CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21829

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review
Complete Response to AE letter

PRODUCT (Generic Name):	Rotigotine
PRODUCT (Brand Name):	NEUPRO
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTHS:	2, 4, 6, [redacted] mg
NDA:	21-829
INDICATION:	Treatment of early stage Parkinson's Disease
NDA TYPE:	Complete response to AE letter
SUBMISSION DATE:	10/2/06, 11/7/06, 12/7/06
SPONSOR:	Schwarz Biosciences
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

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EXECUTIVE SUMMARY

This submission is in response to the approvable letter dated February 28, 2006. The sponsor has responded to all the deficiencies identified in the approvable letter. From the perspective of the Office of Clinical Pharmacology, there was one comment regarding the dissolution specifications that had to be addressed by the sponsor and the sponsor agrees to change the dissolution specifications based on Agency's recommendation. The sponsor's response to this comment is given in the following section on page 4.

The remainder of the review includes a review of three new studies conducted by the sponsor (1 vivo study to evaluate application site differences and 2 in vitro studies to identify pathway of metabolism) and three additional analyses (including pooled analysis to evaluate application site differences and model dependent kinetics to estimate the half life of rotigotine after patch application). The results of all the new studies and analyses are used to support the sponsor's proposed labeling. The new analyses were conducted by the sponsor to address the labeling changes proposed by them. The review of these studies is provided in the Appendix on page 28. Reviewer's labeling recommendations have been made based on the results of these new studies and analyses.

The sponsor has also included a labeling justification document for their proposed changes to the Agency label sent with the approvable letter dated February 28, 2006. The

reviewer's labeling recommendation is based on the sponsor's labeling justification document (in the EDR) and Dr. Kavanaugh's review of the original NDA along with this reviewer's interpretation of the data.

RECOMMENDATION

The sponsor has provided a complete response to the Agency approvable letter dated 2/28/06 as it relates to Clinical Pharmacology issues identified in the letter. The reviewer finds this response acceptable. The reviewer however recommends some changes in the label. The labeling recommendations beginning on page 5 should be conveyed to the sponsor.

Veneeta Tandon, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Ramana Uppoor, Ph.D._____

CLINICAL PHARMACOLOGY COMMENT FROM THE APPROVABLE LETTER

CLINICAL PHARMACOLOGY QUESTION NO. 1:

Please adopt the following proposed dissolution method, specifications, and acceptance criteria for rotigotine transdermal systems as the regulatory method.

Table 1 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	

SPONSOR RESPONSE:

The proposed dissolution method is adopted for the to be marketed product. It applies for all — strengths, i.e. from 4.5 mg / 10 cm^2 to ——— The analytical method, the drug product specifications and acceptance criteria, and the justification of specification are revised accordingly.

In addition, the revision of the specification has been reflected in the related documents, i.e. Pharmaceutical Development - Drug Product - Formulation Development, Batch Analyses and Stability data.

AGENCY COMMENT:

Acceptable. The sponsor has agreed to Agency recommendation.

LABELING RECOMMENDATIONS

22 Page(s) Withheld

_____ Trade Secret / Confidential

__/__ Draft Labeling

_____ Deliberative Process

APPENDIX

REVIEW OF NEW STUDIES AND ADDITIONAL ANALYSES

Assessment of Application Site Differences

Study SP 651: A single-center, randomized, open-label crossover trial to assess the relative bioavailability of rotigotine after multiple-dose applications of rotigotine transdermal patch (18.0mg/40cm2 or 2 x 9.0mg/20 cm2) at different sites of application in subjects with idiopathic Parkinson's disease

This is a new study not previously reviewed.

Objectives:
The objectives of this trial were the following:

- to evaluate the relative bioavailability of rotigotine after application of 1 rotigotine transdermal patch (18.0mg [40cm2]) to 2 patches (9.0mg [20cm2]) in subjects with idiopathic Parkinson's disease
- to evaluate the relative bioavailability of rotigotine after multiple dose applications of the 40cm2 patch at different application sites in subjects with idiopathic Parkinson's disease
- to investigate the safety and tolerability (including local tolerability) and to assess the patch adhesiveness of rotigotine transdermal patch in subjects with idiopathic Parkinson's disease

Study Design:
This was a Phase 1, open-label, randomized, cross-over trial. After a Dose-Escalation Phase doses of rotigotine transdermal patch (18.0 mg [40cm2]) were applied once daily in a random sequence to 6 different application sites (flank, shoulder, upper arm, thigh, hip, and abdomen). Patches were applied to 5 of the 6 application sites, each application lasting 24 hours (Days 16- 20). At the sixth application site, patches were applied in a cross-over design (Days 21 and 22) in which subjects received treatment A (application of one 18.0 mg [40cm2] rotigotine patch for 24 hours) and treatment B (simultaneous application of two 9.0 mg [20cm2] rotigotine patches for 24 hours) in a randomized order. Subsequently, doses were de-escalated in 9.0 mg [10cm2] steps by application of each patch size for 2 days.

