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 ± 0.065	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 ± 213	1305 ± 209
C_{max} (ng equiv/g)	1384 ± 488	1522 ± 574	1294 ± 213	1391 ± 185
T_{max} (h)	0.5	0.25	0.25	0
AUC_{last} (h ng equiv/g)	2505 ± 247	2188 ± 397	2225 ± 87.4	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 carcinal samples per time point were withdrawn
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	4533 ± 382	6734 ± 9158	16092 ± NA
$T_{1/2}$ (h)	23.3 ± 3.38	35.8 ± 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 (n=3) and at 0.75 hours (n=1)
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: 4.2.2.2.5
Study no.: [redacted]-4002/01

b(4)

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	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 1 (Treatment 1)	Day 1 (Treatment 2)	Day 1 (Treatment 3)	Day 1 (Treatment 1)
C_{max} (ng/mL)	4.21 (3.59-5.63)	7.83 (2.39-11.5)	9.30 (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 (13.4-36.0)	33.0 (23.4-150)	3216 (2855-2892)
$T_{1/2}$ (h)	1.92 (1.88-2.37)	2.18 (1.99-2.42)	2.17 (1.89-2.88)	1.45 (1.39-1.84)
F_{abs} (%)	1.34 (1.18-1.39)	1.51 (1.02-2.00)	1.46 (1.21-6.83)	NA

Additional information:
Medians (ranges) are tabulated.
F_{abs} 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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.