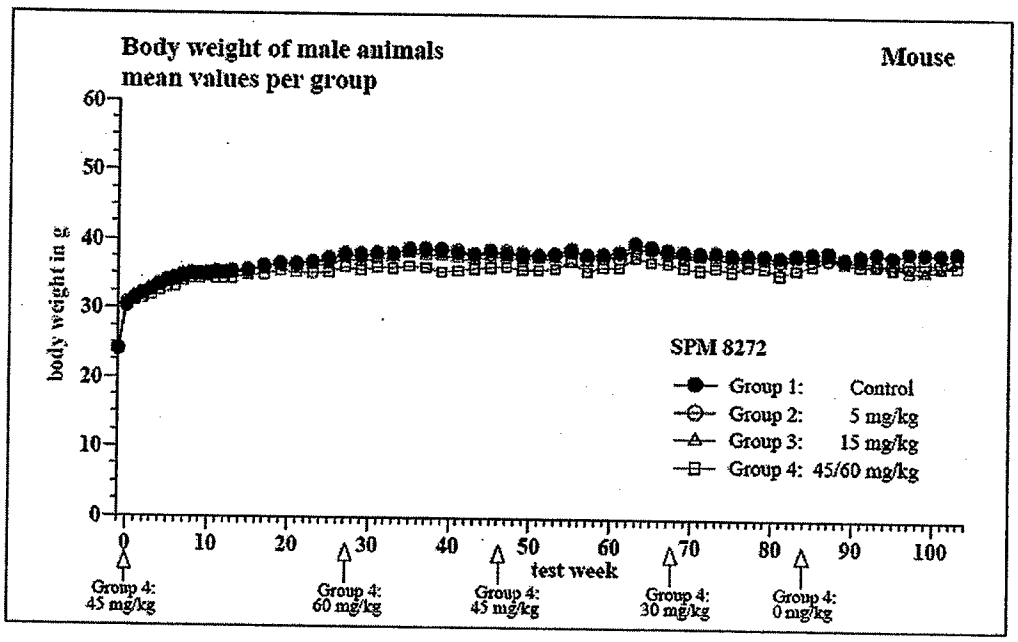


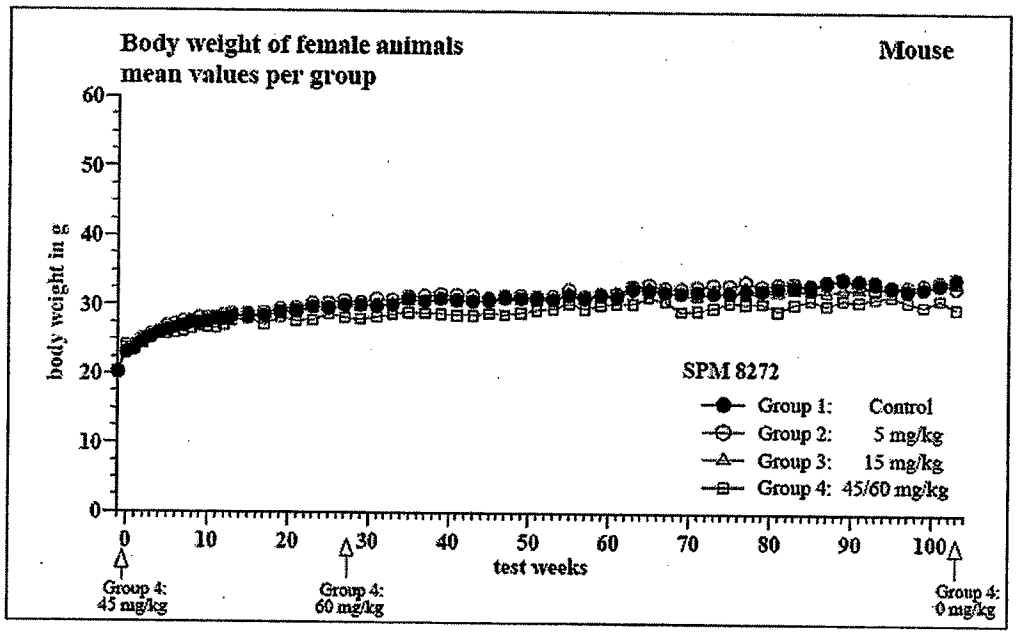


Clinical signs: No treatment- or dose-related effects on behavior or external appearance were observed. No treatment- or dose-related effects on hematology or clinical chemistry were observed.

Body weights:

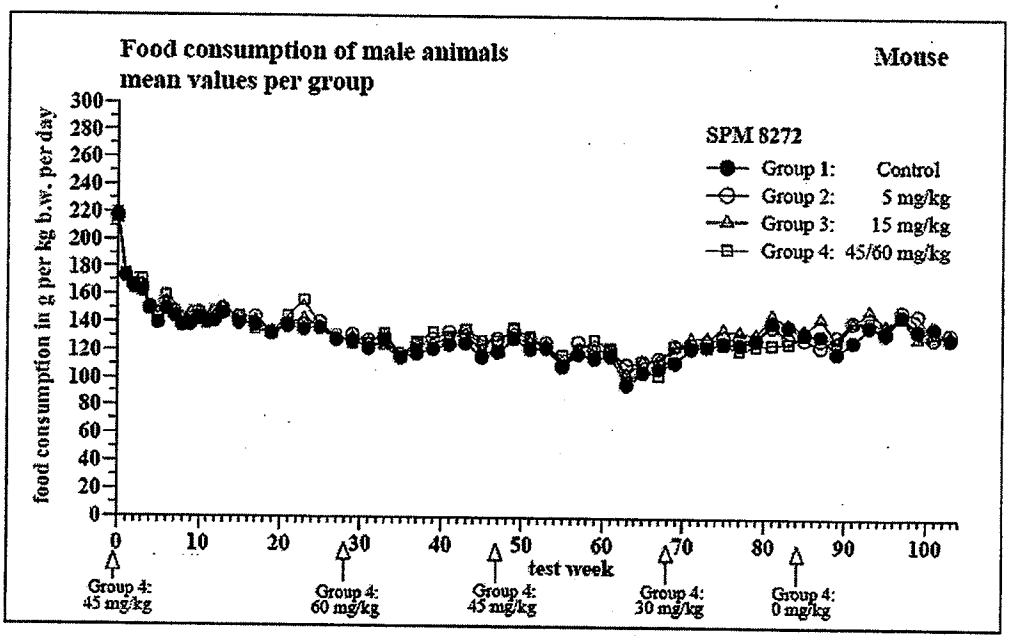
	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Mean body weight (grams)								
__TW 103	38.8	38.3	37.6	36.7	34.1	32.9	33.4	29.8
__TW 0	30.3	30.7	30.7	30.6	23.0	23.9	23.4	23.7
__difference	8.5	7.6	6.9	6.1	11.1	9.0	10.0	6.1
Body weight (% control)	--	-1.3	-3.1	-5.4	--	-3.5	-2.1	-12.6
Body weight gain (% control)	--	-10.6	-18.8	-28.2	--	-18.9	-9.9	-45.0