The overall trial was conducted according to the following scheme:
Eligibility assessment
↓
Days 1 – 3 once daily 4.5 mg(10cm2) : applied to the shoulder in all subjects
↓
Days 4 – 6 once daily 9.0 mg(20cm2): applied to the hip in all subjects
↓
Days 7 – 12 once daily 13.5 mg (30cm2): applied to the shoulder in all subjects
↓
Days 13 – 15 once daily 18.0 mg (40cm2): applied to the shoulder, upper arm and flank in all subjects
↓

Days 16 – 20 once daily (randomized to 5 of 6 different application sites)

Day 21 (randomized to the sixth application site)	Treatment A:	Treatment B:
	1 x 18.0mg (40cm^2)	2 x 9.0mg (20cm^2)
	↓	↓
Day 22 (randomized to the sixth application site)	Treatment B:	Treatment A:
	2 x 9.0mg (20cm^2)	1 x 18.0mg (40cm^2)
	↓	↓

Days 23 – 28 De-Escalation
The trial medication was down-titrated according to the following schedule:
- Days 23 and 24: 13.5 mg rotigotine transdermal patch
- Days 25 and 26 9.0mg rotigotine transdermal patch
- Days 27 and 28 4.5mg rotigotine transdermal patch
- Day 29 no patch application in order to wash-out rotigotine

The Patch-On Period was 24 hours for each patch. To evaluate the apparent dose, the residual amount of rotigotine in used patches was determined. The apparent dose of rotigotine was calculated as the difference between initial drug content and residual drug amounts in the patches.

Trial population:
36 male or female subjects with idiopathic Parkinson's disease (of at least 18 years of age)

Concomitant medications:
The following concomitant medications were not allowed during the trial and within 5 half-lifes prior to Baseline visit:
- Levodopa (in combination with benserazide or carbidopa and/or catechol-O-methyl transferase [COMT] inhibitors)
- Dopamine agonists (eg, ropinirole, pramipexole, pergolide, etc.)
- MAO-A inhibitors (eg, pargyline, phenelzine, tranylcypromine, moclobemide)
- Dopamine-releasing substances (eg, methylphenidate or amphetamine)
- Dopamine-modulating substances (eg, reserpine, alpha-methyldopa)
- Budipine
- Dopamine antagonists: anti-emetics (metoclopramide)

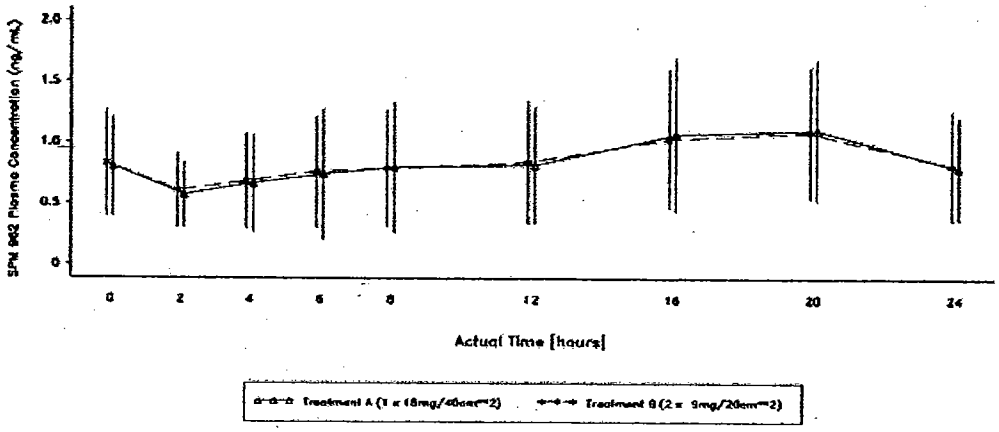
Blood Samples:
Samples were taken immediately prior to patch removal on Days 14 and 15 and at the following time points on Days 16 to 22: 0 (immediately prior to patch removal) 2, 4, 6, 8, 12, 16, 20 and 24 hours post application.

