Table 34 Treatment Emergent Adverse Events by Dose Level in Study SP540

Body System	Preferred Term	Dose Level (mg)				Total
		4.5	9	13.5	18.0	
N – Starting Rx		31	30	30	29	31
D/C		1[a]		1[b]		2
APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	6		4	2	12
SKIN AND APPENDAGES DISORDERS	Erythema	2				2
	Skin Disorder - Any	3	2			5
	Skin Disorder - Mild	2				
	Skin Disorder - Moderate	1	2			
GASTRO-INTESTINAL SYSTEM DISORDERS	NAUSEA - Any	3	3	3	4	10
	NAUSEA - Mild	3	1	1	2	
	NAUSEA - Moderate		2	1	1	
	NAUSEA - Severe			1	1	
	VOMITING - Any		2	1	1	3
	VOMITING - Mild					
	VOMITING - Moderate		2		1	
	VOMITING - Severe			1		
	CONSTIPATION	1				1
	Abdominal Pain		2			2
	Abdominal Cramping	1				1
	DIARRHOEA					
AUTONOMIC NERVOUS SYSTEM DISORDERS	APPETITE DECREASED	1				1
	APPETITE INCREASED					
	Dry Mouth	2				2
	Sweating		1			1
	SINUS BRADYCARDIA					
	SINUS TACHYCARDIA					
HEART RATE AND RHYTHM DISORDERS	Ventricular Extrasystole	1	1	1[b]		3
	ATRIAL BIGEMINY					
	Ventricular BIGEMINY					
	PALPITATION					
CARDIOVASCULAR DISORDERS, GENERAL	HYPERTENSION	1		2		3
	HYPOTENSION ORTHOSTATIC	1				1
CENTR & PERIPH NERV SYST DISORDERS	Chest Pain				1	1
	DIZZINESS	1		3	2	5
	HEADACHE				1	1
	Dyskinesia	1				1
	Paresthesia					
PSYCHIATRIC DISORDERS	Tremor		1	1	1	1
	Anxiety / Irritability	1	2	1		4
	INSOMNIA					
	DREAMING ABNORMAL					
	SLEEP DISTURBED					
BODY AS A WHOLE - GENERAL DISORDERS	FATIGUE					
METABOLIC AND NUTRITIONAL DISORDERS	WEIGHT INCREASE					
RESPIRATORY SYSTEM DISORDERS	Flu Like Syndrome					
	THROAT SORE					

a Discontinued due to noncompliance
b Discontinued due to ventricular extrasystole

3.5.3 Pharmacokinetics / Pharmacodynamics

Table 110 on page 259 summarizes the major pharmacodynamic measures and measurement strategy for the studies submitted. A summary of these appear in the following subsections.

3.5.3.1 Small Phase I and Phase II Dose Ranging Studies

3.5.3.1.1 Efficacy Measurements

Effects of rotigotine on efficacy as measured by the Modified Columbia Rating Scale, (MCRS), were performed for IV rotigotine in studies SP803, SP804, SP805. A summary of the effects in the IV studies may be found in § 3.5.1 beginning on page 62.

Effects on the MCRS were also measured in study SP800. However, this study used the developmental — patch formulation, (Formulation 2), that produced gave extremely low bioavailability. So this study was not reviewed for PK/PD effects relationships.

Effects on the UPDRS and Hae and Young Scores were measure in study SP534, where the change from baseline after dose titration was measured and in study SP540 where the change from baseline at the end of each week of dose titration was measured. Due to the small sample sizes these studies were not reviewed for PK/PD relationships

3.5.3.1.2 Effects on Hormone Concentrations

As a dopamine agonist effects on hormone secretion are expected.

Study SP503 examined the effect of rotigotine on a variety of hormones including Prolactin HGH, LH, FSH, TSH, and aldosterone. Due to limited review time this study was not reviewed, but will be if an approvable letter is issued.

Prolactin levels were also measured in studies SP803 and SP535, and aldosterone was also measured in study SP840.

3.5.3.1.3 Effects on Intra-Ocular Pressure

Effects on intraocular pressure were measured in the IV rotigotine study SP803. This study was also not reviewed due to limited review time, but will be if an approvable letter is issued.

3.5.3.1.4 Effects on Wakefulness and Alertness

Effects on wakefulness and alertness were formally examined in studies SP630, SP512, and SP513 with the Epworth Sleepiness Scale. Due to limited time the PK/PD or dose response of these effects were not reviewed, but may be if an approvable letter is issued.

3.5.3.2 Population PK/PD

3.5.3.2.1 Phase II - Fixed Dose Efficacy Study – Study SP506

Study SP506 was a large phase II randomized, double-blind, placebo-controlled, fixed dose PK/PD efficacy study. Subjects were titrated from a starting dose of 4.5 mg / 10 cm^2 to a dose of 4.5 mg, 9.5 mg, 13.5 mg, or 18 mg daily over a titration period of 4 weeks with titration steps of 4.5 mg at weekly intervals. This was followed by a maintenance phase of 7 weeks for a total drug exposure 11 weeks. Thus there were 5 treatment arms including placebo.

The study design specified a total of 45 patients enrolled per arm for a total of 225 subjects. The sponsor claims that 400 subjects were actually enrolled with 329 completers. However, there were only 63-70 subjects reported enrolled per arm for a calculated total of 265 subjects.
The schedule of PK and PD measures for study SP506 are shown in Table 35.

Table 35 PK And PD Measurements Schedule for Study SP506

Treatment Phase	Baseline	Titration Phase		Maintenance Phase		Follow Up
End of:	-1[a]	Week 2	Week 4	Week 7	Week 11	Week 14
Days	0	14	28	49	77	98
UPDRS	X	X	X	X	X	X
H&Y Score	X		X		X	
24 Hour PK Sample	X		X	X	X	

a For PK sampling from days -4 to -28

It should be noted that only 24 hour PK samples were obtained.

The sponsor did not provide raw individual baseline UPDRS scores so changes from baseline for individual subjects could not be calculated and PD parameter estimates and variability in the PK/PD relationship could not be estimated. Mean UPDRS scores however were provided and exploratory PK and PK/PD plots of the mean data are shown in Figure 16 to Figure 19 on the following pages.

Figure 16 shows a side by side view of a plot of mean UPDRS Score vs. Study Week by dose with a plot of mean 24 hour Rotigotine Concentrations vs. Study Week also shown by dose. According to the medical reviewer the two lower doses of 4.5 mg and 9 mg per day were not statistically different from placebo, whereas the two higher doses of 13.5 mg and 18.0 mg were statistically better than placebo treatment. However, there was no additional benefit seen with the 18 mg dose compared with the 13.5 mg dose. The rotigotine plasma concentration plot suggests that this may be due to a lack of separation in the plasma concentrations in the two arms.

Although Figure 17 shows a linear relationship between mean 24 hour rotigotine concentrations and dose a close examination of the data indicates that the lack of separation in the 13.5 mg and 18 mg concentrations may be due to chance with the subjects receiving the 13.5 mg dose having slightly higher concentrations than expected and the subjects receiving the 18 mg dose having slightly lower concentrations. This is also supported by comparing the data from this study to the exposures seen in other studies, (see §3.7.4 Multiple Dose Pharmacokinetics on page 116).

Figure 16 Comparison of Plots of Mean UPDRS Score and Mean 24 hour Rotigotine Concentrations vs. Study Week by Dose for Study SP506

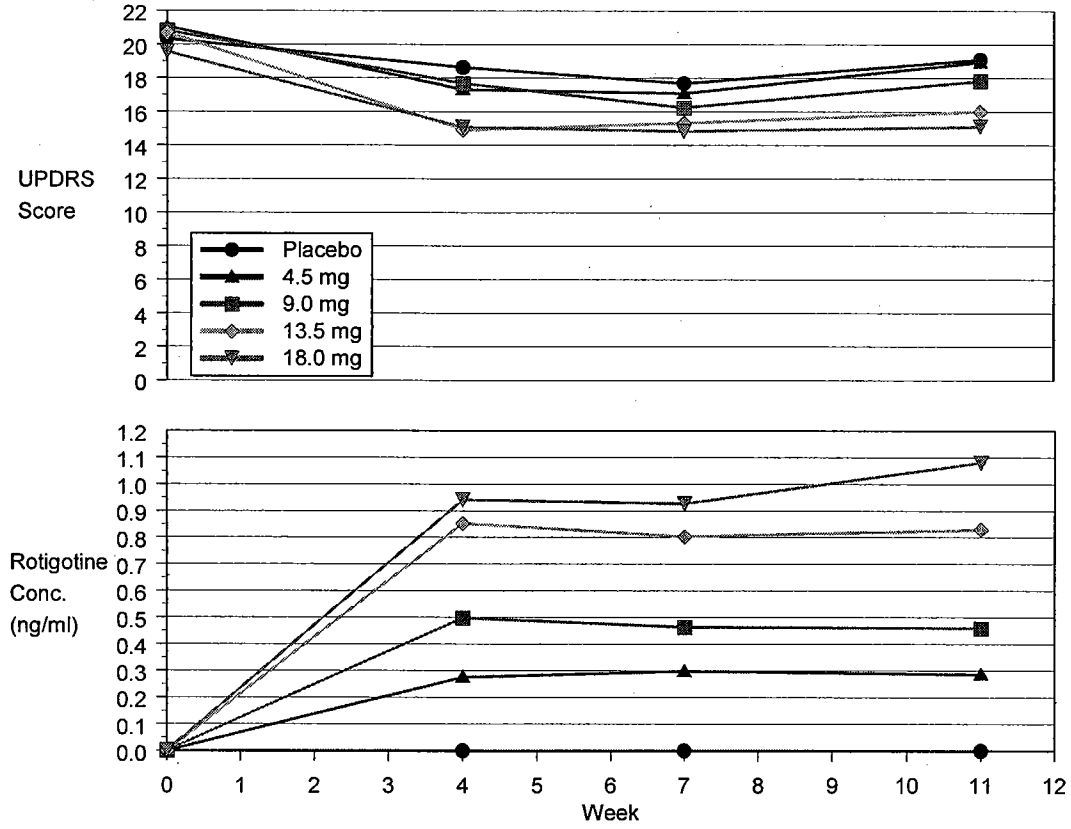


Figure 17 Mean 24 hour Rotigotine Concentration vs. Dose by Study Week for Study SP506

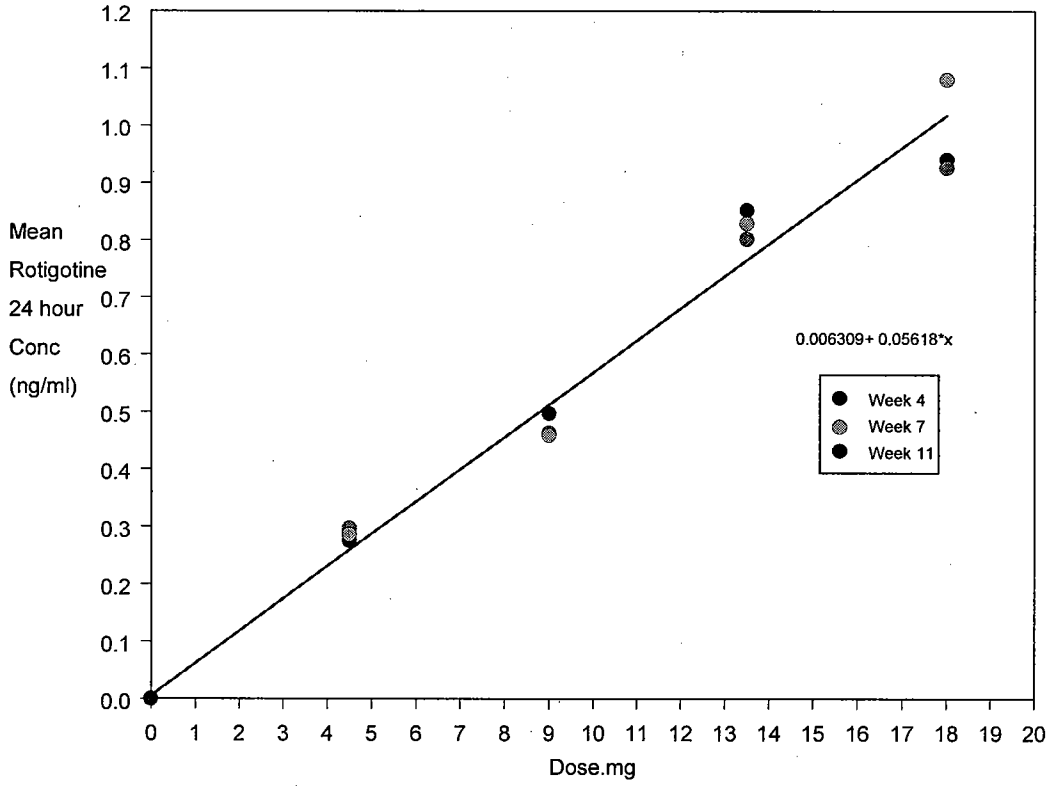


Figure 18 and Figure 19 below show baseline corrected UPDRS scores with and without correction for placebo vs. mean 24 hour rotigotine plasma concentrations.

Figure 18 without correction for placebo suggests that a maximum effect may have been reached with the 13.5 mg dose, whereas when the scores are corrected for the mean placebo response the loess curve suggests that we may still be in a linear response range and the lack of additional effect seen may be due to simple variability, (see Figure 19). Additional data and possibly studies are needed to determine which one is the true situation.

Figure 18 Mean Baseline Corrected UPDRS Scores vs. Mean 24 hour Rotigotine Concentrations by Dose with LOESS Curve for Study SP506

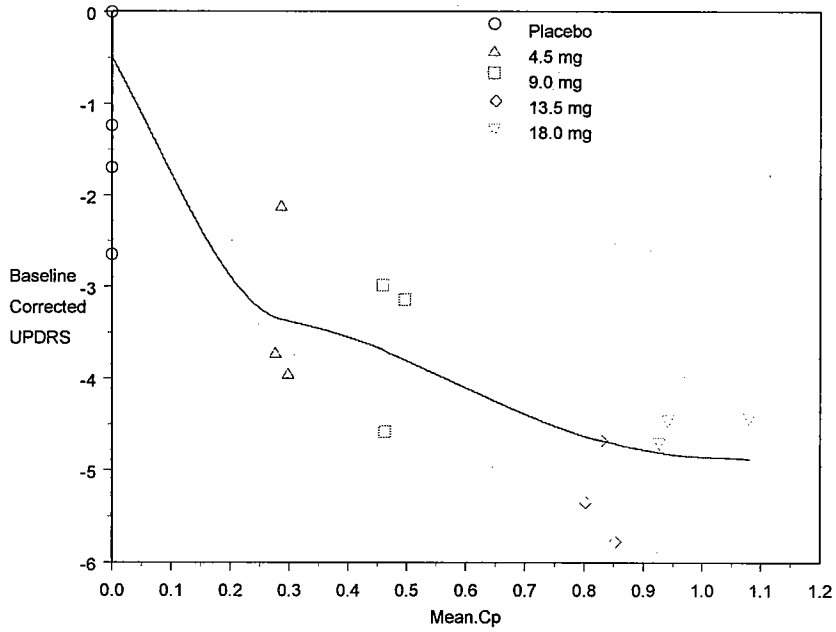
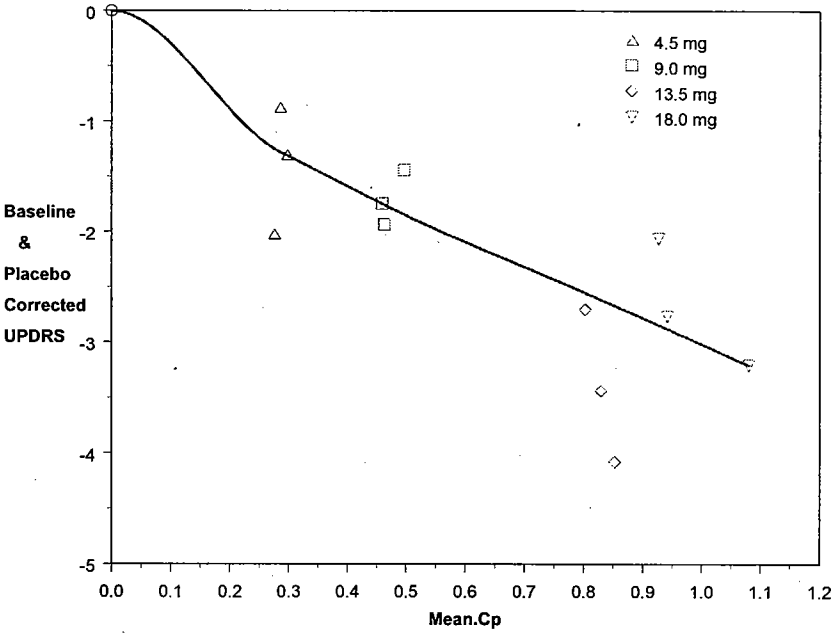


Figure 19 Mean Baseline and Placebo Corrected UPDRS Scores vs. Mean 24 hour Rotigotine Concentrations by Dose with LOESS Curve for Study SP506



If the rest of the raw baseline data is submitted in an amendment, analysis of the data may be performed.

3.5.3.2.2 Phase III – Pivotal Flexible Dose Studies – Studies SP512 and SP513

3.5.3.2.2.1 Part I – Pivotal Efficacy Phase

Studies SP512 and SP513 were phase III pivotal efficacy studies each with two parts, Part I was the initial efficacy evaluation, and Part II was the open-label long term safety extension.

SP512 Part I was a randomized, double-blind, placebo controlled, 2-arm, parallel group flexible dose study in patients with 'early stage' Parkinson's Disease. Subjects were randomized to placebo or rotigotine patches and the dose was titrated 4.5 mg / day to 13.5 mg / day or to a maximally tolerated dose in steps of 4.5 mg occurring at 1 week intervals. After the end of the 4 week titration phase Subjects were then maintained on 13.5 mg / day or their maximally tolerated dose for an additional 24 weeks or until withdrawal due to AEs. Thereafter the dose was deescalated in 4.5 mg steps every 2 days.

SP513 Part I was a randomized, double-blind, placebo and active controlled, double-dummy 3-arm, parallel group flexible flexible dose study in patients with 'early stage' Parkinson's Disease. Subjected were randomized to placebo, rotigotine patches, or ropinirole po. The dose of rotigotine was titrated from 4.5 mg / day to 18.0 mg / day or to either a 100% effective or a maximally tolerated dose in steps of 4.5 mg occurring at 1 week intervals. Subjects randomized to roprinirole were titrated from 0.75 mg to 24 mg in 3 divided doses per day with dosage increased at weekly intervals. The first 4 steps were in increments of 0.75 mg per day, the next four steps were in increments of 1.5 mg per day and the last 5 steps were in increments of 3.0 mg per day. After the end of the 13 week titration phase subjects were maintained on their titrated dose for an additional 24 weeks or until withdrawal due to AEs. Thereafter the dose was deescalated over 12 days.

In Part I of both SP512 and SP513 both PK and PD samples were obtained. The PD measures obtained in each study are shown in Table 36, and the sampling schemes for both PK and PD measures are shown in Table 37.

Table 36 PK and PD Measures Obtained in Part I of the Pivotal Phase III Efficacy Studies SP512 and SP513

	SP512	SP513
UPDRS	X	X
CGI	X	X
H&Y	X	X
Motor Complication Assessment	—	X
Epworth Sleepiness Scale	X	X
Euroqol Quality of Life	X	X
ECG	X	X
Prolactin	—	X

Patch application was rotated among 6 different sites on each side of the body.

Table 37 PK & PD Sampling Schedules for the Pivotal Phase III Efficacy Studies – SP512 and SP513

Study	Phase	Screening	Titration			Maintenance							FU
			Baseline										
SP512	*Visit*	1	2	3	4	5	6	7	8	9	10	11	12
	Week	-4 to -1	1	2	3	4	8	12	16	20	24	28	32
	Day	-28 to -4	1	8	15	22	50	78	106	134	162	190	218
	PK Sample		X	X	X	X		X		X		X	X
	UPDRS	X	X	X	X	X	X	X	X	X	X	X	X
	[redacted]												
	H&Y	X										X	
	Motor Complication Assessment (512 only)	X											
	Epworth Sleepiness Scale	X	X			X			X			X	
	Euroqol Quality of Life	X		X								X	
	ECG	X	X			X			X			X	X
	Prolactin (512 only?)		X		X	X		X		X		X	X

Study	Phase	Screening	Titration									Maintenance							FU
			Baseline																
SP513	*Visit*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Week	-4 to -1	1	2	3	4	5	7	9	11	13	14	18	22	26	30	34	38	42
	Day	-28 to -1	1	8	15	22	29	43	57	71	85	91	120	148	176	204	232	260	288
	PK Sample		X	X	X	X	X	X	X	X	X	X		X		X		X	X
	UPDRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	[redacted]																		
	H&Y	X																X	
	Epworth Sleepiness Scale		X									X			X			X	
	Euroqol Quality of Life		X															X	
	ECG	X	X		X		X					X			X			X	X

The sponsor fit the data using a population PK approach to a first order 1 compartment model with zero order absorption and a 3 hr lag time, and used absorption rate of dose/21 hours in spite of data for previous studies indicating that a zero order absorption and fixing the lag time and absorption rate was inappropriate.

Covariates examined included, age, gender, body weight, ClCr, total Bilirubin, and GGT. Due to the lack of renal elimination Clcr would not expected to be a significant covariate except in perhaps ESRD, if metabolized by CYP2D6, and since subjects were not in either renal or hepatic failure none of the lab values are expected to be significant covariates. Application site was not included as a covariate in the model even though this would be a logical covariate to examine. Lastly samples were only taken prior to patch removal and 1-4 hours post patch change, thus the sampling design is insufficient to define a structural model of error model given the variability in absorption seen with this formulation in other studies.

Study population numbers for both the efficacy and population PK analyses are shown in Table 38. It was unclear exactly how many samples were drawn and used in the pop PK analysis based on the sponsor's written report, thus some of these numbers are estimates. Tabulation of the true values would have required going through each line of the line listings In addition, Table 39 shows that the sponsor excluded a large percentage of samples for a variety of inappropriate reasons, most of which have to do with those samples exhibiting higher inter- or intrasubject variability. Thus even with the sponsor's own model the mean estimates are clearly off and variability is underestimated.

Table 38 Reported or Estimated Subject and PK Sample Disposition for Pivotal Phase III Efficacy Studies – SP512 Part I and SP513 Part I

Study		Efficacy Analysis Groups				PK Subgroup		
		Enrolled	Randomized	Primary Analysis	Completers	Subjects in PK Subgroup	Calculated Total Number of Samples to be taken	Number of Samples Reported as used in Pop PK
SP512	*Planned*	300	250	240		50[a]	600[b]	
	Reported	302	277	273		56	672[b]	449?
SP513	*Planned*	540	470	450		90	2160	
	Reported	610		561	409	26	347	90

a 10-12 subjects per arm
b 12 samples per subject(2 samples per visit) excluding baseline and FU visit
c 24 samples per subject (2 samples per visit) excluding baseline and FU visit

Table 39 Reported PK Sample Exclusion and Calculated Percentages for Pivotal Phase III Efficacy Studies – SP512 Part I and SP513 Part I

Study	Prior Sample's Concentration >2 higher or <0.5	Sample Weight Normalized Concentration >0.2 ng/ml/kg	Dose Normalized Concentration >2x individual's mean Dose Normalized Concentration or <0.5 individual's mean Dose Normalized Concentration	Sample marked as prior to patch change instead of post patch change[a]	Sample marked as post patch change instead of prior to change[a]	Total Number of Samples Excluded from Pop PK Analysis	Number of Samples Calculated or Reported as Obtained	% of Samples Excluded	% of Samples Used
SP512	48	10	84	13	16	171	449	50.9	49.1
SP513		4	134			138	90	60.5	39.5

a Based on reported sampling time

Table 40 shows the 24 Hour mean concentrations by dose during the titration phase as reported by the sponsor. There is some question as to dose proportionality from these numbers however it should be remembered that the sponsor inappropriately excluded data, there is no measure of variability, and for study SP 513 the titration phase went on for 13 weeks thus most samples were at the 18 mg dose. Therefore we can't say anything for certain based on this data.

Table 40 Sponsors' Reported Mean 24 Hour Concentrations by Dose During the Titration Phase for Studies SP512 and 513

Patch Strength (mg)	Dose Ratio	% of Subjects Titrated to Dose	24 hour Concentration During Titration Phase		Ratio of 24 hour Concentration at Each Titration Step	
		SP512	SP512	SP513	SP512	SP513
4.5	1	3%	0.27	0.259	1.00	1.00
9	2	6%	0.51	0.483	1.89	1.86
13.5	3	91%	0.76	0.691	2.81	2.67
18	4	—	—	0.810	—	3.13

Although the sponsor reported summary statistics for concentrations at each sampling time, due to the inappropriate data exclusion these metrics are not reliable and so are not reported here.

Table 41 shows the mean pre and post dose concentrations for maintenance doses in the pivotal phase III studies by dose and gender as calculated by the reviewer excluding concentrations of 0 ng/ml, most of which were clearly in the placebo group. The timing of the samples was inconsistent adding to the difficulty in interpretation. However it's interesting that the number of samples per study, 609 and 487, do not jive with the expected number of samples as calculated in Table 38.

Table 41 Mean Pre and Post Dose Concentrations for Maintenance Doses in Pivotal Phase III Studies by Dose and Gender

Study	512				513			
Dose	13.5 mg / 30 cm^2				18.0 mg / 40 cm^2			
Gender	Female		Male		Female		Male	
Sample	Predose	Postdose	Predose	Postdose	Predose	Postdose	Predose	Postdose
N	119	118	192	180	149	137	104	97
Conc. (ng/ml)	0.865 ± 1.332 (154.0) 0.11 - 13.4 [0.637]	0.713 ± 0.740 (103.8) 0.117 - 6.800 [0.579]	0.652 ± 0.438 (67.2) 0.122 - 2.5 [0.534]	0.821 ± 2.055 (250.2) 0.112 - 26.1 [0.573]	0.920 ± 0.599 (65.1) 0.125 - 2.53 [0.784]	0.915 ± 0.577 (63.1) 0.115 - 2.66 [0.78]	0.635 ± 0.503 (79.2) 0.119 - 3.260 [0.482]	0.683 ± 0.689 (100.9) 0.13 - 5.1 [0.453]

Table 42 shows that no obvious differences by age or sex.

Table 42 Steady-State Trough (pre- and post-dose) Concentrations by Gender and Age in Studies SP512 and SP513

Study	512				513			
Dose	13.5 mg / 30 cm^2				18.0 mg / 40 cm^2			
Age[a]	≥65		<65		≥65		< 65	
	72.4 65 - 84	72.5 67 - 81	56.5 42 - 64	53.6 44 - 63	68.4 66 - 79	67.3 65 - 70	52.0 37 - 62	51.5 41 - 63
Gender	F	M	F	M	F	M	F	M
N	90	84	62	154	53	38	179	121
Summary Statistics	0.953 ± 1.424 (149.4) 0.010 - 13.4 [0.707]	0.602 ± 0.395 (65.7) 0.066 - 2.020 [0.561]	0.885 ± 0.737 (83.3) 0.142 - 5.42 [0.693]	0.805 ± 0.496 (61.6) 0.0642 - 4.95 [0.703]	0.824 ± 0.580 (70.4) 0.108 - 2.000 [0.631]	0.772 ± 0.544 (70.4) 0.200 - 3.260 [0.703]	1.018 ± 0.614 (60.3) 0.017 - 2.660 [1.010]	0.710 ± 0.634 (89.3) 0.121 - 5.010 [0.489]

a Values for age are mean and range

Although Figure 20 and
Figure 21 are boxplots of both pre- and post-dose concentrations, they tend to confirm the sponsor's claim that pre-dose concentrations are stable for at least 6 months. Note that Figure 20 is truncated with regard to concentrations and measured concentrations were much higher, i.e. up to 26.1 ng/ml, (see Table 41).

Figure 20 Rotigotine Concentrations over Time – Study SP512

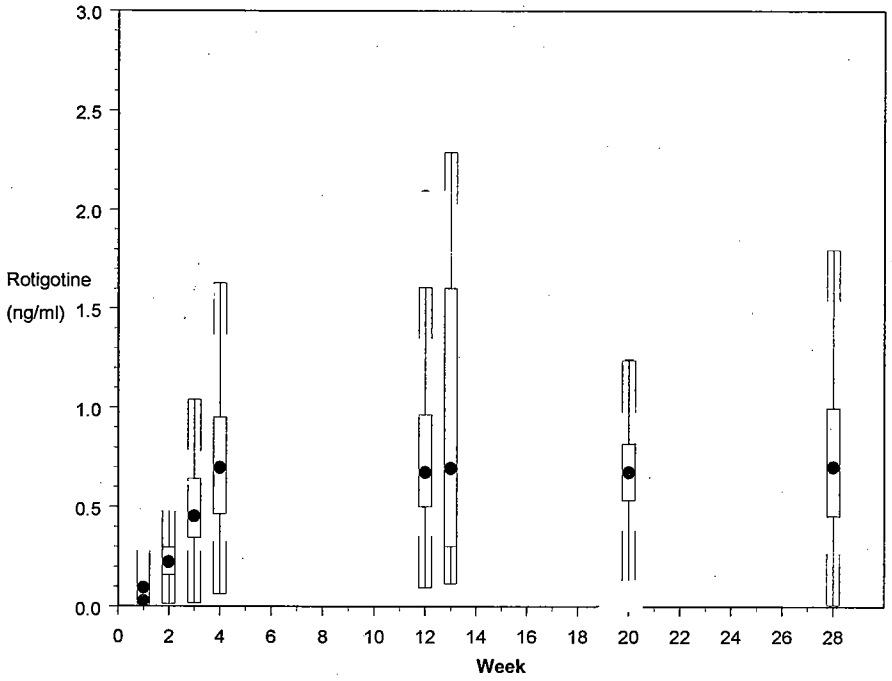
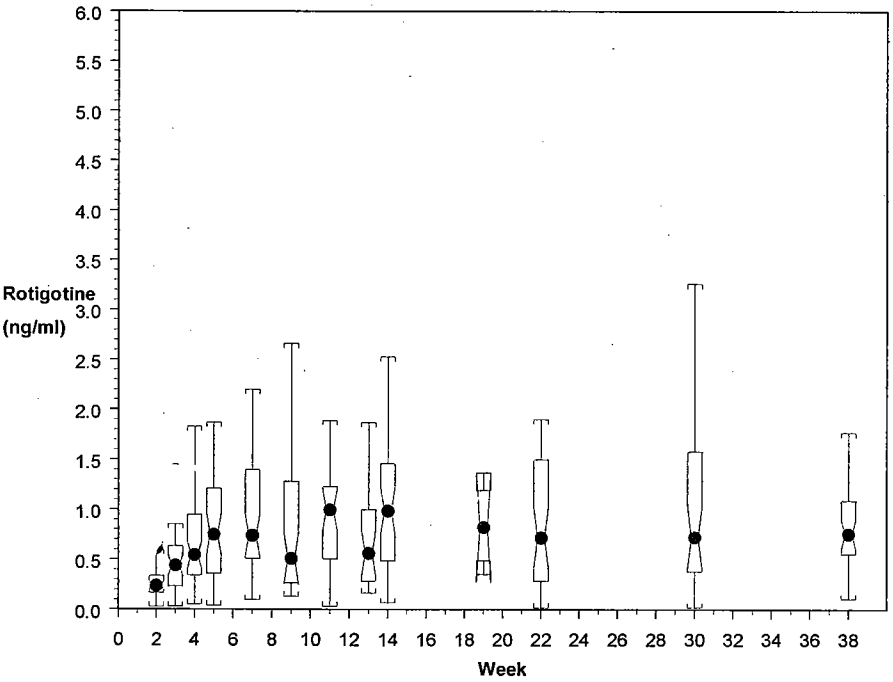


Figure 21 Rotigotine Concentrations over Time – Study SP513



3.5.3.2.2.2 Part II – Open Label Safety Extension Phase

In Part II of study SP512 the dose was retitrated up to 13.5 mg over 28 days, although dose adjustments could be made later, in addition the dose could be titrated up to 36 mg after 1 year or with the sponsor's permission during the first year. Although PK samples are obtained the sampling schedule was not clearly defined.

In Part II of study SP512 the dose was retitrated up to 18 mg over 28 to 40 days, although dose adjustments could be made later, in addition the dose could be titrated up to 36 mg after 1 year or with the sponsor's permission during the first year. PK samples were to be obtained each Visit during the first year of the study only.

So far the sponsor has not reported any PK data from these studies and indicates that the data is to be reported at a future time.

The sponsor should include PK samples beyond 1 year, especially in order to see the PK with the higher doses. Although no PD measures are being obtained, this could also be added to the protocol to allow for PK/PD examination, and correction for disease progression.

3.5.3.3 PK/PD QT Study – SP630

Study Design

Study SP630 was an open-label, multi-site, randomized uncontrolled multiple dose QT study in young and elderly male and female subjects. The planned enrollment was to be 12 subjects per group, (48 total), although the actual numbers were higher at 16 – 19 subjects per group.

Subjects were administered rotigotine via fixed titration schedule starting at a dose of 4.5 mg and increasing in steps of 4.5 mg every 6 days to a maximum dose of 18 mg, (days 1 – 24). This was followed by a 6 day maintenance phase at a dose of 18 mg, (days 25 - 30), and a 6-day de-escalation phase. Patches were applied to 6 different rotating sites, (abdomen, flank, upper arm, shoulder, thigh, and hip). 12 lead ECGs and plasma samples for PK analysis were taken at baseline, (day -1), and at the maximal dose of 18 mg on days 27 and 30. Sampling times for both ECGs and PK samples were at 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 23.5 hours post-application.

In addition, ECGs in triplicate via holter monitoring and PK samples were also taken on days, 25, 26, 28, and 29 at 0, 4, 8, and 12 hours post-application, as well as on a number of other days.

Due to the number of different application sites there are only a limited number of samples taken at each application site. Therefore even though typically there are differences in bioavailability between application sites, due the limited number of samples no differences could be detected.

Individually corrected QT values, (QTcI), were examined where:

$$QTcI = QT/(RR)^{\beta}$$

and the coefficient β is derived separately for each subject by regression of log QT on log RR using only the baseline ECG data. For each subject, a maximum of 48 ECGs, collected on Day -1 were available for this assessment. The mean value for β was then used in the analysis of the effect of rotigotine on QT.

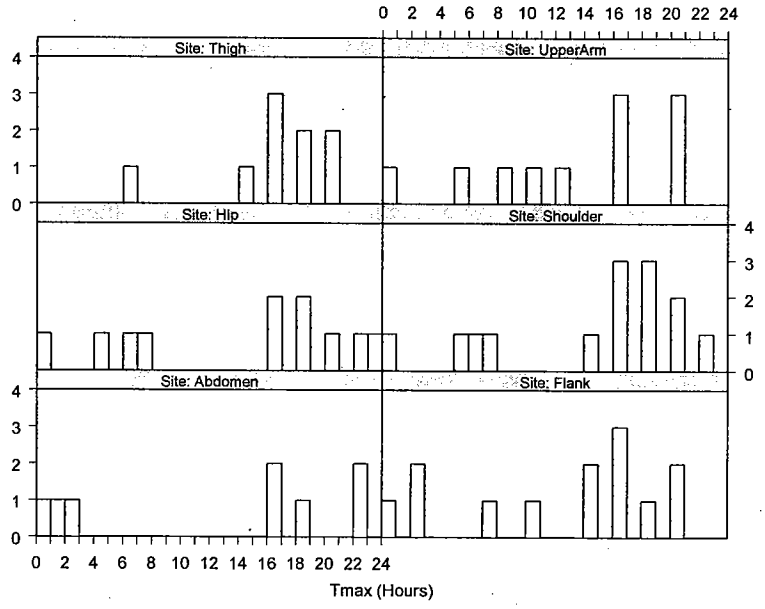
Results

A total of 70 subjects were enrolled and randomized; 63 subjects were analyzed for the primary pharmacokinetic (PK) variables and 58 subjects were analyzed for the primary pharmacodynamic variables. The reason for the difference in evaluable subjects for PK and PD is not clear.

As clear from the study design major design flaws include the lack of an active control group, and not using a high enough dose. Also the use of multiple application sites results in a small number of individuals with patch application at any one site and hides any differences in bioavailability and exposure.

Although the 12 lead ECGs were supposed to be used, the sponsor states that the report of the analysis of the effect of rotigotine on QTc was based on the holter ECG recordings, Based on the sampling schedule the use of holter monitoring is likely to miss the peak concentrations, (see Figure 22), and is unlikely capture the peak effect from any metabolites. Based on the time course of PVCs seen in Figure 12 the possibility of metabolite effects on ECG should be strongly considered.

Figure 22 Histograms of Tmaxs at Different Application Sites – Study SP630



According to the sponsor:

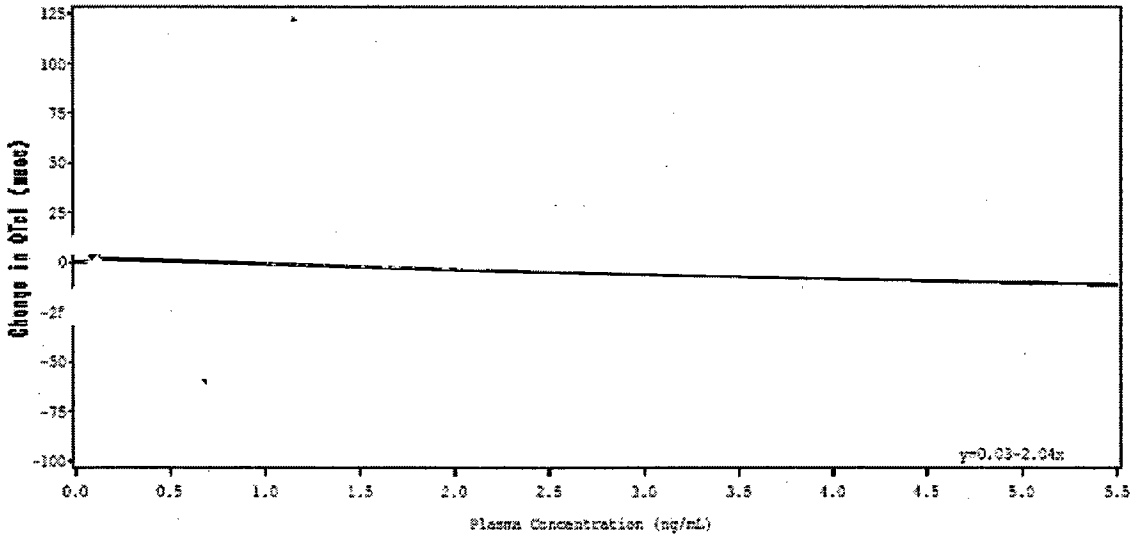
'The overall mean value for β was 0.436, and individual subject values ranged from 0.21 to 0.69. Therefore, at the extremes of this range, there are subjects who have an individual correction with a coefficient that is lower than that used in the Fridericia correction (0.333), and also some for whom the coefficient is higher than that used with the Bazett correction (0.5). While the presence of such extreme variations in the individual correction factors may be due to genuine physiological changes, it can also be related to sampling (statistical) variations and therefore add to the complexity of 'normalizing' the uncorrected QT interval to heart rate.'

In addition the sponsor states:

'Comparison of the subgroups on the basis of the QTcI coefficient shows that the mean value for the <65 years of age group is somewhat higher than that for the ≥65 years of age group (0.455 and 0.418, respectively). There is a larger difference between the gender groups (males = 0.397, females = 0.484). The presence of this difference implies that it might be inappropriate to use a single correction equation for the whole population (ie, QTcP); separate corrections for the male and female subsets might be more appropriate, but such a correction (apart from QTcI) was not pre-specified. The population, or trial-specific, correction QTcP was derived as follows: QTcP = QT/(RR)0.43 This correction factor falls approximately midway between the Fridericia and Bazett correction factors (0.33 and 0.5, respectively).

The sponsor's exploratory plot of QTcI vs. plasma concentration does not show a pattern indicative of QT prolongation, (see Figure 23). Although, the effects on the hERG channel were seen at a concentration of 150 nM whereas the highest concentrations in Figure 23 of around 5 ng/ml correspond to concentrations around one-tenth of that, (i.e. 15.8 nM; 1 ng/ml = 3.17 nM). Based on the Tmaxs in Figure 22, higher concentrations may be seen with an 18 mg dose, and even higher concentrations are likely to be seen with the doses to be used in advanced Parkinson's Disease. In conclusion, additional work and analysis will be needed to confirm the lack of an effect on QTc especially at higher doses.

Figure 23 Correlation of the Change in QTcI and Plasma Concentration of Unconjugated Rotigotine during the Maintenance Phase



Data source: Figure 3-05

Currently another QT study _____ is under development. Due to the possibility of metabolites effecting ECG, the any PK/PD correlation from the planned QT study that does not address specific metabolites would be suspect. With regards to dose, the primary goal for the study is to detect whether there is an effect on the heart or not, therefore lower doses need not be studied. However, if individuals from this study show a positive effect further examinations of dose response in these subjects might be useful. The possibility of skin irritation and increased absorption over time should also be considered in this study.