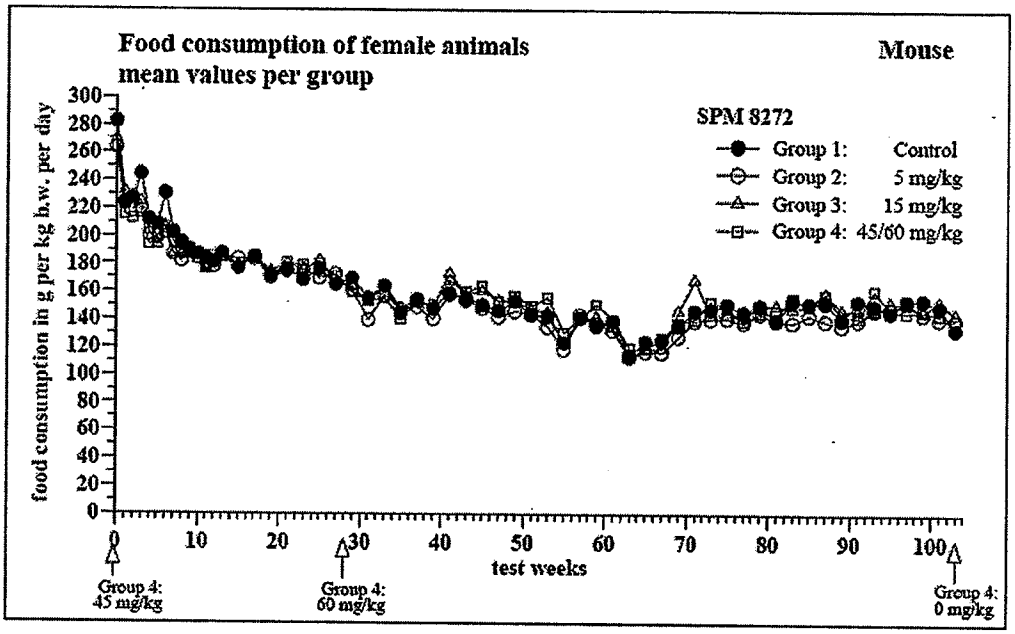




Food consumption:

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/64	0	5	15	45/60
Mean weekly f.c. (g/kg b.w./day)	132.26	136.10	136.07	135.55	164.64	159.02	164.07	163.46





Gross pathology:

N=50	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Tightly filled large intestine	0	4	5	7	0	0	0	6
Tightly filled rectum	0	2	4	10	0	0	0	5

No treatment related absolute or relative changes in organ weight were observed.

Histopathology: Peer review: yes (x), no ( )

Non-neoplastic: females p.1296

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Adrenals								
__hemangioectasia	0	0	0	1	2	0	2	8
Urinary bladder, not emptied	12	10	20	20	2	2	3	5
Ovaries	--	--	--	--				
Colon, dilatation	0	0	2	3				
Rectum, dilatation	0	0	2	4				
Pituitary								
__cyst, adenohypophysis	0	2	0	2				
__hyperplasia, pars distalis	0	0	4	2				
Preputial gland, duct ecstasia	2	3	0	6				
Spleen, atrophy, cell reduction	0	1	2	3				
Kidneys								
__chronic nephropathy	0	3	6	3				
__hydronephrosis	0	2	3	0				
Thyroids								
__follicular cysts, unilat.	7	11	7	13				
__follicular cysts, bilat.	2	4	1	4				
__total	9	15	8	17				

Neoplastic: No treatment related effects were observed (see statistical review by Steve Thomson).

Toxicokinetics:

	Males (mg/kg/day)			Females (mg/kg/day)		
	5	15	30/45/60	5	15	45/60
AUC_{last} (ng·hr/ml)						
__week 26	14.9	96.6	909 (45 mg/kg/day)	21.2	135	1060 (45 mg/kg/day)
__week 52	31.0	149	753 (45 mg/kg/day)	17.8	147	1883 (60 mg/kg/day)
__week77			420 (30 mg/kg/day)			
__week 88			333 (30 mg/kg/day)			
__week 102/104	13.4	99.4		12.5	116	1695 (60 mg/kg/day)
Cmax (ng/ml)						
__week 26	13.1	46.2	483 (45 mg/kg/day)	10.0	125	944 (45 mg/kg/day)
__week 52	15.8	68.3	709 (45 mg/kg/day)	15.5	94.7	1740 (60 mg/kg/day)
__week77			282 (30 mg/kg/day)			
__week 88			216 (30 mg/kg/day)			
__week 102/104	10.4	48.6		10.6	93.7	1740 (60 mg/kg/day)
tmax(hr)						
__week 26	0.5	0.5	0.5	0.5	0.5	0.5
__week 52	0.5	1	0.5	0.5	0.5	0.5
__week 102/104	0.5	0.5		0.5	0.5	0.5

Species:	Mouse, CD-1							Mouse, CD-1					
Gender(M/F)/Number of animals:	15 M, 15 F							12 M, 12 F					
Dose (mg/kg/day):	15							25					
Duration of administration:	26 weeks							26 weeks					
Plasma samples derived from study:	LPT 13359/00							LPT 13348/00					
Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790	SPM 7605		SPM 5509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M F	M	F	M	F	M	F	M	F
PK-Parameters:															
C_{max} (nmol/L)	135	366	163	276	23.7	52.9	127 312	422	753	245	390	60.3	122	235	538
T_{max} (h)	0.5	0.5	0.5	0.5	0.5	0.5	0.5 0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
AUC_{last} (h·nmol/L)	283	397	450	504	69.8	91.5	402 667	847	1402	606	913	184	278	928	1228
Ratio C_{max}	1	1	1.20	0.75	0.18	0.14	0.94 0.85	1	1	0.58	0.52	0.14	0.16	0.56	0.71
Ratio AUC_{last}	1	1	1.59	1.27	0.25	0.23	1.42 1.68	1	1	0.71	0.65	0.22	0.20	1.10	1.09