Pharmacokinetic Results:

Comparison of Treatment A and B:

Rotigotine plasma concentration time profile for the two treatments is shown in the following figure; suggesting that the two treatments (one 18 mg vs two 9 mg doses) were not very different. However, given that this comparison is at steady state, it is not very sensitive to detect differences.

Arithmetic mean and SD of rotigotine plasma concentrations by treatment



The mean apparent doses (7.133 ± 1.915mg for Treatment A vs 7.717 ± 2.132mg for Treatment B) were similar for both treatments.
The PK parameters for the two treatments is shown in the following Table:

Ratio analysis (parametric) of primary PK parameters (Day 21-22)

Parameter	Treatment A	Treatment B	Ratio (A/B) of Geo. Means (%)	90% CI for Ratio (A/B) of Geo. Means (%)	ANOVA CV (%)
$AUC_{(0-24)ss}$ (ng/mL*h)	17.7446	17.8341	99.50	(93.67, 105.69)	15.2
$AUC_{(0-24)ss,norm}$ (ng/mL*h/mg)	2.5792	2.3901	107.91	(102.70, 113.38)	12.5
$C_{max,ss}$ (ng/mL)	1.1330	1.0739	105.51	(98.64, 112.85)	17.0
$C_{max,ss,norm}$ (ng/mL/mg)	0.1647	0.1439	114.42	(107.49, 121.80)	15.8

The mean Tmax for the two treatments is given below:

Parameter	Treatment	Geometric Mean	CV (%)
		Median	Range
$t_{max,ss}$ (hours)	A	16.0	0-24
	B	18.0	0-24

The 90% confidence intervals for the ratios A/B were within the acceptance range for bioequivalence of 80 - 125% for all PK parameters of rotigotine.

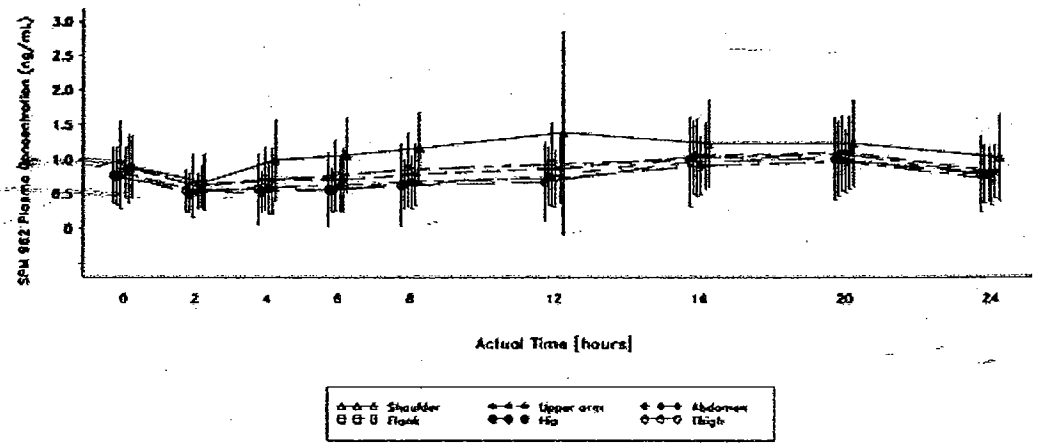
Plasma concentration of rotigotine at different application sites:

The trough levels of rotigotine at Days 14 and 15 were similar, indicating steady-state conditions.

The mean concentration-time profile of rotigotine at steady state was similar for all application sites. Within 2 hours after patch application the mean plasma concentration of rotigotine decreased followed by an increase to plateau plasma concentrations. The highest mean plasma concentrations were generally reached 16 to 20 hours after patch application. Immediately prior to patch removal the mean plasma concentrations of rotigotine were similar to the corresponding concentrations at time of patch removal of the day before. Highest mean plasma concentrations were observed for the patch application site shoulder.

The figure below displays the mean plasma concentration-over-time course separated by application site:

Arithmetic mean and SD of rotigotine plasma concentrations by application site



The higher variability at the application site shoulder at 12 hours is caused by one sample

(Subject 80025). The respective concentration at 12 hours for Subject 80025 was [redacted] ng/mL.