3.6 Drug Metabolism and Human Biomaterial Studies

3.6.1 Protein Binding

Mean (±SD) protein binding in human plasma was 89 (±1) in 5 samples at a rotigotine concentration of 62.5 ng/ml, which is above clinical concentrations.

A displacement interaction was performed with warfarin, however as rotigotine is cationic and warfarin is anionic, no displacement was expected or detected.

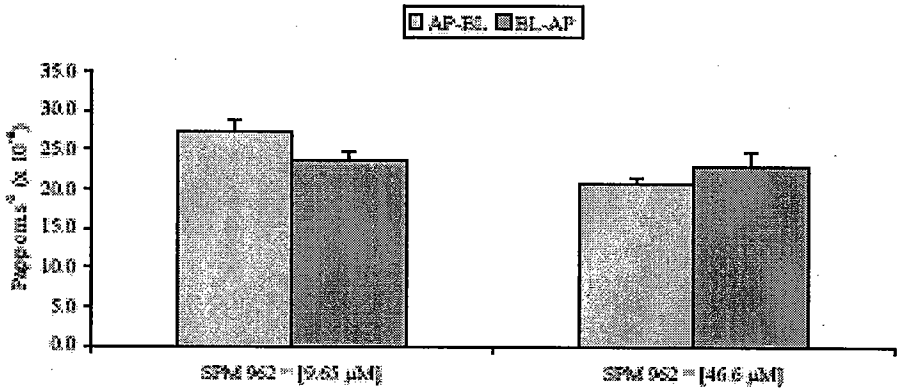
However, rotigotine is cationic and no protein binding studies were performed with α1-acid glycoprotein.

3.6.2 Cell Transport

Permeability experiments with rotigotine, (SPM 962), were conducted in CaCo2 cells. These experiments suggest that rotigotine is not actively transported by pGP nor is it an inhibitor of pGP. However, the experients were conducted at concentrations of approximately 10 and 47 µM, whereas the typical rotigotine peak concentration is around 3.2 nM. In addition, to a high inter-experimental variability some of the control experiments did not work as expected, possibly indicating differences between cells in different experiments. Results from these experiments are shown inFigure 24 to Figure 27.

Figure 24 shows equivalent bidirectional movement of rotigotine in CaCo2 cells indicating passive transport.

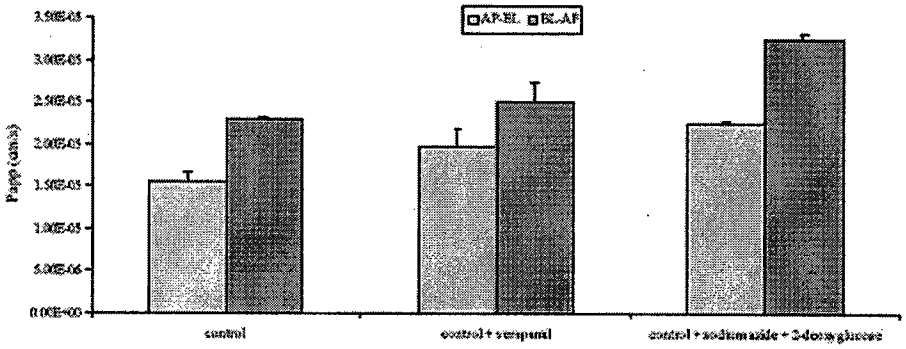
Figure 24 Permeability Coefficients of SPM 962 (9.65 and 46.6 µM) in the AP-BL and BL-AP Directions in CaCo-2 Cells



a Each bar represents the mean of three determinations ± standard deviation

Figure 25 shows the lack of effect of verapamil, an inhibitor of pGP, and sociium azide in combination with 2-deoxyglucose, a non-specific active transport inhibitor on the bidirectional movement of rotigotine.

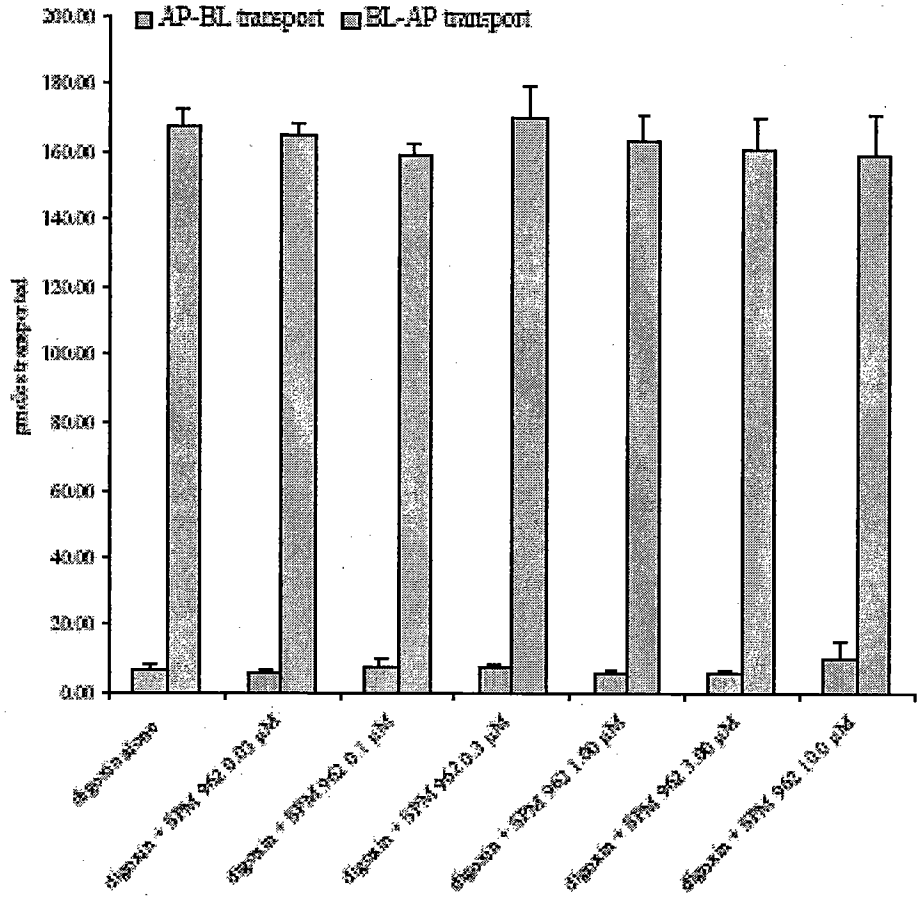
Figure 25 Transport of SPM 962 in the Absence and Presence of verapamil (100 µM) or Sodium Azide (15.0 mM) + 2-Deoxyglucose (50.0 mM).



a Each bar represents the mean ± standard deviation of three determinations. [SPM 962] for control = 46.7 µM; in the presence of verapamil = 46.6 µM; in the presence of sodium azide and 2-deoxyglucose = 47.3 µM

Figure 26 shows the lack of effect of varying concentrations of rotigotine on the active transport of digoxin by pGP.

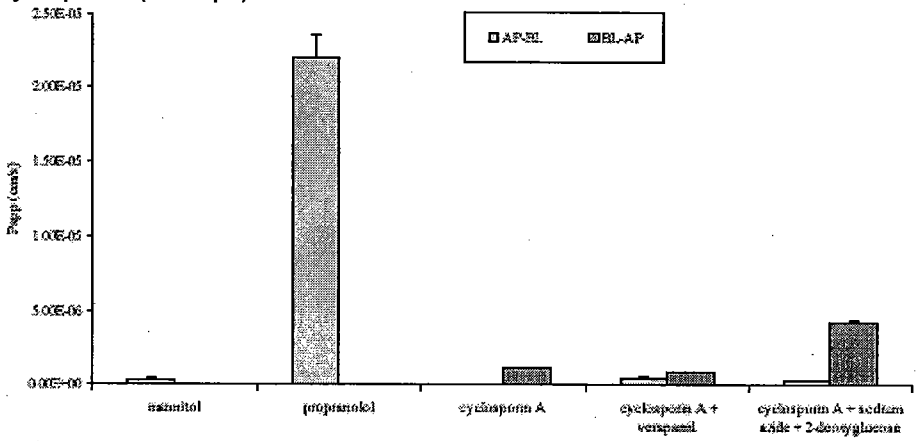
Figure 26 Effect of Varying Concentrations of SPM 962 (0.0300, 0.100, 0.300, 1.00, 3.00 and 10.0 µM) on the AP-BL and BL-AP Transport of [^{3}H]-Digoxin (5.00 µM)



a Each bar represents the mean of three determinations ± standard deviation except for AP-BL transport in the presence of 10.0 µM SPM 962, where n = 2.

Figure 27 shows the results of control experiments in CaCo-2 Cells with mannitol a marker of passive diffusion, propranolol and cyclosporine A, markers of active transport, and cyclosporine A with specific and non-specific active transport inhibitors.

Figure 27 Transport of permeability markers Mannitol (10.1 µM), Propranolol (100 µM) and Cyclosporin A (0.0476 µM) in CaCo-2 Cells



a Each bar represents the mean ± standard deviation of three determinations except for the AP-BL transport of Cyclosporin A where n = 2.

3.6.3 Metabolic Pathways

Figure 28 on the next page shows the metabolic pathways as reported by the sponsor with some possible additional pathways suggested by this reviewer.

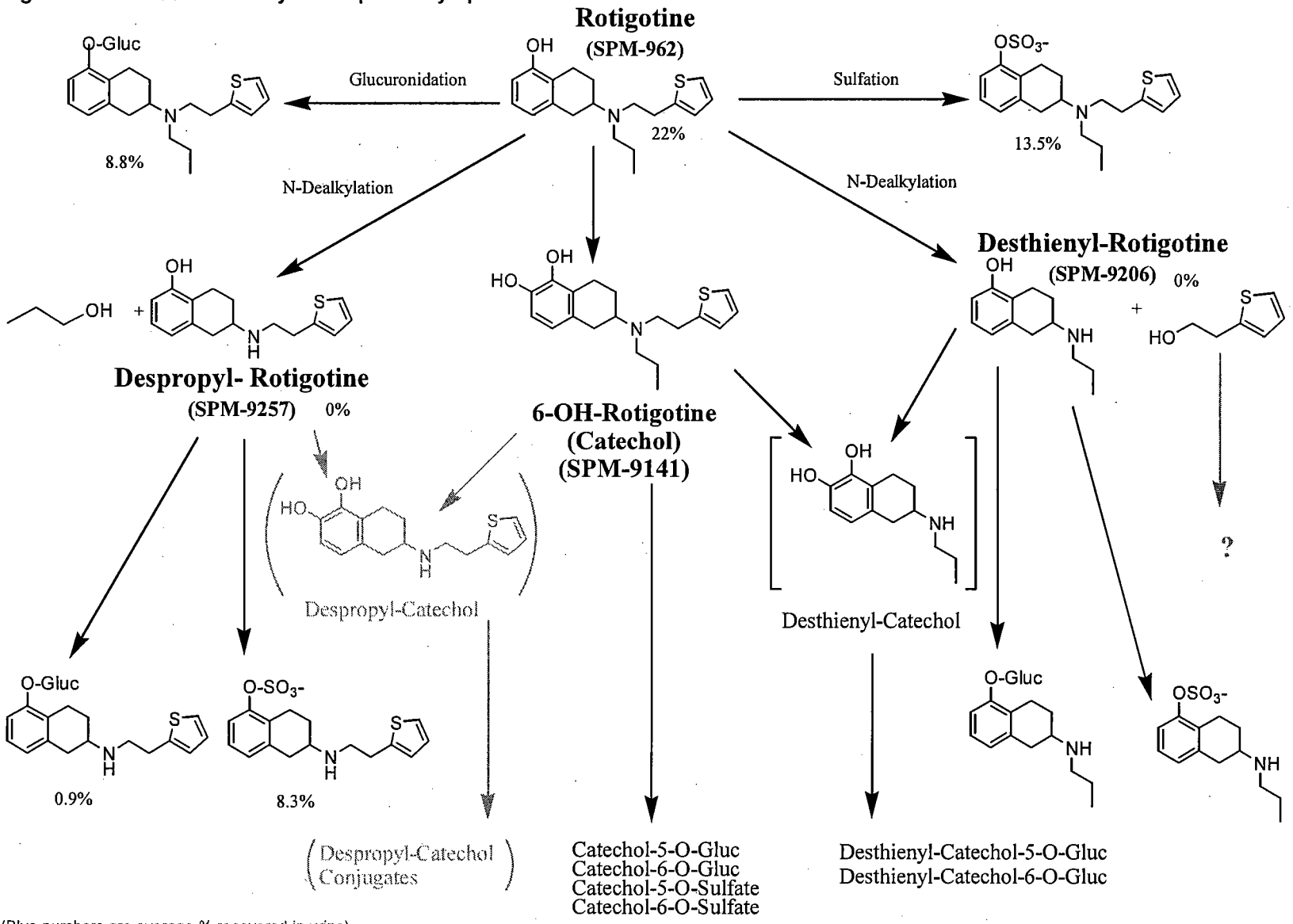
Rotigotine is directly conjugated at the 5 hydroxy to both a glucuronide and sulfate conjugate.

Rotigotine also undergoes N-dealkylation to form both an N-despropyl- and an N-desthienyl-metabolite. Coproducts from these metabolic reactons include propanol and thieny-ethanol respectively. Rotigotine is also oxidized at the 6 position to form a catechol.

The primary N-desalkyl metabolites can be secondarily oxidized to catechols, and all of the oxidative primary or secondary metabolites may be conjugated.

Figure 28 is not the complete metabolic pathway as the elimination of the despropyl-catechol and the thienyl-ethanol has not been described. However, the thienyl-ethanol could be β-oxidized, conjugated, and undergo S-oxidation.

Figure 28 Metabolic Pathways as Reported by Sponsor



(Blue numbers are average % recovered in urine)
(Pink not proposed by Sponsor)

3.6.4 Receptor and Transporter Binding

Except for dopamine receptor binding there did not appear to be any significant binding or inhibition to human receptors or transporters by rotigotine at clinically achieved concentrations. The only metabolites that were tested included the catechol, the despropyl and the desthienyl metabolites and of these, only desthienyl-rotigotine appeared to inhibit any receoptor or metabolite at clinical concentrations, and this was for dopamine D3 and D5 receptors, (see Table 43).

Table 43 Ki Values (nM/L) for Rotigotine and Selected Metabolites with Human Receptors and Transporters Showing Significant Binding[a]

Receptor	Rotigotine	Rotigotine (enantiomer)	*R-Sulfate*	*R-Gluc*	*6-OH cat*	*Cat 5-O-Gluc*	*Cat 6-O-Gluc*	*Cat 5-O-Sulfate*	*Cat 6-O-Sulfate*	Despropyl	*Despropyl Gluc*	*Despropyl Sulfate*	Desthienyl	*Desthienyl-Gluc*	*Desthienyl-Sulfate*	*Desthienyl Cat 5-O-Gluc*	*Desthienyl Cat 6-O-Gluc*
	SPM962 N923	N924			*SPM9141*					SPM9257			SPM9206				
D1	8.1																
D2	10.0																
D3	7.0, 0.71												7.6				
D4.4	15																
D4.2	3.9																
D4.7	5.9																
D5	4.5												9.5				
5HT1A	30																

a Metabolites in blue Italicized text were not tested by the sponsor

APPEARS THIS WAY
ON ORIGINAL

3.6.5 *In Vitro* metabolism

After completion of this section this reviewer found additional *in vitro* metabolism studies with human biomaterials listed in the preclinical pharmacology section of the NDA. This data will also need to be reviewed.

3.6.5.1 Metabolism

In vitro study DHGY-1012-00 examined the metabolic formation of desthienyl-rotigotine, despropyl-rotigotine, and the catechol metabolite by 100 pMol of heterologously expressed human CYP isozymes over 40 minutes in the presence of 70 μM of rotigotine, and the inhibition of these metabolites in pooled human hepatic microsomes. The results are shown in Table 44 and Table 45.

The primary isozymes responsible for metabolism as indicated Table 44 by appear to be CYP1A2, 2C19, and 3A4 although this is not totally consistent with the results of the inhibition experiments shown in Table 45. Extrapolation to clinical dosing may not be appropriate as clinical doses are in the 3 – 30 nM/L range compared to 70 mM in these experiments. Thus metabolism by certain isozymes may not be observed at these lower clinical concentrations.

Table 44 Heterologously Expressed Human CYP Isozymes 70 mM in over 40 min

Metabolite Formed		Heterologous Expressed CYP Isozymes										
Nominal Designation	***Code #***	**1A1**	**1A2**	**2A6**	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A4**	**4A11**
Desthienyl	***9206***	X	X		X	X	X	X	X		X	
Despropyl	***9257***	X						X			X	
Catechol	***9141***		X					X				
Unknown Metabolite								X				

Table 45 Inhibition of Rotigotine Metabolite Formation in Pooled Human Hepatic Microsomes

CYP	Inhibitor	% Inhibition of Metabolite Formation		
		Desthienyl	Despropyl	Catechol
		9206	9257	9141
1A2	Furafylline 10 μM	**41.0**	13.6	**42.2**
2A6	Methoxsalen 2.5 μM	35.1	-14.8	23.7
2C8	Quecetin 10 μM	20.8	16.4	35.0
2C9	Sulphapenazole 10 μM	22.5	22.6	21.8
2C19	Tranylcpromine 50 μM	**58.8**	**50.2**	**40.4**
2D6	Quinidine 1 μM	21.9	27.1	0.512
2E1	Diethyldithiocarbamate 50 μM[a]	***44.3***	5.69	**52.0**
3A4	Ketoconazole 1 μM	34.2	19.0	16.6

a Non selective

3.6.5.2 Inhibition

The ability of rotigotine and various metabolites to inhibit various homozygous expressed human isozymes was examined and an estimate of the IC50 and Ki was made based on an assumption of competitive inhibition. Neither rotigotine nor the 4 metabolites shown inhibit these CYP isozymes at clinically relevant concentrations. However, it should be noted that the reported Ki's for the controls are approximately 1 order of magnitude lower than is typically reported which raises questions as to the reliability of the reported data.

Table 46 Inhibition of Metabolite Formation by Rotigotine and Rotigotine Metabolites in Homozygous Human Isozymes Expressed in Insect Cells[a]

CYP	Ki (nMol/L)									
	SPM 962	SPM 5907	SPM 9257	SPM 9206	SPM 9141	Controls				
	Rotigotine	Rotigotine Glucuronide	Despropyl	Desthienyl	Catechol	Furafylline	Sulfaphenazole	Omeprazole	Quinidine	Ketoconazole
1A2	15,200	ND	ND	ND	44,000	540				
2C9	8600	ND	73,400	ND	1320		170			
2C19	900	ND	69,500	ND	940			1550		
2D6	200	57,000	300	8100	1300				6	
3A4	6600	ND	12000	>100,000	1000					14

a ND – No Inhibition detected

Additional inhibition experiments of rotigotine inhibition of CYP-2C19 and CYP-2D6 were also performed to identify the potential mechanism of inhibition. Full inhibition experiment data was fit by nonlinear regression to competitive, non-competitive, un-competitive, and mixed inhibition models, and the model that best fit the data was selected as the inhibition mechanism. Results are shown in Table 47. Unfortunately fitting data to a limited set of models is not an appropriate method for determination of mechanism.

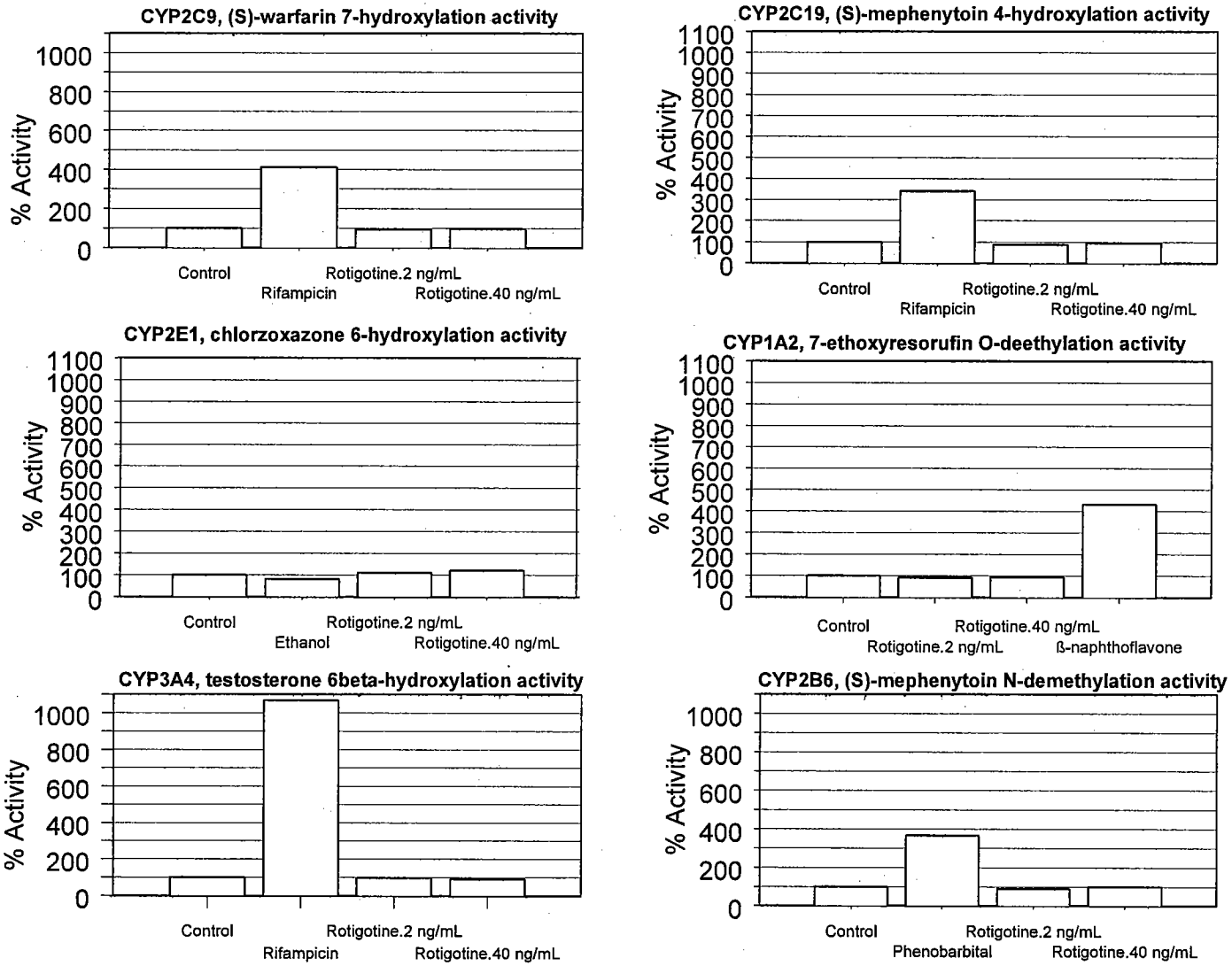
Table 47 Inhibition of Metabolite Formation by Rotigotine and Rotigotine Metabolites in Homozygous Human Isozymes Expressed in Insect Cell Lines

CYP Isozyme	Mechanism	Mean Ki (nMol/L)
2C19	Non-competitive	2200
2D6	Mixed	300

3.6.5.3 Induction

Rotigotine showed no indication of induction of CYP 1A2, 2B6, 2C9, 2C19, or 3A4 isozyme activities in human hepatocytes. There was no increase in of CYP2E1 activity by ethanol; however ethanol is an enzyme stabilizer and there was not enough detail to determine if the experiment was done properly, (see Figure 29).

Figure 29 Plots of Induction of P450 Isozyme Activities by Rotigotine in Human Hepatocytes



3.6.6 *In Vivo* Metabolism

3.6.6.1 Overview

In vivo metabolism was primarily addressed in two studies of radiolabeled drug, studies SP606 and SP610. Study SP606 employed radiolabeled rotigotine in a patch formulation, (formulation 3), and in study SP610 radiolabeled rotigotine administered IV over 12 hours, was compared to unlabeled rotigotine administered in a patch formulation, (formulation 3).

In addition, a number of other PK studies also measured selected metabolites of rotigotine in urine and/or plasma when unlabeled rotigotine was administered via a transdermal formulation, (see Table 48 for an overview of studies in which at least some metabolite PK information was obtained).

Table 48 Studies that Measured Radiolabeled Rotigotine or Rotigotine Metabolites

Study Number	Study Description	Matrices	Analytes	Comment
SP606	Radiolabeled Transdermal Patch Study	Plasma	Total Radioactivity Rotigotine	Radiolabeled Studies
		Urine Feces Skin Wash Skin Strip Patches	Total Radioactivity	
SP610	IV and Transdermal Patch Mass Balance Study	Whole Blood	Total Radioactivity	
		Plasma Urine Feces	Total Radioactivity Rotigotine '2 Major Metabolites'	
SP503	SD PK	Plasma	Rotigotine Catechol Metabolites	Metabolites Measured
SP630	Multiple Dose Rotating Patch Site, ECG Study in Young and Elderly Males & Females with an 18 mg Patch	Plasma	Rotigotine	
		Urine	Rotigotine and main metabs	
SP717	Japanese & Caucasian PK Study	Plasma	Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	
SP718	Japanese & Caucasian PK Study	Plasma	Rotigotine (unconjugated and total),	
SP671	PK in Hepatic Insufficiency	Plasma	rotigotine (unconjugated and total)	
		Urine	Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	
SP672	PK in Renal Insufficiency	Plasma	Rotigotine (unconjugated and total)	
		Urine	Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	
SP627	Cimetidine DDI Study	Plasma	Rotigotine (unconjugated and total)	
		Urine	Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	
SP628	Levodopa / Carbidopa DDI Study	Plasma	Rotigotine (unconjugated and total)	
		Urine	Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	
SP670	Domperidone DDI Study	Plasma	Rotigotine (unconjugated and total)	
		Urine	Catechol Metabolites Rotigotine (unconjugated and total), despropyl- and desthienyl-metabolites (unconjugated and total)	

3.6.6.2 Mass Balance and Radiolabeled Studies

3.6.6.2.1 Radiolabeled Transdermal System Study

Study SP606 measured rotigotine by LC/MS/MS in plasma and the recovery of total radioactivity in urine andfeces over 4 days after transdermal administration of a 4.5 mg patch in 6 individuals.

Figure 30 shows the erratic time course of rotigotine plasma concentrations after transdermal application. Although 4 subjects had peaks at 24 hours when the patch was removed, one subject, (Subject 5), had a peak at 48 hours and another subject had a peak at 12 hours.

The patch itself delivered about 50% of the dose, to the skin, however due washing and skin stripping only 45% of the dose was absorbed. Based on this experiment whether the patient washes the application site after removel or not may change the dose by 10% on average and up to >20%, (see Table 49).

Table 49 also shows that on average 90% of the Absorbed dose is recovered within four days, and that 70% of the absorbed dose is recovered in urine and 20% of the absorbed dose is recovered in feces. Since this study only examined total radioactivity it's not known to what extent rotigotine is metabolized before elimination in urine and feces.

Figure 30 Individual Plasma Concentration vs. Time Profiles of Rotigotine by LC/MS/MS in Study SP606

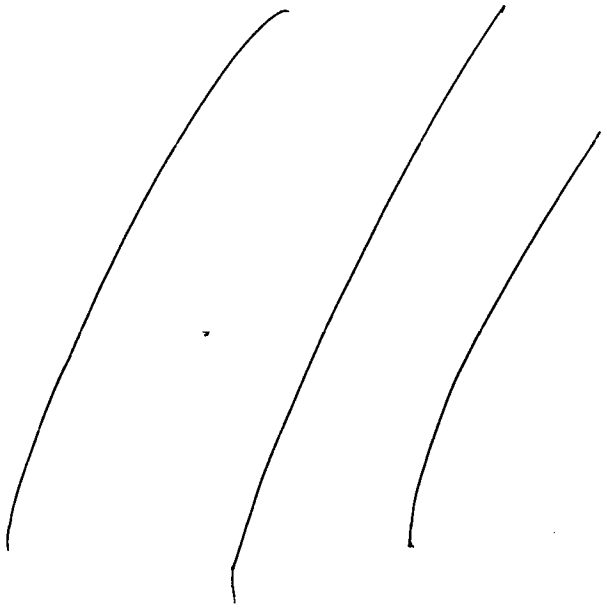


Table 49 Recovery of Radioactivity After a 24 hour Application of a Radiolabeled Rotigotine Transdermal System 4.5 mg / 10 cm^2 – Study SP606

% of Applied Dose Remaining in Patch	% of Applied Dose Delivered	% of Amount Delivered in Skin Wash	% of Amount Delivered in Skin Strip	% of Applied Dose Absorbed	% of Absorbed Dose Recovered in Urine over 4 days	% of Absorbed Dose Recovered in Feces Over 4 days	Total % of Absorbed Dose Recovered in Urine and Feces	Total % of Dose Delivered Recovered in Urine and Feces
49.0 ± 10.4 (21.1)	51.0 ± 10.4 (20.3)	11.6 ± 6.4 (55.2)	0.7 ± 1.1 (155.3)	45.1 ± 11.8 (26.1)	68.0 ± 9.4 (13.9)	22.1 ± 4.3 (19.6)	90.1 ± 7.1 (7.9)	78.8 ± 7.1 (9.1)
33.6 - 60.4 [52.4]	[47.6]	[9.2]	[0.3]	[43.6]	[66.3]	[23.0]	[92.2]	[78.5]

3.6.6.2.2 Radiolabeled IV Rotigotine Study

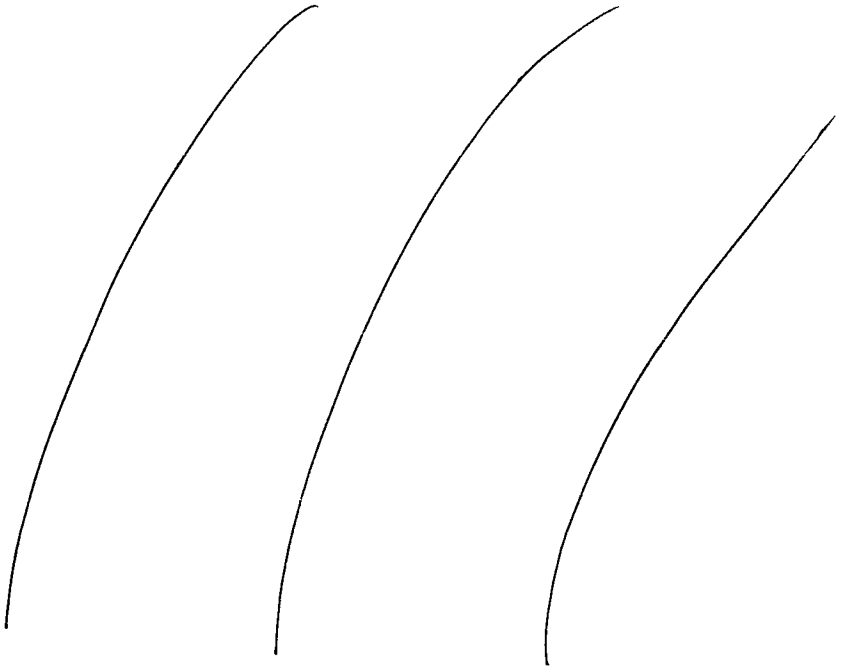
The sponsor also conducted a comparative two-way crossover absolute bioavailability study of 4.5 mg / 10 cm^2 rotigotine transdermal systems compared to IV administration of 1.2 mg of rotigotine infused over 12 hours, study SP610. By infusing ^{14}C labeled rotigotine in the IV arm of the study IV, this study was also able to serve as a mass balance study of rotigotine.

PLASMA EXPOSURES

Transdermal System Arm

Figure 31 shows individual concentration vs. time profiles for the transdermal system. As in the radiolabeled transdermal study SP606, erratic concentration vs. time profiles are observed.

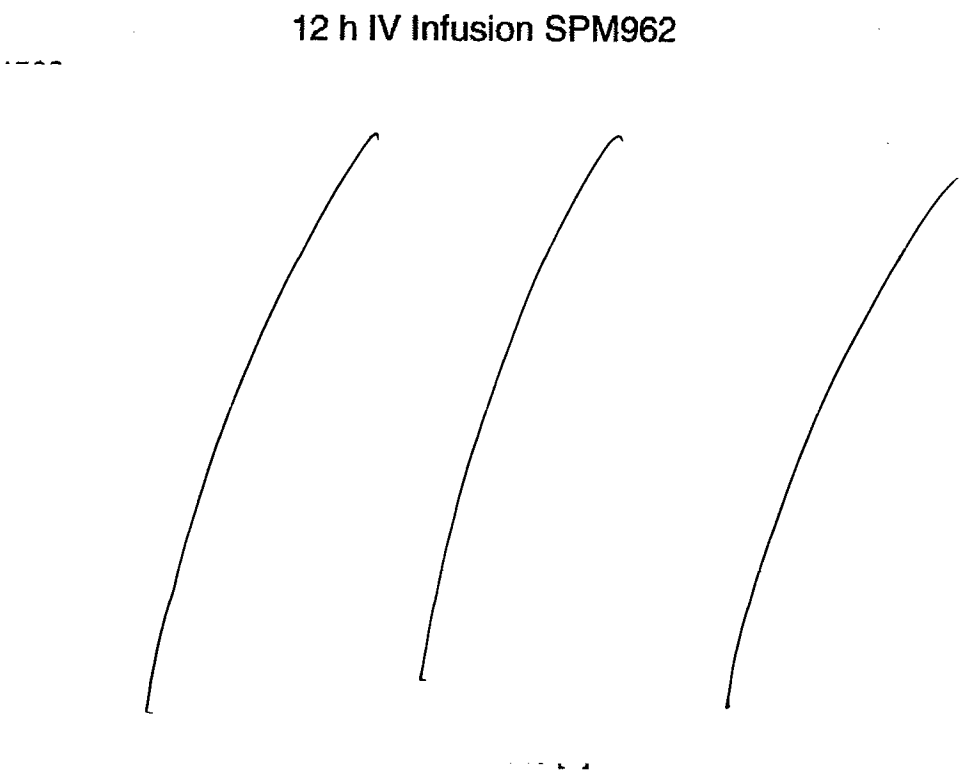
Figure 31 Individual Rotigotine Plasma Concentration vs. Time Profiles for a Single Dose of Rotigotine Transdermal System 4.5 mg / 10 cm^2 in Study SP610



IV Arm

Figure 32 shows concentration vs. time profiles of radiolabeled rotigotine in ng/ml, and selected metabolites in ng.eq/ ml, in pooled plasma samples after IV infusion. The mean exposures as measured by AUCs relative to rotigotine are approximately 3 fold for rotigotine sulfate, 15% - 20% higher for Despropyl-rotigotine sulfate, and lower for other metabolites. It should be noted that based on the total radioactivity recovered in plasma desthienyl sulfate and other conjugates probably refers to Desthienyl glucuronide, as approximate 45% of the total radioactivity in plasma was not assigned to any specific species, (see Table 50).

Figure 32 Pooled Plasma Concentration, (pg eq. / ml), vs. Time Profiles of Rotigotine and Selected Metabolites from 6 Subjects after Administration of 1.2 mg ^{14}C-Rotigotine IV over 12 hours – Study SP610



Value for t = 12 missing for SPM 962 sulfate, despropyl-SPM 962 sulfate and desthienyl-SPM 962 sulfate and other conjugates

Table 50 on the next page shows PK metrics for rotigotine after application of the transdermal system and PK metrics for total radioactivity, metabolites in plasma and whole blood, as well as in plasma for rotigotine and selected after IV administration.

The sponsor's metrics after transdermal administration do not match metrics calculated by the reviewer based on the raw data; however, they're in the same range, (see Table 50).

Radioactivity in plasma and whole blood indicate that there's some but limited penetration into blood cells.

Absolute bioavailability for the patch is estimated around 30% based on mean data. The most obvious discrepancy in the sponsor's data is the clearance estimate for rotigotine which is much higher after transdermal application than after IV administration. This could be due to the reported transdermal clearance being really Cl/F, although when I did the adjustments I got an estimated Cl/F or around 390 L/hr. In addition if the sponsor's mean AUCinf is an underestimate as suggested by my calculations transdermal Cl estimates might be lower. Another problem is that both Cl estimates would indicate that the steady-state concentration should be several ng/ml.

Table 50 Summary PK Metrics for Rotigotine, Total Radioactivity, and Selected Metabolites in Plasma and Whole Blood – Mass Balance Study SP610

Arm	Analyte	Matrix	Dose	Tlag	Tmax	Cmax	AUClast or AUCt	AUCinf[a]	% extrap	t1/2	Cl	
TDS	Rotigotine	Units	mg	hr	hr	ng/ml	ng/ml x hr^{-1}	ng/ml x hr^{-1}	%	hr	L/hr	L/hr/kg
		As reported by sponsor	2.90 ± 0.3 (10.8) 2.5 - 3.4 [2.9]	2.83 ± 1.3 (46.9) 1.0 - 4.0 [3.0]	15.5 ± 5.0 (32.6) 12.0 - 25.0 [14.0]	0.47 ± 0.11 (24.1) 0.38 – 0.65 [4.16]	8.275 ± 2.0 (24.4) 5.7 – 11.4 [8.3]	8.477 ± 2.0 (23.9) 5.9 – 11.7 [8.6]	1.98 ± 1.0 (48.5) 1.1 - 3.6 [1.7]	5.4 ± 1.3 (23.6) 3.7 - 7.3 [5.3]	352.2 ± 60.3 (17.1) 293.0 - 464.3 [339.5]	4.25 ± 1.1 (25.1) 3.5 - 6.3 [4.0]
		As Calculated by Reviewer			16.2 ± 4.8 (29.4) 12 - 25 [16]	0.54 ± 0.2 (30.6) 0.4 - 0.6 [0.5]	8.84 ± 1.9 (21.2) 5.9 - 11.4 [8.9]					
IV	Based on Total Radioactivity expressed as ng equiv. ml	Units	mg	hr	hr	ng eq./ml	ng eq./ml x hr^{-1}	ng eq./ml x hr^{-1}	%	hr		
		Plasma	1.193 ± 0.0 (0.63) 1.185 - 1.2 [1.194]	0.25	10.3 ± 1.5 (14.6) 8.0 - 12.0 [10.0]	4.2 ± 0.6 (14.5) 3.1 - 4.7 [4.3]	65.4 ± 12.3 (18.9) 44.5-79.5 [64.6]	69.7 ± 13.3 (19.1) 47.5 - 84.2 [68.9]	6.2 ± 1.1 (18.5) 4.9-7.6 [5.9]	12.8 ± 5.8 (45.5) 8.1 - 23.5 [11.5]		
		Whole Blood			12.0 ± 1.3 (10.5) 10.0 - 14.0 [12.0]	2.7 ± 0.5 (16.6) 2.1 - 3.3 [2.9]	44.5 ± 10.7 (24.1) 33.0 - 60.2 [43.9]	48.1 ± 11.5 (23.9) 36.0 - 65.7 [46.2]	7.4 ± 2.2 (29.5) 4.6 - 10.5 [7.7]	12.7 ± 5.1 (40.1) 7.3 - 22.3 [11.6]		
		Ratio[b] Whole Blood : Plasma			—	0.66+0.05 (8.2 0.58-0.74 [0.66]	0.69+0.17 23.8 0.41-0.93 [0.69]	0.70+0.17 24.8 0.43-0.97 [0.68]	—	—		
	Pharmacokinetic Metrics of Rotigotine and Selected Metabolites in Pooled Plasma Samples from 6 subjects Administered Radiolabeled Rotigotine IV over 12 hours											
						A[c] B[c] C[c]	A[c] B[c] C[c]	A[c] B[c] C[c]		A		
	Free Rotigotine	Pooled Plasma Samples	1.2	0.5[d]	8	0.51 12.1% **1.0**	5.97 9.1% **1.0**	6.13 8.8% **1.0**		2.48	182.7	
	Rotigotine Sulfate			0.5	8	1.48 35.2% 2.90	17.38 26.6% 2.91	17.7 25.4% 2.89		3.81		
	Despropyl-Rotgotine Sulfate			0.5	10	0.62 14.8% 1.22	6.91 10.6% 1.16	7.15 10.3% 1.17		10.28		
	Desthienyl-Rotigotine Sulfate and other Conjugates			1.0	6	0.29 6.9% 0.57	3.98 6.1% 0.67	e		2.51		
	Rotigotine Glucuronide			0.5	10	0.41 9.8% 0.80	3.36 5.1% 0.56	3.43 4.9% 0.56		3.09		
	Total Analytes			—	—	3.31 78.8% —	37.6 57.1% —	34.41 49.4% 56.1%[f] —				
Fabs	Rotigotine TDS / Rotigotine IV							0.30[g] 0.34[h]				

a AUCinf calculated based on average t1/2
b Some distribution into RBCs
c A – Mean value for analyte; B % = (Mean value for analyte / mean value for total radioactivity in plasma) * 100; C - Metabolite Exposures Relative to Rotigotine after IV Administration
d First sample time for pooled samples 0.5 hours
e Biphasic AUCt probably almost AUCinf
f AUCt of desthienyl metabolite included in total AUCinf calculation
g Mean Fabs = (mean AUCinf TDS/ mean AUCinf IV) x (Dose IV /Mean Delivered Dose po)
h Mean Fabs = (mean AUCinf TDS/ mean AUCinf IV) x (Dose IV /Mean Delivered Dose po*Estimated Fraction absorbed)

Fractional recoveries of radiolabeled rotigotine and rotigotine metabolites in urine and feces after IV administration are shown in Table 51. The sponsor's claimed urine and fecal recovery after IV administration is similar to those reported after transdermal administration, however, when this reviewer tallies the raw data the total recovery in urine is much less, and approximately 40% of the dose is not identified as to what species it is eliminated from the body as.