Species:	Mouse, CD-1							Mouse, CD-1					
Gender(M/F)/Number of animals:	15 M, 15 F							12 M, 12 F					
Dose (mg/kg/day):	45							100 (M) / 125 (F)					
Duration of administration:	26 weeks							26 weeks					
Plasma samples derived from study:	LPT 13359/00							LPT 13348/00					
Analytes:	SPM 7605		SPM 5509		SPM 7789		SPM 7790	SPM 7605		SPM 5509		SPM 7789		SPM 7790	
	M	F	M	F	M	F	M F	M	F	M	F	M	F	M	F
PK-Parameters:															
C_{max} (nmol/L)	1414	2764	580	473	304	466	719 939	4890	8697	565	571	817	1137	1135	1695
T_{max} (h)	0.5	0.5	0.5	1	0.5	0.5	0.5 1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	2
AUC_{last} (h·nmol/L)	2661	3104	1392	1412	600	750	1812 3144	11344	24978	2633	3092	2325	5348	6218	19922
Ratio C_{max}	1	1	0.41	0.17	0.22	0.17	0.51 0.34	1	1	0.12	0.07	0.17	0.13	0.24	0.18
Ratio AUC_{last}	1	1	0.52	0.45	0.23	0.24	0.68 1.01	1	1	0.23	0.13	0.21	0.22	0.56	0.76

Additional information:
Pooled plasma samples (n=3 animals/sex/time) were obtained at 0.5, 2, 6 and 24 hours (LPT 13348/00) or at 0.5, 1, 2, 4, 6 and 12 hours (LPT 13359/00)
SPM 7605 = hydroxy metabolite, SPM 5509 = carboxy metabolite, SPM 7789 = N-desisopropyl metabolite, SPM 7790 = carboxy-N-desisopropyl metabolite

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Examination of the influence of SPM 8272 on the fertility and early embryonic development to implantation of CD-1 mice by oral administration to the animals of the F0 generation

Key findings: At 45 mg/kg/day, no effect on male fertility or the male reproductive system was observed. In females, numbers of corpora lutea, implantation sites, live

fetuses, and uterine weight were decreased at this dose. At 15 mg/kg/day (about 0.7 -1.6 fold the maximum expected clinical exposure), no effects on female fertility, the female reproductive system, or early embryonic development were observed.

Study no.: 12981/00
Conducting laboratory and location: b(4)

Date of study initiation: 27 March 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot # AC 8288, WE 10964, IB 0712, 95.84% pure
Formulation/vehicle: aqua ad injectabilia

Methods:

Species/strain: CD-1/ CD®-1(ICR)BR mice b(4)
Doses employed: 0, 15, 45, and 75 mg/kg/day
Route of administration: oral, gavage, 10 ml/kg
Study design: Males were dosed daily from 10 weeks before mating to the end of the mating period; females were dosed daily from 2 weeks before mating to the 7th day of pregnancy. Untreated animals were used to test male and female fertility separately in separate segments of the study.
Number/sex/group: 20/group + 6/group for toxicokinetics

Results:

Mortality: One female in the high dose group died due to an application error.
Clinical signs: No treatment related effects were observed.
Body weight: The body weight of females in the 45 mg/kg/day group was reduced from gestation day 3 forward. The reduction was attributed to the lower mean number of fetuses in the high dose group.
Food consumption: No treatment related effects were observed.
Toxicokinetics:

	5 mg/kg/day	15 mg/kg/day	45 mg/kg/day
$C_{0.5}$, males			
day 1	7.62-8.62	57.6-48.9	313-414
day 71	19.5-28.3	179-187	605-929
$C_{0.5}$, females			
day 1	9.30-13.0	72.3-77.0	638-647
day 15	18.0-107	43.4-77.3	571-583

Species	Formulation	Dose (mg/kg/day)		C_{max} (ng/mL)	t_{max} (h)	AUC(0-24h) (h·ng/mL)
Mouse [a]	Solution	5	NOEL	11.0, 13.1	0.5 [d]	53.4, 103
	(gavage)	15		36.4 - 77.6	0.5 [d] - 1	113 - 161
		25	NOAEL	176, 374	0.5 [d]	627, 696
		45		373 - 452	0.5 [d]	834 - 1134
		75		631, 1440	0.5 [d]	1960, 3641
		125		1880, 2000	0.5 [d], 1	4037, 7741

In-life observations: No treatment related effects were observed.
Terminal and necroscopic evaluations:

Treated females	0 mg/kg/day	5 mg/kg/day	15 mg/kg/day	45 mg/kg/day
Corpora lutea	14.8	13.2	13.6	12.5*
Implantation sites	14.5	13.1	13.5	12.4*
Live fetuses	13.6	12.3	12.9	11.5*
Uterine weight	8.05	7.01	7.24	6.48*

Embryofetal development

Study title: Study of embryo-fetal development in CD-1 mice with SPM 8272 by oral administration

Key findings: At 75 mg/kg/day (about 6-30 times the expected clinical exposure of an 8 mg dose via AUC), one dam died, and body weight, gravid uterine weight, and the number of live fetuses were decreased. Resorptions were increased. At 45 mg/kg/day, one dam died, but no effect on body weight was observed. The number of live fetuses appeared to be decreased, but did not reach statistical significance. At the lowest dose of 15 mg/kg/day (about 0.7-1.6 times), the number of resorptions was increased and the number of live fetuses was decreased. In addition, 1 fetus with cleft palate was observed in each of the treated groups, but not in the control group. As any of these effects may be considered a symptom of maternal stress, it should be considered that no NoAEL was observed for maternal or fetal effects in this study.

Study no.: 13347/00 b(4)
Conducting laboratory and location: [redacted]

Date of study initiation: 6 July 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #RD 7691/1, WE 11013, IB 0712
Formulation/vehicle: aqua ad injectabilia

Methods:

Species/strain: CD-1/CD®-1(ICR)BR mice b(4)
Doses employed: 0, 15, 45, and 75 mg/kg/day
Route of administration: oral, gavage, 10 ml/kg
Study design: dosing from day 6 to day 15 of pregnancy
Number/sex/group: 20/group + 16/group for toxicokinetics

Results:

Mortality: One dam each in the mid and high dose group died prematurely and one dam in the mid dose group aborted and was sacrificed prematurely.
Clinical signs: No treatment related effects were observed.