The PK parameters at different application sites is given in the following Table:

PK parameters for rotigotine by application site

	Application site					
	Geometric Mean (CV%)					
Parameter	**Shoulder**	**Upper arm**	**Abdomen**	**Flank**	**Hip**	**Thigh**
$AUC_{(0-24)ss}$ (ng/mL*h)	24.1130 (57.4)	18.2763 (63.3)	16.1391 (54.5)	18.5763 (61.8)	16.4484 (56.5)	14.7160 (76.0)
$AUC_{(0-24)ss,norm}$ (ng/mL*h/mg)	2.9232 (47.6)	2.5437 (49.1)	2.5034 (42.3)	2.6273 (50.1)	2.4743 (46.1)	2.1818 (64.2)
$C_{max,ss}$ (ng/mL)	1.440 (61.8)	1.119 (57.6)	0.972 (49.9)	1.176 (56.5)	1.066 (51.4)	0.985 (63.8)
$C_{max,ss,norm}$ (ng/mL/mg)	0.175 (54.2)	0.156 (46.9)	0.151 (40.4)	0.166 (47.3)	0.160 (43.1)	0.146 (53.7)
	Median (Range)					
$t_{max,ss}$ (hours)	12.0 (0-24)	18.0 (0-24)	16.0 (0-24)	16.0 (0-24)	16.0 (0-20)	16.0 (0-24)

Comparable mean $AUC_{(0-24)ss}$ and $C_{max,ss}$ values were obtained for upper arm, abdomen, flank,hip, and thigh. Patch application to shoulder resulted in higher mean $AUC_{(0-24)ss}$ and $C_{max,ss}$. The median $t_{max,ss}$ for shoulder was 12.0 hours and 16 hours for most of the other application sites.

The parameters $AUC_{(0-24)ss,norm}$ and $C_{max,ss,norm}$ normalized by apparent dose were slightly higher for shoulder compared to the other application sites.

The relative bioavailability of rotigotine was compared for different patch application sites. Point estimates (%) for the ratios of different application sites and the respective 90% confidence intervals of the PK parameters based on the results from the ANOVA are provided in the following tables for the parameters and the normalized parameters:

Ratio analysis (parametric) of $AUC_{(0-24)ss}$ (ng/mL*h) by application site

Application Site 1		Application Site 2		Ratio (1/2) of Geo. Mean (%)	90% CI for Ratio (1/2) of Geo. Means (%)
Site	Geo. Mean	Site	Geo. Mean		
Shoulder	24.1130	Upper arm	18.2763	131.91	(117.18, 148.54)
		Abdomen	16.1391	149.41	(132.70, 168.22)
		Flank	18.5763	129.80	115.29, 146.15)
		Hip	16.4484	146.60	(130.21, 165.05)
		Thigh	14.7160	163.86	(145.53, 184.48)
Upper arm	18.2763	Abdomen	16.1391	113.24	(100.58, 127.50)
		Flank	18.5763	98.39	(87.38, 110.77)
		Hip	16.4484	111.11	(98.69, 125.10)
		Thigh	14.7160	124.19	(110.31, 139.83)
Abdomen	16.1391	Flank	18.5763	86.88	(77.17, 97.82)
		Hip	16.4484	98.12	(87.15, 110.47)
		Thigh	14.7160	109.67	(97.41, 123.48)
Flank	18.5763	Hip	16.4484	112.94	(100.31, 127.15)
		Thigh	14.7160	126.23	(112.12, 142.12)
Hip	16.4484	Thigh	14.7160	111.77	(99.27, 125.84)

The ANOVA analysis on log-transformed values is carried out on application sites for 40 cm^2 patches (Days 16 to 20, and from Day 21 or 22, whichever day had a dosing schedule of 1 x 18.0mg/40cm^2)

Ratio Analysis (Parametric) of AUC(0-24)ss,norm (ng/mL*h/mg) (Days 16-22)
Population: Pharmacokinetic Set

Application Site 1			Application Site 2			Ratio (1/2) of	90% CI for Ratio (1/2)	ANOVA CV
Site	n	Geo. Mean	Site	n	Geo. Mean	Geo. Means (%)	of Geo. Means (%) (a)	(%)
Shoulder	36	2.9232	Upper arm	36	2.5437	114.92	(104.72, 126.11)	23.6
	36	2.9232	Abdomen	36	2.5034	116.77	(106.41, 128.14)	
	36	2.9232	Flank	36	2.6273	111.26	(101.39, 122.10)	
	36	2.9232	Hip	36	2.4743	118.14	(107.66, 129.64)	
	36	2.9232	Thigh	36	2.1818	133.98	(122.09, 147.02)	
Upper arm	36	2.5437	Abdomen	36	2.5034	101.61	(92.59, 111.50)	
	36	2.5437	Flank	36	2.6273	96.82	(88.23, 106.24)	
	36	2.5437	Hip	36	2.4743	102.80	(93.68, 112.81)	
	36	2.5437	Thigh	36	2.1818	116.58	(106.24, 127.93)	
Abdomen	36	2.5034	Flank	36	2.6273	95.28	(86.83, 104.56)	
	36	2.5034	Hip	36	2.4743	101.18	(92.29, 111.03)	
	36	2.5034	Thigh	36	2.1818	114.74	(104.56, 125.91)	
Flank	36	2.6273	Hip	36	2.4743	106.18	(96.76, 116.52)	
	36	2.6273	Thigh	36	2.1818	120.42	(109.73, 132.14)	
Hip	36	2.4743	Thigh	36	2.1818	113.40	(103.34, 124.45)	