Table 51 Fractional Recoveries of Radiolabeled Rotigotine and Rotigotine Metabolites post IV Dosing – Study SP610

		% of Dose Recovered											
Matrix		**Total Rotigotine**	**Rotigotine Glucuronide**	**Rotigotine Sulfate**	**Despropyl-Rotigotine**	**Despropyl-Rotigotine Glucuronide**	**Despropyl-Rotigotine Sulfate**	***Total Despropyl-Rotigotine Conjugates (i.e. Despropylation) as Calculated by Reviewer***	**Desthienyl-Rotigotine**	**Other (*"Total"*) Metabolites Recovered as Claimed by Sponsor**	***Total Metabolites Recovered as Calculated by Reviewer***	**Total Parent & Metabolite Recovered as Reported by Sponsor**	**Difference in Total Recoveries as Calculated by Reviewer and Sponsor[b]**
Urine	Summary Stats	22.3 ± 3.5 (15.6) 18.9 – 26.8 [12.1]	8.8 ± 1.4 (16.2) 6.5 – 10.5 [9.0]	13.5 ± 3.5 (26.1) 10.0 – 18.5 [8.2]	BLQ	0.9 ± 0.3 (29.3) 0.6 – 1.3 [0.8]	8.3 ± 3.8 (46.1) 4.3 – 14.0 [9.6]	*9.3 ± 3.9* *(42.1)* *4.9 – 14.9* *[51.3]*	BLQ	11.7 ± 4.5 (38.7) 6.4 – 18.2 [21.0]	*34.6 ± 13.1* *(37.8)* *23.8 – 59.6* *[44.5]*	71.3 ± 8.4 (11.7) 61.1 – 82.1 [47.3]	28.1 ± 13.8 (49.3) 12.5 - 46.0 [23.6]
	Source	Table 4e	Table 4a	Table 4c		Table 4b	Table 4d	*Sum from Tables 4b& 4d*		Table 4f	*Sum of Tables 4a,c, b, d & f*	Table 5 & 6[c]	
Feces	Summary Stats	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ		BLQ	BLQ	—	23.4 ± 7.6 (32.3) 10.3 – 31.9 [59.2]	—
	Source											Table 7 & 8	
Urine and Feces											66.7 ± 16.8 (25.2) 40.5 - 84.8 [73.4]	94.8 ± 7.7 (8.1) 86.5 – 107.7 [95.3]	Ibid.

a BLQ – below limit of quantitation; Amounts of individual species in feces too low to quantify
b Difference = (Sponsor's Reported Value – Reviewer's Calculated Value)
c Values in sponsor's tables 5 and 6 don't match for 3 subjects (table 5 mean is 70.5%)

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Table 52 Recovery post IV dosing sponsor calc based on amt in patch my calcs based on amt delivered

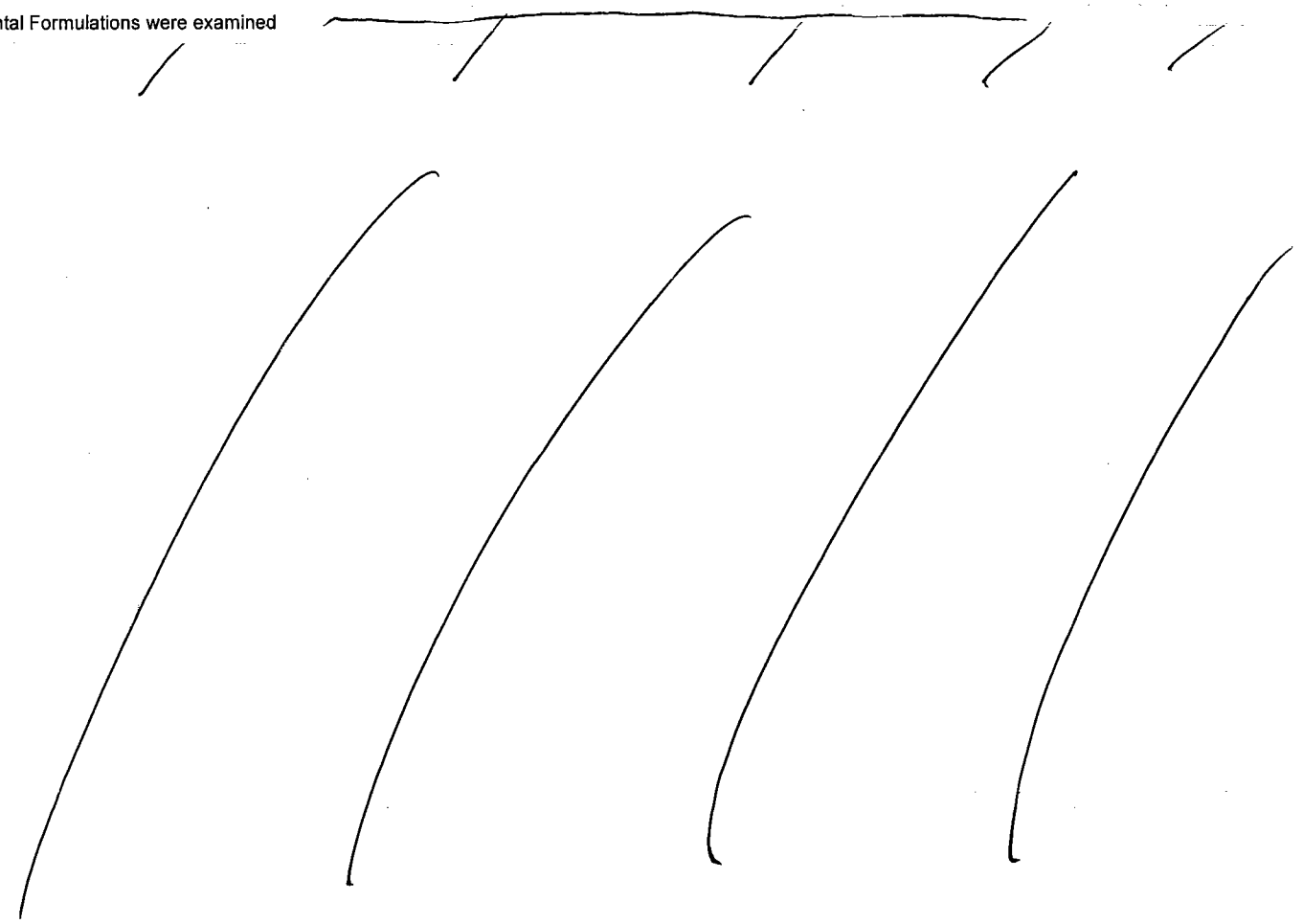
										% of Dose								
Rx	Matrix		Parent					Rotigotine Glucuronide	Rotigotine Sulfate	Despropyl-Rotigotine	Desthienyl-Rotigotine	Despropyl-Rotigotine Glucuronide	Despropyl-Rotigotine Sulfate	Total Metabolites Recovered as Claimed by Sponsor	Total Metabolites Recovered as Calculated by Reviewer	% Dealkylation calculated by Reviewer (i.e. despropylation)	Total Parent & Metabolite Recovered as Calculated by Reviewer	Total Parent & Metabolite % Recovered as Reported by Sponsor
			Total Rotigotine	Free Rotigotine	Rotigotine Conjug	Total Despropyl	Total Desthienyl											
TDS REK Calc	Urine (Renal Recovery)		12.8 ± 2.0 15.6 [redacted] 12.3	0.04 ± 0.03 62.6 [redacted] 0.03				±						3.5 ± 0.6 17.5 [redacted] 3.3				
% dose	Fecal		NR	NR										NR				
606	Urine																	
	Feces																	
	Total																	
									%	0 – 48	hours							
581	Urine	Ref		0.06 ± 0.04 (75.3) [redacted] [0.05]	20.5 ± 6.9 (33.5) [redacted] [19.2]	6.0 ± 2.0 (32.7) [redacted] [5.9]	1.9 ± 0.9 (46.9) [redacted] [1.6]										28.5 ± 7.3 (25.5) [redacted] [27.1]	
		Test		0.06 ± 0.04 (64.7) [redacted] [0.05]	22.8 ± 7.2 (31.8) [redacted] [21.4]	6.2 ± 2.0 (31.9) [redacted] [6.1]	1.9 ± 0.6 (34.1) [redacted] [1.9]				±						31.0 ± 8.1 (26.0) [redacted] [30.4]	

a Amount in Feces too low to quantify

3.7 Pharmacokinetics

3.7.1 Development Formulations

Two developmental Formulations were examined



3.7.2 Study Summaries

Due to the confusing nature of the submission, summary tables of the various aspects of the designs of the studies as well as of the results of various measurements were made. Summaries of the study designs may be found in §5.1 Appendix 1 - Study Designs beginning on page 228 in the following tables:

Table 103 Study Designs - List of Studies, Protocol Numbers, Study Dates, and Study Location
Table 104 Study Designs - Inclusion Criteria by Study
Table 105 Study Designs - Exclusion Criteria
Table 106 Study Designs - Exclusion Criteria
Table 107 Study Designs - Concomitant Medications
Table 108 Study Designs - Patch Application
Table 109 Study Designs - PK Sampling
Table 110 Study Designs - PD Measurements
Table 111 Study Designs - Safety Monitoring
Table 112 Study Designs - Tolerance and Adhesion
Table 113 Study Designs – Assays and Sample Handling

Selected results may be found in §5.2 Appendix 2 - Subject Demographics beginning on page 281, and in §5.3 Appendix 3 - Rotigotine Pharmacokinetic Metrics beginning on page 288 in the following tables:

Table 115 Rotigotine PK Summary Metrics by Study – Part 1
Table 116 Rotigotine PK Summary Metrics by Study – Part 2
Table 117 PK Outliers by Study

3.7.3 Single Dose Pharmacokinetics

In addition, to the radiolabeled studies SP606 and SP610, the single dose pharmacokinetics of the to-be-marketed formulation was examined in healthy volunteers in the studies summarized in Table 54. No single dose studies were performed in patients.

Table 54 Single Dose PK Studies of Rotigotine Transdermal Systems

Study no.	Description	Dose	Application Site
SP502	SD BE study of CTF to — , Development Formulations	4.5 mg	Trunk
SP581	SD Pivotal BE study of TBM to CTF	4.5 mg	Chest
SP503	SD & MD Study	4.5 mg	Trunk
SP606 & SP620	SD Radiolabeled Studies	4.5 mg	Forearm Upper Abdomen
SP596	SD Intrinsic Factor Ethnicity Study (Caucasians & Blacks)	4.5 mg	Abdomen
SP717	SD Intrinsic Factor Ethnicity Study (Caucasians & Japanese)	4.5 mg	Abdomen
SP672	SD Intrinsic Factor Renal Insufficiency Study	4.5 mg	Abdomen
SP626	SD Intrinsic Factor Application Site Study	4.5 mg	Ventral Abdomen Ventral Upper Arm Ventral / lateral upper leg

It should be noted that only the lowest titration dose was used, not the clinically efficacious doses of 13.5 mg and 18 mg.

In addition, several application sites studied in the phase III studies and proposed for labeling were not examined. This is significant as it's well documented that absorption and bioavailability can vary dramatically by application. Application sites studied in phase II and phase III studies are shown in Table 55.

Table 55 Transdermal Application Sites in Phase II and Phase III Studies

Study Numbers	Phase	Application Sites	Studied in Phase I PK Studies
SP506	II	Upper abdomen	X
SP512 SP513	III	Upper abdomen	X
		Lower Abdomen	X
		Thigh	X
		Hip	
		Flank	
		Shoulder	
		Upper Arm	X

Cmax, and AUCs of these single dose PK studies are summarized in Table 56, however, full summaries or pharmacokinetic metrics for these studies may be found in 5.3 Appendix 3 - Rotigotine Pharmacokinetic Metrics on page 288 and in other sections of this review where these studies are discussed in more detail.

Except for an early study that compared the CTF when it was first developed to the [redacted] formulation, most of the PK for exposure are comparable, (see Table 56). In a few cases where AUCs are higher, this is likely due to the application site where the skin may be thinner and the blood vessels closer to the skin. Other reasons for higher AUCs in certain studies may be due to body size, e.g. women vs. men. It's noteworthy that Tmax ranged from 4 to 34 hours.

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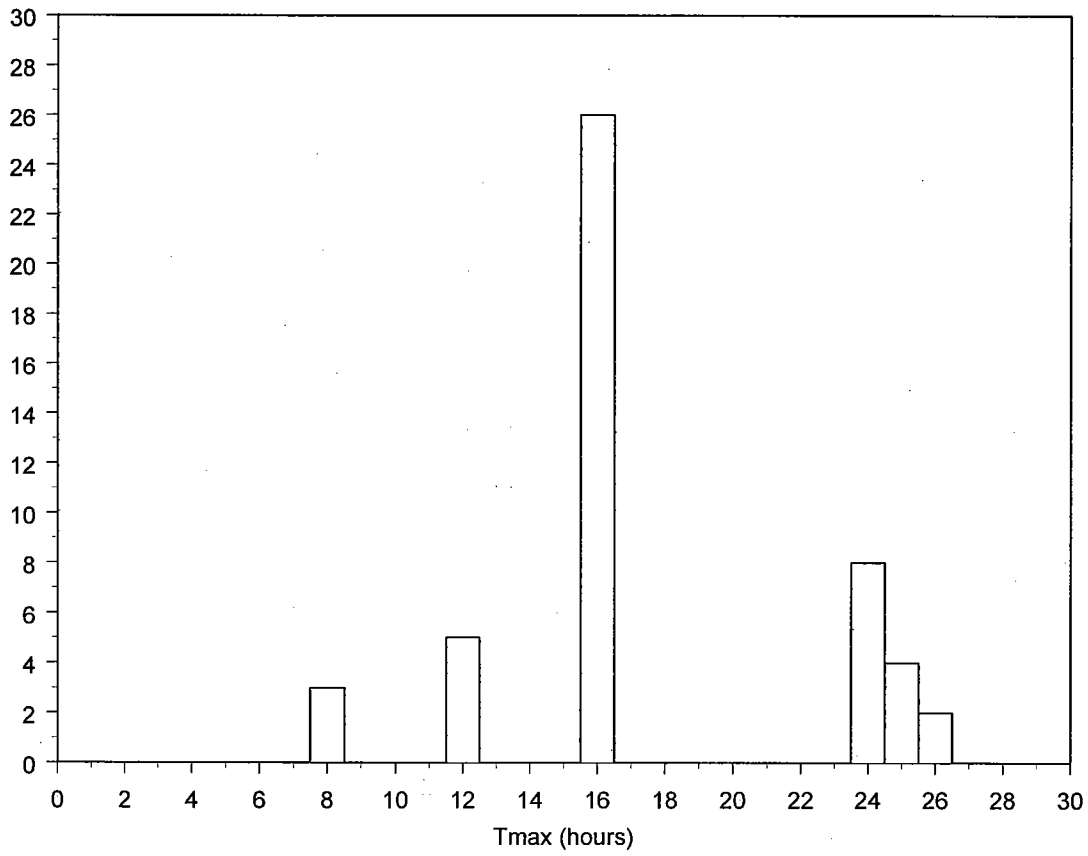
Table 56 Abbreviated Summary Statistics of Single Dose Pharmacokinetic Metrics in Healthy Volunteers

Study no.	Description	Dose	Application Site	Form	Arm/Pop	Tlag (hours)	Tmax (hours)	Cmax (ng/ml)	AUC (ng/ml x hr^{-1})	Detailed Study Report	
										Section	Page
SP502	*SD BA study of CTF to [redacted] Development Formulations*	*4.5 mg*	*Trunk*	*CTF*	*1 TDS*	*3.7 ± 1.3 (35.7) 2 - 6 [4]*	*19.3 ± 5.5 (28.5) 8 - 24 [23]*	*0.56 ± 0.19 (34.0) 0.32 - 0.98 [0.51]*	*11.3 ± 4.2 (36.7) 6.4 - 20.1 [11.2]*	§3.7.1	110
		9.0 mg			*2 TDS*	*3.3 ± 1.3 (39.1) 2 - 6 [4]*	*14.9 ± 6.3 (42.0) 8.0 - 24.0 [15.0]*	*1.19 ± 0.35 (29.4) 0.68 - 1.71 [1.28]*	*24.1 ± 8.6 (35.9) 10.9 - 36.5 [24.7]*		
SP581	SD Pivotal BE study of TBM to CTF	4.5 mg	Chest	TBM		4.1 ± 1.6 (38.0) 2 - 8 [4]	16.8 ± 6.9 (41.0) 4 - 27 [15]	0.31 ± 0.18 (57.4) 0.09 – 0.77 [0.25]	5.72+2.97 (51.9) 2.3 – 13.6 [5.06]		
		4.5 mg		CTF		4.3 ± 1.6 (38.4) 2 - 8 [4]	18.0 ± 6.5 (36.0) 4 - 26 [23]	0.31 ± 0.15 (49.5) 0.1 – 0.74 [0.27]	5.62 +2.68 47.6 2.36 - 13.4 [5.37]		
SP503	SD & MD Study	4.5 mg	Trunk	CTF		4.2 ± 1.8 (42.1) 2 - 12 [4]	20.3 ± 5.6 (27.9) 12.0 - 24.0 [24.0]	0.22 ± 0.23 (101.7) 0.04 - 1.28 [0.16]	4.5 ± 2.9 (64.1) 0.94 - 14.3 [3.7]		
SP606	SD Radiolabeled Studies	4.5 mg	Forearm	CTF		3.3 ± 1 (31) 2 - 4 [4]	23.7 ± 7 29.5 12 - 34 [24]	0.29 ± 0.16 (56.1) 0.11 - 0.56 [0.26]	11.2 ± 7.1 (63.2) 5.5 - 23.5 [8.85]	§3.6.6.2.1	104
SP610	SD Radiolabeled Studies	4.5 mg	Upper Abdomen	CTF		2.83 ± 1.3 (46.9) 1.0 - 4.0 [3.0]	15.5 ± 5.0 (32.6) 12.0 - 25.0 [14.0]	0.54 ± 0.2 (30.6) 0.4 - 0.6 [0.5]	8.5 ± 2.0 (23.9) 5.9 - 11.7 [8.6]	§3.6.6.2.2	105
SP596	SD Intrinsic Factor Ethnicity Study (Caucasians & Blacks)	4.5 mg	Abdomen	CTF	Caucasian	1.7 ± 0.5 (29) 1 - 2 [2]	17 ± 7 (39) 8 - 26 [15]	0.34 ± 0.13 (37) 0.18 – 0.61 [303])	6.4 ± 2.7 (41) 3.2 – 12.4 [5.7]		
					Black	2.9 ± 1.7 (59.7) 1 - 8 [2]	17.6 ± 6.4 (36.7) 8.0 - 27.0 [15]	0.34 ± 0.24 (70.2) 0.88 – 1.21 [0.31]	5.6 ± 2.5 (44.7) 0.94 – 10.8 [5.8]		

SP717	SD Intrinsic Factor Ethnicity Study (Caucasians & Japanese)	4.5 mg	Abdomen	TBM	Caucasian Female	4.3 ± 2.4 (55.1) 2 - 8 [4]	16.2 ± 4.8 (29.9) 8 - 25 [16]	0.29 ± 0.32 (108.4) 0.1 – 1.27 [0.22]	5.9 ± 6.7 (113.5) 0.2 – 26.0 [4.8]		
					Caucasian Male	5.5 ± 2.3 (41.4) 2 - 8 [4]	18.4 ± 6.5 (35.4) 8 - 26 [16]	0.20 ± 0.16 (78.5) 0.08 – 0.68 [0.16]	4.3 ± 3.4 (78.4) 1.8 – 14.7 [3.8]		
					Japanese Female	4.7 ± 2.7 (58.7) 2 - 12 [4]	18.1 ± 4.8 (26.5) 12 - 25 [16]	0.31 ± 0.97 (31.5) 0.1 – 0.51 [0.32]	6.2 ± 2.1 (33.4) 2.8 – 9.3 [6.3]		
					Japanese Male	4.2 ± 1.3 (32.1) 2 - 8 [4]	17.7 ± 4.0 (22.6) 12 - 24 [16]	0.20 ± 0.11 (55.1) 0.08 – 0.39 [0.16]	3.9 ± 1.9 (48.6) 1.6 – 7.4 [3.7]		
SP672	SD Intrinsic Factor Renal Insufficiency Study	4.5 mg	Abdomen	TBM		4.0 ± 1.9 (46.3) 2 - 8 [4]	17.5 ± 4.2 (24.2) 12.0 - 24.0 [16.0]	0.22 ± 0.11 (50.9) 0.09 - 0.43 [0.22]	4.6 ± 2.1 (46.4) 2.1 - 9.1 [4.1]		
SP626	SD Intrinsic Factor Application Site Study	4.5 mg	Ventral Abdomen	CTF		3.5 ± 1.4 (39.7) 2 - 6 [4]	18.5 ± 7.15 (38.6) 6.0 - 24.1 [23.0]	0.40 ± 0.22 (54.5) 0.14 – 0.93 [0.33]	7.8 ± 4.8 (61.5) 2.6 – 21.8 [6.4]		
			Ventral Upper Arm			2.9 ± 1.2 (40.3) 1 - 4 [2]	14.2 ± 7.6 (53.6) 4.0 - 25.0 [12.0]	0.50 ± 0.37 (73.9) 0.17 – 1.83 [0.42]	9.8 ± 6.62 (67.3) 3.3 – 31.5 [7.2]'		
			Ventral / lateral upper leg			2.5 ± 1.0 (41.2) 1 - 4 [2]	16.8 ± 7.72 (45.9) 6.0 - 24.0 [23.0]	0.57 ± 0.37 (65.0) 0.22 – 1.66 [0.43]	10.6 ± 7.3 (68.6) 3.6- 34.4 [8.5]		

Figure 33 shows a histogram of the distribution of Tmaxs after a single 4.5 mg dose in all subjects in study SP717 that was conducted in male and female Caucasian and Japanese subjects.

Figure 33 Distribution Histogram of Tmaxs after a Single 4.5 mg dose in Male and Female Caucasian and Japanese Subjects – Study SP717



3.7.4 Multiple Dose Pharmacokinetics

Table 57 shows a summary of the PK plasma sampling schedules in multiple dose studies, along with the maximum dose studied and treatment duration. This table clearly shows that most of the sampling schemes are clearly inadequate. Based on single dose studies a lack of a 3 hour sample may miss the true trough due to the lag time in absorption, and most of the studies done have samples between 14 and 23.5 or 24 hours. Base on the distribution of Tmaxs seen in the single dose studies, (see Table 56 and Figure 33), a large fraction of the Cmaxs and Tmaxs are a likely to be missed. Lastly, as rotigotine is irritating absorption can increase over time it applied to the same site.

Based on the design, study SP630 is most likely to represent the pharmacokinetics that would be seen with the treatment application used in the phase III studies.

Table 57 Summary of PK Sampling Schemes in Multiple Dose Studies

Study No	Description	Max Dose or Range	Duration of drug Rx[a]	Applic. Site	PK Sampling																										
					During Treatment																			Post D/C								
					Day(s)	Time Post Dose																		Day(s)	Time Post D/C								
						0	1	2	4	5	6	7	8	10	12	14	16	18	20	22	23	23.5	24		0	1	2	3	4	6	8	12	14	16	24	36	48
503	MD study	4.5 mg	13 days	Trunk	13	0			4				8		12								24	14	0	1	2	3	4	6	8		14		24	36	48
630	ECG study	18 mg	30 / 7	Same as Ph III	27 & 30	0	1	2	4	5	6	7	8	10	12	14	16	18	20	22		23.5		—												
718	Ethnicity Caucasian / Japanese	9 mg	6 days	Abdomen (flank)	6	0	1	2	4				8		12		16						24	7	0	1	2		4								48
671	Hepatic Impairment	4.5 mg	3 days	Abdomen (flank)	3	0	1	2	4				8	10	12							23.5	24	4	0		2		4	6		12			24	36	48
627	DDI Cimetidine	9 mg	4 days	Abdomen (stomach)	6	0	1	2	4				8		12							23.5	24	7	0	1	2		4	6	8	12		16	24		
628	DDI CD/LD	9 mg	2 days	Abdomen (flank)		0	1	2	4				8		12		16						24		0		2		4	6		12			24	36	
670	DDI Domperidone	4.5 mg	4 days	Abdomen (stomach)		0	1	2	4				8		12							23.5	24		0		2		4	6		12			24		
534 Part 1	Ph II	4.5 mg – 18 mg	28 / 7	Abdomen (stomach)	1,2-4, 8,15,22	0																		5 29	0 0	1	2		4	6	8	12					
Part 2		4.5 mg - 18 mg	28 / 7	Abdomen (stomach)	1,2-4, 8,15,22	0		2			6				12						23			29	0		2		4	6							
535	Ph II	18 mg	28 / 7	Abdomen (stomach)	1, 8, 15, 22	0		2			6				12						23			29	0		2		4	6							
540	Ph II	18 mg	28 / 6	Abdomen (upper/lower)	22, 27																23	23.5		29		1	2		4		8						
506	Ph II	18 mg	12 weeks		28, 49, 77																		24													
SP512	Ph III	13.5 mg		Back, shoulder area or upper arm, thigh hip	Intermit-tently																		24													
SP513		18 mg																					24													

a For studies reviewed in this section the first number is the total duration of drug treatment, the second number is approximate number of days at each dose level. This only applies thruogh study SP540.

The following studies in advanced PD and RLS were also multiple dose studies but were not reviewed: [redacted]

To minimize duplication only selected studies in Table 57 will be reviewed here. Other multiple dose studies will be reviewed in other sections that are more appropriate to their specific objectives, (see §3.5.3.2 Population PK/PD on 83 for the review of PK for studies SP506, SP512, and SP513).

The following criteria were used to select studies to review in this section:

- Studies with at least 6 days of treatment at the dose levels at which PK samples are drawn
- Studies with multiple blood samples over the dosage interval
- Total duration of treatment $\geq$ 12 days

This leaves the studies highlighted in blue, in addition to study SP630 in purple in Table 57.

Table 58 on the following page shows summary statistics for selected pharmacokinetic metrics for these studies.

It should be noted that the plasma for studies SP534 and SP535 were obtained on the first day of treatment at each dose level consequently the values in Table 58 are likely lower than the steady-state values, in addition, the lack of adequate sampling in these studies may also skew the estimates.

Studies SP503 and SP630 provide the most useful data.

In general we can make the following conclusions about the PK metrics from these studies.

Tmax and Tmin are highly variable and can occur at any time.

For the 18 mg dose the average Cmin is around 0.8 ng/ml, and average Cmax is around 1.5 – 2 ng/ml however Cmax is quite variable and may range up to 15 ng/ml.

More details on the first 3 studies, SP503, SP630, and SP 534 Part I, are presented in the following subsections.

Table 58 Summary Statistics for Some Pharmacokinetic Metrics from Selected Multiple Dose Studies

Study	Dose	Day(s)	N	Tmin (Hours)	Cmin (ng/ml)	Tmax (Hours)	Cmax (ng/ml)	Cmax:Cmin Ratio	AUC (ng/ml x hr^{-1})	R	t1/2 (Hours)
SP503	4.5 mg	13	29	10.5+10.4 (99.6) 0 - 24 [8]	0.18 ± 0.07 (40.1) 0.07 - 0.36 [0.17]	13.5 + 7.0 52.1 4 – 24 12	0.31 ± 0.16 (53.7) 0.08 - 0.93 [0.28]	1.87+0.87 46.5 1.2 - 6.0 [1.72]	6.1 ± 2.8 (46.1) 1.7 - 14.9 [5.6]	1.54 ± 0.51 (33.2) 0.70 - 2.90 [1.60]	4.4 ± 0.8 (16.9) 2.5 - 5.8 [4.3]
SP630	18.0 mg	27, 30	126	6.2 ± 6.5 (103.8) 0.0 - 23.5 [5.0]	0.50 ± 0.27 (54.2) 0.04 - 1.30 [0.43]	13.5 ± 7.4 (55.0) 0.0 - 23.5 [16.0]	1.55 ± 0.90 (58.1) 0.40 - 5.31 [1.29]	3.4 ± 1.5 (44.1) 1.6 - 11.2 [2.9]	22.2 ± 11.5 (51.7) 5.1 - 68.6 [19.1]		
534 Part 1	9.0 mg 13.5 mg				C24 data only, but over 28 days						
SP534 Part II	4.5 mg	1	8			18.9 ± 5.7 (30.2) 12.0 - 23.0 [23.0]	0.51 ± 0.44 (85.0) 0.24 - 1.56 [0.38]		6.2 ± 2.2 (36.1) 3.21 - 9.2 [6.0]		
	9 mg	8	8	1.25 ± 1.04 (82.8) 0.0 - 2.0 [2.0]	0.28 ± 0.13 (45.5) 0.15 - 0.50 [0.28]	11.1 ± 5.6 (50.7) 6.0 - 23.0 [12.0]	1.03 ± 0.39 (37.9) 0.73 - 1.91 [0.94]	3.96 ± 1.12 (28.4) 2.44 - 5.75 [3.99]	17.6 ± 6.7 (38.2) 12.4 - 32.7 [14.8]		
	13.5 mg	15	8	5.63 ± 8.14 (144.7) 0.0 - 23.0 [2.00]	0.64 ± 0.32 (49.7) 0.24 - 1.16 [0.60]	8.1 ± 7.5 (92.7) 0.0 - 23.0 [6.0]	2.45 ± 2.92 (118.9) 1.15 - 9.64 [1.44]	3.67 ± 2.39 (65.1) 1.61 - 8.31 [2.76]	27.0 ± 8.1 (30.2) 15.9 - 42.1 [27.1]		
	18 mg	22	7	2.3 ± 1.8 (78.7) 0.0 - 6.0 [2.0]	0.81 ± 0.21 (26.1) 0.61 - 1.23 [0.75]	7.7 ± 4.5 (58.8) 0.0 - 12.0 [6.0]	1.71 ± 0.55 (32.2) 1.16 - 2.78 [1.54]	2.16 ± 0.72 (33.5) 1.64 - 3.72 [1.90]	30.4 ± 8.3 (27.2) 22.1 - 42.9 [27.8]		
SP535	4.5 mg	1	8	7.9 ± 6.9 (87.0) 2.0 - 23.0 [6.0]	0.13 ± 0.13 (105.6) 0.03 - 0.42 [0.08]	18.9 ± 5.7 (30.2) 12.0 - 23.0 [23.0]	0.34 ± 0.13 (38.0) 0.16 - 0.51 [0.33]	5.52 ± 5.80 (105.1) 1.24 - 18.56 [3.71]	5.2 ± 2.4 (45.9) 1.5 - 8.5 [5.0]		
	9 mg	8	8	1.3 ± 1.0 (82.8) 0.0 - 2.0 [2.0]	0.28 ± 0.13 (45.5) 0.15 - 0.50 [0.28]	11.1 ± 5.6 (50.7) 6.0 - 23.0 [12.0]	1.03 ± 0.39 (37.9) 0.73 - 1.91 [0.94]	3.97 ± 1.12 (28.4) 2.44 - 5.75 [3.99]	17.4 ± 6.8 (39.2) 12.4 - 32.7 [14.7]		
	13.5 mg	15	8	2.8 ± 4.3 (155.2) 0.0 - 12.0 [1.0]	0.62 ± 0.28 (45.2) 0.24 - 0.99 [0.60]	11.8 ± 7.4 (63.2) 6.0 - 23.0 [9.0]	1.42 ± 0.36 (25.8) 0.83 - 2.02 [1.44]	2.75 ± 1.59 (57.9) 1.61 - 6.34 [2.03]	25.9 ± 6.2 (23.9) 15.9 - 33.4 [27.1]		
	18 mg	22	7	2.3 ± 1.8 (78.7) 0.0 - 6.0 [2.0]	0.81 ± 0.21 (26.1) 0.61 - 1.23 [0.75]	8.6 ± 3.2 (37.4) 6.0 - 12.0 [6.0]	1.68 ± 0.57 (34.0) 1.16 - 2.78 [1.54]	2.13 ± 0.75 (35.3) 1.43 - 3.72 [1.90]	30.4 ± 8.3 (27.2) 22.1 - 42.9 [27.8]		

3.7.4.1 Study SP503

Study SP503 was a multiple dose PK study in healthy volunteers that examined the PK of a 4.5 mg dose applied to the trunk on days 1 and 14.

Figure 34 shows the time metrics for a 4.5 mg dose of Rotigotine in study SP503. Tmin and Tmax were not sampled during between 12 – 24 hours when Tmax and Tmin are most likely to occur so these distributions are biased. The distribution of Tlag on day 1 is of most interest showing that a 3-4 hour tlag is common although it can extend up to 12 hours.

Figure 34 Histogram of Rotigotine Time Metrics, (Tlag, Tmin, & Tmax), on Day 1 and 14 of Treatment with 4.5 mg TDS QD– Study 503

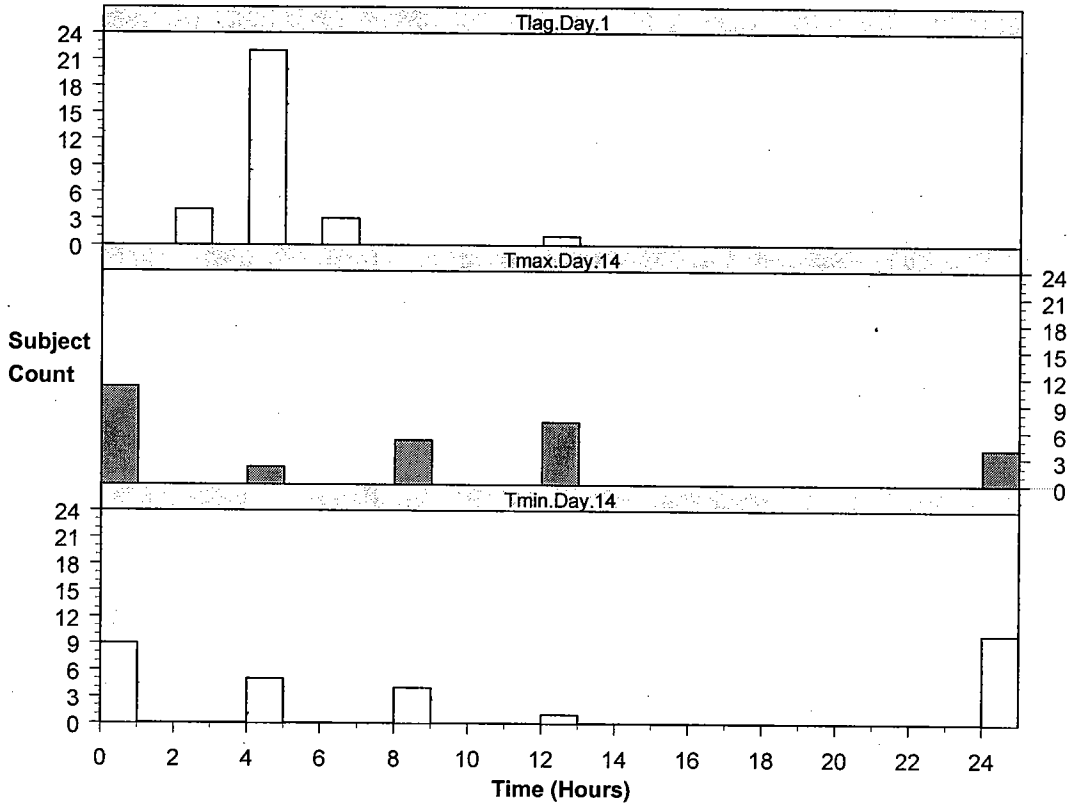


Figure 35 and Figure 36 show plasma concentration profiles for rotigotine 4.5 mg on the first day and 14th days of dosing respectively. The main point of these plots is the approximate 1.5 – 2 fold degree of accumulation. However, the effects after longer treatment periods with higher doses was not examined.

Figure 35 Rotigotine Plasma Concentration vs. Time Profiles on Day 1 of 4.5 mg /day Dosing - Study SP503

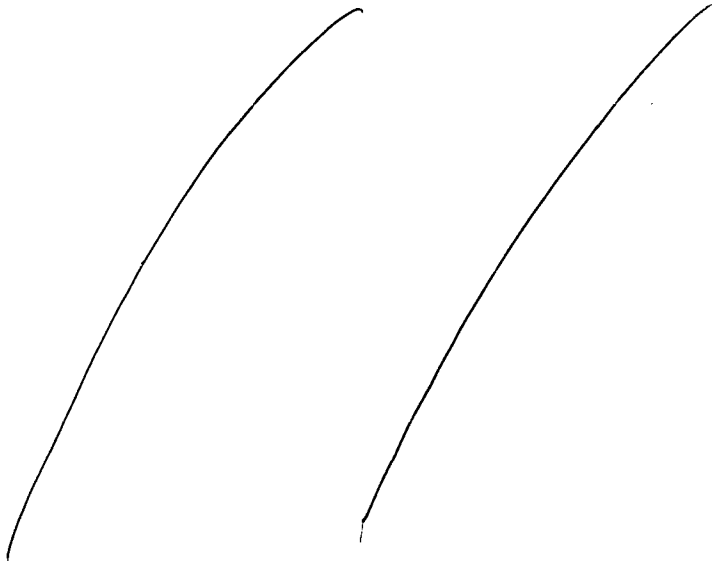


Figure 36 Rotigotine Plasma Concentration vs. Time Profiles on Day 13 of Treatment (4.5 mg / Day) and Days 14 and 15 after discontinuation – Study SP503

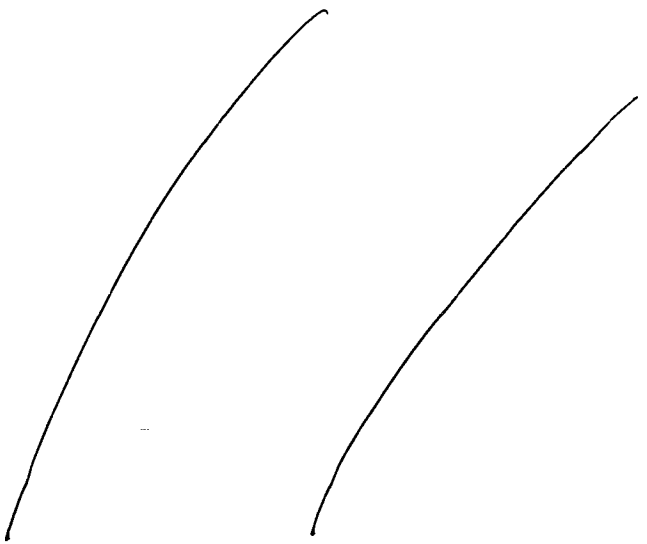
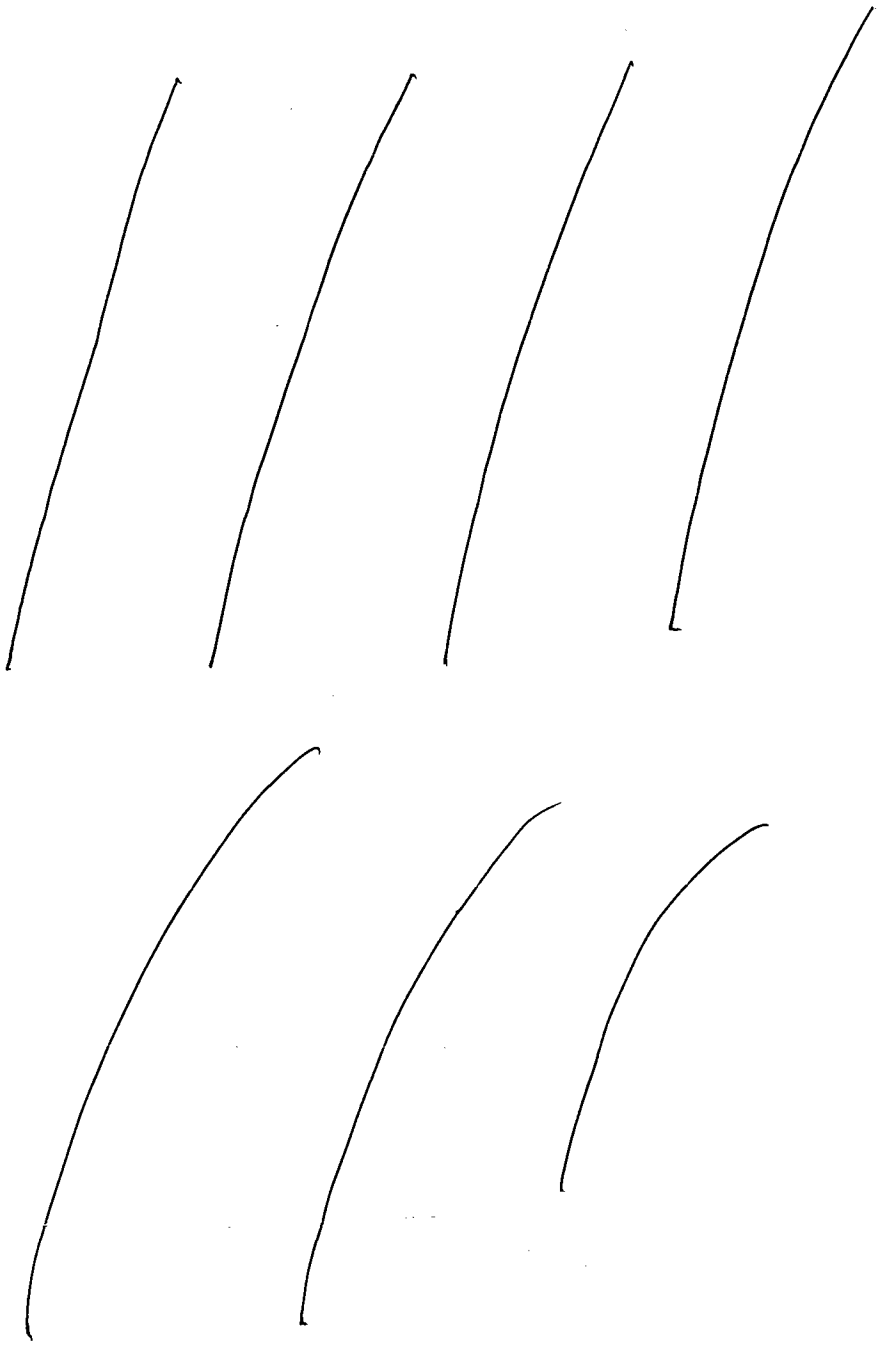


Figure 37 shows the concentration vs. time profiles on the first day, the last day of dosing, and after removal of the last patch, concentration when the patch is changed each day over a 2 week interval. This shows the variability possible when samples are only obtained when the patch is changed.