Body weight: At 75 mg/kg/day, body weight was slightly reduced (up to 7%) during the last days of gestation; the decrease was attributed to the increased resorption rate in this group. No other treatment related effects were observed.
Food consumption: No treatment related effects were observed.
Toxicokinetics:

	0 mg/kg/day	15 mg/kg/day	45 mg/kg/day	75 mg/kg/day
Cmax (ng/ml)				
__gestation day 6	--	42.9-43.5	485-755	663-834
__gestation day 15		70.3-79.7	530-1570	808-1670
$AUD_{0.5-4}$ (ng·hr/ml)				
__gestation day 6	--	61.3-69.7	448.6-554.4	568.2-879.1
__gestation day 15		89.5-147.5	907.3-1839.5	2308.8-2702.5

Species	Formulation	Dose (mg/kg/day)		C_{max} (ng/mL)	t_{max} (h)	AUC(0-24h) (h·ng/mL)
Mouse [a]	Solution	5	NOEL	11.0, 13.1	0.5 [d]	53.4, 103
	(gavage)	15		36.4 - 77.6	0.5 [d] - 1	113 - 161
		25	NOAEL	176, 374	0.5 [d]	627, 696
		45		373 - 452	0.5 [d]	834 - 1134
		75		631, 1440	0.5 [d]	1960, 3641
		125		1880, 2000	0.5 [d], 1	4037, 7741

Terminal and necroscopic evaluations:

Dams:

	0 mg/kg/day	15 mg/kg/day	45 mg/kg/day	75 mg/kg/day
Gravid uterine weight (g)	21.3	20.2	19.5	17.4**
Implantation sites				
__total	264	256	243*	264
__per dam	13.2	12.8	12.8	12.6
Preimplantation loss (mean %)	2.4	2.7	5.9	5.4
Postimplantation loss (mean %)	3.4	7.1	6.5	16.6
Resorptions				
__total	8	19*	15	37**
__per dam	0.4	1.0	0.8	1.8
Early resorptions				
__total	5	7	8	14
__per dam	0.3	0.4	0.4	0.7
Late resorptions				
__total	3	12	7	23
__per dam	0.2	0.6	0.4	1.1
Dead fetuses	1	0	1	2
Live fetuses				
__total	255	237*	228	226**
__per dam	12.8	11.9	12.0	11.3

Offspring:

	0 mg/kg/day	15 mg/kg/day	45 mg/kg/day	75 mg/kg/day
Cleft palate				
__fetal incidence (percent)	0	1 (0.4)	1 (0.4)	1 (0.4)
__litter incidence (percent)	0	1 (5.0)	1 (5.3)	1 (5.0)
Exancephaly			1 (from dam which aborted prematurely)	
Sternebrae fused (slight)				
__fetal incidence (percent)	2 (1.6)	1 (0.8)	1 (0.9)	6 (5.3)
__litter incidence (percent)	2 (10.0)	1 (5.0)	1 (5.3)	2 (10.0)
Sternebrae misaligned (slight)				
__fetal incidence (percent)	5 (3.9)	4 (3.4)	3 (2.6)	6 (5.3)
__litter incidence (percent)	2 (10.0)	3 (15.0)	2 (10.5)	6 (30.0)
Total fetal skeletal variations				
__fetal incidence (percent)	11 (8.6)	8 (6.7)	6 (5.2)	14 (12.3)
__litter incidence (percent)	8 (40.0)	7 (35.0)	4 (21.1)	9 (45.0)
Total fetal skeletal retardations				
__fetal incidence (percent)	113 (88.3)	106 (89.1)	110* (95.7)	108 (94.7)
__litter incidence (percent)	20 (100.0)	20 (100.0)	19 (100.0)	19 (95.0)
Liver hemorrhagic foci				
__fetal incidence (percent)	1 (0.8)	1 (0.8)	1 (0.9)	2 (1.9)
__litter incidence (percent)	1 (5.0)	1 (5.0)	1 (5.3)	2 (10.0)

Study title: Study of Embryo-fetal Development in Rabbits with SPM 8272 by Oral Administration

Key findings: At 27 mg/kg/day (about 4-12 times the expected clinical exposure of an 8 mg dose via AUC), one dam died following dosing. Resorptions were increased at this dose and the total number of live fetuses was decreased. The number of fetuses with incompletely ossified sternebrae were increased. At 9 mg/kg/day (about 0.2-0.3 times the expected clinical exposure), one dam aborted and was sacrificed. Although, the number of fetuses with incompletely ossified sternebrae appeared to be increased, statistical significance was not reached. A no effect level for maternal and fetal toxicity was not clearly identified in this study.

Study no.: 13178/00
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 22 May 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #RD 7691/1, WE no. SPM: WE 11013
Formulation/vehicle: aqua ad injectabilia

Methods:

Species/strain: Himalayan rabbit
Doses employed: 0, 3, 9, and 27 mg/kg/day

Route of administration: oral gavage
Study design: administration from gestation day 6 to day 20 (satellite animals from day 6 to day 28)
Number/sex/group: 10 females per group plus 2 per group for toxicokinetics

Results:

Mortality/clinical signs: One high dose dam died 20 minutes following dosing. One mid dose dam aborted on gestation day 26 and was sacrificed prematurely. No treatment related clinical signs were observed.
Body weight: No treatment related effects were observed.
Food consumption: No treatment related effects were observed.
Toxicokinetics:

	0 mg/kg/day	3 mg/kg/day	9 mg/kg/day	27 mg/kg/day
Cmax (ng/ml)				
__gestation day 6	--	2.32-4.26	15.2-37.1	162-528
__gestation day 20		3.99-7.38	7.78-13.5	305-529
__gestation day 28		6.08-8.71	5.89-57.3	62.5-100
$AUD_{0.5-5}$ (ng·hr/ml)				
__gestation day 6	--	3.61-6.27	21.4-23.5	337.6-690.8
__gestation day 20		7.36-11.4	16.7-28.6	559.2-1034.6

Terminal and necroscopic evaluations:

Dams:

	0 mg/kg/day	3 mg/kg/day	9 mg/kg/day	27 mg/kg/day
Resorptions				
__total	7	10	3	22**
__per dam	0.4	0.5	0.2	1.1
Dams with all resorptions	0	1	0	1
Early resorptions				
__total	3	10*	2	18
__per dam	0.2	0.5	0.1	0.9
Late resorptions				
__total	4	0*	1	4
__per dam	0.2	0.0	0.1	0.2
Dead fetuses	0	0	0	0
Live fetuses				
__total	108	110	116	97**
__per dam	5.4	5.8	6.1	5.1
__% live males	48	47	44	44
Pre-implantation loss (mean %)	23.1	20.8	20.5	27.5
Post implantation loss (mean %)	5.2	8.6	2.1	17.1

Offspring:

	0 mg/kg/day	3 mg/kg/day	9 mg/kg/day	27 mg/kg/day
Sternebrae incompletely ossified or reduced				
__fetal incidence (percent)	68 (63.1%)	76 (69.1%)	83 (71.6%)	82** (84.5%)
__litter incidence (percent	16 (80.0%)	18 (94.7%)	18 (94.7%)	19 (100%)
Sternebrae misaligned (slight)				
__fetal incidence (percent)	1 (0.9%)	1 (0.9%)	3 (2.6%)	2 (2.1%)
__litter incidence (percent	1 (5.0%)	1 (5.3%)	3 (15.8%)	2 (10.5%)

Study title: Study of embryo-fetal development in rabbits with SPM 8272 by subcutaneous administration

Key study findings: At 4.5 mg/kg/day by subcutaneous administration (about 10-12 times the expected clinical exposure of an 8 mg dose via AUC of the active entity SPM 7605), mortality was observed in dams in conjunction with clonic convulsions, dyspnea, miosis, and a decrease in body weight and food consumption. No effects on number of corpora lutea, implantation sites, resorptions, placental and fetal weights, or number of live fetuses were observed. No external or skeletal malformations were observed. No treatment related external or skeletal variations were observed. No treatment related skeletal retardations were observed except incomplete ossification of the sternebra(e). At 1.5 mg/kg/day (about 3-4 times), no maternal or fetal effects were observed except for a decrease in maternal food consumption. At 0.5 mg/kg/day, no maternal or fetal effects were observed.

Study no.: 15408/02
Conducting laboratory and location:

b(4)

Date of study initiation: 22 October 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SPM 8272 (fumarate salt), Batch no. RD 7778/1, WE No. SPM: 11809,

Methods

Doses: 0, 0.5, 1.5, and 4.5 mg/kg/day
Species/strain: rabbit, Himalayan, 4-5 months, 2.20-2.88 kg
Number/sex/group: 20/group
Route, formulation, volume, and infusion rate: subcutaneous bolus injection under the dorsal skin, in aqua ad injectabilia (2 ml/kg)
Satellite groups used for toxicokinetics: 2 animals each in groups 1, 3, 4
Study design: dosing from the 6th to 20th day of gestation with sacrifice on , in the main study group, and dosing from the 6th to the 28th day of gestation in the satellite animals

Results

Mortality (dams):

	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
Mortality (#)	0	0	0	4
Mortality (%)	0	0	0	17

Clinical signs (dams):

	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
Clonic convulsions	0	0	0	2
Dyspnea	0	0	0	2
Lateral position	0	0	0	1
Miosis	0	21	20	24

Body weight (dams):

Kg	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
Day 0	2.479	2.480	2.453	2.403
Day 3	2.523	2.549	2.507	2.468
Day 6	2.571	2.588	2.527	2.502
Day 9	2.575	2.552	2.482	2.440*
Day 12	2.591	2.557	2.467	2.422**
Day 15	2.619	2.602	2.506	2.439**
Day 18	2.681	2.643	2.563	2.469**
Day 21	2.689	2.651	2.570	2.479**
Day 24	2.733	2.706	2.638	2.554**
Day 27	2.768	2.749	2.709	2.600**
Day 29	2.792	2.791	2.736	2.647*

Food consumption (dams):

Gms/Kg	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
Day 4	51.5	47.9	48.3	50.1
Day 7	48.8	44.8	33.4**	32.2**
Day 8	49.7	40.3*	30.7**	26.3**
Day 12	44.9	37.9	28.8**	26.8**
Day 18	44.0	38.0	32.3**	27.7**
Day 24	38.4	37.0	37.8	44.1
Day 29	31.7	33.7	33.2	39.8**

Toxicokinetics: Exposure to SPM 7605 increased in approximate proportion to the dose in the pregnant rabbit; SPM 7605 crossed the placental barrier.

N=2, individual data	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
$AUD_{0.5\text{-}6h}$ (ng·hr/ml)				
Administration 1 (Day 6)			264, 289	919, 999
Administration 15 (Day 20)			289, 312	974, 1042
Cmax (ng/ml)				
Administration 1 (Day 6)			93.8, 109	374, 391
Administration 15 (Day 20)			102, 106	391, 484
Tmax (hr)				
Administration 1 (Day 6)			0.5, 1	0.5, 1
Administration 15 (Day 20)			1, 1	0.5, 0.5

Terminal and necroscopic evaluations:C-section data : No treatment related effects were observed on number of corpora lutea, implantation sites, resorptions, placental and fetal weights, or number of live fetuses.

Offspring : No external or skeletal malformations were observed. No treatment related external or skeletal variations were observed. No treatment related skeletal retardations were observed except incomplete ossification of the sternebra(e).

Skeletal retardations	Dams (mg/kg/day)			
	0	0.5	1.5	4.5
Incomplete ossification of the sternebra(e)				
fetal incidence	32	31	33	46*
litter incidence	14	14	12	16
Total skeletal retardations (litter incidence, %)	16	18	16	17

Study title: Examination of SPM 8272 for effects on the pre- and postnatal development (including maternal function) following oral administration to the dams of CD-1 mice of the F0 Generation.

Key findings: At 60 mg/kg/day (estimated to be about 5-24 times the expected exposure of an 8 mg clinical dose via AUC), one dam was found dead during the lactation period and decreased maternal body weight and food consumption were observed. Decreased litter weight and developmental delay (time to ear opening) were observed in the F1 generation. At 30 mg/kg/day (about 2-12 times), decreased maternal body weight was observed. A decrease in litter weight did not reach statistical significance at this dose, but developmental delay (time to ear opening) and increased activity level (not significant, but present at 60 mg/kg/day) were observed in the F1 generation. At 10 mg/kg/day, no effects on dams or the F1 generation were observed. No effects on reproductive performance of the F1 generation were observed nor any effects on the F2 generation, at any dose.