Note: Geo. Mean = Geometric mean
Note: The ANOVA analysis on log-transformed values is carried out on application sites for 40 cm**2 patches (Days 16 to 20, and from Day 21 or 22, whichever day had a dosing schedule of 1 x 18.0mg/40cm**2)
Note: Geometric means are back-transformed from LS means from an ANOVA on log-transformed values, which includes sequence, period, and treatment as fixed effects, and subject within sequence as a random effect.
Note: Sequence = one of 12 possible randomized application site sequences over Days 16-22.
Note: (a) The 90% confidence interval is the classic (shortest) confidence interval

Ratio analysis (parametric) of $C_{max,ss}$ (ng/mL) by application site

Application Site 1		Application Site 2		Ratio (1/2) of Geo. Mean (%)	90% CI for Ratio (1/2) of Geo. Means (%)
Site	Geo. Mean	Site	Geo. Mean		
Shoulder	1.4405	Upper arm	1.1188	128.75	(113.28, 146.32)
		Abdomen	0.9716	148.25	(130.44, 168.49)
		Flank	1.1755	122.54	(107.82, 139.27)
		Hip	1.0662	135.10	(118.87, 153.55)
		Thigh	0.9846	146.30	(128.73, 166.27)
Upper arm	1.1188	Abdomen	0.9716	115.15	(101.32, 130.87)
		Flank	1.1755	95.18	(83.74, 108.17)
		Hip	1.0662	104.94	(92.33, 119.26)
		Thigh	0.9846	113.63	(99.98, 129.15)
Abdomen	0.9716	Flank	1.1755	82.65	(72.73, 93.94)
		Hip	1.0662	91.13	(80.18, 103.57)
		Thigh	0.9846	98.68	(86.83, 112.16)
Flank	1.1755	Hip	1.0662	110.25	(97.01, 125.31)
		Thigh	0.9846	119.39	(105.05, 135.69)
Hip	1.0662	Thigh	0.9846	108.29	(95.28, 123.07)

The ANOVA analysis on log-transformed values is carried out on application sites for 40 cm^2 patches (Days 16 to 20, and from Day 21 or 22, whichever day had a dosing schedule of 1 x 18.0mg/40cm^2)

Ratio Analysis (Parametric) of Cmax,ss (ng/mL) (Days 16-22)
Population: Pharmacokinetic Set

Application Site 1			Application Site 2			Ratio (1/2) of Geo. Means (%)	90% CI for Ratio (1/2) of Geo. Means (%) (a)	ANOVA CV (%)
Site	n	Geo. Mean	Site	n	Geo. Mean			
Shoulder	36	1.4405	Upper arm	36	1.1188	128.75	(113.28, 146.32)	33.0
	36	1.4405	Abdomen	36	0.9716	148.25	(130.44, 168.49)	
	36	1.4405	Flank	36	1.1755	122.54	(107.82, 139.27)	
	36	1.4405	Hip	36	1.0662	135.10	(118.87, 153.55)	
	36	1.4405	Thigh	36	0.9846	146.30	(128.73, 166.27)	
Upper arm	36	1.1188	Abdomen	36	0.9716	115.15	(101.32, 130.87)	
	36	1.1188	Flank	36	1.1755	95.18	(83.74, 108.17)	
	36	1.1188	Hip	36	1.0662	104.94	(92.33, 119.26)	
	36	1.1188	Thigh	36	0.9846	113.63	(99.98, 129.15)	
Abdomen	36	0.9716	Flank	36	1.1755	82.65	(72.73, 93.94)	
	36	0.9716	Hip	36	1.0662	91.13	(80.18, 103.57)	
	36	0.9716	Thigh	36	0.9846	98.68	(86.83, 112.16)	
Flank	36	1.1755	Hip	36	1.0662	110.25	(97.01, 125.31)	
	36	1.1755	Thigh	36	0.9846	119.39	(105.05, 135.69)	
Hip	36	1.0662	Thigh	36	0.9846	108.29	(95.28, 123.07)	