Figure 37 Individual Subject Concentration vs. Time Profiles for Rotigotine 4.5 mg over 2 weeks – Study SP503



Time (Hours)

3.7.4.2 Study SP630

Study SP630 was a multiple dose PK/PD QT study in healthy volunteers. Subjects were from 4 subgroups as follows:

Males < 65 yo
Females < 65 yo
Males ≥ 65 yo
Females ≥ 65 yo

The plan was to complete 12 subjects per group although more subjects in each group actually completed the study for a total of 63 subjects. Subjects were titrated up to a dose of 18 mg / day in steps of 4.5 mg in weekly intervals.

The patch was applied in a rotating sequence to one of six bilateral sites. Consequently, the effect of application site cannot be adequately assessed due to the limited number of subjects, and will add to the variability in exposure and PK metrics.

Twentyfour hour concentrations were obtained after 1 or 6 days of dosing at each of the 3 lower doses, (4.5 mg, 9 mg, 13.5 mg), and more extensive sampling was performed at the 18 mg dose. Table 59 shows these 24 hour concentrations along with the 24 hour concentrations after the first and last dose of 18 mg /day. When the outlier at 13.5 mg is excluded it appears that there is likely linearity with dose.

Table 59 Linearity of Twenty-four Hour Concentrations with Dosages from 4.5 mg to 18.0 mg – SP630

Dose (mg)	4.5 mg / 10 cm^2	9.0 mg / 20 cm^2	13.5 mg / 30 cm^2		18.0 mg (2 x 9.0 mg / 20 cm^2)	
Day of Rx	6	13	19		25	30
Day of Rx with Dose	6	7	6		6	11
N	63	63	63	62	63	63
C_{24} (ng/ml)	0.168 ± 0.100 (59.6) [0.143]	0.413 ± 0.313 (75.7) [0.318]	0.829 ± 1.782 (214.9) [0.559]	0.609 ± 0.339 (55.7) [0.546]	0.790 ± 0.500 (63.4) [0.684]	0.811 ± 0.368 (45.3) [0.760]

Pre-dose data along with all pre-dose concentrations at 18 mg are plotted by dose in Figure 38 and Figure 39. Figure 38 shows the total variability in pre-dose concentrations seen, i.e. up to ~14.5 ng/ml, and Figure 38 along with Figure 39 show the apparent dose linearity in pre-dose concentrations.

Figure 38 Rotigotine Pre-dose Concentrations by Dose Level - Study SP630

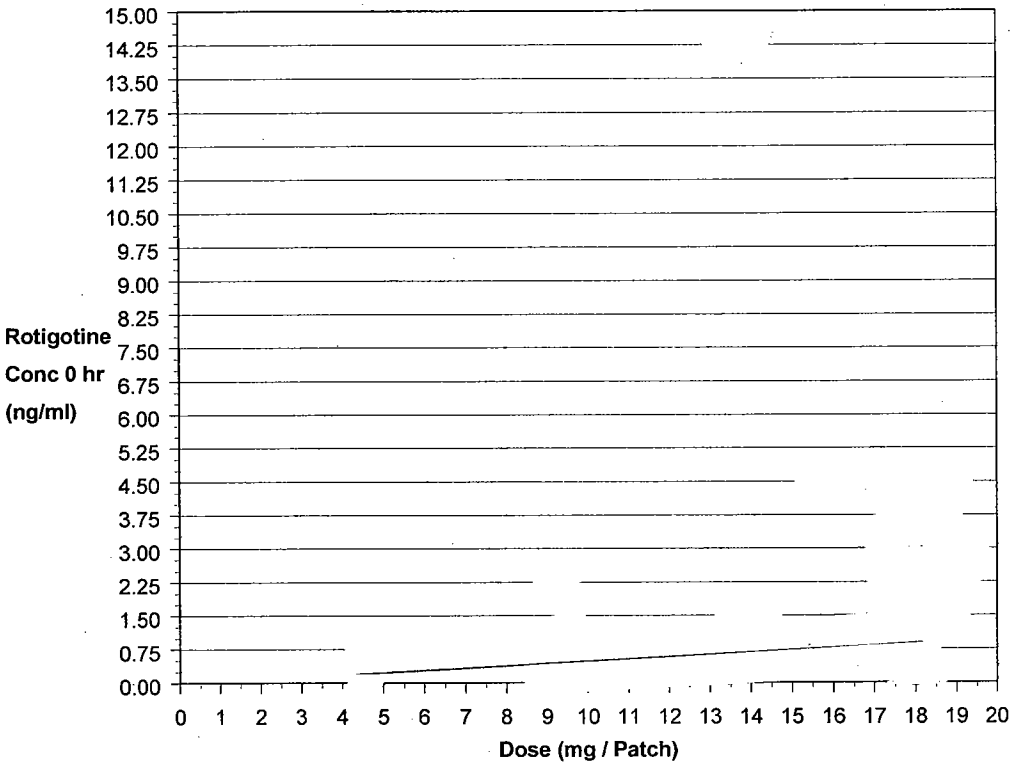
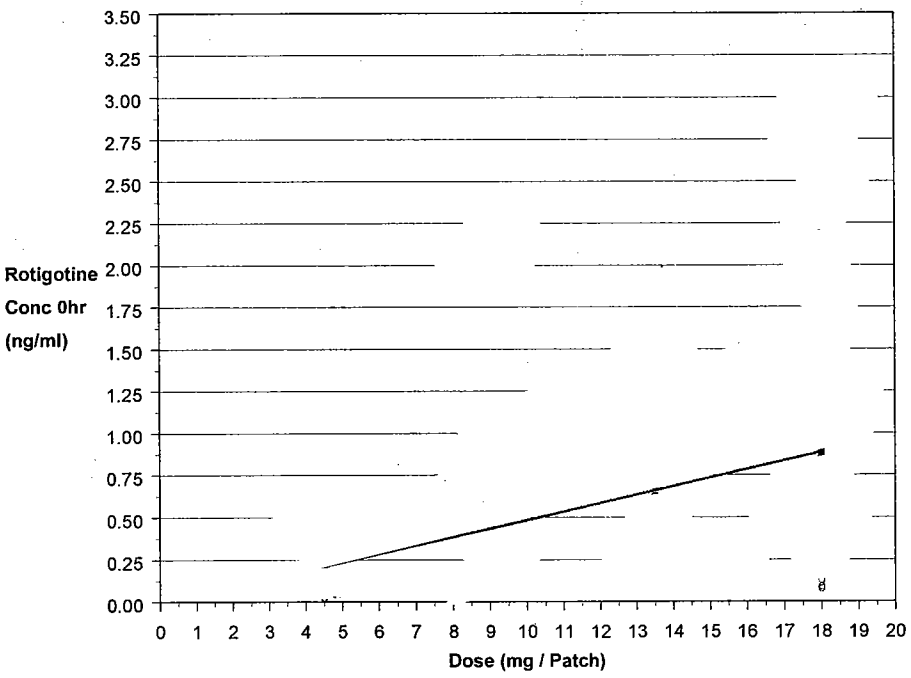


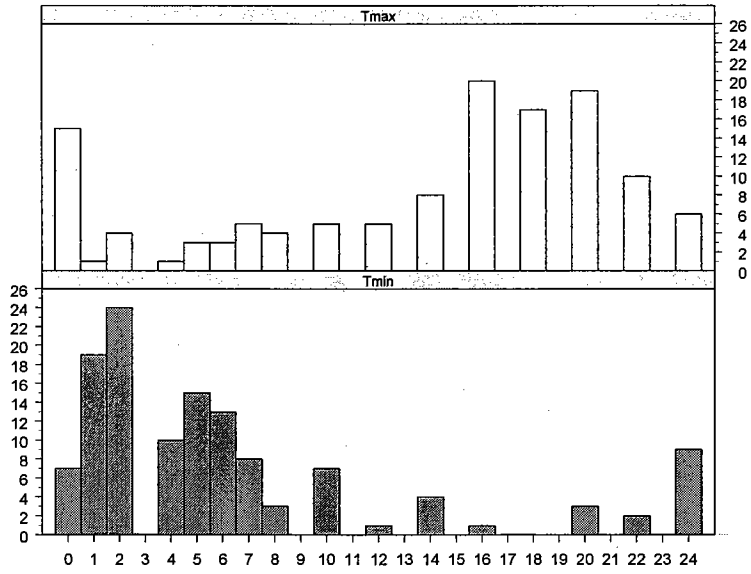
Figure 39 Truncated Rotigotine Pre-Dose Concentrations by Dose Level- Study SP630



Full PK profiles were obtained at the highest dose, (18 mg) on days 27 and 30. Histograms of time metrics and of Cmax and Cmin from these profiles are shown in Figure 40 and Figure 41 respectively.

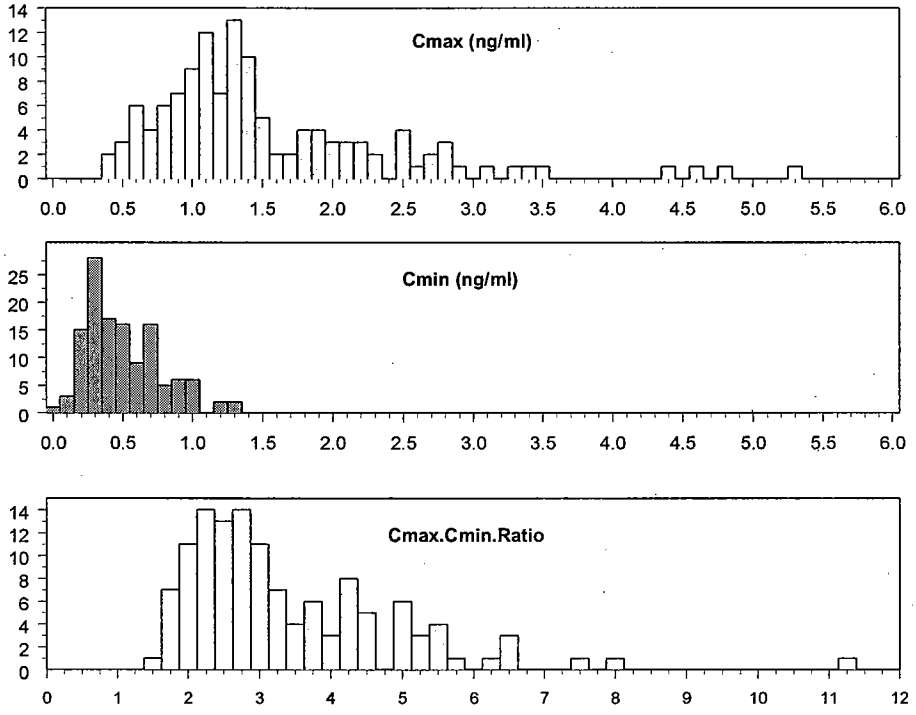
Although Cmax and Cmin may occur at any time, most Tmaxs occur between 16 and 24 hours post-dose, and most Tmins occur between 0 to 8 hours post-dose.

Figure 40 Histograms of Rotigotine Time Metrics during a 24 hour Dosage Interval for All Subjects on Days 27 and 30 (n = 126) – Study SP630



Cmaxs are typically just above 1 ng/ml, although many are up to 3 ng/ml (see Figure 41), and some individuals may have Cmaxs up to 15 ng/ml, (see Figure 38). Cmins are typically less than 1 ng/ml, weith Cmax to Cmin ratios typically around 2.5 although they range up to >11 fold, (see Figure 41).

Figure 41 Histograms of Rotigotine Maximum and Minimum Concentrations during a 24 hour Dosage Interval and Cmax:Cmin Ratios for all Subjects on Days 27 and 30 (n = 126) – Study SP630



Most individuals have rotigotine concentrations between 0.5 - 1.5 ng/ml as shown by the concentration vs. time profiles by group in Figure 42 to Figure 45. With the variability in the time course of plasma concentrations over a day shown in Figure 46 to Figure 49.

6 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

3.7.4.3 Study SP534 – Part I

Figure 50 and Figure 51 respectively show the concentration vs. time profiles in study SP534 part I whenfor a 4.5 mg and 13.5 mg dose applied to the abdoment on the first day of treatment, then pre-dose concentrations through day 4 followed by concentration decline post-patch removal, (period I).

After a 3 day washout on days 5-7 pre-dose concentrations at the same dose levels are shown on days 15, 22, and 29 (i.e. maintanence phase).

Although not shown inspection of the data from each individual subject shows that the pre-dose concentrations in the maintenance phase is consistently higher than during the first several days. This indicates that either skin irritation is increasing bioavailability over time or there is auto-inhibition, although the increasing bioavailability is the most likely explanation.

Figure 50 Rotigotine Plasma Concentrations (arithmetic mean ± sd, n = 5 for period 1, n = 4 other periods) over Time in Group I 4.5 mg / 10 cm^2 QD—Study SP534 Part I

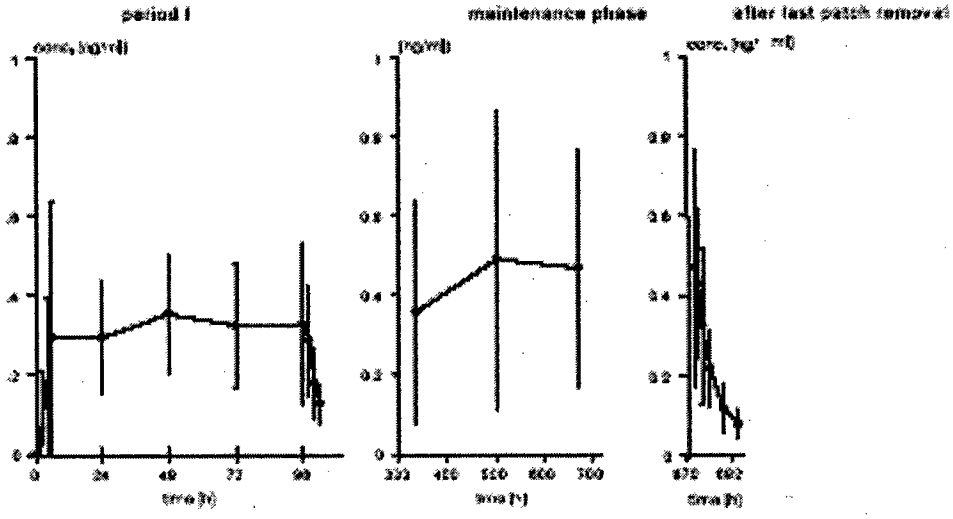
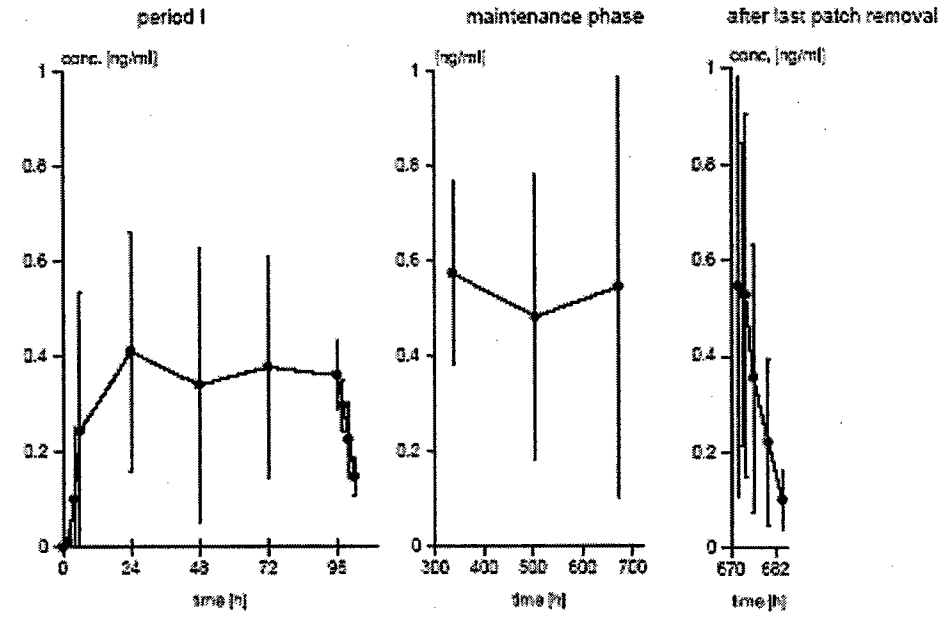


Figure 51 Rotigotine Plasma Concentrations (arithmetic mean ± sd, n = 5 for period 1, n = 3 other periods) over Time in Group II 13.5 mg / 20 cm^2 QD—Study SP534 Part I



3.7.5 Population Pharmacokinetics

The sponsor performed separate population pharmacokinetic analyses on data from the phase III clinical efficacy studies SP512 and SP513 at the titrated maintainance dose.

Plasma samples were obtained pre-dose or within a short time after the patch was changed, and a one-compartment model with zero order input rate of dose/ 21 hours, first order elimination, and a lag-time of 3 hours was used as PK model for the evaluation of population PK. The sponsor also censured data as shown in Table 60.

Table 60 Sponsor's Reported Censuring of Data for Pop PK Analyses

Study	SP512	SP513	Comments / Rationale Provided
Number of Subjects in Pop PK Subgroup	56	?	
Expected number of steady-state samples per subject	5	12	
Total Records	1297	1409	
Sample Exclusion Criteria			
dose level = 0 mg	?	862	
Net number of samples	?	547	
prior/past values was >2 or the ratio of prior/past values was <0.5	48	4	
dose-normalized plasma concentrations >0.2ng/mL/mg	10		SP506 mean trough plasma concentrations plus 2-times standard deviation divided by dose [mg] were between 0.1 and 0.15ng/mL/mg.
dose normalized concentrations < 0.5X or >2X the individual mean of dose-normalized concentrations	84	130	reproducible intra-individual stability of drug absorption (and stabile plasma concentration profile, as reported in trial SP718
marked as "prior" in the source data, although the time of blood sampling was after patch application or vica versa	29		
Number of samples used in pop PK analysis	504	413	
% of samples inappropriately excluded	?	24%	

Possible covariates examined include:

- age
- gender
- body weight
- creatinine clearance
- total bilirubin
- GGT

Age was identified as the only covariate to explain the variability of the total drug clearance. This was found in study SP513, but not study SP512.

However, the pop PK analysis is so flawed that no conclusions should be drawn from it. Major flaws include the following:

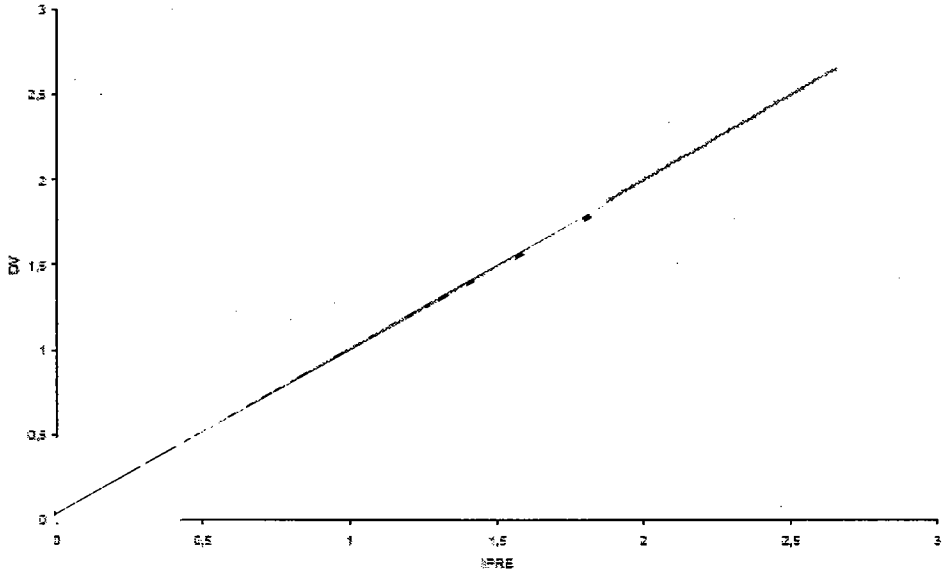
Drug depletion from the patch a first order absorption model is more appropriate than a zero order model and Tlag should not have been fixed. The structural model was thus clearly inappropriate, however based on the highly variable absorption characteristics previously seen it's unlikely any structural model could be defined.

Sampling was also clearly inadequate over the dosage interval to assess the pop PK even if an appropriate structural model could be found.

Samples were inappropriately excluded, and would result in a smaller variability and fit of the data. Finally examination of the fit of the observed concentrations vs. the predicted concentrations reveals approximately a 2-fold variability both above and below the predicted concentrations, (see Figure 52). Based on the variability seen in the Cmin this is not really a very good predictor or estimate of PK parameters.

With respect to age there was only 2 subjects from both studies who was >80 years of age, (i.e. 81 and 82 yo), and who had reliable PK samples, one other subject, (84 yo), only had PK samples taken at a single visit and thus can't be considered compliant.

Figure 52 Regression of Observed vs. Predicted Rotigotine Concentrations Based on Pop PK Model for Study SP513



3.7.6 Intrinsic Factors

3.7.6.1 Effect of Application Site

Study SP626 was an open-label, single-dose, randomized, 3-way, cross-over study in 24 healthy young Caucasian males 18 – 50 years old of the bioequivalence of rotigotine 4.5 mg patches applied to the ventral abdomen, the ventral upper arm, and the ventral / lateral upper leg. A number of samples were excluded from analysis by the sponsor due to 'pharmacokinetic implausibility', and were likewise excluded by the reviewer to check the sponsor's calculations. Even with this data excluded, Table 61 shows that these 3 sites are clearly not bioequivalent to each other. The sponsor's mean concentration vs. time profiles for the different application sites are shown in Figure 53 and as semi-log plots in Figure 54. Figure 54 seems to indicate biphasic elimination. Inspection of individual plots confirms this but not in all individuals, (see Figure 55). Mean half-lives for these two phases are approximately 2.4 and 5.7 hours.

Table 61 Summary Statistics for Pharmacokinetic Metrics for a Single Dose of Rotigotine 4.5 mg TDS by Application Site – Study SP626

	Metrics	Summary Statistics[a]			Geometric Means			Geometric Mean Ratios (90% Confidence Interval)		
		A	B	C	A	B	C	B: A	C: A	B:C
		Ventral Abdomen	Ventral Upper Arm	Ventral / Lateral Upper Leg	Ventral Abdomen	Ventral Upper Arm	Ventral / Lateral Upper Leg	Ventral Upper Arm : Ventral Abdomen	Ventral / Lateral Upper Leg : Ventral Abdomen	Ventral / Lateral Upper Leg : Ventral Upper Arm
	n	21	21	22	21	21	22			
Reviewer's Calculations	Tlag (hrs)	3.5 ± 1.4 (39.7) 2 - 6 [4]	3.0 ± 1.0 (34.7) 2 - 4 [4]	2.6 ± 1.0 (36.2) 2 - 4 [4]						
	Tmax (hrs)	17.9 ± 7.5 (41.8) 6 - 24 [23]	13.5 ± 8.0 (59.7) 0 - 24 [24]	16.2 ± 8 (49.4) 4 - 24 [24]						
	Cmax (ng/ml)	0.393 ± 0.211 (53.8) 0.136 - 0.930 [0.324]	0.488 ± 0.357 (73.1) 0.120 - 1.830 [0.819]	0.589 ± 0.374 (63.5) 0.218 - 1.660 [1.160]	0.350	0.408	0.499	116.5	142.6	81.8
	AUCt (ng/ml x hr^{-1})[b]	6.98 ± 4.22 (60.5) 2.58 - 20.06 [5.76]	9.13 ± 6.24 (68.3) 1.81 - 31.32 [16.17]	10.30 ± 6.93 (67.2) 3.62 - 34.19 [18.24]	6.07	7.66	8.76	126.2	144.3	87.4
Sponsor's Reported Values	Tmax (hrs)	18.5	14.2	16.8						
	Cmax (ng/ml)	0.397	0.505	0.568	0.357	0.416	0.485	116.5 97.1, 139.9	135.8 114, 161	85.9 72, 103
	AUC∞ (ng/ml x hr^{-1})	7.76	9.84	10.64	6.6	8.59	9.27	130.0 109.1, 155.0	140.3 119.4, 164.8	92.7 78.3, 109.7

a mean ± SD, (CV%), min – max, [median]
b n=21 for $AUCt^{C}$

Figure 53 Mean Rotigotine TDS Concentration vs. Time Profiles vs. Application Site – SP626

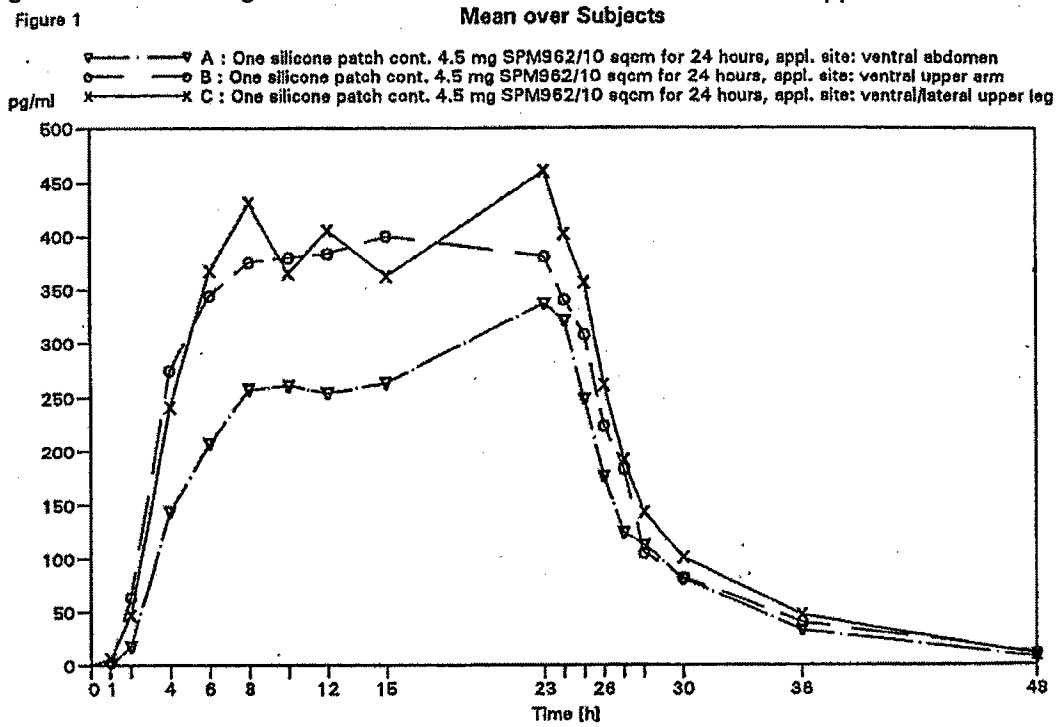


Figure 54 Mean Rotigotine TDS Semi-log Concentration vs. Time Profiles vs. Application Site – SP626

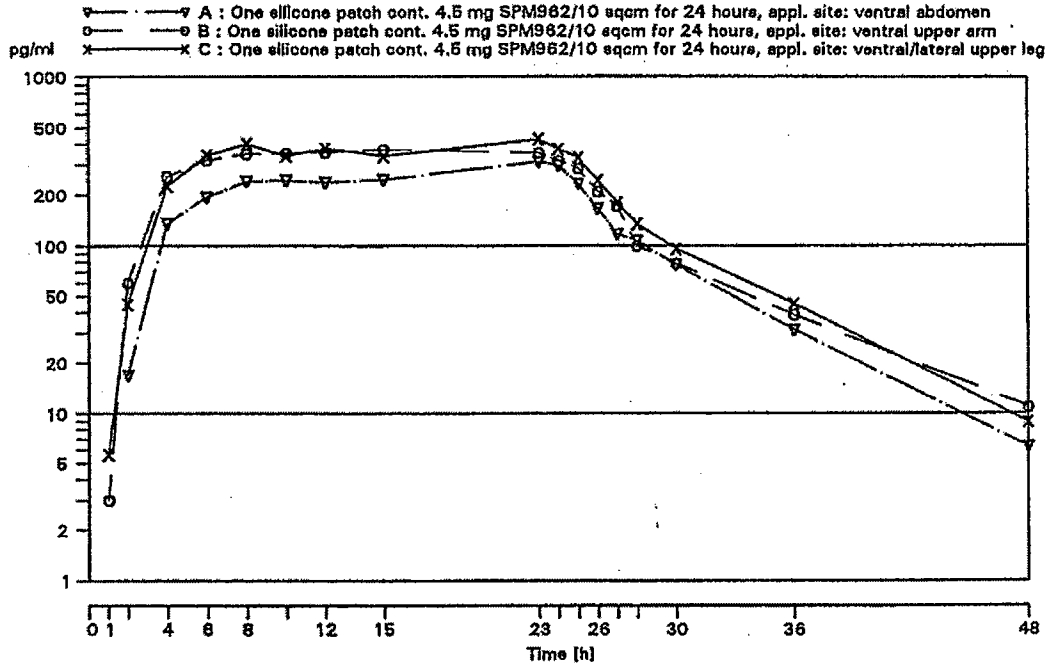
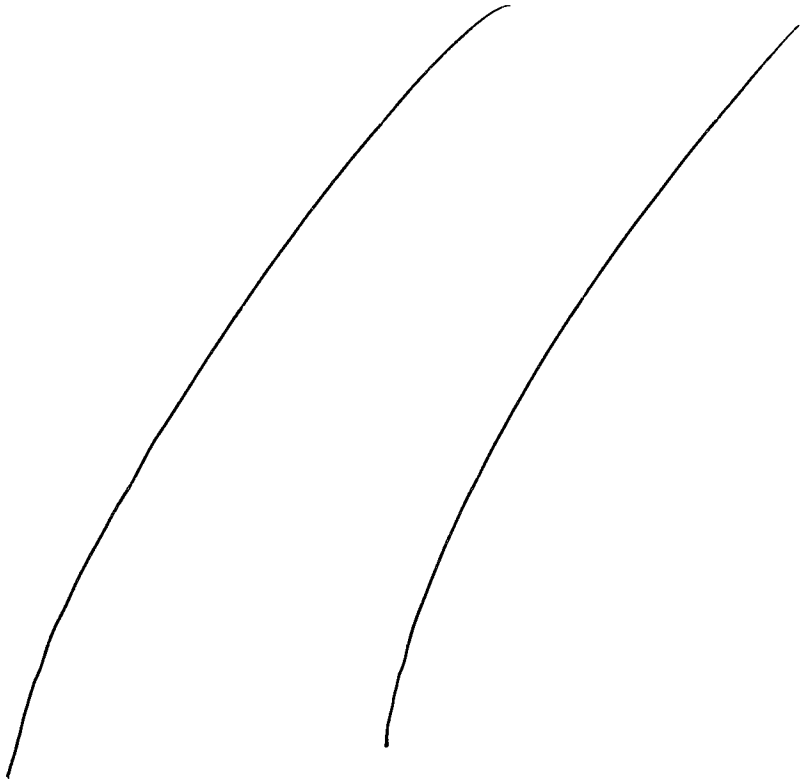


Figure 55 Individual Rotigotine TDS Semi-log Concentration vs. Time Profiles when Applied to the Ventral Abdomen – SP626



3.7.6.2 Effect of Age, Gender, and Application Site

Exploratory plots of the unnormalized and dose and weight normalized Cmax and AUCtau vs. Age by application site and gender failed to reveal any consistent patterns. Any regression patterns appear to be simply due to the small number of subjects and intersubject variability, (see Figure 56 to Figure 67).

Figure 56 Dose vs. Age in Male Subjects by Application Site – SP630

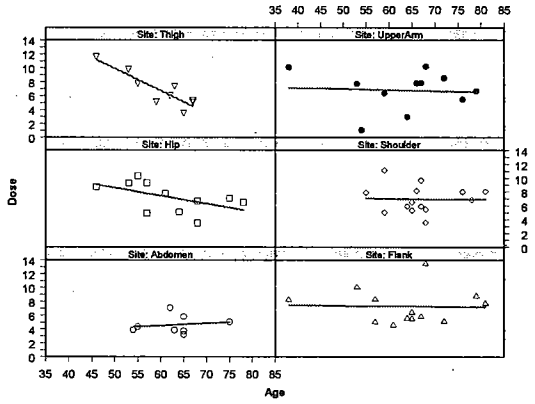


Figure 57 Weight and Dose Normalized AUCtau vs. Age in Male Subjects by Application Site – SP630

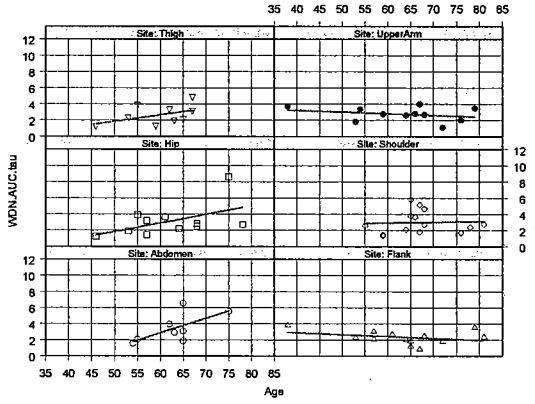


Figure 58 Weight and Dose Normalized Cmax vs. Age in Male Subjects by Application Site – SP630

Figure 59 Dose vs. Age in Female Subjects by Application Site – SP630

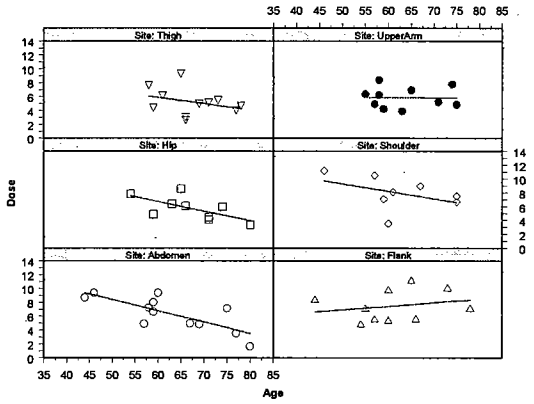


Figure 60 Weight and Dose Normalized AUCtau vs. Age in Female Subjects by Application Site – SP630

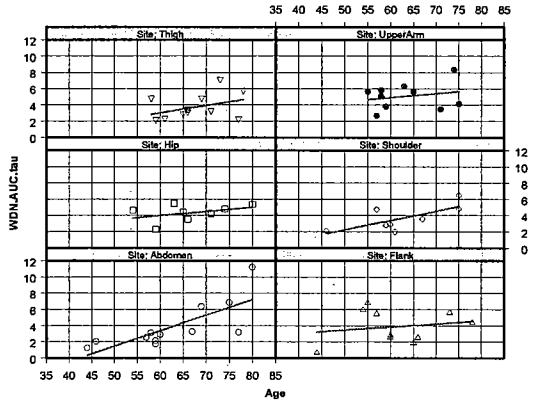


Figure 61 Weight and Dose Normalized Cmax vs. Age in Female Subjects by Application Site – SP630

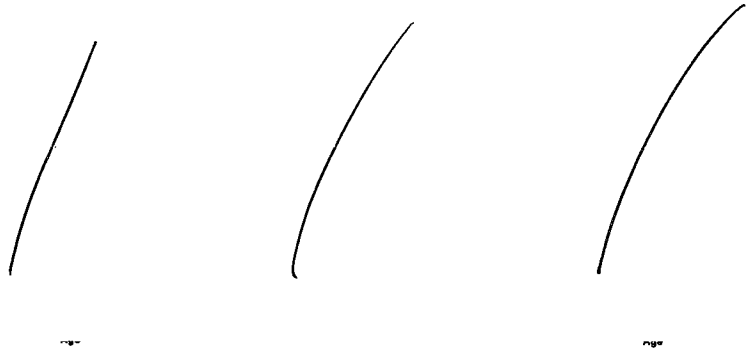


Figure 62 AUCtau vs. Age in Male Subjects by Application Site – SP630

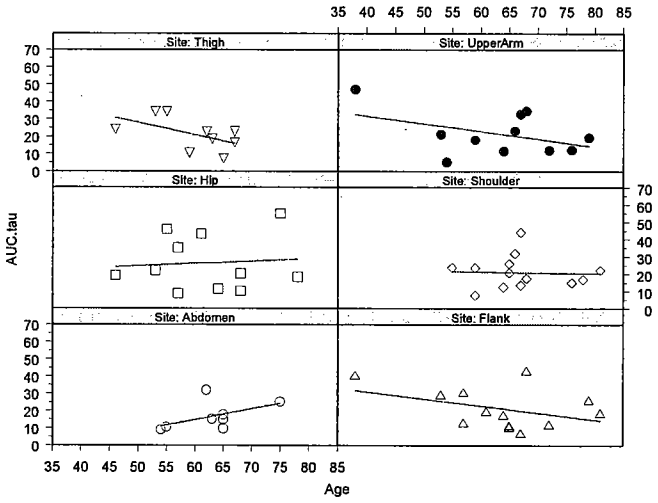


Figure 63 Cmax vs. Age in Male Subjects by Application Site – SP630

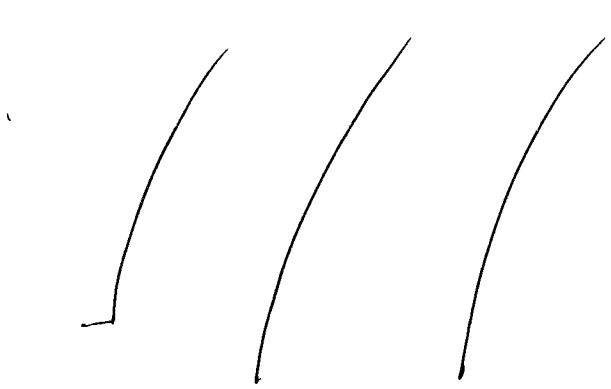


Figure 64 AUCtau vs. Age in Female Subjects by Application Site – SP630

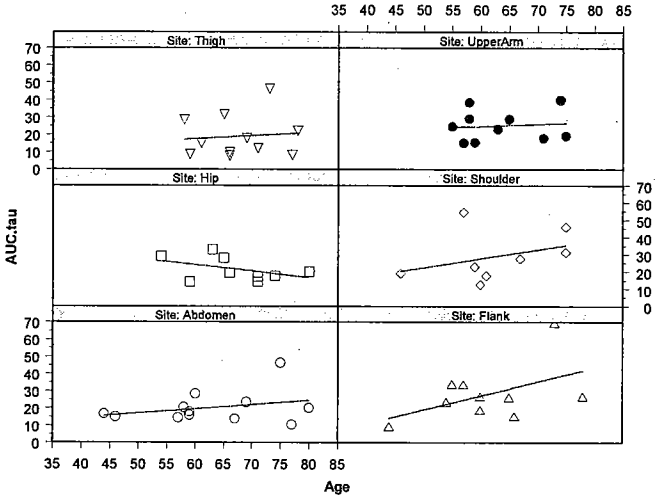


Figure 65 Cmax vs. Age in Female Subjects by Application Site – SP630

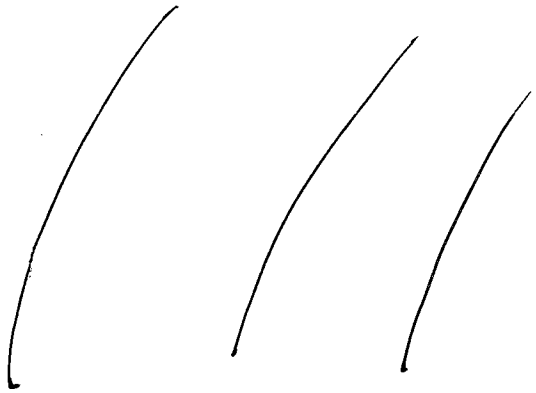


Figure 66 Rotigotine Tmax by Application Site in Males – Study SP630

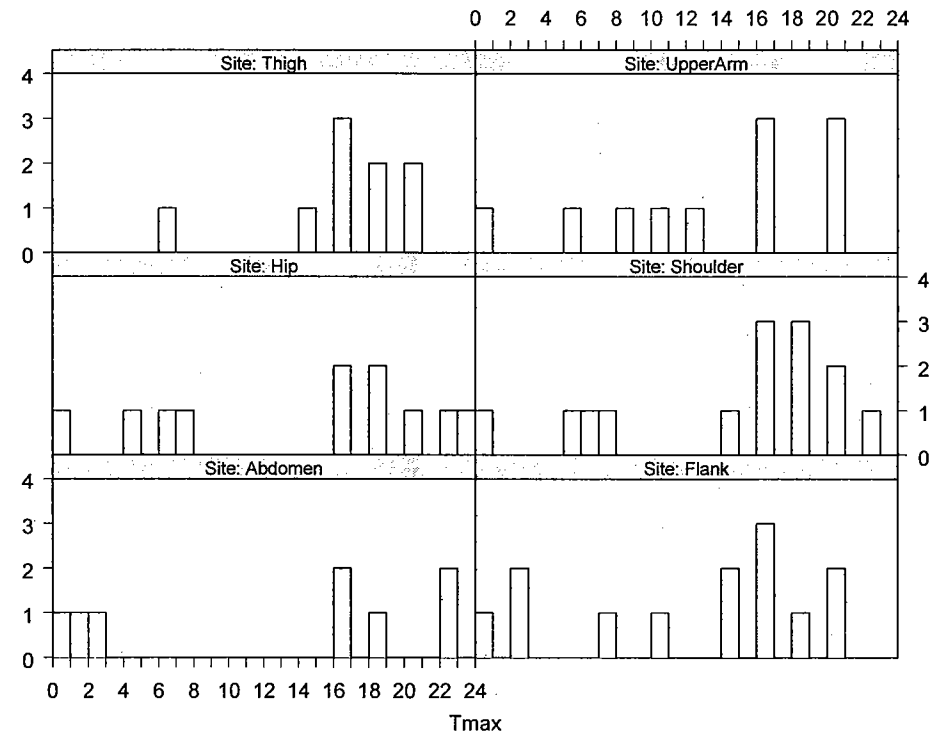
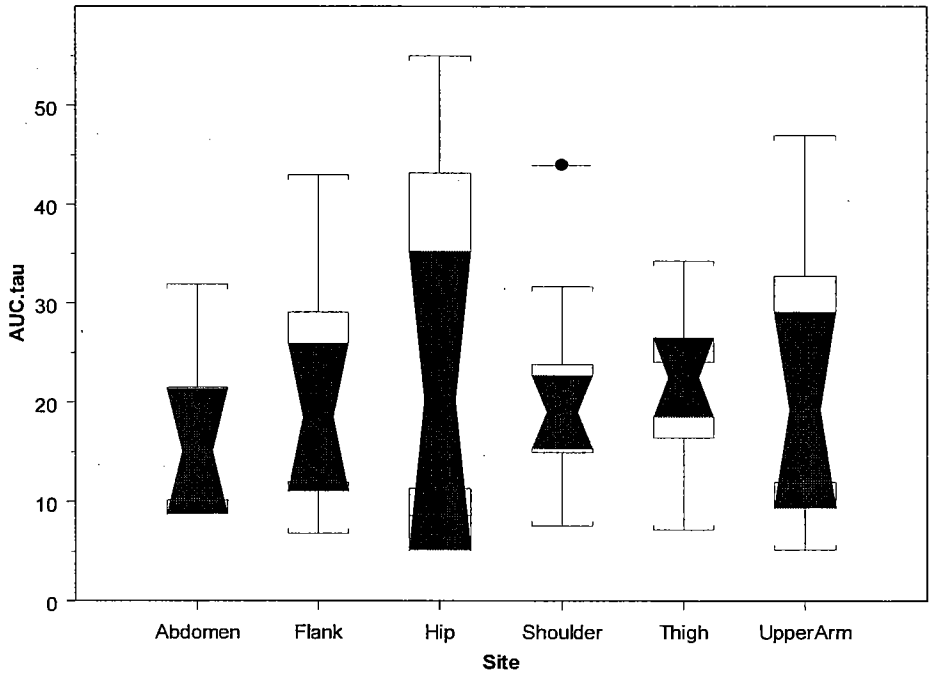


Figure 67 Box Plots of AUCtau by Application Site in Males – Study SP630



3.7.6.3 Effect of Race

3.7.6.3.1 African Americans and Caucasians

Study SP596 examined the single dose pharmacokinetics of rotigotine 4.5 mg in two groups of healthy young males, one Black and one Caucasian. Pharmacokinetic metrics were similar between the two groups and there were no apparent differences by race, (see Table 62).