Study no.: 13249/00
Submission #001, volume #35, and page #1
Conducting laboratory and location: b(4)

Date of study initiation: 27 June 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #RD 7691/1, WE 11013, IB 0712, 97.75% pure
Formulation/vehicle: aqua ad injectibilia

Methods:

Species/strain: CD-1/CD®-1(ICR)BR mice b(4)
Doses employed: 0, 10, 30, and 60 mg/kg/day
Route of administration: oral, gavage
Study design: F0 generation dosed from implantation (gestation day 6) until weaning (lactation day 21)

Number/sex/group: 20/group

Results:

Mortality: One high dose dam was found dead on lactation day 4. No other mortalities or treatment related clinical signs were observed.

Body weight: Body weight was slightly decreased in the 60 mg/kg/day dams from gestation day 10, becoming significant during lactation weeks 1 and 2 (11% and 10%, respectively). Body weight was also decreased in the 30 mg/kg/day group during lactation week 1 (~8%).

Food consumption: In the 60 mg/kg/day group, food consumption was transiently decreased on gestation days 7 and 8 and on lactation weeks 1, 2, and 3.

In-life observations:

Offspring:

	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	60 mg/kg/day
Mean number of live pups per litter				
__day 0 of lactation	12.8	12.1	12.4	11.1
__day 21 of lactation	12.0	11.4	11.8	9.6
Litters, at birth, losing >1 pup	0	0	2	1
Litters, day 0-4, losing >3 pups	0	0	1	1
Litters, day 4-21, losing >1 pup	3	0	2	5
Litters, day 0-21, losing >4 pups	0	0	2	3
Litter weights (g)				
__day 1	19.8	18.9	18.0	16.4
__day 4	27.3	26.6	24.6	20.9*
__day 21	96.7	101.9	88.0	74.1*
__males, day 22-27	73.6	82.9	77.7	54.4
__females, day 25-30	105.6	94.3	94.3	94.3
Ear opening, mean day of life	13.6	13.7	14.3*	14.3*
Eye opening, mean day of life	16.0	15.8	16.4	16.4
Cleavage of the belanopreputial gland, mean	24.5	24.6	25.2	25.0
Vaginal opening, mean day of life	30.7	30.1	31.4	31.3
Negative mid-air righting reflex, day 14 mean	0.0	0.0	5.0	5.0
Negative auditory startle reflex, day 14 mean	23.4	9.6	31.5	46.3
Negative passive avoidance, day 27 mean	16.4	10.6	14.8	21.1
Open field test, sectors entered	96.5	98.6	110.0*	100.6
Reproductive performance	--	No effects	No effects	No effects

Terminal and necroscopic evaluations:

Dams:

	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	60 mg/kg/day
Implantation sites	13.1	12.9	13.1	11.7

2.6.6.7 Local tolerance

Study title: Acute skin irritation test (patch test) of SPM 8272 in rabbits

Study no.: 13554-00

Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 24 November 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch 3 AC 8340/1 (WE 11386), 96.14% pure
Formulation/vehicle: 0.9% NACl

Study design: Three rabbits were exposed to 500 mg SPM 8272/patch on intact and abraded skin for 4 hours. Substance-related lesions were recorded at l, 24, 48 and 72 hours after patch removal and at 4, 5 and 6 days after patch removal from abraded skin.

Results:

Erythema (grade 1) was noted 1 hour after patch removal on the intact skin in 2 of 3 animals. The erythema disappeared after 24 hours. Erythema (grade 1) and edema (grade 1) were noted 1 hour after patch removal from abraded skin in all three animals. After 48 hours the edema disappeared. The erythema disappeared between day 4 and 6 in all animals. There was no observation of systemic intolerance.

SPM 8272 was judged to be non-irritating to skin under the conditions of this study.

Study title: Acute eye irritation study of SPM 8272 by instillation into the conjunctival sac of rabbits

Study no.: 13555/00
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 5 December 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch # AC 8340/1 (WE 11386), 96.14% pure

Study design: A single administration of 100 mg SPM 8272/animal was made to the conjunctival sac of the right eye of 3 female rabbits.

Results:

Corneal opacity was noted 24 hours after instillation in animal no. 1 (grade 2) and animal nos. 2 and 3 (grade 1). Corneal opacity (grade 1) was observed 48 hours after application in all animals and lasted 5 days after instillation in animal no. 2., 6 days in animal no. 1 and 7 days in animal no. 3.

A fluorescein test at 24 hours revealed corneal staining; more than 3/4 of the corneal surface was affected in animal no. 1 and 3 and between half and 3/4 of the corneal surface was affected in animal no. 2. A fluorescein test at seven days revealed corneal staining in animal no. 3; less than 1/4 of the surface was affected.

Irritation at the iris (grade 1) was noted in all animals 24 hours after instillation, lasting 5 days in animal no. 2 and 6 days in animal nos. 1 and 3.

Conjunctival redness (grade 1) was observed in animal no.2, 24 hours after instillation.

Chemosis (grade 2) was noted in all animals 1 hour after instillation, lasting 24 hours. Chemosis (grade 3) was observed in animal nos. 1 and 3, 48 hours after application and lasting 72 hours in animal no. 1 and 5 days in animal no. 3.

SPM 8272 was judged to be irritating to the eyes under the conditions of this study.

Study title: Local tolerance test of SPM 8272 and SPM 7605 in rabbits after a single intravenous, intraarterial, paravenous, subcutaneous and intramuscular administration.

Study no.: 15546/02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 5 September 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch no. 20206056 (104.3% pure) and 20206052 (102.0% pure)
Formulation/vehicle: 0.9% NaCl

Study design:

One male and one female Himalayan rabbit per group were administered one of the following and observations extended for 14 days:

intravenous infusion into the marginal vein of the ear (4 hour infusion of 10 ml/kg, 1.4 mg/kg SPM 8272 or 0.9 mg/kg SPM 7605)
intramuscular injection into the gastrocnemius muscle (4 hour infusion of 0.5 ml/kg, 0.07 mg/animal SPM 8272 or 0.45 mg/animal SPM 7605)
intraarterial infusion into the central artery of the ear (10 ml/kg, 1.4 mg/kg SPM 8272 or 0.9 mg/kg SPM 7605)
paravenous injection beside the vena saphena parva (2.0 ml/kg, 0.28 mg/animal SPM 8272 or 0.18 mg/animal SPM 7605)
subcutaneous injection under the dorsal ski(2.0 ml/kg, 0.28 mg/animal SPM 8272 or 0.18 mg/animal SPM 7605)

Results:

No SPM 8272 or SPM 7605 related local or systemic toxicity was observed following i.v., i.a., p.v., or s.c. administration. The effects observed following a single intramuscular

injection (mild focal necrosis, mild to moderate histiocytic infiltration, minimal focal giant cells, minimal mixed cell infiltrate) were reversible after 14 days.