Note: Geo. Mean = Geometric mean
Note: The ANOVA analysis on log-transformed values is carried out on application sites for 40 cm**2 patches (Days 16 to 20, and from Day 21 or 22, whichever day had a dosing schedule of 1 x 18.0mg/40cm**2)
Note: Geometric means are back-transformed from LS means from an ANOVA on log-transformed values, which includes sequence, period, and treatment as fixed effects, and subject within sequence as a random effect.
Note: Sequence = one of 12 possible randomized application site sequences over Days 16-22.
Note: (a) The 90% confidence interval is the classic (shortest) confidence interval

The ratios of geometric means for pair wise comparisons between 5 of the 6 application sites were around 100% indicating a comparable bioavailability. For the comparison of shoulder with the other applications sites, higher ratios of geometric means were observed.

The mean apparent dose determined for the different application sites, ranged between 6.6mg (abdomen) and 8.5mg (shoulder).

Patch Adhesiveness:

Prior to patch removal, between 60% and 81% of the patches adhered with ≥90% adhesiveness. Most other patches adhered with at least 50 to ≤75% adhesiveness. Patch attachments <50% were rare (0-4.2%); 8.3-14% of patches were not assessable due to fixation by the hypoallergenic tape. The patch adhesiveness was similar for the different patch sizes (see Table below).

The patch adhesiveness was similar for all application sites and for the different treatments.

Summary of patch adhesiveness prior to patch removal by patch size

Patch size	Patch adhesiveness							
	0 n(%)	1 n(%)	2 n(%)	3 n(%)	4 n(%)	5 n(%)	6 n(%)	Total n(%)
10 cm^2	29 (81)	4 (11)	2 (5.6)	0	1 (2.8)	0	0	36 (100)
20 cm^2	17 (47)	7 (19)	3 (8.3)	3 (8.3)	1 (2.8)	5 (14)	0	36 (100)
30 cm^2	26 (72)	4 (11)	3 (8.3)	0	0	3 (8.3)	0	36 (100)
40 cm^2	207 (64)	33 (10)	20 (6.2)	13 (4.0)	5 (1.5)	46 (14)	0	324 (100)
2 x 20 cm^2	26 (72)	4 (11)	1 (2.8)	0	0	5 (14)	0	36 (100)

Note: Patch Adhesiveness: 0: >=90% adhered; 1: 75-<90% adhered; 2: 50-<75% adhered; 3: <50% adhered;
4: patch detached; 5: not assessable due to fixation by hypoallergenic tape;
6: not assessable due to new patch administration
Note: The frequencies displayed in this table are based on patches applied

Pharmacokinetics Conclusions:

- The bioavailability for one 18mg (40cm2)-patch was similar to that of two 9mg (20cm2)-patches.
- The application sites hip, flank, upper arm, abdomen, and thigh provided similar $AUC_{(0-24)ss}$ and $C_{max,ss}$ values. The ratio of geometric means for $AUC_{(0-24)ss}$, and $C_{max,ss}$ were around 100%.
- For shoulder, the mean plasma concentrations and PK parameters were higher compared to the other application sites. Mean $AUC_{(0-24)ss}$ was 24.1130ng/mL*h

for shoulder compared to 14.7160-18.5763ng/mL*h for the other application sites; mean $C_{max,ss}$ was 1.440ng/mL for shoulder and 0.972-1.176ng/mL for the other application sites.

- The difference between shoulder and the other application sites was reduced comparing $AUC_{(0-24)ss}$ (111.26% – 133.98%) and $C_{max,ss}$ (105.03% – 119.62%) normalized by apparent dose indicating a higher absorption of rotigotine at the application site shoulder.

Reviewer's Comment:

The sponsor has not reported arithmetic means at each application site.

Pooled analyses to evaluate application site differences

A pooled analysis of the relative bioavailability of rotigotine at 6 different application sites based on $AUC_{(0-24)ss}$ data obtained in SP630 (Pharmacokinetic Set: 63 subjects) and SP651 (Pharmacokinetic Set: 36 subjects) was conducted to obtain more reliable estimates on the relative bioavailability of rotigotine at different application sites based on a larger sample size (99 subjects). The results of this analysis are presented in this report.

Clinical trial SP630 was conducted to investigate the 24-hour plasma concentration profile of rotigotine under steady-state conditions in subjects with early-stage Parkinson's disease. Subjects received the ——— dose of 18.0mg/day rotigotine as a combination of two 20cm2 patches. In the Maintenance Phase, the patch application site was randomized for each subject for the Days 25 to 30 (6 days in total, each application site only once). On Days 27 and 30, plasma concentrations were measured at 16 sampling points (0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, and 23.5 hours) to obtain detailed 24-hour PK profiles, while on the other days reduced profiles of 5 blood samples were taken (0, 4, 8, 12, and 23.5 hours).