Table 62 Summary Statistics for Rotigotine 4.5 mg Single Dose Pharmacokinetic Metrics in Blacks and Caucasians – Study SP596.

Race	N	Tlag (hrs)	Cmax (ng/ml)	Tmax (hrs)	$AUC_{0-\infty}$ ($ng/ml \times hr^{-1}$)	%extrap.	$t_{1/2}$ (hr^{-1})
Black	24	1.7 ± 0.5 (29) 1 - 2 [2.0]	0.34 ± 0.13 (37) 0.18 - 0.62 [0.30]	17 ± 7 (39) 8 - 26 [15.0]	6.4 ± 2.66 (41) 3.17 - 12.35 [5.7]	3.2 ± 2.4 (73) 1.1 - 12.4 [2.7]	6.49 ± 3.65 (56) 1.71 - 19.7 [6.09]
Caucasian	23	2.9 ± 1.7 (59.7) 1.0 - 8.0 [2.0]	0.34 ± 0.24 (70.2) 0.09 - 1.21 [0.31]	17.6 ± 6.4 (36.7) 8.0 - 27.0 [15.0]	5.59 ± 2.50 (44.7) 0.94 - 10.80 [5.8]	5.2 ± 4.1 (78.6) 1.0 - 20.3 [4.0]	7.6 ± 3.1 (41.0) 2.5 - 16.0 [7.0]

3.7.6.3.2 Japanese and Caucasians

Two studies looked at the comparative pharmacokinetics of Rotigotine after single and multiple doses, 3 days), in Male and Female Caucasian and Japenses Volunteers. There were no consistent differences observed in both studies in pharmacokinetic metrics between genders or between Caucasian and Japanese, (see Table 63 to Table 67).

It should be noted that the results for renal elimination are orders reported as fraction of the apparent dose in Table 64 to Table 67, whereas it's reported as % of dose in the IV mass balance study reported in Table 51.

Table 63 Summary Statistics for Unconjugated Rotigotine PK Metrics in Caucasian and Japanese Volunteers after a Single Dose of Rotigotine 4.5 mg – Study 717

Race	Gender	N	Weight (kg)	Apparent dose (mg)	Tlag (hr)	Tmax (Hr)	Cmax (pg/mL)	Cmax weight and dose normalized (ng.kg/ (mL.mg))	AUC(0-t) (pg.h/mL)	AUC(0-inf) (pg.h/mL)	CL/f (by apparent dose) (L/h)	CL/f (by apparent dose) (L/(h.kg)) weight normalized	t ½ (hr)	Renal clearance (L/h)	Renal clearance (mL/(h.kg)) weight normalized	Fraction excretedof apparent dose (%))	Apparent volume of distribution (L)	Apparent volume of distribution (L/kg) weight normalized
Caucasian	Female	12	58.0 ± 5.7 (9.8) 49.0 - 68.0 [55.5]	2.3 ± 0.5 (24.1) 1.7 - 3.5 [2.0]	4.3 ± 2.4 (55.1) 2.0 - 8.0 [4.0]	16.2 ± 4.8 (29.9) 8.0 - 25.0 [16.0]	294.4 ± 319.2 (108.4) 98.9 - 1270.0 [222.0]	7.1 ± 4.9 (69.4) 3.0 - 20.2 [5.4]	6025.0 ± 6470.7 (107.4) 1501.2 - 25709.5 [4631.9]	5908.4 ± 6705.7 (113.5) 213.0 - 26023.0 [4766.7]	294.1 ± 144.8 (49.2) 104.9 - 488.5 [335.8]	4.9 ± 2.2 (45.0) 1.9 - 7.9 [5.5]	5.8 ± 2.6 (44.6) 3.4 - 10.8 [4.5]	0.227 ± 0.177 (77.877) 0.055 - 0.670 [0.169]	3.9 ± 2.7 (70.1) 1.0 - 9.9 [3.1]	0.04 ± 0.03 (69.34) 0.01 - 0.11 [0.03]	3852 ± 1892 (49) 1908 - 7693 [3246]	64.2 ± 27.7 (43.1) 34.1 - 113.1 [50.6]
Caucasian	Male	12	68.3 ± 6.5 (9.5) 57.0 - 78.0 [69.0]	1.9 ± 0.6 (29.8) 1.1 - 3.3 [1.8]	5.5 ± 2.3 (41.4) 2.0 - 8.0 [4.0]	18.4 ± 6.5 (35.4) 8.0 - 26.0 [16.0]	197.7 ± 155.3 (78.5) 83.8 - 675.0 [158.0]	6.8 ± 3.0 (44.6) 3.5 - 14.8 [6.0]	4181.7 ± 3398.3 (81.3) 1724.6 - 14641.9 [3665.8]	4321.2 ± 3386.4 (78.4) 1810.1 - 14739.4 [3809.5]	213.9 ± 85.3 (39.9) 72.8 - 389.0 [215.6]	3.1 ± 1.1 (36.2) 1.3 - 5.3 [3.1]	5.6 ± 1.8 (32.6) 3.5 - 9.0 [5.0]	0.265 ± 0.135 (51.121) 0.061 - 0.480 [0.267]	3.9 ± 2.0 (52.1) 0.9 - 6.8 [3.6]	0.06 ± 0.03 (62.47) 0.01 - 0.13 [0.04]	4157 ± 1829 (44) 1604 - 7066 [3781]	60.3 ± 23.9 (39.6) 22.0 - 97.0 [55.8]
Japanese	Female	12	53.3 ± 8.4 (15.7) 44.0 - 75.0 [51.5]	2.0 ± 0.5 (26.1) 1.4 - 3.1 [1.9]	4.7 ± 2.7 (58.7) 2.0 - 12.0 [4.0]	18.1 ± 4.8 (26.5) 12.0 - 25.0 [16.0]	307.0 ± 96.7 (31.5) 133.0 - 507.0 [319.5]	8.1 ± 2.3 (27.8) 3.8 - 12.5 [8.1]	6051.4 ± 2041.5 (33.7) 2643.3 - 9216.1 [6108.1]	6204.5 ± 2069.5 (33.4) 2745.9 - 9340.5 [6269.8]	155.6 ± 56.2 (36.1) 81.3 - 277.0 [140.1]	2.9 ± 0.9 (30.9) 1.6 - 5.2 [2.8]	5.5 ± 2.5 (44.7) 3.3 - 12.4 [4.7]	0.198 ± 0.093 (47.155) 0.088 - 0.361 [0.197]	3.7 ± 1.9 (49.6) 1.7 - 8.2 [3.9]	0.06 ± 0.03 (48.08) 0.01 - 0.10 [0.07]	2624 ± 940 (36) 1814 - 4847 [2223]	51.4 ± 22.6 (43.9) 24.2 - 96.9 [44.3]
Japanese	Male	12	62.4 ± 4.4 (7.1) 56.0 - 74.0 [62.5]	2.0 ± 0.5 (25.4) 0.9 - 2.8 [2.0]	4.2 ± 1.3 (32.1) 2.0 - 8.0 [4.0]	17.7 ± 4.0 (22.6) 12.0 - 24.0 [16.0]	198.9 ± 109.6 (55.1) 74.5 - 390.0 [158.0]	6.0 ± 2.2 (36.0) 3.0 - 9.8 [5.6]	3797.4 ± 1915.3 (50.4) 1457.7 - 7226.4 [3556.9]	3948.4 ± 1918.5 (48.6) 1620.4 - 7383.1 [3706.6]	242.9 ± 96.9 (39.9) 121.2 - 478.1 [249.6]	3.9 ± 1.5 (38.9) 2.0 - 7.5 [4.2]	5.1 ± 2.5 (49.0) 2.4 - 10.7 [4.1]	0.343 ± 0.220 (64.203) 0.086 - 0.791 [0.271]	5.5 ± 3.5 (63.7) 1.4 - 12.6 [4.4]	0.06 ± 0.03 (48.65) 0.02 - 0.11 [0.05]	3942 ± 1533 (39) 1486 - 6683 [4017]	62.7 ± 22.5 (35.9) 25.6 - 92.0 [63.8]

Table 64 Summary Statistics for Total Rotigotine PK Metrics in Caucasian and Japanese Volunteers after a Single Dose of Rotigotine 4.5 mg – Study 717

Race	Gender	N	Weight (kg)	Apparent dose (mg)	Tlag (hr)	Tmax (hr)	Cmax (pg/mL)	Cmax weight and dose normalized (ng.kg/ (mL.mg))	AUC(0-t) (pg.h/mL)	AUC(0-inf) (pg.h/mL)	t ½ (hr)	Renal clearance (L/h)	Renal clearance (mL/(h.kg)) weight normalized	Fraction excreted (of apparent dose)
Caucasian	Female	12	58.0 ± 5.7 (9.8) 49.0 - 68.0 [55.5]	2.3 ± 0.5 (24.1) 1.7 - 3.5 [2.0]	2.3 ± 1.3 (55.8) 1.0 - 4.0 [2.0]	18.5 ± 4.6 (24.9) 12.0 - 26.0 [16.0]	1405.0 ± 707.2 (50.3) 471.0 - 2950 [1395.0]	34.6 ± 12.5 (36.0) 13.1 - 56.9 [35.1]	31747.3 ± 17311.4 (54.5) 9034.1 - 69125.6 [28308.3]	32613.7 ± 17836.2 (54.7) 9197.8 - 71361.9 [28942.6]	10.0 ± 2.1 (21.0) 7.5 - 13.1 [10.0]	8.2 ± 4.1 (49.9) 2.8 - 18.2 [7.6]	139 ± 75 (54) 52 - 331 [127]	0.11 ± 0.03 (31.08) 0.04 - 0.15 [0.10]
Caucasian	Male	12	68.3 ± 6.5 (9.5) 57.0 - 78.0 [69.0]	1.9 ± 0.6 (29.8) 1.1 - 3.3 [1.8]	3.3 ± 1.8 (53.3) 2.0 - 8.0 [3.0]	17.5 ± 4.9 (28.0) 8.0 - 26.0 [16.0]	1214.6 ± 578.8 (47.7) 715.0 - 2890.0 [1085.0]	43.7 ± 11.5 (26.3) 27.5 - 63.6 [43.8]	26576.7 ± 10687.1 (40.2) 14110.8 - 56966.7 [25823.0]	27117.5 ± 10677.1 (39.4) 14581.1 - 57394.8 [26376.1]	9.1 ± 1.7 (18.9) 5.9 - 12.4 [8.9]	7.9 ± 3.0 (38.1) 3.8 - 13.8 [7.1]	116 ± 40 (34) 52 - 184 [114]	0.11 ± 0.04 (40.36) 0.06 - 0.20 [0.09]
Japanese	Female	12	53.3 ± 8.4 (15.7) 44.0 - 75.0 [51.5]	2.0 ± 0.5 (26.1) 1.4 - 3.1 [1.9]	3.5 ± 1.7 (49.5) 2.0 - 8.0 [4.0]	18.3 ± 4.3 (23.6) 16.0 - 28.0 [16.0]	1819.4 ± 600.3 (33.0) 803.0 - 3410.0 [1770.0]	48.1 ± 13.0 (26.9) 26.2 - 72.8 [46.6]	38695.2 ± 9972.9 (25.8) 19599.7 - 56686.1 [38049.7]	39682.6 ± 10142.5 (25.6) 22053.1 - 59382.9 [38905.2]	9.4 ± 2.0 (21.2) 7.2 - 14.6 [9.1]	6.2 ± 2.7 (44.4) 2.9 - 9.7 [5.5]	116 ± 47 (41) 57 - 200 [116]	0.12 ± 0.05 (45.45) 0.06 - 0.20 [0.11]
Japanese	Male	12	62.4 ± 4.4 (7.1) 56.0 - 74.0 [62.5]	2.0 ± 0.5 (25.4) 0.9 - 2.8 [2.0]	4.0 ± 1.5 (36.9) 2.0 - 8.0 [4.0]	17.8 ± 5.4 (30.2) 8.0 - 25.0 [16.0]	1651.1 ± 644.1 (39.0) 535.0 - 3110.0 [1740.0]	51.5 ± 14.9 (29.0) 34.2 - 86.4 [47.0]	33903.6 ± 10289.0 (30.3) 12027.5 - 43241.8 [37616.8]	34303.4 ± 10314.4 (30.1) 12202.1 - 43556.5 [38024.1]	7.9 ± 1.3 (16.4) 6.0 - 9.8 [8.0]	7.4 ± 5.2 (70.1) 4.0 - 23.2 [5.6]	119 ± 81 (68) 63 - 363 [94]	0.12 ± 0.05 (43.15) 0.07 - 0.27 [0.10]

Table 65 Summary Statistics for Total Despropyl-Rotigotine PK Metrics in Caucasian and Japanese Volunteers after a Single Dose of Rotigotine 4.5 mg – Study 717

Ethnic Origin	Gender	N	Weight (kg)	Apparent dose (mg)	Tlag (hr)	Tmax (hr)	Cmax (ng/mL)	Cmax weight and dose normalized (ng.kg/ (mL.mg))	AUC(0-t) (ng.h/mL)	Cumulative amount (ng)	Fraction excreted (of apparent dose)
Caucasian	*Female*	*12*	58.+ 5.7 (9.8) 49.0 - 68.0 [55.5]	2.3 ± 0.5 (24.1) 1.7 - 3.5 [2.0]	3.6 ± 2.9 (82.0) 1.0 - 8.0 [3.0]	18.9 ± 7.1 (37.7) 8.0 - 26.0 [24.0]	0.48 ± 0.32 (68.12) 0.15 - 1.34 [0.37]	11.8 ± 5.9 (50.1) 3.3 - 21.5 [10.8]	7.9 ± 9.2 (116.3) 0.6 - 33.5 [4.4]	149 ± 69 (47) 63 - 293 [139]	0.071 ± 0.020 (28.972) 0.033 - 0.098 [0.069]
Caucasian	*Male*	*12*	68.3 ± 6.5 (9.5) 57.0 - 78.0 [69.0]	1.9 ± 0.6 (29.8) 1.1 - 3.3 [1.8]	3.8 ± 3.4 (89.6) 0.0 - 8.0 [2.5]	23.6 ± 12.9 (54.6) 8.0 - 60.0 [24.0]	0.39 ± 0.30 (76.46) 0.00 - 0.97 [0.35]	13.3 ± 7.3 (55.0) 0.0 - 26.7 [13.3]	5.6 ± 6.1 (107.6) 0.0 - 18.7 [4.0]	125 ± 87 (70) 49 - 348 [102]	0.071 ± 0.030 (41.840) 0.041 - 0.124 [0.064]
Japanese	*Female*	*12*	53.3 ± 8.4 (15.7) 44.0 - 75.0 [51.5]	2.0 ± 0.5 (26.1) 1.4 - 3.1 [1.9]	5.3 ± 4.4 (83.2) 1.0 - 16.0 [4.0]	21.8 ± 13.8 (63.4) 8.0 - 60.0 [24.0]	0.43 ± 0.26 (61.11) 0.00 - 0.81 [0.46]	11.2 ± 6.7 (60.1) 0.0 - 22.9 [13.1]	8.1 ± 6.4 (79.5) 0.0 - 17.5 [9.1]	137 ± 54 (39) 43 - 213 [127]	0.077 ± 0.020 (25.725) 0.030 - 0.109 [0.077]
Japanese	*Male*	*12*	62.4 ± 4.4 (7.1) 56.0 - 74.0 [62.5]	2.0 ± 0.5 (25.4) 0.9 - 2.8 [2.0]	6.9 ± 6.0 (86.2) 1.0 - 24.0 [6.0]	22.7 ± 4.2 (18.5) 12.0 - 26.0 [24.0]	0.48 ± 0.23 (47.82) 0.11 - 0.83 [0.54]	15.0 ± 6.3 (42.3) 3.9 - 27.3 [16.1]	9.5 ± 5.5 (57.9) 0.2 - 17.9 [10.4]	147 ± 102 (69) 55 - 448 [120]	0.086 ± 0.053 (61.728) 0.047 - 0.245 [0.077]

Table 66 Summary Statistics for Total Desthienyl-Rotigotine PK Metrics in Caucasian and Japanese Volunteers after a Single Dose of Rotigotine 4.5 mg – Study 717

Ethnic Origin	Gender	N	Weight (kg)	Apparent dose (mg)	Tlag (hr)	Tmax (hr)	Cmax (ng/mL)	Cmax weight and dose normalized (ng.kg/ (mL.mg))	AUC(0-t) (ng.h/mL)	Cumulative amount(ng)	Fraction excreted (of apparent dose)
Caucasian	*Female*	*12*	58.0 ± 5.7 (9.8) 49.0 - 68.0 [55.5]	2.3 ± 0.5 (24.1) 1.7 - 3.5 [2.0]	6.9 ± 7.1 (102.7) 1.0 - 25.0 [6.0]	26.7 ± 17.0 (63.6) 8.0 - 60.0 [24.0]	0.26 ± 0.22 (85.50) 0.00 - 0.77 [0.24]	6.2 ± 4.2 (68.4) 0.0 - 12.3 [6.5]	4.3 ± 5.7 (131.4) 0.0 - 19.4 [2.3]	50.2 ± 23.9 (47.6) 22.6 - 90.7 [50.2]	0.03 ± 0.01 (38.84) 0.02 - 0.05 [0.03]
Caucasian	*Male*	*12*	68.3 ± 6.5 (9.5) 57.0 - 78.0 [69.0]	1.9 ± 0.6 (29.8) 1.1 - 3.3 [1.8]	5.3 ± 4.7 (88.8) 1.0 - 12.0 [3.0]	34.6 ± 16.3 (47.2) 24.0 - 60.0 [26.0]	0.23 ± 0.20 (86.21) 0.00 - 0.65 [0.23]	7.7 ± 5.9 (76.8) 0.0 - 17.7 [8.5]	4.8 ± 5.4 (112.1) 0.0 - 16.0 [3.2]	63.4 ± 32.8 (51.8) 30.5 - 133.7 [52.2]	0.05 ± 0.02 (35.83) 0.03 - 0.09 [0.04]
Japanese	*Female*	*12*	53.+3 8.4 (15.7) 44.0 - 75.0 [51.5]	2.0 ± 0.5 (26.1) 1.4 - 3.1 [1.9]	7.5 ± 6.8 (90.2) 1.0 - 26.0 [8.0]	26.4 ± 11.7 (44.2) 8.0 - 60.0 [25.0]	0.24 ± 0.16 (64.34) 0.00 - 0.55 [0.24]	6.2 ± 3.7 (60.2) 0.0 - 13.3 [5.9]	4.3 ± 4.2 (96.2) 0.0 - 13.4 [3.5]	46.7 ± 19.2 (41.1) 21.1 - 76.6 [43.1]	0.04 ± 0.02 (41.94) 0.01 - 0.06 [0.03]
Japanese	*Male*	*12*	62.4 ± 4.4 (7.1) 56.0 - 74.0 [62.5]	2.0 ± 0.5 (25.4) 0.9 - 2.8 [2.0]	10.5 ± 8.4 (79.9) 1.0 - 33.0 [8.0]	27.9 ± 10.1 (36.3) 24.0 - 60.0 [25.0]	0.35 ± 0.18 (53.02) 0.00 - 0.59 [0.42]	10.5 ± 5.3 (50.9) 0.0 - 17.9 [11.8]	6.1 ± 4.1 (68.3) 0.0 - 12.2 [6.5]	41.6 ± 16.0 (38.5) 26.4 - 86.5 [35.9]	0.03 ± 0.01 (35.17) 0.02 - 0.06 [0.03]

Table 67 Summary Statistics for Rotigotine PK Metrics in Caucasian and Japanese Volunteers after a Multiple Doses of Rotigotine 4.5 mg and 9 mg

		N	Day 3 2.25 mg / 5 cm²					Day 6 4.5 mg / 10 cm²					Day 9 9.0 mg / 20 cm²				
			Cmin (pg/ml)	Cmax (pg/ml)	Cmax:Cmin	Tmin (hrs)	Tmax (hrs)	Cmin (pg/ml)	Cmax (pg/ml)	Cmax:Cmin	Tmin (hrs)	Tmax (hrs)	Cmin (pg/ml)	Cmax (pg/ml)	Cmax:Cmin	Tmin (hrs)	Tmax (hrs)
Unconjugated Rotigotine																	
Caucasian	Female	6	72.9 ± 19 (26.1) 50.7 - 94.9 [72.5]	126 ± 29 (22.7) 86 - 171 [127]	1.75 ± 0.18 (10.1) 1.47 - 1.99 [1.75]	3.3 ± 4.5 (133.7) 0.0 - 12.0 [1.5]	12.7 ± 8.9 (70.4) 0.0 - 24.0 [16.0]	125.7 ± 12.2 (9.7) 111 - 142 [128]	285.3 ± 90.2 (31.6) 174 - 420 [252]	2.24 ± 0.56 (24.9) 1.57 - 3.16 [2.10]	9.3 ± 11.4 (122.5) 0.0 - 24.0 [3.0]	8.7 ± 5.9 (67.9) 0.0 - 16.0 [10.0]	282 ± 65.7 (23.3) 194 - 373 [289]	770 ± 333.5 (43.3) 362 - 1370 [725]	2.79 ± 1.26 (45.3) 1.87 - 4.98 [2.12]	9.2 ± 11.5 (126.0) 1.0 - 24.0 [2.5]	15.3 ± 5.3 (34.7) 8.0 - 24.0 [16.0]
Caucasian	Male	6	55.7 ± 25 (44.9) 30.4 - 102 [51.6]	108 ± 59 (55.1) 61 - 222 [88]	1.90 ± 0.30 (16.0) 1.57 - 2.32 [1.88]	4.2 ± 4.0 (96.5) 1.0 - 12.0 [3.0]	12.2 ± 9.6 (78.6) 1.0 - 24.0 [8.0]	118.7 ± 59.7 (50.2) 47.7 - 198 [106.2]	229.8 ± 94.4 (41.1) 90.9 - 344 [251]	2.02 ± 0.36 (18.0) 1.43 - 2.47 [1.98]	5.8 ± 9.0 (155.0) 0.0 - 24.0 [3.0]	10.0 ± 7.9 (79.0) 0.0 - 16.0 [14.0]	223.2 ± 77.7 (34.8) 108 - 303 [233.5]	552 ± 207.9 (37.7) 366 - 908 [526]	2.60 ± 0.86 (33.2) 1.69 - 4.09 [2.38]	4.5 ± 4.6 (102.1) 1.0 - 12.0 [2.5]	6.7 ± 6.5 (98.0) 0.0 - 16.0 [6.0]
Japanese	Female	7	54.1 ± 18 (33.3) 31.8 - 80.7 [44.7]	120 ± 62 (52) 76.1 - 252 [87]	2.18 ± 0.47 (21.7) 1.73 - 3.12 [2.00]	4.3 ± 3.7 (86.0) 1.0 - 12.0 [4.0]	8.1 ± 9.1 (111.8) 0.0 - 24.0 [8.0]	92.4 ± 33.4 (36.2) 54.3 - 134 [78.6]	246.1 ± 123.2 (50) 157 - 513 [228]	2.69 ± 0.72 (26.8) 1.79 - 3.83 [2.41]	1.6 ± 1.4 (88.9) 0.0 - 4.0 [2.0]	16.6 ± 4.3 (25.8) 12.0 - 24.0 [16.0]	265.7 ± 94.3 (35.5) 170 - 430 [253]	747 ± 367.8 (49.2) 366 - 1390 [743.5]	3.12 ± 2.21 (70.8) 1.55 - 7.47 [2.44]	0.5 ± 0.8 (167.3) 0.0 - 2.0 [0.0]	6.7 ± 3.3 (49.0) 4.0 - 12.0 [6.0]
Japanese	Male	6	64 ± 25.8 (40.3) 34.2 - 109 [56.1]	144 ± 48 (33.5) 98 - 217 [128]	2.38 ± 0.73 (30.8) 1.73 - 3.63 [2.09]	9.5 ± 11.3 (118.7) 1.0 - 24.0 [3.0]	14.0 ± 3.3 (23.9) 8.0 - 16.0 [16.0]	122.7 ± 33.8 (27.5) 83.8 - 161 [121]	213.3 ± 39.2 (18.4) 155 - 269 [215]	1.79 ± 0.31 (17.3) 1.47 - 2.27 [1.71]	3.7 ± 2.7 (72.5) 0.0 - 8.0 [4.0]	8.8 ± 8.0 (90.1) 0.0 - 16.0 [10.0]	264.7 ± 163.8 (61.9) 118 - 538 [207.5]	695.8 ± 230.9 (33.2) 397 - 918 [750.5]	3.24 ± 1.84 (56.9) 1.54 - 6.77 [2.69]	1.0 ± 0.9 (89.4) 0.0 - 2.0 [1.0]	12.7 ± 7.3 (57.9) 4.0 - 24.0 [12.0]
Total Rotigotine																	
Caucasian	Female	6	819 ± 202 (24.7) 456 - 1020 [901]	1484 ± 428 (28.9) 683 - 1880 [1520]	1.79 ± 0.21 (11.8) 1.50 - 2.05 [1.79]	2.8 ± 2.8 (98.4) 1.0 - 8.0 [1.5]	11.3 ± 6.4 (56.5) 0.0 - 16.0 [14.0]	1527 ± 362 (23.7) 924 - 1990 [1535]	3133 ± 1049 (33.5) 1380 - 4430 [3305]	2.03 ± 0.50 (24.6) 1.49 - 2.97 [1.90]	6.3 ± 9.0 (142.9) 1.0 - 24.0 [2.0]	16.0 ± 0.0 (0.0) 16.0 - 16.0 [16.0]	3318.3 ± 995.2 (30) 1670 - 4380 [3515]	7478 ± 2468 (33) 3440 - 10400 [7540]	2.25 ± 0.35 (15.7) 1.87 - 2.82 [2.12]	8.8 ± 11.8 (134.0) 0.0 - 24.0 [2.5]	15.3 ± 6.4 (41.8) 4.0 - 24.0 [16.0
Caucasian	Male	6	484 ± 119 (24.7) 280 – 611 [480]	1016 ± 254 (25) 688 - 1360 [978]	2.14 ± 0.38 (17.9) 1.61 - 2.58 [2.20]	2.5 ± 1.6 (65.7) 1.0 - 4.0 [2.5]	17.3 ± 3.3 (18.8) 16.0 - 24.0 [16.0]	1196.8 ± 302 (25.2) 701 - 1530 [1220]	2370 ± 467.7 (19.7) 1850 - 3150 [2370]	2.06 ± 0.48 (23.5) 1.27 - 2.78 [2.09]	3.5 ± 4.2 (119.5) 1.0 - 12.0 [2.0]	16.7 ± 3.9 (23.6) 12.0 - 24.0 [16.0]	2591.7 ± 393.4 (15.2) 2160 - 3020 [2585]	5383 ± 1408 (26.2) 4200 - 7930 [4880]	2.08 ± 0.41 (19.8) 1.51 - 2.74 [1.99]	4.7 ± 4.5 (95.5) 1.0 - 12.0 [3.0]	15.3 ± 6.4 (41.8 4.0 - 24.0 [16.0]
Japanese	Female	7	562 ± 151 (26.9) 418 - 822 [518]	1131 ± 345 (30.5) 783 - 1730 [1110]	2.00 ± 0.13 (6.6) 1.77 - 2.14 [2.04]	6.0 ± 8.1 (134.4) 1.0 - 24.0 [4.0]	9.7 ± 7.3 (74.6) 0.0 - 16.0 [12.0]	1076 ± 406 (37.8) 728 - 1680 [860]	2341.4 ± 846.8 (36.2) 1510 - 3650 [2000]	2.20 ± 0.32 (14.6) 1.80 - 2.62 [2.17]	1.4 ± 1.3 (89.1) 0.0 - 4.0 [1.0]	14.3 ± 6.5 (45.3) 0.0 - 20.0 [16.0]	2706.7 ± 500.2 (18.5) 2280 - 3500 [2465]	6078 ± 1102 (18.1) 4840 - 7960 [5935]	2.29 ± 0.49 (21.3) 1.79 - 3.17 [2.12]	0.7 ± 0.5 (77.5) 0.0 - 1.0 [1.0]	8.0 ± 5.1 (63.2) 4.0 - 16.0 [6.0]
Japanese	Male	6	489 ± 197 (40.2) 245 - 745 [464]	1077 ± 323 (30) 817 - 1680 [964]	2.37 ± 0.73 (30.8) 1.74 - 3.75 [2.14]	2.3 ± 1.4 (58.6) 1.0 - 4.0 [2.0]	13.3 ± 6.5 (49.0) 0.0 - 16.0 [16.0]	980.3 ± 379.8 (38.7) 588 - 1630 [950]	1816.7 ± 405.7 (22.3) 1160 - 2230 [1940]	1.97 ± 0.48 (24.2) 1.37 - 2.62 [1.82]	5.2 ± 9.2 (178.8) 1.0 - 24.0 [1.5]	10.7 ± 8.3 (77.5) 0.0 - 16.0 [16.0]	2307 ± 1041 (45.1) 1130 - 3650 [2125]	5511.7 ± 2287 (41.5) 2930 - 8000 [5760]	2.48 ± 0.71 (28.7) 2.02 - 3.85 [2.12]	1.3 ± 0.5 (38.7) 1.0 - 2.0 [1.0]	10.7 ± 6.0 (56.5) 4.0 - 16.0 [12.0]
Conjugated Rotigotine																	
Caucasian	Female	6	741 ± 185 (25) 397 - 906 [822]	1376 ± 391 (28.4) 632 - 1709 [1431]	1.84 ± 0.21 (11.4) 1.59 - 2.11 [1.82]	2.8 ± 2.8 (98.4) 1.0 - 8.0 [1.5]	11.3 ± 6.4 (56.5) 0.0 - 16.0 [14.0]	1384 ± 347 (25.1) 795 - 1818 [1405.5]	2901.2 ± 974 (33.6) 1256 - 4010 [3082]	2.07 ± 0.48 (23.3) 1.58 - 2.99 [1.93]	5.2 ± 9.2 (178.8) 1.0 - 24.0 [1.5]	16.0 ± 0.0 (0.0) 16.0 - 16.0 [16.0]	3019 ± 940 (31.1) 1476 - 4057 [3135.5]	6838 ± 2329 (34.1) 3078 - 9558 [6844]	2.26 ± 0.32 (14.0) 1.85 - 2.74 [2.19]	8.8 ± 11.8 (134.0) 0.0 - 24.0 [2.5]	15.3 ± 6.4 (41.8) 4.0 - 24.0 [16.0]
Caucasian	Male	6	416 ± 106 (25.4) 250 - 531 [412.4]	931 ± 229 (24.6) 649 - 1297 [883]	2.30 ± 0.49 (21.2) 1.66 - 2.96 [2.36]	2.5 ± 1.6 (65.7) 1.0 - 4.0 [2.5]	17.3 ± 3.3 (18.8) 16.0 - 24.0 [16.0]	1042 ± 263 (25.2) 648 - 1356 [986]	2157.9 ± 370.7 (17.2) 1757.1 - 2806 [2141.5]	2.16 ± 0.50 (23.3) 1.30 - 2.87 [2.19]	3.5 ± 4.2 (119.5) 1.0 - 12.0 [2.0]	16.7 ± 3.9 (23.6) 12.0 - 24.0 [16.0]	2366.7 ± 370.9 (15.7) 1857 - 2759 [2381]	4971.2 ± 1319.5 (26.5) 3721 - 7304 [4551]	2.10 ± 0.43 (20.3) 1.53 - 2.82 [2.01]	4.7 ± 4.5 (95.5) 1.0 - 12.0 [3.0]	15.3 ± 6.4 (41.8) 4.0 - 24.0 [16.0]
Japanese	Female	7	504 ± 136 (27.1) 376 - 741 [474]	1014 ± 296 (29.2) 695 - 1478 [1036]	2.00 ± 0.14 (7.0) 1.78 - 2.18 [2.04]	6.6 ± 8.0 (122.3) 1.0 - 24.0 [4.0]	9.7 ± 7.3 (74.6) 0.0 - 16.0 [12.0]	927.7 ± 327.1 (35.3) 646.5 - 1561 [773.7]	2118.1 ± 770.8 (36.4) 1314 - 3433 [1891]	2.29 ± 0.33 (14.4) 1.81 - 2.74 [2.43]	4.9 ± 8.5 (175.7) 0.0 - 24.0 [2.0]	14.3 ± 6.5 (45.3) 0.0 - 20.0 [16.0]	2423.7 ± 500.2 (20.6) 1955 - 3183 [2209]	5373.5 ± 825.3 (15.4) 4427 - 6639 [5347.5]	2.26 ± 0.40 (17.7) 1.71 - 2.86 [2.23]	0.7 ± 0.5 (77.5) 0.0 - 1.0 [1.0]	10.0 ± 8.3 (82.9) 4.0 - 24.0 [6.0]
Japanese	Male	6	411 ± 163 (39.6) 210 - 639 [404]	945 ± 278 (29.4) 686 - 1463 [883]	2.47 ± 0.77 (31.0) 1.88 - 3.92 [2.17]	2.3 ± 1.4 (58.6) 1.0 - 4.0 [2.0]	13.3 ± 6.5 (49.0) 0.0 - 16.0 [16.0]	828.8 ± 362 (43.7) 495.8 - 1460 [747.5]	1617 ± 384.2 (23.8) 983 - 2023 [1709.5]	2.11 ± 0.59 (28.1) 1.39 - 2.87 [1.89]	5.2 ± 9.2 (178.8) 1.0 - 24.0 [1.5]	10.7 ± 8.3 (77.5) 0.0 - 16.0 [16.0]	1987.5 ± 927.3 (46.7) 935 - 3268 [1856]	4875.3 ± 2123.5 (43.6) 2364 - 7086 [5148.5]	2.55 ± 0.80 (31.4) 2.07 - 4.09 [2.12]	1.3 ± 0.5 (38.7) 1.0 - 2.0 [1.0]	10.7 ± 6.0 (56.5) 4.0 - 16.0 [12.0]

3.7.6.4 Hepatic Impairment

Study SP671 was an open-label, parallel group, multiple dose trial with transdermal administration of rotigotine 4.5 mg TDS daily for 3 days in 8 healthy volunteers and 8 subjects with moderate hepatic impairment. All subjects were Caucasian men 18 to 65-year olds, with a BMI between 20 and 34 kg/m^2.

The study was begun in [redacted] however due to performance irregularities with the first subject the trial was moved to a site in [redacted] The subject from [redacted] was not analyzed for pharmacokinetics but was included in the safety evaluation.

In subjects with moderate hepatic impairment there does not appear to be a need to adjust the dose, although there does appear to possibly be shunting from an unidentified metabolic pathway or more likely inhibited metabolism of desthienyl-rotigotine.

The following are the sponsor's conclusions:

"There were no relevant differences in the pharmacokinetic profile of rotigotine between healthy subjects and subjects with hepatic impairment. For unconjugated rotigotine, Cmax, AUC(0-24), tmax and t½ were lower in subjects with hepatic impairment than in healthy subjects, while Vss was higher in subjects with hepatic impairment. However, the differences between healthy subjects and subjects with hepatic impairment with regard to extent and rate of absorption were not statistically significant. For total rotigotine, Cmax, AUC(0-24), and tmax were higher in subjects with hepatic impairment than in healthy subjects, while t½, and Vss were lower in subjects with hepatic impairment."