Study title: Examination of SPM 8272 in the skin sensitization test in guinea pigs according to Magnusson and Kligman (maximization test)

Study no.: 13553/00
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 12 December 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch no. AC 8340/1 (WE 11386), 96.14% pure
Formulation/vehicle: aqua ad injectibilia

Study design: In Dunkin-Hartley guinea pigs (N=15 males), a 0.1 ml of 1% SPM 8272 in was used in the 1st induction stage (intracutaneous, shoulder). The skin was coated with sodium lauryl sulfate before stage 2 induction (topical, shoulder)(day 6 after the first induction), since a preliminary test revealed no irritating potential for a 25% concentration of SPM 8272, the maximum soluble concentration. A challenge (topical, flank) was made on day 21 with 2 ml SPM 8272/animal (as a 25% concentration in aqua ad injectabilia).

Results: A 1% solution of SPM 8272 produced a discrete or patchy erythema (grade 1) after 25 hours and a moderate and confluent erythema after 48 hours in all animals. A moderate and confluent erythema was noted in all animals 1 h and 24 hours after patch removal following stage 2 (topical) induction (day 7 after the first induction). The challenge on day 21 revealed no skin irritation in any animal. No significant change in body weight gain was observed. Positive (Benzocaine) and negative controls responded as expected.

2.6.6.8 Special toxicology studies

Study title: In vitro assessment of the phototoxicity of SPM 7605 in cultured BALB/c 3T3 NRU cells

Key study findings: SPM 7605 exhibited no phototoxicity under the conditions of this assay.

Study no.: 19387/05

Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 17 September 2005
GLP compliance: yes

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Batch no. DY908.05004, 98.4% pure
Formulation/vehicle: Earl's balanced salt solution

Methods

Doses: 0, 6.25, 12.5, 25, 50, and 100 µg/ml SPM 7605

Study design: Cytotoxicity (reduction in the uptake of the vital dye Neutral red) was compared in the presence and absence of UVA/visible light (50 minutes at 1.7 mW/cm^2 or 5 J/cm^2) after 24 hours of exposure to SPM 7605. Chlorpromazine (0.01, 0.1, 1, and 10 µg/ml) was used as a positive control.

Results: No phototoxicity was observed up to 100 µg/ml of SPM 7605. A photo-irritation factor (PIF) of 1 was calculated for SPM 7605, in comparison to a PIF of 8.9 calculated for the positive control.

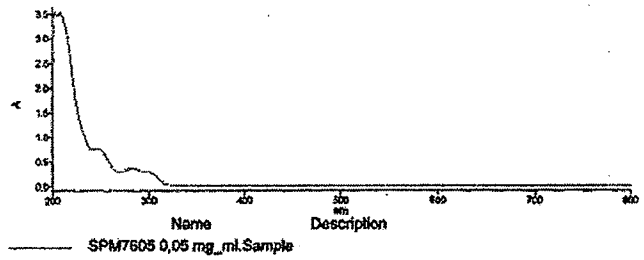
Study title: UV/VIS absorption of SPM 7605
Study no.: 335

Methods

Doses: 0.02, 0.03, 0.04, and 0.05 mg/ml

Study design: SPM 7605 was dissolved in water and its UV/visible spectrum taken against water

Results: The spectrum shows strong absorption at around 200 nm and local absorption maxima at 247 and 284 nm, with a broad shoulder on the latter at around 300 nm. No absorbance was observed between 320 and 800 nm. The absorption of the peak at 284 nm was taken as the upper limit for the absorption in the range of 290-700 nm, and the molar absorptivity was calculated to be $\varepsilon = 2131$ L mol^{-1} cm^{-1} and the specific absorbance $A^{1\%}_{1cm}$ was calculated to be $A^{1\%}_{1cm} = 62.4$ L g^{-1} cm^{-1}.



Study title: 28-day immunotoxicological study of SPM 8272 by repeated oral administration to CD-1 mice-plaque forming colony test

Key study findings: SPM 8272 did not exhibit immunotoxicity under the conditions of this study

Study no.: 17778/04
Conducting laboratory and location: b(4)

Date of study initiation: 13 April 2004
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: batch # RD-7778/1, 92.8% pure
Vehicle: aqua ad injectibilia

Methods

Doses: 0, 25,75, and 100 mg/kg/day SPM 8272 or hexachlorobenzene (100 mg/kg ip on test days 21 and 22)(immunostimulant) or cyclophosphamide (40 mg/kg ip on test days 28 and 29)(immunosuppressant) in 10 ml/kg

Study design: Mice (CD®-1 / CD1®) (10 animals/sex/group) were administered b(4) test item or control substances as described above. For the PFC test, all animals were pre-treated 4 days before sacrifice with 200 µl/animal 10% sheep red blood cells in Hanks buffered salt solution (i.v.) to induce an IgM and IgG response to test item.

Results: Administration of 75 mg/kg/day of SPM 8272 for 28 days caused a slight decrease in body weight, but no effect was observed in the Plaque forming Colony test (no changes in antibody response to IgM and IgG, no change in the number of spleen cells or in the number of plaques) at any dose tested. Spleen cell viability ranged from 96.7 to 99.5%. Positive and negative controls responded as expected.

Study title: Examination of SPM 8272 and SPM 7605 (infusion solutions) for compatibility and hemolytic properties in citrate-anticoagulated human blood (*in vitro*)

Study no.: 15547/02
Conducting laboratory and location: b(4)

Date of study initiation: 19 July 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: SPM 8272 batch no. 20206055 (100.0% pure) and SPM 7605 batch no. 20206051 (101.5% pure)
Vehicle: 0.9% NaCl

Methods

Doses: 0.2 mg/ml SPM 8272 and SPM 7605 (corresponding to the approximate plasma concentration of a clinical formulation)

Study design: Fresh citrate-coagulated blood was obtained from three volunteers. All tests were conducted in triplicate.