Clinical trial SP651 has been described previously in this review.

According to the sponsor, pooling of these data is considered to be adequate based on the following:

- Similar bioavailability of 18mg/day rotigotine administered as 2x20cm2 and 1x40cm2 transdermal patches (SP651)
- Adequate estimation of $AUC_{(0-24)ss}$ based on the reduced PK sampling
- Similar absolute $AUC_{(0-24)ss}$ values in both trials
- Complete $AUC_{(0-24)ss}$ data set available for all application sites for each subject

For the comparison of the different application sites, log-transformed $AUC_{(0-24)ss}$ of rotigotine determined from plasma concentrations was analyzed using an analysis of variance (ANOVA). The ANOVA model included "application site sequence" and

"application site" as fixed effects and "subject within application site sequence" as random effect. Based on these analyses, point estimates (LS-Means) and 90% confidence intervals were calculated.

Results of pooled analysis:

The ratio for the comparison "reduced versus complete profile" in SP630 was 0.95 with a 90% confidence interval of (0.93, 0.97) over all application sites (Table 3). For separate application sites, this statistical evaluation resulted in ratios of 0.91 (90% confidence interval of [0.88, 0.95]) to 1.00 (90% confidence interval of [0.96-1.04]). These data clearly indicate that the reduced profiles are adequate to compare $AUC_{(0-24)ss}$ for all 6 application sites. Example for a few subjects is shown in the following Table:

Subject AUC(0-24)ss after Administration of 15mg/day/40cm² Rotigotine Patches

Trial	Subject Number	Sequence Group	Day	Application Site	AUC(0-24)ss [ng/mL*h] Reduced	Full	Reduced/Full [%]
630	630080101	UA SH TH AB FL HI	25	Upper arm	37.432	37.432	100.0
			26	Shoulder	34.300	34.300	100.0
			27	Thigh	22.397	23.860	93.9
			28	Abdomen	28.802	28.802	100.0
			29	Flank	20.584	20.584	100.0
			30	Hip	17.021	19.014	89.5
	630080102	UA TH HI AB FL SH	25	Upper arm	11.244	11.244	100.0
			26	Thigh	11.154	11.154	100.0
			27	Hip	10.454	11.268	92.8
			28	Abdomen	8.974	8.974	100.0
			29	Flank	11.948	11.048	100.0
			30	Shoulder	11.391	12.228	91.7
	630080103	SH AB HI TH UA FL	25	Shoulder	44.548	44.548	100.0
			26	Abdomen	36.256	36.256	100.0
			27	Hip	48.485	42.145	115.0
			28	Thigh	22.364	22.364	100.0
			29	Upper arm	22.104	22.104	100.0
			30	Flank	16.504	19.074	86.5
	630080104	UA TH FL AB SH HI	25	Upper arm	27.378	27.378	100.0
			26	Thigh	19.028	19.028	100.0
			27	Flank	26.959	28.891	93.3

Note: Trial SP630: reduced profile (hours 0, 4, 8, 12, and 23.5) is utilised for days 27 and 30.
Note: Trial SP651: only randomisation scheme at days 21 and 22 for the 1x40cm² patch was taken into account.
Note: AB = Abdomen, HI = Hip, FL = Flank, SH = Shoulder, TH = Thigh, UA = Upper arm

Comparison of Full and Reduced Profiles for AUC(0-24)ss

Parameter	Site	Geo. LSMean Reduced	Full	Ratio (%)	90% 2-sided Conf. Limits Lower	Upper
AUC(0-24)ss [ng*h/ml]	H: Hip	19.162	20.466	0.94	0.90	0.98
	S: Shoulder	21.896	23.190	0.94	0.91	0.98
	UA: Upper Arm	19.633	19.618	1.00	0.96	1.04
	T: Thigh	14.270	15.160	0.94	0.90	0.98
	AB: Abdomen	16.404	17.258	0.95	0.91	0.99
	F: Flank	17.646	19.323	0.91	0.88	0.95
	All	18.001	19.002	0.95	0.93	0.97

The geometric means of $AUC_{(0-24)ss}$ ranged between 15.28ng/mL*h and 21.58ng/mL*h in SP630 and between 14.72ng/mL*h and 24.11ng/mL*h in SP651. In the pooled analysis, the geometric means of $AUC_{(0-24)ss}$ ranged between 15.07ng/mL*h and 22.47ng/mL*h as shown in the table below.