"In terms of urine pharmacokinetic parameters, for unconjugated rotigotine, there was no relevant difference between groups while for total rotigotine, the rate of renal clearance was similar in both groups, but the amount excreted was higher in subjects with hepatic impairment than in healthy subjects. There was limited urinary excretion of unconjugated metabolites of rotigotine (despropyl rotigotine and desthienyl rotigotine) in both groups. Excretion of total despropyl rotigotine and desthienyl rotigotine (Aess (0-72)) was higher in subjects with hepatic impairment than in healthy subjects. Median fu, (fraction unbound in plasma at 23.5 hours post dose), *values of 10.45 % (range: 7.7, 12.5) and 12.0 % (range: 8.6, 18.0) were observed in healthy subjects (n=8) and subjects with hepatic impairment (n=6), respectively."*

"Application site reaction was the most frequently reported adverse event, reported by 4 (50.0%) healthy subjects and 2 (22.2%) subjects with hepatic impairment; this adverse event was considered highly probably related to trial medication. There were no deaths, serious or significant adverse events. There were no clinically relevant changes in clinical chemistry, hematology and urinalysis variables in either group. There were no clinically relevant changes in vital signs, physical examination or ECG findings from baseline to the end of treatment. No clinically relevant skin reactions like erythema or edema were seen."

Table 68 shows a modified Child-Pugh classification by subject. Quick time was used to evaluate coagulopathies which is unusual. In addition, results of the quick time are not always reported so the actual Child-Pugh classication cannot be ascertained although the Sponsor's assessment of moderate impairment for all subjects does appear to be likely.

The sponsor's summary statistics for the pharmacokinetics of rotigotine and total rotigotine in plasma, and despropyl- and desthienyl-rotigotine in urine are shown Table 69 to Table 72. Although individual values are not shown, inspection of the individual data does not reveal any obvious between the groups or individual outliers, this includes for total rotigotine half-life.

Although the sponsor reported geometric mean, (GM), and geometric standard deviations, (GSD), the reported GSD does not appear to have been back transformed however, this was not checked.

Table 68 Child-Pugh Scoring in Subjects with Hepatic Impairment

Subj No.	Ascites	Ascites Points	Encephalopathy	Encephalopathy Points	Bilirubin [µmol/L]	Bilirubin Points	Albumin [g/L]	Albumin Points	Quick Test (%)[a]	Points	Total Points[b]	Degree of Impairment[b]
80001	Slight	2	Slight	2	17.5	1	43.1	1	94.3	1	7	Moderate
80002	Slight	2	Slight	2	20	1	44.5	1	80	1	7	Moderate
80005	Slight	2	Slight	2	17.5	1	43.9	1	100	1	7	Moderate
80007	Slight	2	Slight	2	19.9	1	41.7	1	94.3	1	7	Moderate
80009	Slight	2	Slight	2	20.6	1	36.3	1			6+?	Moderate?
80011	Slight	2	Slight	2	14.8	1	47.1	1			6+?	Moderate?
80012	Slight	2	Slight	2	52.1	3	35.5	1			8+?	Moderate?
80013	Slight	2	Slight	2	15.7	1	44.4	1			6+?	Moderate?
90001[b]	None	1	None	1	46	2	25	3			7+?	Moderate?

a Typically the INR is currently used to assess coagulopathies in hepatic impairment. The Quick test is a one-step test for the amount of prothrombin present in blood plasma and for determination of prothrombin clotting time. In the 1930's Quick used thromboplastin derived from rabbit brains to prove that patients with bleeding abnormalities secondary to obstructive jaundice was due to a deficiency of prothrombin. Points assigned by Reviewer

b Due to lack of quick time total points could not be assigned in some subjects. For these subjects Total points are give by total for other markers and '+?' for the number of points for coagulopathies.

c Not included in PK analysis, although PK metrics in this individual did not appear different than for others.

Subject 90001 (from [redacted] had several major protocol deviations including:

- ECGs recorded with a mixture of 10, 25, and 50 mm/s and <8 - 10 s stripes. ECGs are not clearly identifiable.The device was inadequate and not regularly checked.
- PK blood sample of Day 4 / 30 h post has been centrifuged between 17 and 0°C and not according to the Protocol (4°C).
- Intake of medication (to prevent ascites) started Aug 06, 2002. Therefore intake not stable for 3 weeks before enrollment.
- Reticulocytes, Albumin, Globulin ratio, Creatinine clearance, Leucocytes, blood in urinalysis (stick) were not analyzed according to the protocol.
- Uncooled transfer of used patches from [redacted]
- Unused trial medication was stored at up to 32°C. Should have been stored between 15 to 25°C.

Table 69 Sponsor's Summary of Pharmacokinetic Metrics for Unconjugated Rotigotine post-Rotigotine 4.5 mg TDS Daily for 3 Days in Healthy Volunteers and Subjects with Hepatic Impairment – Study SP671

Population	N	Parameter	Tmax [h]	Cmax,ss (pg/ml)	AUCss(0-24) [pg/ml x hr^{-1}]	t½ [h]	MRTss [h]	Vss [L]	Ae,ss(0-24) [µg]	CLt [L/h]	CLr [L/h]	CLnr [L/h]	Fu [%]
Healthy Volunteers	8	Mean ± SD (CV%) Range [Median]	15 ± 10.0 (66.9) 0 - 24 [17]	491 ± 219 (44.77) 249 - 935 [459]	8538 ± 3496 (40.95) 3023 - 13572 [8102]	7.4 ± 3.4 (45.6) 3.2 - 12.5 [6.7]	6513 ± 2826 (43.39) 4097 - 12122 [5464.8]	1.04 ± 0.76 (72.69) 0.4 - 2.8 [0.85]	363 ± 172 (47.5) 178 - 688 [298]	0.13 ± 0.07 (56.44) 0 - 0.3 [0.11]	363 ± 172 (47.5) 178 - 688 [298]	10.29 ± 2.04 (19.86) 7.7 - 12.5 [10.45]	10.3 ± 2.0 (19.9) 7.7 - 12.5 [10.4]
		GeoMean GeoSD CV%		453 1.53 44.5	7807 1.62 51.1	6.7 1.58 48.5	6077.12 1.46 39.55	0.87 1.86 68.43	332 1.57 47.2	0.11 1.8 64.1	331.45 1.57 47.21	10.11 1.23 20.52	10.11 1.23 20.52
Hepatic Impaired Subjects	8	Mean ± SD (CV%) Range [Median]	12.8 ± 9.9 (77.7) 0 - 24 [10]	456 ± 181 (39.6) 255 - 793 [406]	7730± 3368 (43.57) 2876 - 13352 [7180]	6.2 ± 3.6 (58.4) 3.7 - 14.7 [5.2]	7097 ± 2014 (28.38) 5029 - 10506 [6752]	0.98 ± 0.74 (76.07) 0.1 - 2.5 [0.94]	384 ± 80.8 (21.02) 306 - 497 [345]	0.14 ± 0.09 (69.15) 0 - 0.3 [0.1]	384 ± 80.8 (21.0) 305.5 - 497.2 [345]	12.78 ± 4.17 (32.6) 8.6 - 18 [12]	12.8 4.2 ± (32.6) 8.6 - 18 [12]
		GeoMean GeoSD CV%		426 1.48 41.0	7047.47 1.61 50.77	5.6 1.56 46.5	6858 1.32 28.4	0.71 2.58 120.6	377.4 1.23 20.7	0.1 2.7 130.1	377 1.23 20.7	12.23 1.39 33.6	12.23 1.39 33.6

a n = 6 fu% in hepatic impaired

Table 70 Sponsor's Summary of Pharmacokinetic Metrics for Total Rotigotine post-Rotigotine 4.5 mg TDS Daily for 3 Days in Healthy Volunteers and Subjects with Hepatic Impairment – Study SP671

Population	N	Parameter	Tmax [h]	Cmax,ss (pg/ml)	AUCss(0-24) [pg/ml x hr^{-1}]	t½ [h]	MRTss [h]	Vss [L]	Ae,ss(0-24) [µg]	CLt [L/h]	CLr [L/h]	CLnr [L/h]
Healthy Volunteers	8	Mean ± SD (CV%) Range [Median]	11.5 ± 10.6 (92.4) 0 - 24 [7]	1724 ± 336 (19.5) 1320 - 2200 [1630]	34047 ± 6951 (20.4) 23718 - 46655 [32492]	13.7 ± 5.8 (42.2) 5 - 23.9 [13.4]	24 ± 4.08 (16.98) 17.4 - 29.8 [23.71]	1866 ± 375 (20.11) 1381 - 2493.2 [1873]	302 ± 173 (57.3) 122 - 686 [261]	78.4 ± 13.3 (17.01) 62.2 - 99 [77.5]	8.4 ± 3.0 (35.4) 5.1 - 14.7 [7.25]	70 ± 15 (21.43) 47.4 - 89.6 [70.3]
		GeoMean Geo SD CV%		1695 1.21 [19.6]	33438 1.23 [20.6]	12.5 1.61 [50.2]	23.7 1.19 [17.6]	1834 1.22 [20.3]	268 1.66 [54.2]	77.4 1.19 [17.11]	8.0 1.38 [32.9]	68.5 1.25 [22.7]
Hepatic Impaired Subjects	8	Mean ± SD (CV%) Range [Median]	7.8 ± 5.1 (65.3) 0 - 12 [9]	2516 ± 962 (38.2) 1670 - 4640 [2245]	46891 ± 19370 (41.3) 32466 - 90050 [37002]	12.7 ± 5.5 (43.5) 7.9 - 25.2 [10.5]	21.53 ± 1.91 (8.9) 18.3 - 24.1 [21.77]	1333 ± 332 (24.9) 726 - 1660 [1430]	3967 ± 195 (49.1) 131 - 736 [385]	61.8 ± 14.7 (23.8) 39.8 - 75.9 [65.2]	9.0 ± 5.1 (56.7) 3.6 - 20 [7.4]	52.8 ± 12.7 (24.0) 33.3 - 68 [53.4]
		GeoMean Geo SD CV%		2388 1.39 [33.9]	44206 1.41 [35.7]	11.9 1.44 [37.8]	21.45 1.09 [9.1]	1290 1.33 [29.2]	353 1.73 [58.9]	60.16 1.29 [26.1]	7.98 1.68 [55.2]	51.36 1.3 [26.6]

Table 71 Sponsor's Summary of Amount of Despropyl-Rotigotine Eliminated in Urine in Subjects with Hepatic Impairment and Healthy Volunteers – Study SP671

Parameter	N	$Ae,ss_{(0-24)}$ [µg]			
		Unconjugated Despropyl-Rotigotine		Total Despropyl-Rotigotine	
		Healthy Volunteers	Hepatic Impaired Subjects	Healthy Volunteers	Hepatic Impaired Subjects
Mean ± SD (CV%) Range [Median]	8	0.01 ± 0.03 (282.8) 0 - 0.1 [0]	0.02 ± 0.04 (197.5) 0 - 0.1 [0]	123.7 ± 71.0 (57.4) 30 - 272 [115.8]	164.9 ± 77.4 (46.9) 34.7 - 279.1 [182.8]
GeoMean Geo SD CV%	8	0.09[a]	0.07[b] 1.6 49.74	105.7 1.9 (71.0)	141.1 1.98 (77.1)

a n = 1
b n = 2

Table 72 Sponsor's Summary of Amount of Desthienyl-Rotigotine Eliminated in Urine in Subjects with Hepatic Impairment and Healthy Volunteers – Study SP671

Parameter	N	$Ae,ss_{(0-24)}$ [µg]			
		Unconjugated Desthienyl-Rotigotine		Total Desthienyl-Rotigotine	
		Healthy Volunteers	Hepatic Impaired Subjects	Healthy Volunteers	Hepatic Impaired Subjects
Mean ± SD (CV%) Range [Median]	8	0	0	15.8 ± 8.6 (54.6) 0.9 - 26.6 [16.42]	21.6 ± 9.5 (43.9) 5.2 - 34.8 [23.4]
GeoMean Geo SD CV%	8	—	—	11.6 3.0 (156.8)	19.0 1.8 (68.05)

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3.7.6.5 Renal Impairment

Study SP672 was an open-label, 5-arm parallel group, single-dose trial, comparing the single dose pharmacokinetics of Rotigotine in healthy subjects and subjects with varying degrees of renal insufficieny. Subjects were 18- to 75-year-old male and female Caucasians (white) with a body mass index between 18 and 34 kg/m^2.

Subjects in the 5 arms included:

- 8 healthy subjects: ClCr $\geq$ 80 ml/min
- 1 subject with mild renal impairment: ClCr $\geq$ 50 - < 80 ml/min
- 7 subjects with renal moderate impairment: ClCr $\geq$ 30 - < 50 ml/min
- 8 subjects with renal severe impairment: ClCr < 30 ml/min
- 8 subjects with endstage renal disease requiring dialysis: ClCr < 15 ml/min

The exposure to unconjugated rotigotine is similar between healthy subjects, subjects with moderate or severe renal impairment, and subjects with endstage renal impairment. Renal clearance decreased with creatinine clearane, (ClCr), however as Clr is a small fraction of total body clearance, total body clearance was unchanged, (see Table 73).

Plasma concentrations of total rotigotine increased with degree of renal impairment, approximately doubling in subjects with severe renal impairment, (see Figure 68), although the amount of both unconjugated as well as total rotigotine eliminated in urine was decreased indicating decreased renal clearance, (see Table 76). However, total rotigotine exposures in subjects with ESRD on dialysis were more similar to subjects with moderate renal impairment. Values for total rotigotine total body clearance also decreased with the degree for renal impairment, although the reason for this is unclear, (see Table 74 and Table 75)

Concentrations for total despropyl and total desthienyl metabolites in plasma were higher for all renal impairment groups compared to the healthy subjects, although the amounts of total despropyl and total desthienyl metabolites eliminated in the urine were unchanged indicating formation is unchanged but renal clearance is decreased in endstage renal impairment and moderate renal impairment compared with healthy subjects and subjects with severe renal impairment, (see Table 76).

As expected with drugs with large volumes of distribution, plasma levels of unconjugated rotigotine did not decrease under extracorporal dialysis indicating that rotigotine is not extracted by dialysis. Protein binding for subjects with renal impairment was also comparable to that of healthy subjects.

Overall it appears that in patients with severe renal impairment not on dialysis have a 2-fold increase in exposure to rotigotine and rotigotine conjugates however the clinical significance of this is not known.

Table 73 Sponsor's Reported Pharmacokinetic Metric Summary Statistics for Unconjugated Rotigotine by Degree of Renal Insufficiency – Study SP672

Group	ClCr	N	Tmax [h]	Cmax [ng/mL]	Cmax norm [ng/mL*kg/mg]	AUC(0-inf) [ng/mL*h]	AUC (0-inf) norm [ng/mL*h*kg/mg]	CL/F [L/h]	CLren [L/h]	Clren ml/min	MRT [h]	Ae [mcg]	t1/2 [h]	Vz/F [L]	Fu [ng/mL]
1	≥80 ml/min	8	17.5 ± 4.2 (24.2) 12.0 - 24.0 [16.0]	0.22 ± 0.11 (50.9) 0.09 - 0.43 [0.22]	6.75 ± 2.26 (33.6) 3.30 - 9.90 [6.35]	4.63 ± 2.15 (46.4) 2.14 - 9.11 [4.07]	139.6 ± 30.3 (21.7) 85.8 - 187.2 [135.2]	1147 ± 488 (42.6) 494 - 2104 [1113]	0.25 ± 0.11 (45.3) 0.11 - 0.46 [0.23]	4.2 ± 1.9 (45.3) 1.9 - 7.6 [3.75]	21.7 ± 4.4 (20.3) 18.2 - 31.6 [20.3]	1.03 ± 0.49 (47.9) 0.55 - 2.06 [0.95]	7.9 ± 4.5 (56.5) 3.9 - 17.1 [6.8]	12838 ± 9350 (72.8) 56501 - 33377 [8883]	
2	50 – 79 ml/min	1	16	0.213	7.9	3.176	118.5	1417	0.20797	3.5	17.9	0.66	4.3	8757	
3	30 – 49 ml/min	7	17.1 ± 5.0 (29.2) 12.0 - 24.0 [16.0]	0.21 ± 0.10 (46.8) 0.05 - 0.37 [0.22]	7.69 ± 2.53 (33.0) 3.00 - 10.90 [7.60]	4.02 ± 1.60 (39.9) 1.20 - 6.42 [4.43]	148.1 ± 44.1 (29.8) 66.7 - 201.0 [157.6]	1438 ± 1049 (73.0) 701 - 3765 [1015]	0.14 ± 0.06 (43.7) 0.06 - 0.24 [0.14]	2.3 ± 1.0 (43.7) 1.1 - 2.9 [2.3]	20.4 ± 2.4 (11.6) 17.7 - 23.9 [19.6]	0.50 ± 0.23 (45.1) 0.27 - 0.89 [0.45]	5.4 ± 2.0 (37.3) 3.1 - 8.1 [5.1]	12356 ± 12320 (99.7) 3136 - 39154 [10114]	0.06+
4	<30 ml/min & Not requiring dialysis[a]	8	22.0 ± 3.7 (16.8) 16.0 - 24.0 [24.0]	0.25 ± 0.09 (34.3) 0.13 - 0.35 [0.28]	7.78 ± 1.96 (25.3) 4.90 - 11.40 [8.00]	5.01 ± 1.56 (31.1) 2.76 - 6.39 [5.85]	157.6 ± 41.6 (26.4) 104.1 - 246.4 [157.4]	1004 ± 394 (39.2) 704 - 1628 [771]	0.16 ± 0.14 (92.8) 0.04 - 0.45 [0.10]	2.6 ± 2.4 (92.8) 0.6 - 7.5 [1.73]	22.0 ± 3.5 (15.9) 18.2 - 28.1 [22.5]	0.78 ± 0.85 (108.3) 0.15 - 2.48 [0.41]	7.4 ± 3.25 (43.7) 3.7 - 11.8 [7.5]	10990 ± 6969 (63.4) 4128 - 23718 [9463]	0.12 ± 0.01 (12.3) 0.11 - 0.13 [0.12]
5	ESRD (<15 ml/min)	8	23.25 ± 1.0 (4.5) 22.0 - 24.0 [24.0]	0.28 ± 0.14 (49.4) 0.11 - 0.55 [0.27]	10.01 ± 3.89 (38.9) 4.70 - 13.80 [12.05]	4.71 ± 2.46 (52.2) 2.12 - 9.65 [4.16]	166.2 ± 55.8 (33.6) 93.5 - 241.4 [181.5]	1162 ± 528 (45.4) 466 - 2125 [1081]	0.02 ± 0.02 (90.4) 0.01 - 0.04 [0.02]	0.4 ± 0.36 (90.4) 0.14 - 0.66 [0.4]	23.3 ± 3.2 (13.5) 19.5 - 27.3 [23.7]	0.11 ± 0.09 (80.4) 0.05 - 0.18 [0.11]	7.1 ± 2.2 (30.3) 3.6 - 10.5 [6.8]	12353 ± 7353 (59.5) 4097 - 25387 [12457]	0.08 ± 0.02 (26.7) 0.06 - 0.11 [0.08]

a 4 subjects with ClCr 20 – 30 and 4 subjects with ClCr <20 ml/min

Table 74 Sponsor's Reported Pharmacokinetic Metric Summary Statistics for Total Rotigotine by Degree of Renal Insufficiency – Study SP672

Grp	ClCr	N	Tmax [h]	Cmax [ng/mL]	Cmaxnorm [ng/mL*kg/mg]	AUC(0-inf) [ng/mL*h]	AUC(0-inf)norm [ng/mL*h*kg/mg]	CL/F [L/h]	CLren [L/h]	CLren [ml/min]	MRT [h]	Ae [mcg]	t1/2 [h]	Vz/f [L]
1	≥80 ml/min	8	20.5 ± 4.9 (23.8) 16.0 - 26.0 [20.0]	0.74 ± 0.28 (37.3) 0.53 - 1.34 [0.60]	23.69 ± 7.37 (31.1) 15.40 - 33.90 [23.35]	16.98 ± 7.54 (44.4) 9.55 - 33.42 [14.38]	536 ± 185 (34.5) 345 - 779 [512]	302 ± 104 (34.4) 135 - 471 [313]	10.0 ± 3.5 (35.1) 4.4 - 14.2 [10.1]	167.5 ± 58.75 (35.1) 73.8 - 237.3 [168.6]	23.5 ± 3.0 (12.9) 20.1 - 29.1 [22.9]	177.8 ± 117.8 (66.3) 41.1 - 395.6 [148.6]	9.5 ± 2.4 (25.3) 6.7 - 13.8 [8.5]	4039 ± 1438 (35.6) 2408 - 6198 [3817]
2	50 – 79 ml/min	1	16	0.847	31.6	26.414	986	170.3663	8.3	138.9	33.3	190.6	18.8	4615
3	30 – 49 ml/min	7	24.0 ± 0.0 (0.0) 24.0 - 24.0 [24.0]	0.80 ± 0.31 (38.3) 0.53 - 1.39 [0.74]	30.54 ± 8.25 (27.0) 16.10 - 40.50 [33.10]	17.47 ± 6.02 (34.5) 11.51 - 29.99 [17.43]	667 ± 161 (24.1) 381 - 874 [642]	279 ± 76 (27.3) 150 - 391 [258]	1.9 ± 0.9 (47.7) 0.8 - 3.6 [1.9]	31.0 ± 14.8 (47.7) 14.1 - 60.7 [33.0]	24.3 ± 2.9 (12.0) 21.3 - 28.8 [24.2]	29.9 ± 14.6 (49.0) 20.3 - 61.5 [24.9]	8.1 ± 2.2 (27.2) 5.3 - 10.7 [8.85]	3225 ± 1106 (34.3) 1500 - 4307 [3649]
4	<30 ml/min & Not requiring dialysis[a]	8	22.25 ± 3.9 (17.6) 16.0 - 26.0 [24.0]	1.62 ± 1.17 (72.0) 0.55 - 3.86 [1.30]	54.89 ± 46.82 (85.3) 17.40 - 154.40 [43.85]	35.70 ± 21.27 (59.6) 11.76 - 69.33 [32.60]	1176 ± 793 (67.4) 428 - 2773 [1101]	180 ± 114 (63.1) 65 - 383 [152.13]	1.8 ± 1.8 (101.1) 0.8 - 6.1 [1.1]	31.7 ± 31.4 (98.8) 14.4 - 101.5 [18.7]	25.0 ± 2.0 (8.0) 23.0 - 29.3 [24.6]	53.9 ± 40.9 (75.9) 11.0 - 110.6 [42.2]	10.5 ± 1.2 (11.1) 9.2 - 12.4 [10.5]	2717 ± 1715 (63.1) 895 - 5992 [2462]
5	ESRD (<15 ml/min)	8	23.25 ± 1.5 (6.4) 22.0 - 26.0 [23.0]	1.03 ± 0.48 (46.0) 0.41 - 1.62 [1.10]	36.39 ± 14.65 (40.3) 22.90 - 64.60 [33.40]	21.41 ± 9.30 (43.4) 8.64 - 32.27 [23.46]	746 ± 236 (31.6) 481 - 1085 [731]	262 ± 142 (54.3) 139 - 521 [197]	0.14 ± 0.11 (79.3) 0.02 - 0.27 [0.13]	2.3 ± 1.85 (79.3) 0.4 - 4.5 [2.2]	25.4 ± 3.4 (13.4) 21.6 - 31.4 [26.4]	3.2 ± 3.7 (113.9) 0.24 - 8.5 [2.0]	8.8 ± 1.1 (12.7) 7.1 - 10.4 [8.9]	3384 ± 2158 (63.8) 1653 - 7813 [2258]

Figure 68 Mean (±SD) Concentration vs. Time Profiles of Total Rotigotine in Healthy Volunteers (ClCr ≥ 80 ml/min) and Subjects with Severe Renal Insufficiency not Requiring Dialysis (ClCr < 30 ml/min)

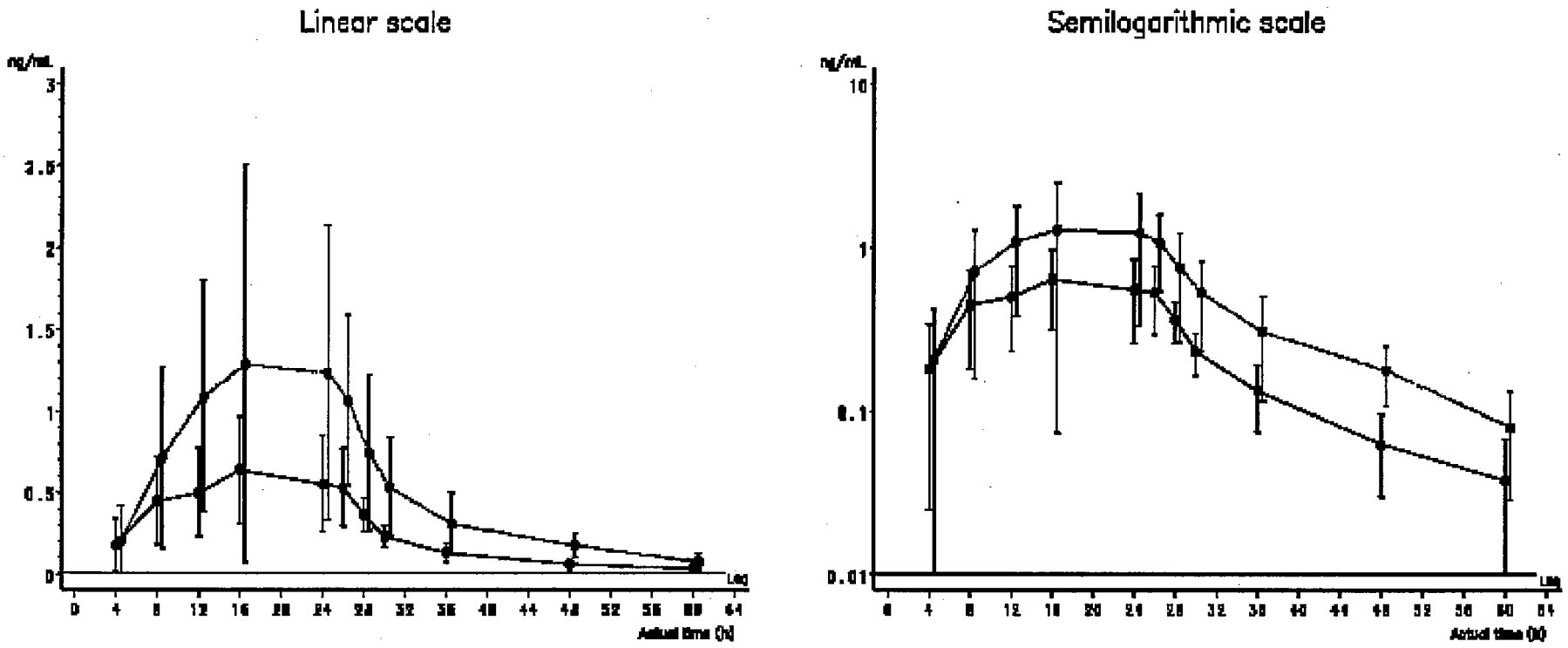

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Table 75 Exposure Ratios of Total Rotigotine to Unconjugated Rotigotine by Degree of Renal Insufficiency

Group	ClCr	AUC_{0-inf} (ng/ ml x hr^{-1})		AUC_{0-inf} Ratio	Cmax (ng/ml)		Cmax Ratio
		Rotigotine	Total Rotigotine	Total Rotigotine : Rotigotine	Rotigotine	Total Rotigotine	Total Rotigotine : Rotigotine
1	≥80 ml/min	8	8	8	8	8	8
		4.63 ± 2.15 (46.4) 2.14 - 9.11 [4.07]	16.98 ± 7.54 (44.4) 9.55 - 33.42 [14.38]	3.93 ± 1.42 (36.2) 2.44 - 6.36 [3.78]	0.22 ± 0.11 (50.9) [0.22]	0.74 ± 0.28 (37.3) [0.60]	4.10 ± 2.64 (64.3) 1.79 - 9.78 [2.94]
2	50 – 79 ml/min	1	1	1	1	1	1
		3.176	26.414	8.32	0.213	0.847	3.98
3	30 – 49 ml/min	7	7	7	7	7	7
		4.02 ± 1.60 (39.9) 1.20 - 6.42 [4.43]	17.47 ± 6.02 (34.5) 11.51 - 29.99 [17.43]	4.91 ± 2.19 (44.6) 3.00 - 9.64 [4.36]	0.21 ± 0.10 (46.8) [0.22]	0.80 ± 0.31 (38.3) [0.74]	4.48 ± 2.45 (54.8) 2.27 - 9.85 [3.80]
4	<30 ml/min & Not requiring dialysis[a]	8	8	8	8	8	8
		5.01 ± 1.56 (31.1) 2.76 - 6.39 [5.85]	35.70 ± 21.27 (59.6) 11.76 - 69.33 [32.60]	7.18 ± 3.58 (49.9) 2.88 - 11.97 [7.60]	0.25 ± 0.09 (34.3) [0.28]	1.62 ± 1.17 (72.0) [1.30]	6.70 ± 4.34 (64.9) 2.11 - 13.50 [5.71]
5	ESRD (<15 ml/min)	7	8	7	8	8	8
		4.71 ± 2.46 (52.2) 2.12 - 9.65 [4.16]	21.41 ± 9.30 (43.4) 8.64 - 32.27 [23.46]	4.65 ± 2.11 (45.4) 2.65 - 8.04 [3.49]	0.28 ± 0.14 (49.4) [0.27]	1.03 ± 0.48 (46.0) [1.10]	4.36 ± 2.90 (66.6) 1.69 - 9.64 [2.98]

Table 76 Sponsor's Reported Recovery of Rotigotine and Selected Rotigotine Metabolites in Urine by Degree of Renal Insufficiency

Group	ClCr	Unconjugated Desthienyl-Rotigotine [mcg]	Total Desthienyl-Rotigotine [mcg]	Unconjugated Despropyl-Rotigotine [mcg]	Total Despropyl-Rotigotine [mcg]	Unconjugated Rotigotine [mcg]	Total Rotigotine [mcg]	Total Urine Recovery [mcg]	Apparent Dose		% of Apparent Dose Recovered in Urine
									mg	mcg	
1	≥80 ml/min	—	8	—	8	8	8	8	8	8	8
		—	21.8 ± 22.0 (100.6)	—	63.57 ± 55.76 (87.7)	1.03 ± 0.49 (47.9)	177.85 ± 117.84 (66.3)	263.27 ± 193.84 (73.6)	2.27 ± 0.67 (29.5)	2270 ± 670 (29.5)	11.34 ± 7.12 (62.8)
			[14.7]		[51.50]	[0.95]	[148.64]	[214.36]	[2.10]	[2095]	[11.26]
2	50 – 79 ml/min	—	1	—	1	1	1	1	1	1	1
		—	54.3	—	114.201	0.66	190.557	359.1	2.09	2420	14.84
3	30 – 49 ml/min	—	7	1	7	7	7	7	7	7	7
		—	5.6 ± 2.4 (43.7)	0.008	25.29 ± 18.66 (73.8)	0.502 ± 0.226 (45.083)	29.89 ± 14.64 (49.0)	60.77 ± 33.19 (54.6)	2.05 ± 0.46 (22.4)	2054 ± 461 (22.4)	3.23 ± 2.27 (70.1)
			[5.1]		[19.59]	[0.454]	[24.87]	[49.52]	[2.21]	[2210]	[1.94]
4	<30 ml/min & Not requiring dialysis[a]	—	8	1	8	7	8	8	8	8	8
		—	20.5 ± 17.0 (82.9)	0.121	60.05 ± 38.85 (64.7)	0.784 ± 0.849 (108.285)	53.94 ± 40.92 (75.9)	134.50 ± 88.86 (66.1)	2.29 ± 0.44 (19.0)	2285 ± 435 (19.0)	5.83 ± 3.87 (66.4)
			[19.6]		[67.36]	[0.413]	[42.18]	[132.97]	[2.39]	[2385]	[6.17]
5	ESRD (<15 ml/min)	—	3	—	4	2	4	8	8	8	8
		—	1.4 ± 1.4 (97.4)	—	1.17 ± 1.57 (133.7)	0.114 ± 0.091 (80.367)	3.20 ± 3.65 (113.9)	2.73 ± 5.18 (189.7)	1.95 ± 0.40 (20.4)	194.5 ± 398 (20.4)	0.12 ± 0.20 (174.5)
			[0.8]		[0.53]	[0.114]	[2.04]	[0.19]	[1.90]	[1900]	[0.01]

3.7.7 Extrinsic Factors

3.7.7.1 Application of Heat

The effect of heat application on bioavailability was not studied. When heat has been applied to other transdermal products the rate and extent of absorption has increased several fold. In the absence of a study, and due to the heat instability of the drug product, labeling should advise that heat should not be applied to the patch.

3.7.7.2 Drug-Drug Interaction Studies

Three drug-drug interaction studies were performed, cimetidine for general metabolic DDI's, carbidopa/levodopa because rotigotine is likely to be administered in concomitantly, and domperidone as it was used as a rescue medication for the nausea and vomiting due to rotigotine.

3.7.7.2.1 Cimetidine – SP627

This was a multiple dose, randomized, open-label, 2 arm crossover study of the effect of cimietidine 400 mg q12 hr on the pharmacokinetics of rotigotine 9 mg in 12 healthy young adult males, 18 – 45 years old.

For treatment A: rotigotine 4.5 mg patches were applied for 2 days, followed by 9 mg patches for 4 days.

For treatment B: rotigotine patches were administered as per treatment A. However cimetidine 400 mg q12 hr was also administered for 7 days. It's not clear from the protocol if cimetidine dosing began on the same day as rotigotine dosing or the day before.

Rotigotine plasma samples were obtained on the last day of dosing, and the day after the removal of the last patch. Twentyfour hour urine samples for rotigotine and selected metabolites were also obtained on the last day of dosing.

The sponsor provided the following rationale for the study:

Drug Interactions:
Cimetidine, apparently through inhibition of hepatic microsomal enzyme systems, reduces the hepatic metabolism of some drugs including coumarin anticoagulants (e.g., warfarin), phenytoin, propranolol, some benzodiazepines (see Drug Interactions: Cimetidine, in the Benzodiazepines General Statement 28:24.08), lidocaine, metronidazole, triamterene, some tricyclic antidepressants, terfenadine, and theophylline, thereby decreasing elimination and increasing blood concentrations of these drugs. Cimetidine may also decrease hepatic blood flow and thereby increase the bioavailability of drugs with high hepatic extraction ratios. Clinically important effects have occurred when cimetidine and coumarin anticoagulants were administered concomitantly; if the drugs must be administered concurrently, prothrombin time should be carefully monitored and dosage adjustment of the anticoagulant may be necessary. Adverse clinical effects have also been reported when cimetidine was administered concomitantly with phenytoin, lidocaine, or theophylline. In one trial in patients receiving 300 mg of an extended-release theophylline preparation twice daily concomitantly with cimetidine 800 mg at bedtime or 300 mg 4 times daily, steady-state peak serum theophylline concentrations and area under the serum concentration-time curve were increased less substantially with the bedtime regimen than the 4-times-daily regimen. Dosage of drugs metabolized by microsomal enzyme systems or those with high hepatic extraction ratios may require adjustment when concomitant cimetidine therapy is initiated or discontinued, especially drugs with low therapeutic ratios or in patients with renal and/or hepatic impairment.
Cimetidine has reduced hepatic and renal clearances of triamterene probably via inhibition of cytochrome P-450 microsomal hydroxylation and competition for renal tubular secretion respectively. Minimal alteration in the natriuretic and potassium-sparing effects of triamterene occurred, but the possibility of a clinically important interaction during concomitant use should be considered.

Oral Dosage:
Duodenal Ulcer: For the treatment of active duodenal ulcer, the usual adult oral dosage of cimetidine is 800 mg daily at bedtime. Because clinical studies have shown that reduction of noctunal gastric acid secretion is the most important factor in healing duodenal ulcers, there does not appear to be a rationale, except for familiarity of use, for dosing regimens other than once-daily administration of cimetidine at bedtime.
For maintenance therapy following healing of acute duodenal ulcer to reduce ulcer recurrence, the usual oral dosage of cimetidine is 400 mg daily at bedtime in adults. Maintenance therapy with higher dosages or more frequent administration does not increase efficacy. For the purpose of this trial a treatment of 400 mg b.i.d. was considered suitable.

Inspection of pharmacokinetic metrics does not reveal any apparent interaction, (see Table 76 and Table 77).

Table 77 Summary Statistics for Rotigotine Pharmacokinetic Metrics in the Presence and Absence of Cimetidine – SP627

Treatment	Tmaxss (hrs)	Cmaxss (ng/ml)	Tminss (hrs)	Cminss (ng/ml)	Cmax:Cmin Ratio	AUCtau (ng/ml x hr^{-1})	T1/2 (hrs)
A: Rotigotine 9 mg	6.7 ± 7.5 (112.2) 0.0 - 23.5 [4.0]	0.53 ± 0.21 (39.9) 0.18 - 0.92 [0.51]	10.5 ± 10.5 (99.6) 1.0 - 24.0 [4.0]	0.23 ± 0.12 (50,3) 0.06 - 0.47 [0.19]	2.60 ± 1.24 (47.9) 1.44 - 5.73 [2.04]	9.1 ± 3.5 (38.1) 2.7 - 15.5 [9.4]	6.8+1.2 (17.7) 5.0 – 9.0
B: Rotigotine 9 mg & Cimetidine 400 mg q12h	4.5 ± 4.5 (100.8) 1.0 - 12.0 [2.0]	0.53 ± 0.20 (38.7) 0.13 - 0.85 [0.57]	11.9 ± 11.4 (95.7) 0.0 - 23.5 [8.0]	0.21 ± 0.11 (51.4) 0.06 - 0.43 [0.21]	2.99 ± 1.96 (65.7) 1.53 - 7.94 [2.21]	8.6 ± 3.1 (36.5) 2.0 - 13.4 [9.4]	6.6+1.3 (19.8) 4.8 – 9.2

Table 78 Renal Clearance and Urinary Recovery of Rotigotine and Selected Metabolites in the Presence and Absence of Cimetidine – SP627

Treatment	N	Unconjugated Rotigotine		Total Rotigotine	N-Despropyl-Rotigotine	N-Desthienyl-Rotigotine
		Clr	Ae(0-24)	Ae(0-24)		
		(ml/min)	ng	mcg		
A: Rotigotine 9 mg	12	2.21 ± 1.38 (62.5) 0.45 - 4.67	1114 ± 810 (72.7)	772 ± 312 (43.2)	248 ± 100 (40.2)	100 ± 36.4 (36.4)
B: Rotigotine 9 mg & Cimetidine 400 mg q12h	12	2.1 ± 1.63 (77.3) 0.16 - 6.18	988 ± 551 (55.8)	659 ± 376 (57.1)	228 ± 119 (52.2)	91 ± 43 (47.3)

3.7.7.2.2 Carbidopa – Levodopa – SP628

Study SP628 was an open-label, parallel-group, drug-drug interaction study of rotigotine TDS and levodopa/carbidopa in 24 subjects, (M/F 12/12), with idiopathic Restless Legs Syndrome.

Treatments by group along with the PK sampling scheme are shown in Table 79.

Table 79 Treatments by Treatment Groups and PK Sampling Scheme for Rotigotine / Carbidopa / Levodopa DDI Study – SP628

Group	Treatments	Day												
		1	2	3	4	5	6	7	8	9	10	11	12	13
A	Rotigotine 4.5 mg / 10 cm^2													
	Rotigotine 9 mg / 20 cm^2						PK[a]			PK[a]	PK[b]			
	CD/LD 2 x (25/100) qd									PK[c]			PK[c]	
B	Rotigotine 4.5 mg / 10 cm^2													
	Rotigotine 9 mg / 20 cm^2								PK[a]			PK[a]	PK[b]	
	CD/LD 2 x (25/100) qd		PK[c]						PK[c]					

a Plasma samples: 0, 1, 2, 4, 8, 12, 16, 24; Urine samples 0- 24 hr
b Plasma samples 0, 2, 4, 6, 12, 24, 48 post patch removal; Urine samples 0-24 hrs post patch removal
c 0, 0.25, 0.5, 0.75, 1, 1.25, 2, 3, 4, 6, 8, 12

Based on summary statistics of pharmacokinetic parameters shown in Table 80 to Table 85 no obvious interaction was detected. However the dose of Rotigotine is relatively low and will not stress the system. This is also true for the carbidopa / levodopa combination which was even less than the labeled starting dose of CD/LD 25/100 tid, and it was certainly less than the maximum labeled dose of 200 mg / 2000 mg per day. Consequently no firm conclusions can be reached regarding an interaction between rotigotine and Carbidopa or Levodopa. In addition, at these doses carbidopa is considered subtherapeutic and the AE profile may not be realistic in this study.