Results: No effect on hematocrit of the erythrocyte suspensions, no change in red cell morphology, and no precipitates were observed at 0.2 mg/ml SPM 8272 or SPM 7605. No hemolysis was observed under these conditions. No changes in osmolality were observed, and no coagulation was observed macroscopically or microscopically.

2.6.6.9 Discussion and Conclusions

Long term toxicology assays were conducted in mice and dogs. Exaggerated pharmacological effects (including mydriasis and increased heart rate) were the primary limiting toxicity for both mice and dogs. No treatment related histopathological changes were observed after treatment for 6 months in mice or 9 months in dogs.

Cardiac toxicity, including QT prolongation, was studied in dogs. A clinical QT study was also conducted.

Fesoterodine was negative for genotoxicity and/or mutagenicity in a battery of *in vitro* and *in vivo* assays and negative for carcinogenicity in two year assays in mice and rats

Male and female fertility studies were conducted in mice. Embryo-fetal studies were conducted in mice and rabbits by oral administration and in rabbits by subcutaneous administration (to increase systemic exposure by overcoming the peaks and troughs of drug exposure). No teratogenicity was observed in mice or rabbits at the doses tested, but non-specific effects were observed at low multiples of the expected clinical exposure. Developmental studies were conducted in mice. There was adequate exposure to each of the major human metabolites in these studies.

Elimination of drug-related materials from the eyes of pigmented rats was evident after 168 hours, but no drug accumulation or drug related ocular toxicity was observed in toxicology studies. Fesoterodine exhibited no phototoxicity in *in vitro* and *in vivo* assays.

2.6.6.10 Tables and Figures: see under individual studies

2.6.7 TOXICOLOGY TABULATED SUMMARY

Type of study	Species and strain	Method of administration	Duration of dosing	Doses (mg/kg)[a]	GLP compliance
Single-dose toxicity	NMRI mice	Oral (gavage)	-	100, 215, 464	Yes
		Intravenous (bolus)	-	4.64, 10.0, 21.5, 46.4	Yes
	Sprague-Dawley rats	Oral (gavage)	-	100, 215, 464, 1000	Yes
		Intravenous (bolus)	-	4.64, 10.0, 21.5, 46.4	Yes
Repeat-dose toxicity	NMRI mice	Oral (gavage)	1 week	0, 30, 169[b], 266	Yes
	CD-1 mice	Oral (gavage)	13 weeks	0, 5, 25, 75, 125	Yes
		Oral (gavage)	13 weeks	0, 15[c], 45	Yes
		Oral (gavage)	26 weeks	0, 5, 25, 75 (100/125)[b]	Yes
		Intravenous infusion	3 days	5, 10, 20[b]	Yes
Repeat-dose toxicity	CD-1 mice	Intravenous infusion	14 days	0, 2, 6[c], 18	Yes
	Sprague-Dawley rats	Oral (gavage)	1 week	0, 10[b], 30[b], 100	Yes
		Oral (gavage)	13 weeks	0, 5[c], 25, 75	Yes
		Oral (gavage)	13 weeks	0, 15[c], 45	Yes
	Beagle dogs	Oral	3 days each; 1 week[d]	1, 3, 10, 30; 18[d]	Yes
		Oral	13 weeks	0, 0.5[c], 2.5, 10	Yes
		Oral	39 weeks	0, 0.5, 2.5, 13.5	Yes
		Oral; intravenous infusion	2 weeks	Oral: 0, 8, 32; iv: 1.5, 6[c]	Yes
		Intravenous infusion	3 days	1[c], 5, 10	Yes
		Intravenous infusion	2 weeks	0, 0.6, 2, 6	Yes
		Intravenous infusion	13 weeks	0, 0.5, 1.5, 4.5[b]	Yes
Type of study	Species and strain	Method of administration	Duration of dosing	Doses (mg/kg)[a]	GLP compliance
Genotoxicity	S. typhimurium and E. coli	In vitro	-	31.6-3160 µg/plate	Yes
	S. typhimurium	In vitro	-	31.6-3160 µg/plate	Yes
	Mammalian V79 cells	In vitro	-	31.25-2500 µg/mL culture	Yes
	Human lymphocytes	In vitro	-	125-2000 µg/mL culture	Yes
	Human lymphocytes	In vitro	-	125-2000 µg/mL culture	Yes
	NMRI mice	In vivo	-	62.5, 125, 250	Yes
Carcinogenicity	CD-1 mice	Oral (gavage)	104 weeks	0, 5, 15, 45/60[b]	Yes
	CD rats	Oral (gavage)	104 weeks	0, 5, 15, 45/60[c]	Yes

a – unless specified otherwise. For carcinogenicity studies, the highest non-carcinogenic dose is underlined.
b – from test week 28 onwards: 60 mg/kg; gradual reduction of the dose to 30 mg/kg from test week 47 onwards (males). Termination of dosing for males and females after the mortality rate reached 60%.
c – from test week 30 onwards: 60 mg/kg

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There is no impediment to approval of this submission from a pharmacology/toxicology perspective.

Unresolved toxicology issues: No issues are considered to be unresolved.

Recommendations: There are no recommendations for further nonclinical studies.

Suggested labeling: see detailed suggestions on page 3.

APPENDIX/ATTACHMENTS: NA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie McLeod
12/12/2006 12:14:50 PM
PHARMACOLOGIST

Lynnda Reid
12/12/2006 05:26:15 PM
PHARMACOLOGIST

NDA: 22030 11 May 2006

45 Day Filing Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA.	X		Studies include chronic toxicity studies (up to 6 months in mice and up to 9 months in dog), a battery of genetic toxicity assays, 2-year carcinogenicity assays in rats and mice, reproductive and developmental studies in mice and rabbits, pharmacology and pharmacokinetic studies.
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the-art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and	X		

ITEM	YES	NO	COMMENT
submitted reviewable supportive data (ie. adequate repeat studies using the marketed product and /or adequate justification for why such repetition would not be necessary)?			
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	X		Formatted for pre-June 30 stamp date
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item #10 below why it is not.	X		
10) Reasons for refusal to file:			

Reviewing Pharmacologist / Date

Supervisory Pharmacologist/Date

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/s/

Laurie McLeod
5/11/2006 11:58:25 AM
PHARMACOLOGIST

Lynnda Reid
5/11/2006 12:59:40 PM
PHARMACOLOGIST