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Table 80 Pharmacokinetic Metrics Summary Statistics of Unconjugated Rotigotine after Various Treatments – CD/LD DDI Study SP628

	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	CL/f (ml/min)	t1/2 (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	CL/f (ml/min)	t1/2 (hrs)
	Treatment CD/LD & Rotigotine					Treatment Rotigotine				
N		23	23	23	11		23	23	23	11
Mean	7.1964	906.8	16845	4662.57	9.262	8.8746	954	16968	4913.13	9.6682
%CV	74.9	41.3	37.8	26.3	22.4	66	51.5	47.5	24	22.9
Minimum	0	263	4752.5	3240.09	5.9338	0	315	6075	3218.4	5.277
Maximum	24	1870	29064	7364.54	13.932	16	2010	31930	7873.8	12.732
Median	8	948	16360	4424.26	8.9058	8	793	16194	4667.67	9.3264
geoMean		826.3	15463	4520.19	9.0616		839	15103	4785.04	9.4094
geo%CV	23	49.2	47.9	25.5	22.1	23	56.6	54.1	23.6	25.8
	Treatment CD/LD & Rotigotine									
	Group B Day 8					Group A Day 9				
N		11	11	11	0		12	12	12	11
Mean	6.5924	881.4	16227	4813.14	.	7.75	930.1	17411	4524.56	9.262
%CV	65	44.3	43.7	31.1	.	82.4	40.3	33.8	21.4	22.4
Minimum	0	263	4752.5	3240.09	.	1	354	6922.8	3309.64	5.9338
Maximum	11.85	1490	26131	7364.54		24	1870	29064	6813.28	13.932
Median	8	997	15605	4524.02		6	937	17919	4406.1	8.9058
geoMean		788	14548	4610.82	.		863.1	16352	4438.67	9.0616
geo%CV	11	57.1	56.5	31.3	.	12	43.3	40.8	20.3	22.1
	Treatment Rotigotine									
	Group A Day 6					Group B Day 11				
N		12	12	12	0		11	11	11	11
Mean	8.8431	993.1	17843	4701.62	.	8.9091	911.5	16014	5143.87	9.6682
%CV	68.9	51.3	46.7	18.7	.	66.1	53.9	50.4	28.2	22.9
Minimum	1	315	6603.5	3664.35	.	0	321	6075	3218.4	5.277
Maximum	16	1940	31930	6259.31		16	2010	29565	7873.8	12.732
Median	8	844.5	17237	4620.08		8	782	13569	4672.66	9.3264
geoMean		873.1	15931	4630.47	.		803.3	14249	4959.54	9.4094
geo%CV	12	58.9	55.7	18.2	.	11	56.8	54.7	29.1	25.8

Table 81 Pharmacokinetic Metrics Summary Statistics of Total Rotigotine after Various Treatments – CD/LD DDI Study SP628

Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	CL/f (ml/min)	t1/2 (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	CL/f (ml/min)	t1/2 (hrs)
Treatment CD/LD & Rotigotine					**Treatment Rotigotine**				
23	23	23	23	11	23	23	23	23	10
9.072	7.529	137.58	597.05	11.001	8.087	7.663	140.08	647.92	12.892
55.4	48.3	43.6	33.8	14.5	72.5	50.9	49.3	59.2	34
1	1.36	30.249	330.79	8.4777	0	1.05	18.548	360.84	7.9299
16	16	257.66	1157.05	13.723	16	17.5	328.82	2282.43	21.713
8	7.41	137.13	594.26	11.07	8	7.38	139.52	530.48	11.626
	6.626	122.72	569.54	10.894		6.665	121.91	592.79	12.292
	60.3	57.5	31.4	14.9		64.7	65.4	39.1	32.7
Treatment CD/LD & Rotigotine									
Group B Day 8					**Group A Day 9**				
11	11	11	11		12	12	12	12	11
8.788	7.314	138.97	584.06		9.333	7.727	136.31	608.96	11.001
67.5	56	49.3	38.5		46	43.2	39.6	30.9	14.5
1	1.36	30.249	330.79		4	2.46	35.585	413.9	8.4777
16	16	257.66	1157.05		16	14.9	225.47	1119.39	13.723
8	6.72	132.13	594.26		8	7.62	145.13	596.72	11.07
	6.22	121.77	550.86			7.02	123.6	587.23	10.894
	72.2	64.1	36.2			51	54.4	27.6	14.9
Treatment Rotigotine									
Group A Day 6					**Group B Day 11**				
	12	12	12	0		11	11	11	10
10.17	7.571	144.22	694.73	.	5.818	7.765	135.57	596.85	12.892
59	53.5	53.4	73.5	.	86.2	50.6	46.2	29.5	34
0	1.05	18.548	391.81	.	0	2.81	47.515	360.84	7.9299
16	17.5	328.82	2282.43		16	16.9	245.88	1006.7	21.713
10	7.77	150.95	529.91		4	7.1	115.96	605.49	11.626
	6.397	121.03	609.53	.		6.97	122.89	575.05	12.292
12	78.3	81.3	48.2	.	11	51.9	50.3	29	32.7

Table 82 Pharmacokinetic Metrics Summary Statistics of Carbidopa after Various Treatments – CD/LD DDI Study SP628

Parameter	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)
	Treatment CD/LD					Treatment CD/LD & Rotigotine				
N		23	23	23	23		23	23	23	23
Mean	2.13	161.24	815.02	0.3128	2.255	2.6	170.7	838.94	0.3138	2.24
%CV	44.9	33.5	35.8	12.8	14.5	40.6	36.7	35.1	11.5	12.8
Minimum	0.75	70.1	358.01	0.216	1.814	1.25	91.9	419.28	0.2259	1.889
Maximum	5	281	1524.3	0.382	3.208	4	343	1476.5	0.367	3.068
Median	2	161	763.25	0.3174	2.184	3	169	746.08	0.314	2.207
geoMean		151.8	763.67	0.3102	2.235		160.47	789.4	0.3117	2.224
Geo%CV	23	38.2	39.2	13.6	13.6	23	37	37.3	12.2	12.2
	Treatment CD/LD									
	Group B Day 2					Group A Day 12				
N		11	11	11	11		12	12	12	12
Mean	2.2	173.6	870.47	0.3228	2.194	2.06	149.92	764.19	0.3036	2.312
%CV	32.4	33.9	36.2	14.6	16.1	56.4	32.5	35.7	10.3	13.2
Minimum	1.25	85.6	402.24	0.2455	1.814	0.75	70.1	358.01	0.216	2.094
Maximum	4	281	1524.3	0.382	2.823	5	210	1229.8	0.3311	3.208
Median	2	176	834.87	0.3264	2.124	2	159.5	701.29	0.3139	2.208
geoMean		164.26	818.45	0.3195	2.169		141.21	716.69	0.3018	2.296
geo%CV	11	36.7	38.9	15.5	15.5	12	39.7	40.1	11.7	11.7
	Treatment CD/LD & Rotigotine									
	Group B Day 8					Group A Day 9				
N		11	11	11	11		12	12	12	12
Mean	2.48	182.48	924.64	0.3146	2.254	2.71	159.89	760.39	0.3131	2.227
%CV	35.1	38.3	35.2	15	16.8	45.4	35	33.2	7.8	8.2
Minimum	1.25	96.3	419.28	0.2259	1.889	1.25	91.9	454.65	0.265	2.019
Maximum	4	343	1476.5	0.367	3.068	4	252	1173	0.3434	2.615
Median	3	177	942.27	0.3243	2.137	2.5	147	672.85	0.3101	2.235
geoMean		171.32	866.53	0.3112	2.228		151.13	724.75	0.3122	2.22
geo%CV	11	38.4	41	16	16	12	36.2	32.8	8	8

Table 83 Pharmacokinetic Metrics Summary Statistics of Levodopa after Various Treatments – CD/LD DDI Study SP628

Parameter	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)
	Treatment CD/LD					Treatment CD/LD & Rotigotine				
N	23	23	23	23	23	23	23	23	23	23
Mean	0.676	1655.7	2691	0.4666	1.513	0.663	1685.4	2617.5	0.4711	1.494
%CV	80.9	33.7	21.7	14.5	13.6	51.6	30.1	20.8	12.6	12.7
Minimum	0.25	758	1842.5	0.3489	1.051	0.25	855	1474.1	0.3636	1.209
Maximum	3	2960	3941.3	0.6595	1.987	1.5	2610	3545.6	0.5732	1.906
Median	0.5	1630	2622.6	0.4631	1.497	0.5	1490	2514.5	0.4598	1.508
geoMean		1562.5	2631.8	0.4622	1.5		1611.8	2561.4	0.4675	1.483
Geo%CV		36.8	21.8	14	14		31.7	21.9	12.7	12.7
	Treatment CD/LD									
	Group B Day 2					Group A Day 12				
N		11	11	11	11		12	12	12	12
Mean	0.845	1495.4	2807.9	0.435	1.617	0.521	1802.8	2583.8	0.4956	1.418
%CV	90.1	31.2	22	12.7	12.8	24.7	34.1	21.4	13.6	11.3
Minimum	0.5	758	2000.5	0.3489	1.332	0.25	872	1842.5	0.4486	1.051
Maximum	3	2290	3941.3	0.5204	1.987	0.75	2960	3555.7	0.6595	1.545
Median	0.5	1500	2664.7	0.4264	1.626	0.5	1685	2349.2	0.4657	1.488
geoMean		1424.3	2745.8	0.4318	1.605		1700.8	2531.5	0.4919	1.409
Geo%CV	11	34.7	22.6	12.8	12.8	12	38	21.2	12.4	12.4
	Treatment CD/LD & Rotigotine									
	Group B Day 8					Group A Day 9				
N		11	11	11	11		12	12	12	12
Mean	0.75	1743.2	2732.1	0.4828	1.458	0.583	1632.5	2512.5	0.4604	1.527
%CV	53.7	30.2	20.4	12.8	13.5	46	31	21.3	12.4	12.2
Minimum	0.5	855	2112.1	0.3782	1.249	0.25	1020	1474.1	0.3636	1.209
Maximum	1.5	2330	3545.6	0.5551	1.833	1.25	2610	3156	0.5732	1.906
Median	0.5	1740	2537.2	0.5038	1.376	0.5	1455	2430	0.455	1.524
geoMean		1662.2	2682.1	0.4791	1.447		1567	2455.6	0.4572	1.516
Geo%CV	11	34.6	20.3	13.2	13.2	12	30.1	23.3	12.3	12.3

Table 84 Pharmacokinetic Metrics Summary Statistics of 3-O-Methyldopa after Various Treatments – CD/LD DDI Study SP628

Parameter	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCss (ng/ml x hr^{-1})	Kel (hr^{-1})	t1/2 (hrs)
	Treatment CD/LD					Treatment CD/LD & Rotigotine				
N		23	23	21	21		23	23	21	21
Mean	3.87	1351	14177	0.0518	13.68	3.26	1268	13041	0.0499	14.32
%CV	40	24.6	23.6	14.2	17	40.5	22.7	20.8	17.4	18.5
Minimum	2	893	9410.8	0.035	10.78	0.5	841	8556	0.0331	10.86
Maximum	8	2210	22515	0.0643	19.81	6	2160	20370	0.0639	20.96
Median	4	1340	13930	0.0526	13.18	3	1230	12716	0.0506	13.69
geoMean		1314	13814	0.0513	13.52		1239	12781	0.0492	14.1
geo%CV	23	24.4	23.5	15.6	15.6	23	21.8	20.7	18.1	18.1
	Treatment CD/LD									
	Group B Day 2					Group A Day 12				
N		11	11	9	9		12	12	12	12
Mean	4.55	1306	13699	0.0538	13.02	3.25	1393	14616	0.0503	14.18
%CV	38.6	21.7	19.2	11	11.5	32.5	27.3	27.1	16.4	19.4
Minimum	2	893	9683.3	0.0427	10.78	2	924	9410.8	0.035	11.02
Maximum	8	1890	18955	0.0643	16.24	5	2210	22515	0.0629	19.81
Median	4	1360	14636	0.0541	12.82	3	1325	13770	0.0512	13.54
geoMean		1278	13470	0.0535	12.95		1347	14137	0.0496	13.96
geo%CV	11	21.8	19.5	11.3	11.3	12	27.2	27.4	18	18
	Treatment CD/LD & Rotigotine									
	Group B Day 8					Day 9 Group A				
N		11	11	9	9		12	12	12	12
Mean	3.36	1315	13376	0.0459	15.6	3.17	1225	12735	0.0529	13.36
%CV	20	26.2	22.2	19.7	19.2	55.2	19	20.1	14.1	14.8
Minimum	2	954	9813.9	0.0331	11.2	0.5	841	8556	0.0389	10.86
Maximum	4	2160	20370	0.0619	20.96	6	1570	16638	0.0639	17.81
Median	3	1370	13842	0.0443	15.64	3	1215	12577	0.0514	13.48
geoMean		1279	13103	0.0452	15.34		1204	12492	0.0524	13.23
geo%CV	11	24.4	21.2	19.6	19.6	12	19.8	20.9	14.5	14.5

Table 85 Urinary Recoveries and Renal Clearance of Rotigotine and Selected Metabolites from CD/LD DDI Study SP628

Analyte	Rx	Group	Day	Metric	N	Mean	%CV	Min	Median	Max	geoMean	geo%CV
total rotigotine	NR			Clr (ml/min)	23			43.93	127.63	330.86	126.99	49.1
				Ae(0-T) (µg)	23				923.94		1042.0	46.0
				Ae%	23				24.37		23.37	28.9
	R			Clr (ml/min)	23			52.71	146.82	472.55	135.62	48.0
				Ae(0-T) (µg)	23				926.01		1105.4	49.5
				Ae%	23				24.20		23.84	28.4
	NR	Group B	Day 8	Clr (ml/min)	11			79.27	122.42	196.05	120.11	28.6
				Ae(0-T) (µg)	11				864.00		948.95	39.7
				Ae%	11				20.74		22.15	18.8
		Group A	Day 9	Clr (ml/min)	12			43.93	151.98	330.86	133.65	65.3
				Ae(0-T) (µg)	12				1168.5		1127.3	49.8
				Ae%	12				26.67		24.49	34.8
	R	Group A	Day 6	Clr (ml/min)	12			52.71	138.01	472.55	131.04	62.2
				Ae(0-T) (µg)	12				885.16		1075.3	56.1
				Ae%	12				21.70		22.46	29.4
		Group B	Day 11	Clr	11			87.31	154.06	217.49	140.80	31.1
				Ae(0-T)	11				938.68		1138.2	44.5
				Ae%	11				25.33		25.36	27.3
unconjugated rotigotine	NR			Clr (ml/min)	23			0.90	2.476	6.71	2.523	63.0
				Ae(0-T) (ng)	23				2312.6		3152.7	83.8
				Ae%	23				0.05		0.07	67.0
	R			Clr (ml/min)	23			0.65	2.385	5.57	2.276	58.9
				Ae(0-T) (ng)	23				1916.8		2870.1	90.4
				Ae%	23				0.05		0.06	67.2
	NR	Group B	Day 8	Clr (ml/min)	11			0.90	3.069	6.71	2.707	75.8
				Ae(0-T) (ng)	11				2128.0		3519.0	93.1
				Ae%	11				0.05		0.08	77.4
		Group A	Day 9	Clr (ml/min)	12			1.00	2.351	5.00	2.366	52.8
				Ae(0-T)	12				2338.0		2817.0	70.5
				Ae%	12				0.05		0.06	44.2
	R	Group A	Day 6	Clr	12			0.65	2.105	5.31	2.174	55.4
				Ae(0-T) (ng)	12				1871.8		2678.4	91.5
				Ae%	12				0.05		0.05	55.9
		Group B	Day 11	Clr (ml/min)	11			0.70	2.772	5.57	2.392	65.4
				Ae(0-T) (ng)	11				2430.0		3079.3	92.5
				Ae%	11				0.05		0.06	76.1
total despropyl-rotigotine	NR			Ae(0-T) (µg)	23	406.62	50.6		401.83			
				Ae%	23	10.73	43.5		10.82			
	R			Ae(0-T) (µg)	23	390.62	49.5		378.50			
				Ae%	23	10.00	37.0		11.19			
	NR	Group B	Day 8	Ae(0-T) (µg)	11	408.34	46.2		436.10			
				Ae%	11	11.12	39.9		9.74			
		Group A	Day 9	Ae(0-T)	12	405.04	56.4		381.43			
				Ae%	12	10.37	48.5		10.87			
	R	Group A	Day 6	Ae(0-T) (µg)	12	362.01	54.6		346.82			
				Ae%	12	9.25	43.9		9.80			
		Group B	Day 11	Ae(0-T) (µg)	11	421.83	45.7		405.85			
				Ae%	11	10.82	30.1		11.48			
total desthienyl-rotigotine	NR			Ae(0-T) (µg)	23	98.19	45.4		91.20			
				Ae%	23	3.53	39.4		3.30			
	R			Ae(0-T) (µg)	23	87.56	45.1		75.73			
				Ae%	23	3.01	33.3		2.90			

Ae(0-T): total amount excreted [ug]
Ae%: total amount excreted as percentage of the dose [%]
NR = CD/LD + Rotigotine; R = Rotigotine

3.7.7.2.3 Domperidone – SP670

Study SP670 was and open, randomized, two-way crossover study in 16 healthy male volunteers 18 – 45 yo that evaluated the effect of domperidone 10 mg po tid x 5 days on the pharmacokinetics rotigotine 4.5 mg qd x 4 days. Both treatments were begun on the same day.
Inspection of summary statistics for rotigotine pharmacokinetic metrics does not reveal any evidence of an effect of domperidone on rotigotine. Unfortunately the dose was below the maximum recommended dose of 20 mg q4h for nausea and vomiting in Parkinson's Disease. It is noteworthy that one subject experienced syncope during the study.

Table 86 Summary Statistics for Pharmacokinetic Metrics for Unconjugated Rotigotine in the Presence and Absence of Domperidone 10 mg po tid – SP670

Traetment Arm		N	$T_{max,ss}$ (h)	$C_{max,ss}$ (pg/mL)	C_{min} (pg/mL)	C_{av} (pg/mL)	AUC_{ss} (h•pg/mL)	AUC_{0-t} (h•pg/mL)	$t_{1/2}$ (h)	A_e (µg)	Cl_{ren} (mL/min)
A	Rotigotine 4.5 mg + Domperidone 10 mg tid	16	15.6 ± 8.8 (56) 0.0 - 24.0 [17.8]	302 ± 162 (54) 114 - 596 [241]	161 ± 75 (46) 64 - 302 [155]	247 ± 130 (53) 98 - 465 [202]	5923 ± 3112 (53) 2361 - 11152 [4836]	7381 ± 3669 (50) 3089 - 13133 [6407]	5.6 ± 1.7 (31) 2.4 - 7.9 [5.6]	1.51 ± 1.10 (73) 0.45 - 4.16 [1.20]	4.56 ± 3.12 (68) 1.56 - 11.16 [3.68]
B	Rotigotine 4.5 mg	16	15.3 ± 9.4 (61) 0.0 - 24.0 [17.8]	306 ± 145 (47) 108 - 557 [275]	153 ± 69 (45) 47 - 296 [157]	249 ± 121 (49) 78 - 467 [227]	5980 ± 2909 (49) 1868 - 11199 [5443]	7430 ± 3490 (47) 2266 - 13376 [6688]	5.3 ± 1.6 (30) 2.8 - 7.9 [5.8]	1.44 ± 0.86 (60) 0.37 - 2.99 [1.27]	4.31 ± 2.10 (49) 1.52 - 8.81 [4.81]
A:B Ratio or A – B for		16		**0.99 ± 0.25 (25) 0.52 - 1.61 [0.93]**			**1.00 ± 0.25 (25) 0.55 - 1.63 [0.95]**			**0.07 ± 0.87 (1243) -0.90 - 2.26 [-0.13]**	

Table 87 Summary Statistics for 24 hour Urine Rocoveries for Rotigotine and Selected Metabolites in the Presence and Absence of Domperidone – SP670

Treatment Arm		N	Unconjugated Rotigotine (ng)	Total Rotigotine (µg)	Total Desthienyl-Rotigotine (µg)	Total Despropyl-Rotigotine (µg)
A	Rotigotine 4.5 mg + Domperidone 10 mg tid	16	1.508 ± 1.097 (72.7) 0.448 - 4.165 [1.199]	437.3 ± 213.6 (48.8) 177.1 - 985.3 [412.0]	49.0 ± 42.3 (86.2) 13.5 - 168.8 [30.7]	131.2 ± 67.8 (51.6) 58.0 - 300.1 [114.5]
B	Rotigotine 4.5 mg	16	1.438 ± 0.857 (59.6) 0.368 - 2.989 [1.275]	423.7 ± 163.0 (38.5) 203.1 - 702.4 [419.1]	48.4 ± 24.7 (51.1) 16.4 - 113.6 [41.3]	121.5 ± 52.3 (43.0) 60.9 - 233.0 [118.2]
A:B Ratio		16	1.149 ± 0.750 (65.3) 0.350 - 2.879 [0.903]	1.074 ± 0.448 (41.7) 0.518 - 2.150 [0.927]	1.039 ± 0.608 (58.5) 0.191 - 2.477 [0.797	1.173 ± 0.541 (46.1) 0.471 - 2.065 [1.062]

3.8 Clinical Pharmacology

Two clinical pharmacology studies, SP629, SP673 were performed to specifically examine the tolerability and adhesive characteristics of rotigotine transdermal systems, although tolerability was assessed in most other studies.

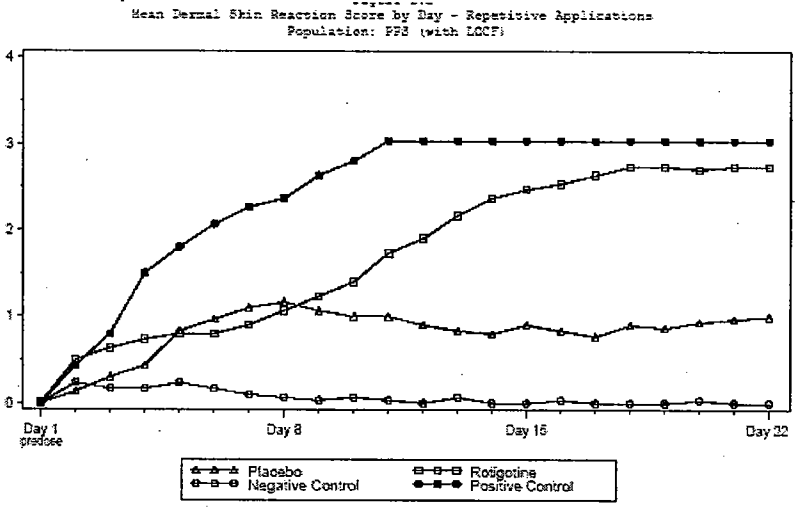
The dermal tolerability scoring systems used may be found in Table 112 in §5.1 Appendix 1 - Study Designs.

3.8.1 Tolerability and Sensitization

3.8.1.1 Study SP629

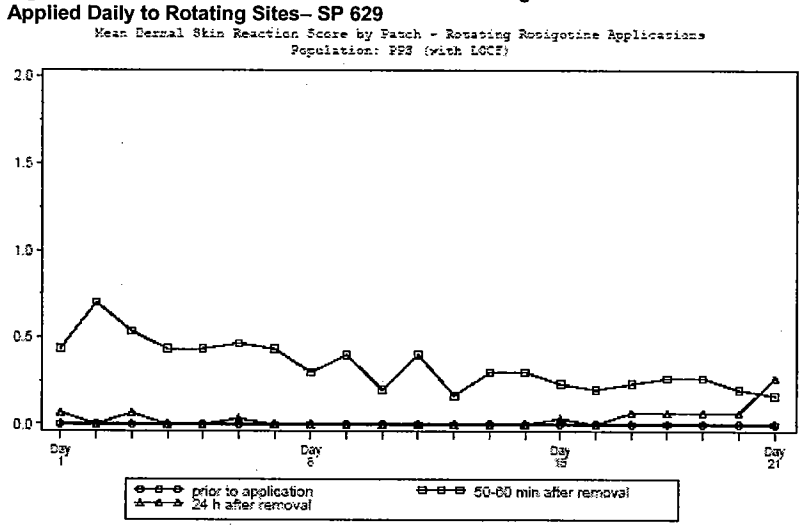
Study SP629 examined the tolerability to a rotigotine 2.25 mg / 5 cm^2 patch applied to the same site for 21 days. As shown in Figure 69 under these conditions rotigotine is clearly a dermal irritant and after application to the same site for 2 – 3 weeks results in almost the same degree of irritancy as the positive control. More importantly 4 of the 40 subjects had evidence of possible allergic sensitization.

Figure 69 Mean Dermal Skin Reaction Score for Rotigotine 5 cm^2 Patches Applied Daily to the Same Site Compared to Controls – SP 629



Even when the patch site was rotated there was still significant irritancy. This is particulary noteworthy as the 5 cm^2 patch not even proposed for Parkinson's Disease and is much smaller than the 40 cm^2 patch proposed for use, and typically irritation increases with patch size. See Table 91 for a summary of the incidence of various scores for this study. There is a significant number of applications with grade 3 erythema and grade 1 edema.

Figure 70 Mean Dermal Skin Reaction Score for Rotigotine 5 cm^2 Patches Post-Removal when Applied Daily to Rotating Sites– SP 629



3.8.1.2 Study SP673

Study SP673 was a two-site, placebo-controlled trial investigating the sensitization potential of rotigotine transdermal patch 1.125 mg / 2.5 cm^2 compared to a placebo patch.

The treatment phase consisted of an induction phase where both patches were administered 3 times weekly for 3 weeks to the same skin site, a rest phase with no patch administration and a challenge phase where patches were applied once to intact skin sites for 48 hours.

Sensitization was assessed by the investigator at the end of the challenge phase using a skin reaction scoring system.

Skin reactions were assessed in accordance with the standards of the International Contact Dermatitis Research Group at 30 minutes (±5 minutes) and at 24, 48, and 72 hours (±1 hour) after the patch removal.

The sponsor's results are shown in Table 88.

Table 88 Summary of Skin Reactions during challenge phase (FAS)

Time after patch removal	Number (%) of subjects					
	Rotigotine (N=221)			Placebo (N=221)		
	Negative (score 0)	Doubtful[1] (score 1)	Weakly positive[2] (score 2)	Negative (score 0)	Doubtful[1] (score 1)	Weakly positive[2] (score 2)
30 minutes	133 (60.2)	73 (33.0)	15 (6.8)	120 (54.3)	90 (40.7)	11 (5.0)
24 hours	172 (77.8)	47 (21.3)	2 (0.9)	190 (86.0)	30 (13.6)	1 (0.5)
48 hours	217 (98.2)	4 (1.8)	—	218 (98.6)	3 (1.4)	—
72 hours	221 (100.0)	—	—	221 (100.0)	—	—

1 faint erythema only
2 erythema, infiltration, possibly papules

According to the sponsor: *"For both treatments, no skin reaction higher than score 2 (ie, erythema, infiltration, possible papules) was observed (Table 11.1 and Figure 3.1). Thirty minutes after patch removal, weak positive reactions were observed for the rotigotine patch in 6.8% of subjects and for the placebo patch in 5% of subjects. The intensity of these reactions decreased quickly, and 24 hours later weak positive reactions were observed in only 0.9% of subjects with the rotigotine patch and in 0.5% with the placebo patch. Until the next reading 48 hours after patch removal (Day 40), these reactions disappeared completely (Figure 1.1 and Figure 1.2). Individual skin reactions during the challenge phase are listed in Listing 9.3."*

This appears to be a positive signal for sensitization, and the incidence or severity with patch sizes used therapeutically might be higher.

3.8.1.3 Study SP630

Study SP630 is the multiple dose PK study that assessed the effect of age, gender, and application site. Dermal tolerability in this study was assessed with the smallest patch, 10 cm^2, on 2 days, and with the largest patch, (40 cm^2), on 6 days. Results for the largest patch strength are shown in Table 89.

Table 89 Summary of Dermal Irritation with Rotigotine 18 mg TDS over 5 Days when Applied to Different Sites – Study SP630

Dermal Response Score								
# of Patches	0	1	2	3	4	5	6	7
	No Irritation	Minimal Erythema	Definite	Erythema and Papules	Definite Edema	Erythema, Edema, & Papules	Vesicular Eruption	Strong Reaction Spreading Beyond Test Site
252 (100.0)	144 (57.1)	97 (38.5)	10 (4.0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)

Other Effects							
# of Patches	None	A	B	C	F	G	H
	No Other Effects	Slight Glazed Appearance	Marked Glazing	Glazing with Peeling and Cracking	Glazing with Fissures	Film of Dried Serous Exudates covering all or part of the patch site	Small Petechial Erosions or Scabs
252 (100.0)	201 (79.8)	37 (14.7)	13 (5.2)	1 (0.4)	0 (0)	0 (0)	0 (0)

Other Site Reactions				
# of Patches	W	X	Y	Z
	Any other Site Reactions	Itching at application site	Pain at application site	Other at application Site
252 (100.0)	31 (12.3)	29 (11.5)	0 (0.0)	2 (0.8)

3.8.1.4 Other Studies

Most other studies that assessed tolerability used only the 10 cm^2 patch for a single 24 hour application. The scoring system most commonly used is shown in Table 90.

Table 90 Tolerability Scoring System Commonly Used by Sponsor in Studies

Redness	Edema
0 None	0 None
1 Slight	1 Marginal
2 Evident	2 Slight (i.e. elevated)
3 Papular	3 Evident (≤ 1 mm)
4 Vesiculation	4 Severe (> 1 mm) & extending

Typically anywhere from 50% - 100% of subjects in each study experienced slight redness, 18% -43% experienced marginal edema, and 5% - 33% experienced slight edema, i.e elevated skin.

It's also noteworthy that in the pivotal phase III efficacy study, SP513, 8% of subjects discontinued therapy due to application site reactions.

Table 91 summarizes dermal tolerability and adhesion scores from many studies. However, it should be noted that this table is incomplete.

Table 91 Summary of Rotigotine Transdermal System Dermal Tolerability and Adhesion from Clinical Studies

	Trial Objective(s)	Rx	N	Erythema								Edema								Adhesion								
				0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	0+1	0	1	2	3	4	5	6	7	8
Study No																											Detach	Not Adfixed
	Initial Exploratory PK/PD Proof of Concept Studies																											
SP803	Evaluate safety and efficacy																											
SP804	Evaluate safety and efficacy																											
SP805	Evaluate safety and efficacy																											
	Formulation Development																											
SP799	Evaulate safety and PK in healthy volunteers																											
SP800	Define PK and evaluate safety																											
SP801	Define PK and safety in healthy volunteers																											
SP802	Define PK, dose response, evaluate efficacy and safety in subjects with advanced Parkinson's disease																											
SP502	Comparative BA of [redacted] vs. silicone patches in healthy volunteers	[redacted] 1 edema	12	2 (17)	10 (83)									1 (8)					67	3 (25)	5 (42)	2 (17)	1 (8)	1 (8)			0	
		1 silicone	14	4 (29)	8 (57)	2 (14)													85	9 (64)	3 (21)	2 (14)					1 (7)	
		2 silicone	24	12 (50)	8 (33)	4 (8)													83	14 (58)	6 (25)	2 (8)	1 (4)	1 (4)			1 (4)	
	Mass Balance																											
SP610	Absorption, metabolism and excretion of 14C-SPM 962 in healthy volunteers																											
SP606	Absorption and excretion of 14C-SPM 962 in healthy volunteers	1 silicone	6		6 (100)							4 (67)	2 (37)							6 (100)							0	
	Healthy Subject PK and Initial Tolerability Trial Reports																											
SP503	Evaluate PK, safety and tolerability in healthy volunteers	1 silicone	409-411	66 (16)	286 (70)	56 (14)	2 (0.5)					405 (98.5)	5 (1.2)	1 (0.2)						222 (54)	122 (30)	40 (10)	17 (4)	7 (2)			9 (2)	
		PBO	60	24 (40)	31 (52)	5 (8)						60 (100)								45 (75)	9 (15)	3 (5)	2 (3)				0	
	Intrinsic Factors																											
SP630	Define PK with rotating patch application sites, evaluate ECG effects, safety and tolerability																			N	≥90%	75%-<90%	50%-<75%	<50%	Detach	NA Tape	NA new patch	
		4.5 /10																		129	103 (80)	12 (9)	3 (2.3)	1 (0.8)	0 (0)	10 (8)	0 (0)	
		9 /20																		63	47 (75)	11 (18)	2 (3)	1 (2)	0 (0)	2 (3)	0 (0)	
		13.5 / 30																		62	33 (53)	20 (32)	4 (6.5)	0 (0)	1 (1.6)	4 (6.5)	0 (0)	
		18 / 40																		377	230 (61)	72 (19)	19 (5)	1 (0.3)	0 (0)	54 (14)	1 (0.3)	
																				None	Edge Lift	1-19%	20-49%	50-79%	80-100%			
SP596	Evaluate the relative BA and PK in Caucasian vs. Black subjects	Not reviewed	47																	ibid								

	Trial Objective(s)	Rx	N	Erythema								Edema								Adhesion								
				0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	0+1	0	1	2	3	4	5	6	7	8
Study No																											Detach	Not Adfixed
		image file sd 4.5 mg/10 cm2																										
SP717	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects																											
SP718	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects																											
SP671	Evaluate PK, safety and tolerability in subjects with impaired hepatic function																											
SP672	Evaluate PK, safety and tolerability in subjects with impaired renal function																											
	Extrinsic Factors																											
SP626	Investigate influence of application site on the bioavailability of rotigotine	4.5 mg/10 cm^2	65	34 (52.4)	31 (47.7)							50 (76.9)	12 (18.5)	3 (4.6)						43 (66.2)	9 (13.8)	9 (13.8)	3 (4.6)	0	1 (1.5)			
SP627	Evaluate influence of cimetidine on PK of rotigotine in healthy volunteers																											
SP628	Evaluate PK of rotigotine and levodopa/ carbidopa in subjects with RLS																											
SP670	Evaluate influence of domperidone on PK, safety and tolerability of rotigotine in healthy volunteers																											
	Clinical Pharmacology																											
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites)	Diff Grading System	805	541 (67.2)	243 (30.2)	15 (1.9)	5 (0.6)	1 (0.1)				737 (91.6)	66 (8.2)	2 (0.2)						804 (99.75)								2 (0.25)
SP673	Sensitization potential in healthy volunteers																											
	Pivotal Bioequivalence Studies																											
SP581	BE evaluation of rotigotine from two different batches of silicone patches in healthy volunteers	A	30	2	28							15 (50)	9 (30)	5 (16.7)						22	5	3						
		B	30	1	29	1						6 (20)	13 (43)	10 (33)	1					21	5	4						
	Patient PD and PK /PD Trial Reports																											
	Patient PK and Initial Tolerability Trial Reports by Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II,																											

	Trial Objective(s)	Rx	N	Erythema								Edema								Adhesion								
				0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	0+1	0	1	2	3	4	5	6	7	8
Study No																											Detach	Not Adfixed
	SP535, SP506, SP540, (SP533, and SP591 – Advanced PD).																											
SP534 Part 1	Evaluate safety and tolerability of fixed doses																											
SP534 Part 2	Evaluate safety and tolerability of dose escalation																											
SP535	Evaluate safety and tolerability																											
SP506	Evaluate efficacy, safety and tolerability																											
SP540	Evaluate efficacy and safety																											
	Population PK/PD Trial Reports																											
SP512	Evaluate PK																											
SP512 Part I	Evaluate efficacy, safety, and PK compared to placebo																											
SP513 Part I	Evaluate efficacy safety, and PK of rotigotine compared to placebo and ropinirole,																											
	Uncontrolled Clinical Trials																											
SP512 Part IId SP702	Evaluate long-term safety																											
SP513 Part IId SP716	Evaluate long-term safety																											
	Other Trial Reports																											
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease																											
SP511	Assess dose groups of rotigotine in subjects with advanced Parkinson's disease																											
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease																											
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's disease																											
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease																											
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS																											

	Trial Objective(s)	Rx	N	Erythema								Edema								Adhesion								
				0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	0+1	0	1	2	3	4	5	6	7	8
Study No																											**Detach**	**Not Adfixed**
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS																											

a Daily dose, unless otherwise specified.
b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.
c Population PK analyses were done in SP512 (Part 1) and SP513 (Part 1) which appear under "Controlled Clinical Trials."
d Report includes data available as of 31 Dec 2003.
e The protocol and clinical trial report for SP540 refers to the trial as a single-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.
f The protocol and clinical trial report for SP533 refer to the trial as a double-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.

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3.8.2 Adhesion

Adhesion was not well studied. Several different adhesion rating systems were used but can be grouped into 3 general categories.

1. Early studies where adhesion is graded qualitatively.
2. Study SP630 – Where a rating scale similar to scales suggested by FDA and used by other sponsors is used in the large MD gender and age study with all patch strengthes.
3. The sponsor's own new scoring system, that is less sensitive discriminating. – This system was only used with small 10 cm^2 patches.

Descriptions of the last two scoring systems are shown in Table 92.

Table 92 Descriptions of Selected Patch Adhesion Scoring Systems Used by the Sponsor

Nominal Score	Degree of Lift					
	0	1	2	3	4	5
Scale 2 (Similar to Other Sponsors)	≥90% adhered (essentially no lift off of the skin)	75% - <90% adhered (some edges only lifting off of the skin)	50 - <75% adhered (less than half the system lifting off of the skin)	<50% adhered (more than half the system lifting off of the skin without falling off)	patch detached (patch completely off the skin)	—
Scale 3 (Sponsor's New Scoring System)	No Lift	Some Edge Lift	1%-19%	20% - 49%	50%-79%	80%-100%

The adhesion data is presented in Table 91. The best adhesion data is from study SP630 which is the multiple dose PK study that assessed the effect of age, gender, and application site. In this study, as expected, adhesion tended to decrease as the patch size increased. At the largest two patch sizes, (30cm^2 and 40 cm^2), , there is greater than 10% lift in 40% - 50% of patches, and greater than 25% lift in 15% - 30% of patches. This indicates a poorly adhesive patch as most patches applied for a 24 hour period typically have greater than 10% lift in only 5% or so of patches and greater than 25% lift in less than 10% of patches.

In addition, up to 14.6% of the 40 cm^2 patches couldn't be assessed as the patches were taped down due to extensive lift. Thus it's possible that some of these patches could have become detached. In fact in the pivotal BE study 10% of 10 cm^2 patches did become detached.

Studies using scale 3 are typically those studies that evaluated adhesion under ideal conditions, i.e. the smallest patch size, short duration, and possibly inpatient studies.

3.9 Biopharmaceutics

3.9.1 Pivotal Bioequivalence (TBM vs. CTF Formulations) – SP581

Study SP581 was an open-label, single dose, two-arm, crossover study evaluating the bioequivalence of the a 4.5 mg / 10 cm^2 patch of the to-be-marketed formulation to the pivotal clinical trial formulation when appliled to the fore axillary line of the chest in 30 healthy male volunteers 18 – 50 years of age. Data from 3 of 30 subjects, (10%), was excluded due to patch lift of 50% – 80%.

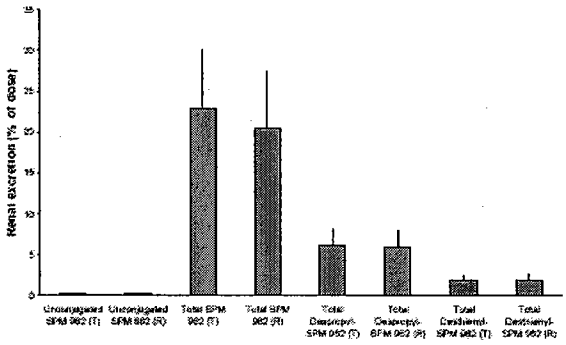
Based on the data in Table 93 the patches appear perform similarly although appropriate geometric means, ratios, and 90% confidence interals have not been calculated. As the CTF and TBM formulations are qualitatively and quantitatively similar, and as the manufacturing changes should not effect bioavailability, there does not appear to be a need for this BE study. However, the batch sizes indicate that the test product used was manufactured at pilot scale and not on the commercial equipment. Plus the TBM formulation used has a much faster dissolution than any other CTF or TBM batch, (see Table 96). In addition, it's unclear if the site of application was studied in any other study, i.e. those whose application site is the fore axillary area of the abdomen. In any case this site was not explicitly stated as used in either the phase I dose ranging study or the pivotal phase III studies.

Table 93 Summary Statistics[a] for Pharmacokinetic Metrics for Rotigotine 4.5 mg / 10 cm^2 Pivotal Bioequivalence Study – SP581

Treatment	Material Code	Batch No	Batch (kg)	Tlag (hrs)	Tmax (hrs)	Cmax (ng/ml)	AUCinf (ng/ml x hr^{-1})	t½ (hrs)
Reference CTF 4.5 mg / 10 cm^2	ND0531	WE11114 (also used in SP506)	35.3	4.3 ± 1.6 (38.4) 2 - 8 [4]	18.0 ± 6.5 (36.0) 4 - 26 [23]	0.308 ± 0.152 (49.5) 0.098 - 0.737 [268.5]	5.51 ± 2.65 (48.1) 2.36 – 13.07 [5.03]	6.4 ± 2.6 (40.4) 1.6 - 10.7 [6.3]
Test TBM 4.5 mg / 10 cm^2	ND0754	WE11249	4.8	4.1 ± 1.6 (38.0) 2.0 - 8.0 [4.0]	16.8 ± 6.9 (41.0) 4 - 27 [15]	0.310 ± 0.177 (57.2) 0.093 - 0.766 [0.248]	5.54 ± 3.02 (54.6) 1.47 – 13.59 [4.89]	6.1 ± 2.2 (36.0) 3.1 - 12.1 [5.6]
Geometric Mean Test[b]						284.1	4949	
Geometric Mean Reference[b]						276.6	5220	
Geometric Mean Test:Reference[b]					-0.5 hr	103%	104%	

a Based on 27 completers
b Sponsor's calculations based on 30 and 27 subjects respectively;90% CI not reported

Figure 71 Renal Elimination of Rotigotine and Selected Metabolites – Study SP581
Cumulative amounts excreted within 48h [percentage of apparent dose]



3.9.2 Dissolution

3.9.2.1 Sponsor's Proposed Dissolution Method

The following in vitro drug release conditions were applied:

- **Apparatus:** Paddle over Disk
- **Test medium:** Phosphate Buffer pH 4.5
- **Volume:** 900 mL
- **Temperature:** 32 ± 0.5°C
- **Speed:** 50 rpm
- **Sampling Times:** 15 min, 30 min, 60 min, 120 min, 180 min.
- **Number of Samples:** 6
- **Analytic Method:** HPLC

According to the sponsor in the beginning of the development samples were usually only withdrawn after 30, 60, and 180 minutes.

3.9.2.2 Sponsor's Proposed Dissolution Specifications

The sponsor only proposed specifications in units of milligrams released the % labeled content was calculated by the reviewer.

Table 94 Sponsor's Proposed Dissolution Specifications

Sampling Time (hours)	Milligrams Released			% LC
	4.5 mg / 10 cm^2	9.0 mg / 20 cm^2	13.5 mg / 30 cm^2	All Strengths
				NLT

3.9.2.3 Sponsor's Proposed Dissolution Acceptance Criteria

Evaluation according to USP<724> Acceptance Table 4

3.9.2.4 Reviewer's Proposed Dissolution Method, Specifications, and Acceptance Criteria

The sponsor provided all dissolution data and proposed specifications in milligrams released and these needed to be converted to % labeled content, (%LC).

Rotigotine batches listed by the studies they were used in are shown in Table 100. Batches used in the Phase II dose ranging study SP506 are shown in green. The pivotal BE batches are shown in violet, and the batches used in the pivotal phase III studies or the QTc study are shown in red, blue, and pink.

Summary dissolution data for Rotigotine TDS batches used in the phase II fixed-dose, dose-ranging study, SP506, and in the pivotal Phase III and Pivotal BE studies are shown in Table 96.

It's noteworthy that the final formulation batch used in the pivotal BE study was produced at — scale, and had significantly faster dissolution than all other CTF and TBM batches listed.

Summary dissolution data of Rotigotine TDS batches used in the pivotal Phase III studies sorted by patch strength are shown in Table 97.

Table 98 shows overall dissolution statistics for rotigotine TDS patches used in the pivotal phase III studies grouped by patch strength, and Table 99 shows overall dissolution statistics for rotigotine TDS patches used in the pivotal phase III studies for all patch strengths combined.

Based on the data in Table 96 to Table 98, the reviewer has proposed the regulatory dissolution method, specifications, and acceptance criteria shown in Table 95.

Table 95 Proposed Regulatory Dissolution Method, Specifications, and Acceptance Criteria for Rotigotine Transdermal Systems

Applicable Strengths:	4.5 mg / 10 cm^2 9.0 mg / 20 cm^2 13.5 mg / 30 cm^2 —	
Apparatus:	Paddle over Disk (Apparatus 5)	
Test medium:	Phosphate Buffer pH 4.5	
Volume:	900 mL	
Temperature:	32 ± 0.5 °C	
Speed:	50 rpm	
Sampling Times:	0.25, 1.0, 2.0 hours	
Specifications:	***Sampling Times (Hours)***	***% Labeled Content***
	0.25 1.0 2.0	— — NLT —
Acceptance Criteria:	Per USP XXIX / NF 24 <724> Acceptance Table 4	

Table 96 Dissolution of Rotigotine TDS Batches Used in Phase II Study SP506 and in Pivotal Phase III and BE Studies

Form	Date	Use	Size (kg)	Batch	Strength (mg/cm²)	% LC				
						15 min	30 min	60 min	120 min	180 min
CTF	Feb-99	SP503 Init MD PK		WE10893	4.5/10	20.9 ± 0.2 (1.2)	34.6 ± 0.1 (0.3)	55.2 ± 0.2 (0.4)	84.7 ± 0.3 (0.4)	100.5 ± 0.5 (0.5)
	Aug-99	Ph II SP506		WE10927	4.5/10	—	34.5 ± 1.2 (3.4)	57.0 ± 1.2 (2.0)	—	94.8 ± 1.3 (1.4)
		Ph II SP506		WE10938	4.5/10	—	31.6 ± 0.6 (1.9)	52.2 ± 0.6 (1.1)	—	91.3 ± 0.6 (0.7)
	Jan-00	Ph II SP506 Pivotal BE		WE11114	4.5/10	—	38.1 ± 0.4 (1.0)	57.9 ± 0.4 (0.8)	—	93.3 ± 0.8 (0.9)
		Ph II SP506		WE11113	9/20	—	39.1 ± 0.6 (1.6)	59.0 ± 0.6 (1.1)	—	94.8 ± 1.0 (1.1)
	Jun-00	Ph II SP506		WE11346	4.5/10	—	41.7 ± 0.6 (1.4)	62.7 ± 0.6 (1.0)	—	104.1 ± 0.6 (0.6)
TBM	2000	Pivotal BE		WE11249	4.5/10	—	59.6 ± 1.3 (2.2)	86.7 ± 1.3 (1.6)	—	101.6 ± 1.7 (1.7)
TBM	2000	Phase III SP512		WE11682	4.5/10	—	45.3 ± 2.0 (4.5)	63.3 ± 1.1 (1.8)	—	97.8 ± 1.0 (1.1)
		Phase III SP512		WE11683	9/20	—	45.5 ± 0.2 (0.4)	65.7 ± 0.2 (0.4)	—	104.3 ± 0.7 (0.7)
		Phase III SP512		WE11684	13.5/30	—	43.9 ± 0.2 (0.5)	63.7 ± 0.2 (0.3)	—	97.0 ± 0.5 (0.6)
		Stability		WE11685	18/40	—	44.2 ± 0.2 (0.5)	63.8 ± 0.2 (0.4)	—	99.2 ± 1.4 (1.4)
	2001	Phase III		2010618370	4.5/10	—	43.3 ± 0.4 (1.0)	62.1 ± 0.4 (0.6)	88.4 ± 0.6 (0.7)	99.6 ± 0.3 (0.4)
		Phase III		2010718440	9/20	—	43.2 ± 0.4 (0.9)	63.2 ± 0.3 (0.4)	90.3 ± 0.3 (0.3)	101.2 ± 1.7 (1.6)
		Phase III		2010618360	13.5/30	—	42.8 ± 0.4 (0.9)	61.8 ± 0.3 (0.5)	88.5 ± 0.3 (0.4)	101.4 ± 0.5 (0.4)
		Phase III		2071718430	18/40	—	44.0 ± 0.2 (0.4)	63.6 ± 0.2 (0.4)	90.1 ± 0.3 (0.4)	101.4 ± 1.8 (1.7)
	2002	Phase III		2020318300	4.5/10	—	42.5 ± 0.3 (0.8)	61.2 ± 0.3 (0.5)	87.9 ± 0.3 (0.3)	99.9 ± 0.3 (0.3)
		Phase III		2020318240	9/20	—	42.3 ± 0.2 (0.5)	61.8 ± 0.3 (0.4)	89.0 ± 0.1 (0.1)	100.0 ± 1.4 (1.4)
		Phase III		2020318370	13.5/30	—	42.7 ± 0.2 (0.5)	62.1 ± 0.3 (0.5)	88.9 ± 0.3 (0.3)	100.5 ± 0.3 (0.3)
		Phase III		2020318390	18/40	—	43.8 ± 0.3 (0.7)	63.6 ± 0.2 (0.4)	90.5 ± 0.3 (0.3)	100.7 ± 1.0 (1.0)
	Feb-2003	Phase III		WE12606	4.5/10	31.2 ± 0.2 (0.6) 30.9 - 31.4	43.3 ± 0.5 (1.1)	61.0 ± 0.3 (0.4)	86.9 ± 0.4 (0.5)	96.4 ± 0.6 (0.7)
				WE12606	4.5/10	29.5 ± 0.5 (1.8) 29.2 - 30.6	—	—	—	—
				WE12607	9/20	32.1 ± 0.4 (1.4) 31.5 - 32.5	44.2 ± 0.3 (0.6)	63.0 ± 0.4 (0.6)	88.9 ± 0.3 (0.3)	96.2 ± 0.5 (0.5)
				WE12578	13.5/30	34.3 ± 1.2 (3.5) 32.5 - 36.0	44.6 ± 0.4 (1.0)	63.5 ± 0.4 (0.6)	89.7 ± 0.5 (0.5)	97.3 ± 0.9 (1.0)
				WE12608	18/40	30.3 ± 0.4 (1.4) 29.7 - 30.8	44.4 ± 0.4 (0.8)	63.3 ± 0.4 (0.6)	90.0 ± 0.4 (0.5)	98.6 ± 0.9 (0.9)
	Jul-2003	Phase III		WE12787	4.5/10	29.5 ± 0.8 (2.6) 28.9 - 31.0	43.6 ± 0.8 (1.9)	63.7 ± 0.8 (1.2)	90.8 ± 1.0 (1.1)	100.5 ± 0.9 (0.9)
				WE12786	9/20	28.8 ± 0.4 (1.4) 28.2 - 29.2	43.0 ± 0.4 (1.0)	62.9 ± 0.6 (0.9)	90.2 ± 0.7 (0.8)	103.6 ± 2.8 (2.7)
				WE12785	13.5/30	28.7 ± 0.5 (1.6) 28.0 - 29.1	43.1 ± 0.4 (0.9)	63.4 ± 0.5 (0.7)	90.9 ± 0.6 (0.7)	102.0 ± 1.9 (1.9)
				WE12874	18/40	28.9 ± 0.3 (1.1) 28.6 - 29.5	43.5 ± 0.1 (0.3)	63.5 ± 0.1 (0.2)	90.8 ± 0.2 (0.2)	102.7 ± 0.7 (0.7)

Table 97 Dissolution of Rotigotine TDS Batches Used in Pivotal Phase III Studies Sorted by Patch Strength

Date	Batch	Strength (mg)	% LC				
			Sampling Time (minutes)				
			15	30	60	120	180
2001	2010618370	4.5	—	43.3 ± 0.4 (1.0)	62.1 ± 0.4 (0.6)	88.4 ± 0.6 (0.7)	99.6 ± 0.3 (0.4)
2002	2020318300	4.5	—	42.5 ± 0.3 (0.8)	61.2 ± 0.3 (0.5)	87.9 ± 0.3 (0.3)	99.9 ± 0.3 (0.3)
2000	WE11682	4.5	—	45.3 ± 2.0 (4.5)	63.3 ± 1.1 (1.8)	—	97.8 ± 1.0 (1.1)
Feb-2003	WE12606	4.5	31.2 ± 0.2 (0.6) 30.9 - 31.4	43.3 ± 0.5 (1.1)	61.0 ± 0.3 (0.4)	86.9 ± 0.4 (0.5)	96.4 ± 0.6 (0.7)
Feb-2003	WE12606	4.5	29.5 ± 0.5 (1.8) 29.2 - 30.6	—	—	—	—
Jul-2003	WE12787	4.5	29.5 ± 0.8 (2.6) 28.9 - 31.0	43.6 ± 0.8 (1.9)	63.7 ± 0.8 (1.2)	90.8 ± 1.0 (1.1)	100.5 ± 0.9 (0.9)
2001	2010718440	9	—	43.2 ± 0.4 (0.9)	63.2 ± 0.3 (0.4)	90.3 ± 0.3 (0.3)	101.2 ± 1.7 (1.6)
2002	2020318240	9	—	42.3 ± 0.2 (0.5)	61.8 ± 0.3 (0.4)	89.0 ± 0.1 (0.1)	100.0 ± 1.4 (1.4)
2000	WE11683	9	—	45.5 ± 0.2 (0.4)	65.7 ± 0.2 (0.4)	—	104.3 ± 0.7 (0.7)
Feb-2003	WE12607	9	32.1 ± 0.4 (1.4)	44.2 ± 0.3 (0.6)	63.0 ± 0.4 (0.6)	88.9 ± 0.3 (0.3)	96.2 ± 0.5 (0.5)
Jul-2003	WE12786	9	28.8 ± 0.4 (1.4)	43.0 ± 0.4 (1.0)	62.9 ± 0.6 (0.9)	90.2 ± 0.7 (0.8)	103.6 ± 2.8 (2.7)
2001	2010618360	13.5	—	42.8 ± 0.4 (0.9)	61.8 ± 0.3 (0.5)	88.5 ± 0.3 (0.4)	101.4 ± 0.5 (0.4)
2002	2020318370	13.5	—	42.7 ± 0.2 (0.5)	62.1 ± 0.3 (0.5)	88.9 ± 0.3 (0.3)	100.5 ± 0.3 (0.3)
2000	WE11684	13.5	—	43.9 ± 0.2 (0.5)	63.7 ± 0.2 (0.3)	—	97.0 ± 0.5 (0.6)
Feb-2003	WE12578	13.5	34.3 ± 1.2 (3.5)	44.6 ± 0.4 (1.0)	63.5 ± 0.4 (0.6)	89.7 ± 0.5 (0.5)	97.3 ± 0.9 (1.0)
Jul-2003	WE12785	13.5	28.7 ± 0.5 (1.6)	43.1 ± 0.4 (0.9)	63.4 ± 0.5 (0.7)	90.9 ± 0.6 (0.7)	102.0 ± 1.9 (1.9)
2002	2020318390	18	—	43.8 ± 0.3 (0.7)	63.6 ± 0.2 (0.4)	90.5 ± 0.3 (0.3)	100.7 ± 1.0 (1.0)
2001	2071718430	18	—	44.0 ± 0.2 (0.4)	63.6 ± 0.2 (0.4)	90.1 ± 0.3 (0.4)	101.4 ± 1.8 (1.7)
Feb-2003	WE12608	18	30.3 ± 0.4 (1.4)	44.4 ± 0.4 (0.8)	63.3 ± 0.4 (0.6)	90.0 ± 0.4 (0.5)	98.6 ± 0.9 (0.9)
Jul-2003	WE12874	18	28.9 ± 0.3 (1.1)	43.5 ± 0.1 (0.3)	63.5 ± 0.1 (0.2)	90.8 ± 0.2 (0.2)	102.7 ± 0.7 (0.7)

Table 98 Overall Dissolution Statistics for Rotigotine TDS Patches Used in Pivotal Phase III Studies by Patch Strength

Strength		% LC				
	Sampling Time (minutes)	15	30	60	120	180
4.5 mg / 10 cm^2	N	18	30	30	24	30
	Mean SD (%CV) Range [median]	30.1 ± 1.0 (3.3) [29.5]	43.6 ± 1.3 (3.1) [43.3]	62.3 ± 1.3 (2.0) [61.9]	88.5 ± 1.6 (1.8) [88.1]	98.8 ± 1.7 (1.7) [99.4]
9.0 mg / 20 cm^2	N	12	30	30	24	30
	Mean SD (%CV) Range [median]	30.5 ± 1.8 (5.8) [30.4]	43.6 ± 1.2 (2.7) [43.4]	63.3 ± 1.4 (2.1) [63.1]	89.6 ± 0.7 (0.8) [89.4]	101.1 ± 3.3 (3.3) [101.8]
13.5 mg / 30 cm^2	N	12	30	30	24	30
	Mean SD (%CV) Range [median]	31.5 ± 3.1 (9.8) [30.8]	43.4 ± 0.8 (1.9) [43.3]	62.9 ± 0.8 (1.3) [63.2]	89.5 ± 1.0 (1.1) [89.1]	99.6 ± 2.3 (2.3) [100.2]
18.0 mg / 40 cm^2	N	12	24	24	24	24
	Mean SD (%CV) Range [median]	29.6 ± 0.8 (2.8) [29.6]	43.9 ± 0.4 (0.9) [43.8]	63.5 ± 0.3 (0.4) [63.5]	90.3 ± 0.5 (0.5) [90.4]	100.9 ± 1.9 (1.9) [101.5]

Table 99 Overall Dissolution Statistics for Rotigotine TDS Patches Used in Pivotal Phase III Studies for all Patch Strengths Combined

All Strengths		% LC				
	Sampling Time (minutes)	15	30	60	120	180
	N	54	114	114	96	114
	Mean SD (%CV) Range [median]	30.4 ± 1.9 (6.2) [29.5]	43.6 ± 1.0 (2.4) [43.5]	63.0 ± 1.1 (1.8) [63.3]	89.5 ± 1.2 (1.4) [89.6]	100.1 ± 2.5 (2.5) [100.0]

Table 100 Rotigotine Batches Used in Clinical Studies

Form	Batch no.	Batch no. LTS	Manufacturing date	Patch (cm^2)	Batch size (kg)	No. TDS	Primary package	Studies Used In																				
								SP502 Comp BA Form 2 & Form 3	SP503 MD PK	SP506 Ph II Efficacy PK/PD	SP511 Ph II Advanced PD	SP512 Pivotal Ph III	SP513 Pivotal Ph III	SP540 Titration Schedule	SP581 Pivotal BE	SP591 Dose Ranging Advanced PD	SP596 Blacks	?	SP610 Radio-labeled	SP626 Applic Site BE	SP627 DDI Cimetidine	SP628 DDI CD/LD	SP630 MD PK ECG Sat Sys	SP650 Advanced PD Ph III ?	SP670 DDI Domperidone	SP671 Renal	SP672 Hepatic	SP717 Japanese	SP718 Japanese	Stability
							7	SP502																					
														SP540															
								SP502																					
3	WE10893	8290259	22 FEB 1999	10	7	8570			SP503					SP540															stability
3	WE10894	8290249	22 FEB 1999	20		15200								SP540															stability
3	WE10927	8290975	02 AUG 1999	10		65100				SP506	SP511			SP540															stability
3	WE10938	8291039	02 AUG 1999	10		6805				SP506																			
3	WE10930	8291229	12 AUG 1999	20		58720					SP511			SP540															stability
3	WE10931	8290969	12 AUG 1999	20		56400					SP511																		stability
3	WE11114	8290156	22 JAN 2000	10		64408				SP506					SP581				SP610	SP626	SP627								
3	WE11113	8290150	22 JAN 2000	20		64400				SP506						SP591													
3	WE11182	8290460	22 JAN 2000	10		51430										SP591	SP596												
3	WE11345	81100800	09 JUN 2000	20		43639										SP591													
3	WE11346	81100806	09 JUN 2000	10		44290				SP506																			
3	WE11504	81104200	01 AUG 2000	20		29650																							
3	WE11505	81104100	01 AUG 2000	10		22130																							
final	WE11249	8290550	14 APR 2000	10		2905									SP581														
final	WE11634	7054920	17 OCT 2000	5		168000																							stability
final	WE11669	7054990	17 OCT 2000	10		180000																							stability
final	WE11670	7055950	17 OCT 2000	20		633600																							stability
final	WE11681	7060520	15 NOV 2000	5		100800																							stability
final	WE11683	7060430	15 NOV 2000	10		253700						SP512												SP650	SP670				stability
final	WE11684	7061033	15 NOV 2000	20		229600						SP512	SP513											SP650					stability
final	WE11685	7061193	15 NOV 2000	40		26400						SP512																	stability
final	WE11685	7061190	15 NOV 2000	40		26400																							stability
final	WE11705	7061610	15 NOV 2000	5		100000																							stability
final	WE11706	7061600	15 NOV 2000	10		25000																							stability
final	WE11707	7061590	15 NOV 2000	20		25600																							stability
final	WE11708	7061580	15 NOV 2000	30		25200																							stability
final	WE11709	7061570	15 NOV 2000	40		25350																							stability
final	20107184S0	7027321	29 MAY 2001	5		25000																							stability
final	20107184S0	7027241	29 MAY 2001	10		55800						SP512	SP513									SP628		SP650				SP717		stability
final	20107184S0	7027261	29 MAY 2001	20		25200						SP512	SP513									SP628								stability
final	20107184S0	7027521	29 MAY 2001	30		25500						SP512	SP513											SP650						stability
final	20107184S0	7027531	29 MAY 2001	40		25200						SP512												SP650						stability
final	20112186	7039221	29 MAY 2001	10		25200																							stability
final	20112186	7039231	29 MAY 2001	20		25200																							stability
final	20112186	7039241	29 MAY 2001	30		25200																							stability
final	20112186	7039251	29 MAY 2001	40		25200																							stability
final	20203183	7016472	20 FEB 2002	5		26400																						SP718	stability
final	20203183	7016573	20 FEB 2002	10		142200						SP512	SP513											SP650		SP671	SP672		SP718	stability
final	20203183	7016583	20 FEB 2002	20		278100						SP512	SP513											SP650					SP718	stability
final	20203183	7016593	20 FEB 2002	30		131400						SP512	SP513											SP650						stability
final	20203183	7016482	20 FEB 2002	40		25300						SP512												SP650						stability
final	WE12465	7052982	20 FEB 2002	20		94882						SP512	SP513											SP650						
final	WE12292	7029235	20 FEB 2002	30		161100						SP512	SP513											SP650						
final	WE12293	7029242	20 FEB 2002	40		233800						SP512	SP513											SP650						
final	WE12677	7016573	11 FEB 2003	10		215700						SP512	SP513											SP650						stability
final	WE12687	7016583	11 FEB 2003	20		248400						SP512	SP513	SP515										SP650						stability
final	WE12676	7016593	11 FEB 2003	30		236400						SP512	SP513	SP515										SP650						stability
final	WE12668	7016643	11 FEB 2003	40		23656						SP512	SP513											SP650						stability
final	WE12670	7019453	11 FEB 2003	10		24749																								stability
final	WE12671	7019463	11 FEB 2003	20		26400																								stability
final	WE12672	7019473	11 FEB 2003	30		25500																								stability
final	WE12673	7019483	11 FEB 2003	40		25200																								stability
final	WE12787	7046943	22 JUL 2003	10		81296						SP512											SP630	SP650						stability
final	WE12786	7046947	22 JUL 2003	20		49750						SP512		SP515									SP630	SP650						stability
final	WE12787	7046963	22 JUL 2003	30		253500						SP512	SP513	SP515									SP630	SP650						stability
final	WE12788	7046973	22 JUL 2003	40		253200						SP512	SP513	SP515										SP650						stability
final	WE12945	7016714	13 FEB 2004	20		231000						SP512												SP650						stability
final	WE12967	7016734	13 FEB 2004	30		206500							SP513																	stability
final	WE12966	7016724	13 FEB 2004	40		85600							SP513																	stability

3.9.3 Drug Delivery

Apparent drug delivery was determined in a number of studies by measuring the amount of rotigotine remaining in used patches. Most studies examined drug delivery from 4.5 mg patches and in these studies delivery from the 4.5 mg / 10 cm^2 patches typically averaged around 2.5 mg per day, (i.e. 55% delivery), however average deliveries ranged from 2 mg to 2.9 mg per day and individual patches delivered up to 4.1 mg. Only one study examined delivery from a 9 mg patch and it was 5.2 mg/day. One study, SP630, examined delivery from an 18 mg patch at steady-state in male and female middle aged and elderly patients using the proposed rotating application sites. In this study mean drug delivery was 6.6 mg with individual drug delivery again ranging up to double the mean delivery, (see Table 102). This data indicates that drug delivery is not linear with drug content. The sponsor has proposed nominal drug deliveries that are linearly related to drug content, (i.e. slope = 0.444), these proposed nominal rates and the approximate mean observed delivery rates are summarized in Table 101.

Table 101 Approximate Mean 24 hour Drug Delivery by Rotigotine Patch Strength

TDS Strength	4.5 mg / 10 cm^2	9.0 mg / 20 cm^2	13.5 mg / 30 cm^2
Approximate Average Drug Delivery (mg/day)	2.5	5.2	NR[a]
Proposed Nominal Delivery Rate (mg/day)	2.0	4.0	6.0

a NR – Not reported

Figure 73, Figure 72, and Figure 74 shows the total variability in drug delivery, and the variability by application site and patient group for the 18 mg strength patch.

Although the sponsor's proposed drug delivery is not accurate it is approximately the mean % delivery across various strengths, because of this and for ease in prescribing the sponsor's proposed delivery rates are acceptable.

Figure 72 Histogram of Dose Delivered in mg from a 18 mg Rotigotine TDS - Study SP630

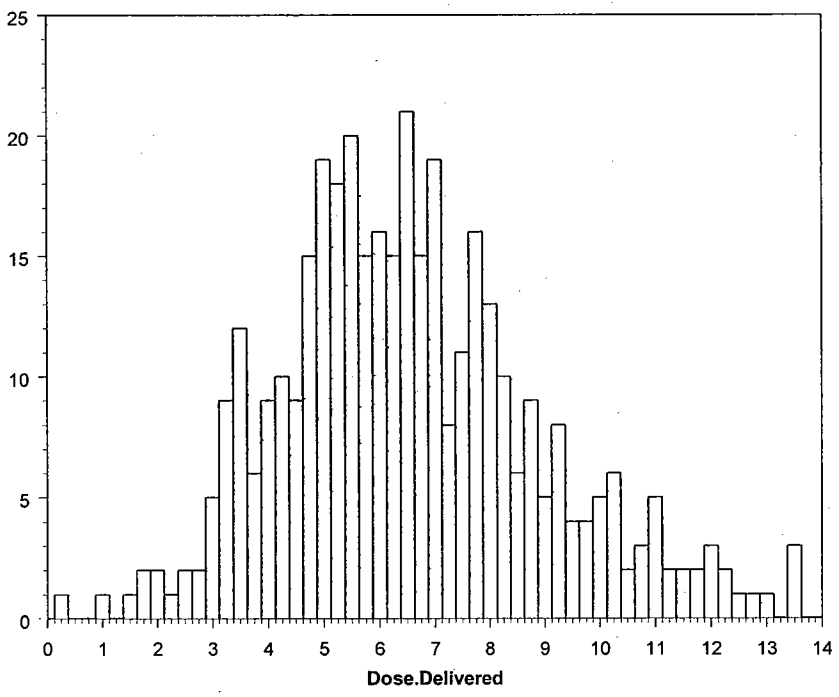


Figure 73 Box Plots of Dose Delivered in mg from a 18 mg Rotigotine TDS by Age, Gender, and Application Site – Study SP630

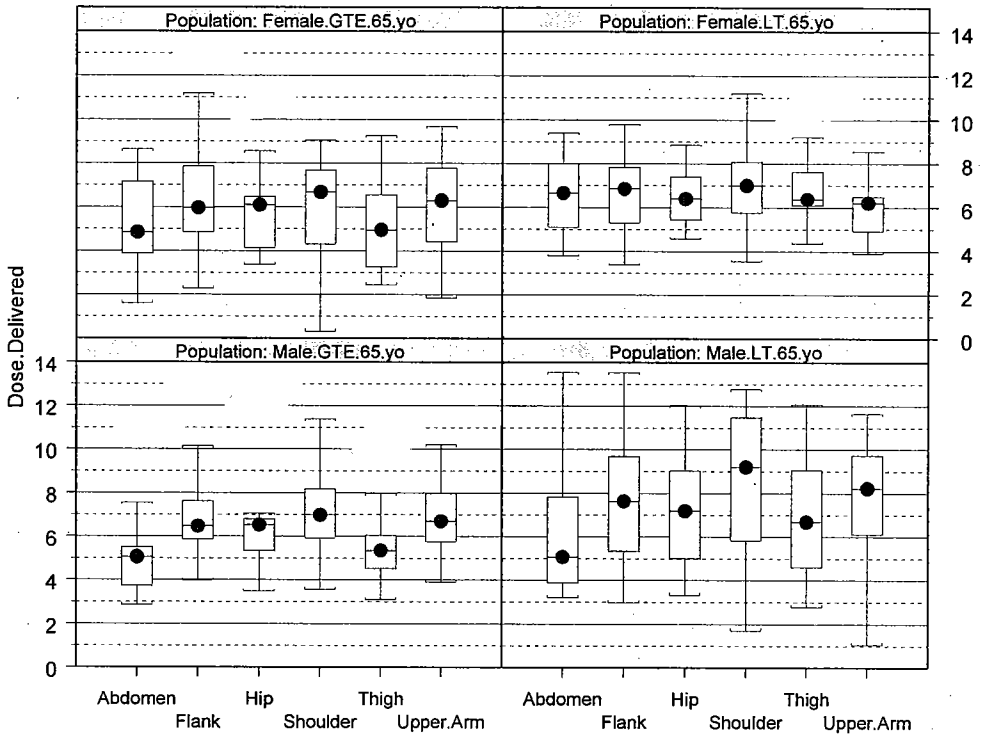


Figure 74 Histogram of Dose Delivered in mg from a 18 mg Rotigotine TDS by Age and Gender – Study SP630

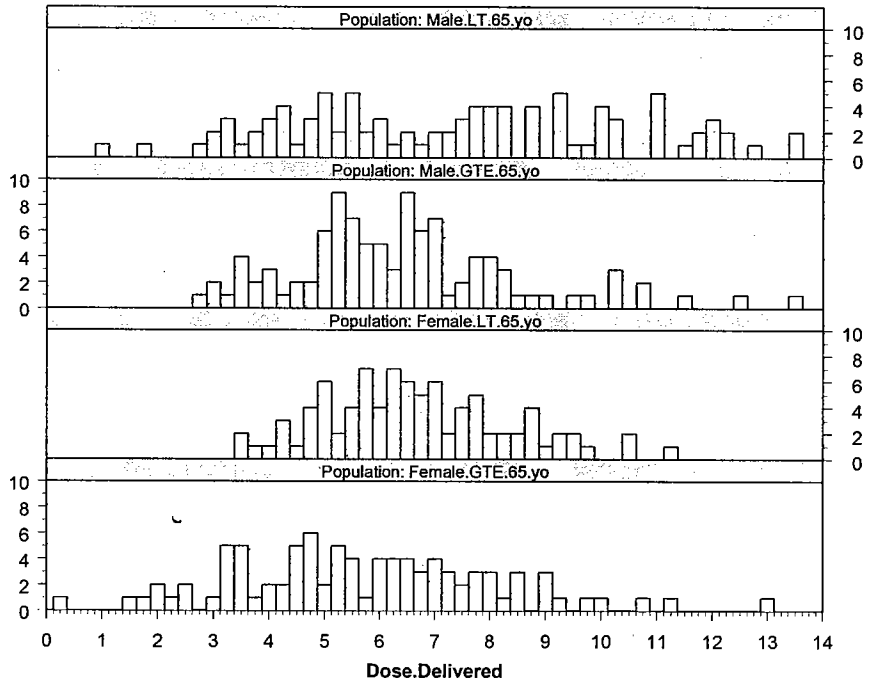


Table 102 Summary of Drug Delivery from Rotigotine Transdermal Systems

Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm^2 / day	mcg / cm^2 / hr
IV Studies																
SP803	IV PK/PD Studies				NA	NA				NA						
SP804					NA	NA				NA						
SP805					NA	NA				NA						
Formulation Development																

Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm^2 / day	mcg / cm^2 / hr
Mass Balance METAB																
SP610	Mass Bal TDS vs IV			TDS				Silicone Form 4	4.5 mg / 10 cm^2	1		2.9 ± 0.3 10.8 2.5 - 3.4 2.9	61.4 ± 6.6 10.8 52.8 - 72.7 60.4	34.6 ± 5.4 (15.5) 28.5 - 41.8 34.8 ng/kg	0.29 ± 0.03 10.8 0.25 - 0.34 0.285	12.1 ± 1.3 10.8 10.4 - 14.3 11.9
				IV				—	—			1.2	—	**14.4 ± 1.5 (10.1) 12.2 - 16.2 [14.5]**		—
SP605	Mass Bal TDS				Volar surface of Forearm			Silicone Form 4	4.5 mg / 10 cm^2	1	4.5 est	2.3 ± 0.5 20.3 1.8 - 3.0 2.1	51 ± 10.4 20.3 39.6 - 66.4 47.6	0.0307 ± 0.0077 25.2 0.0221 - 0.0441 0.0288	0.23 ± 0.05 20.3 0.18 - 0.30 0.21	9.6 ± 1.9 20.3 7.4 - 12.5 8.9
											Skin wash					
									% delivery corrected for % in skin wash	4.5 est	**4.8+1.5 31.1 3.2 - 7.2 4.5**	2.1 ± 0.5 23.0 1.6 - 2.7 2.0	**46.1 ± 10.6 23.0 34.8 - 60.4 43.6**		**0.21 ± 0.05 23.0 0.16 - 0.27 0.20**	**8.7 ± 2.0 23.0 6.5 - 11.3 8.2**

Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm² / day	mcg / cm² / hr
Healthy Subject PK and Initial Tolerability Trial Reports																
SP503				Day 1	Medial axillar region of trunk alt sides	24 hr	28	Silicone Form 3	4.5 / 10 cm²	1 / Day	4.67	2.30 ± 0.72 (31.2) 0.62 - 3.75 [2.36]	49.2 ± 15.3 31.2 13.3-80.3 50.4	28.1 ± 9.7 (34.6) 7.5 - 55.0 [29.3]	0.23 ± 0.07 (31.2) 0.06 – 0..38 [0.24]	9.6 ± 3.0 (31.2) 2.6 - 15.6 [9.8]
				Day 14			30					2.56 ± 0.84 (32.8) 0.82 - 3.96 [2.46]	54.9 ± 18.0 32.8 17.6-84.8 52.7	30.1 ± 10.8 34.7 8.6-57.9 29.9	0.26 ±0.08 (32.8) 0.08 – 0.4 [0.25]	10.7 ± 3.5 32.8 3.4-16.5 10.3
				Overall Days 1 - 14			392					2.57 ± 0.76 (29.7) 0.43-4.55 [2.54]	55.0 ± 16.3 29.7 9.2-97.4 54.3	31.3 ± 10.0 32.0 5.7-66.7 30.6	0.26 ± 0.08 (29.7) 0.04-0.46 [0.25]	10.7 ± 3.2 29.7 1.8-19.0 10.6
Intrinsic Factors																
SP630	Age Gender and Dose Linearity some time effect		All	Days 26 - 30	All 6	24 hr	377	Silicone Form 4 TBM	18.0 mg / 40 cm²	1 / Day	18.0 mg	6.6 ± 2.4 36.1 0.3 - 13.5 6.4	36.5 ± 13.2 36.1 1.7 – 75.2 35.4	89.6 ± 35.2 39.3 4.6 - 201.8 86.5	0.16 ± 0.06 36.1 0.01 – 0.34 0.16	6.8 ± 2.5 36.1 0.3 – 14.1 6.6
			F < 65 yo				89					6.7 ± 1.7 (25.1) 3.4 - 11.2 [6.4]	37.0 ± 9.3 (25.1) 18.8 - 62.2 [35.7]	97.0 ± 36.2 (37.3) 41.6 - 201.8 [87.4]	0.17 ± 0.04 (25.1) 0.08 - 0.28 [0.16]	6.9 ± 1.7 (25.1) 3.5 - 11.7 [6.7]
			M <65 yo				96					7.4 ± 3.0 (40.0) 1.1 - 13.5 [7.4]	41.0 ± 16.4 (40.0) 5.9 - 75.2 [41.3]	81.6 ± 34.3 (42.1) 10.3 - 169.5 [77.6]	0.18 ± 0.07 (40.0) 0.03 - 0.34 [0.19]	7.7 ± 3.1 (40.0) 1.1 - 14.1 [7.7]
			F ≥65 yo				90					5.8 ± 2.3 (40.5) 0.3 - 13.1 [5.6]	32.1 ± 13.0 (40.5) 1.7 - 72.3 [31.0]	92.3 ± 39.9 (43.3) 4.6 - 198.6 [92.7]	0.14 ± 0.06 (40.5) 0.01 - 0.33 [0.14]	6.0 ± 2.4 (40.5) 0.3 - 13.7 [5.8]
			M ≥65 yo				102					6.4 ± 2.1 (32.0) 2.9 - 13.5 [6.3]	35.7 ± 11.4 (32.0) 15.9 - 75.1 [34.6]	88.4 ± 28.9 (32.7) 31.4 - 172.2 [87.3]	0.16 ± 0.05 (32.0) 0.07 - 0.34 [0.16]	6.7 ± 2.1 (32.0) 3.0 - 14.1 [6.5]
SP596	Effect of Race Black							Silicone patch 'Phase II' Form 3								
SP717	Race & Sex		CF			24 hr	12	Silicone Form 4 TBM	4.5 / 10 cm²			2.28 ± 0.55 (24.1) 1.73 - 3.46 [2.00]	50.7 ± 12.2 (24.1) 38.4 - 76.9 [44.4]	39.5 ± 9.2 (24.7) 27.5 - 62.9 [37.4]	0.23 ± 0.05 (24.1) 0.17 - 0.35 [0.20]	9.5 ± 2.3 (24.1) 7.2 - 14.4 [8.3]
			CM				12					1.88 ± 0.56 (29.8) 1.14 - 3.32 [1.82]	41.7 ± 12.4 (29.8) 25.3 - 73.8 [40.3]	27.4 ± 7.6 (27.3) 19.9 - 45.5 [24.1]	0.19 ± 0.06 (29.8) 0.11 - 0.33 [0.18]	7.8 ± 2.3 (29.8) 4.8 - 13.6 [7.6]

Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm^2 / day	mcg / cm^2 / hr
			JF				12					2.03 ± 0.53 (26.1) 1.35 - 3.05 [1.86]	45.0 ± 11.8 (26.1) 30.0 - 67.8 [41.7	37.9 ± 7.0 (18.5) 29.3 - 46.8 [37.8]	0.20 ± 0.05 (26.1) 0.14 - 0.31 [0.19]	8.4 ± 2.2 (26.1) 5.6 - 12.7 [7.8]
			JM				12					1.97 ± 0.50 (25.4) 0.94 - 2.75 [2.01]	43.8 ± 11.1 (25.4) 20.9 - 61.1 [44.6]	31.9 ± 9.1 (28.6(15.7 - 45.7 [32.1]	0.20 ± 0.05 (25.4) 0.09 - 0.28 [0.20]	8.2 ± 2.1 (25.4) 3.9 - 11.5 [8.4
SP718	Effect of Race							Silicone Form 4 TBM	2.5 mg / 5 cm^2	75		1.5	67.1	21.4	0.30	1.3
									4.5 mg / 10 cm^2	76		2.5 ± 0.6 22.1 1.5 - 4.0 2.5	56.4 ± 12.4 22.1 32.9 – 98.0 55.3	42.5 ± 10.0 23.5 26.9 – 71.7 41.3	0.25 ± 0.06 22.1 0.15 - 0.40 0.25	1.1 ± 0.2 22.1 0.6 - 1.7 1.0
									9.0 mg / 20 cm^2	72						
SP671	Hepatic Impairment Study		NI	Days 1 - 3			8	Silicone Form 4 TBM				2.40 ± 0.34 14.1 1.90 - 3.18 2.3	50.7 ± 7.1 14.0 40.2 - 67.2 48.5	28.7 ± 4.4 15.4 22.9 - 37.9 27.2		10.0 ± 1.4 14.1 7.9 - 13.3 9.6
				Day 3 Only			8					2.69 ± 0.92 34.3 1.43 - 4.06 2.73	56.9 ± 19.6 34.4 30.2 - 86.3 57.7	31.4 ± 9.32 29.7 17.9 - 43.0 32.7		11.2 ± 3.85 34.3 6.0 - 17.0 11.4
			Hep Insuff	Days 1 - 3								2.4 ± 0.34 14.1 1.9 - 3.18 2.3	50.7 ± 7.1 14.0 40.2 - 67.2 48.5	28.7 ± 4.4 15.4 22.9 - 37.9 27.2		10.0 ± 1.4 14.1 7.9 - 13.3 9.6
				Day 3 Only								2.62 ± 0.41 15.5 2.03 - 3.18 2.75	56.3 ± 8.6 15.5 42.9 - 67.2 58.2	31.4 ± 5.6 17.6 23.9 - 37.9 33.0		10.9 ± 1.7 15.5 8.5 13.2 - 11.5
SP672	Renal Impairment Study							Silicone patch CTF / TBM Form 4	4.5 mg some taped down	32		2.14 ± 0.49 23.0 1.38 – 3.60 2.12	45.2 ± 10.4 23.0 29.2 - 76.1 44.9	29.6 ± 7.6 25.5 17.9 – 48.6 27.3	0.21 ± 0.49 23.0 0.14 – 0.36 0.21	8.9 ± 2.1 23.0 5.8 – 15.0 8.8
Extrinsic																
SP626	3 sites	Not Done						Silicone patch 'Phase II' Form 3								
SP627								Silicone patch 'Phase II' Form 3								
SP628	DDI LD/CD							Silicone patch CTF / TBM								