Descriptive statistics of $AUC_{(0-24)ss}$ at different application sites – pooled analysis

Application site	N	Geometric mean (ng/mL*h)	CV (%)
Abdomen	99	16.7960	56.9
Flank	99	18.3188	60.6
Hip	99	16.7757	66.8
Shoulder	99	22.4705	60.3
Thigh	99	15.0709	63.6
Upper arm	99	19.2771	58.2

In the pooled analysis (as well as in SP630 and SP651), the mean $AUC_{(0-24)ss}$ was lowest after administration of the rotigotine transdermal system to the thigh and highest after administration to the shoulder.

Mean values of $AUC_{(0-24)ss}$ for each application site were compared in an ANOVA. The results of the pairwise comparisons from the pooled analysis are summarized in the table below.

Summary of the analysis of variance of log-transformed $AUC_{(0-24)ss}$ – pooled analysis

Ratio of application sites	Estimate	90% confidence interval
Shoulder / Upper Arm	1.1657	(1.0871, 1.2499)
Shoulder / Abdomen	1.3378	(1.2477, 1.4345)
Shoulder / Flank	1.2266	(1.1440, 1.3153)
Shoulder / Hip	1.3395	(1.2492, 1.4363)
Shoulder / Thigh	1.4910	(1.3905, 1.5987)
Upper arm / Abdomen	1.1477	(1.0704, 1.2307)
Upper arm / Flank	1.0523	(0.9814, 1.1284)
Upper arm / Hip	1.1491	(1.0717, 1.2321)
Upper arm / Thigh	1.2791	(1.1929, 1.3715)
Abdomen / Flank	0.9169	(0.8551, 0.9831)
Abdomen / Hip	1.0012	(0.9337, 1.0736)
Abdomen / Thigh	1.1145	(1.0394, 1.1950)
Flank / Hip	1.0920	(1.0184, 1.1709)
Flank / Thigh	1.2155	(1.1336, 1.3033)
Hip / Thigh	1.1131	(1.0381, 1.1936)

Reviewer's Comment:

This study SP 630 was considered not suitable for assessing application site differences by the original Clinical Pharmacology reviewer Dr Kavanaugh, due to the following reason:
"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"

The sponsor has given reasons why pooling data from Study SP 630 to data with the new study SP 651 is acceptable, due to difference in sampling times etc, which is acceptable, because the sponsor has shown that the estimate of AUC with full and reduced sampling are similar. However, the patch was applied to each site only once in a limited number of subjects, therefore, not robust to estimate application site differences. Moreover, pooling can minimize differences seen across different application sites. Since Study SP651 has been conducted in adequate number of subjects (N=36); the application site differences obtained from this study should be reported in the label.

Therefore, this pooled analysis can only be used as supportive information, but statistical numbers on the differences due to application sites should be taken from the definitive study SP 651.

Comparison of clinical efficacy in SP506 and SP512/SP513

In order to estimate the impact of inter-day-variability due to different application sites on efficacy, the results of trials SP506 and SP512 and SP513 were compared. In the first trial (SP506), the subjects were asked to use the abdomen as the sole application site. In the 2 latter trials (SP512 and SP513), application sites were changed daily among 6 different body sites (shoulder, upper arm, hip, flank, thigh, and abdomen).

In trial SP506, 1 of 4 target doses of rotigotine (4.5, 9.0, 13.5, or 18.0mg/day) or placebo was used. In trial SP512, most subjects used a target dose of 13.5mg/day, and in trial SP513, a target dose of 18.0mg/day was used by the majority of subjects.
The following table displays the net effects of rotigotine (UPDRS Parts II+III) across the 3 trials.

Efficacy: Placebo-substracted rotigotine effect – SP506, SP512, and SP513

UPDRS Parts II + III score	SP506		SP512	SP513
	13.5mg/day[a]	18.0mg/day[a]		
Change from baseline[b]	-4.91	-5.04	-5.28	-4.49
20% responder	28.4%	23.9%	28.7%	21.7%

ANCOVA=analysis of covariance, FAS=Full Analysis Set, UPDRS=Unified Parkinson's Disease Rating Scale
a. FAS as randomized
b. ANCOVA results

Sponsor's Conclusions:

Although in SP512 and SP513 rotation of application sites across 6 different body parts was performed and in SP506 only abdomen as an application site was used, rotigotine patch showed similar efficacy across all 3 trials. These results indicate that the site of application does not have a clinically relevant impact on efficacy.

Reviewer's Comment:

This should also be evaluated by the Medical Officer.

Model Dependent Pharmacokinetics of rotigotine to estimate the half life:

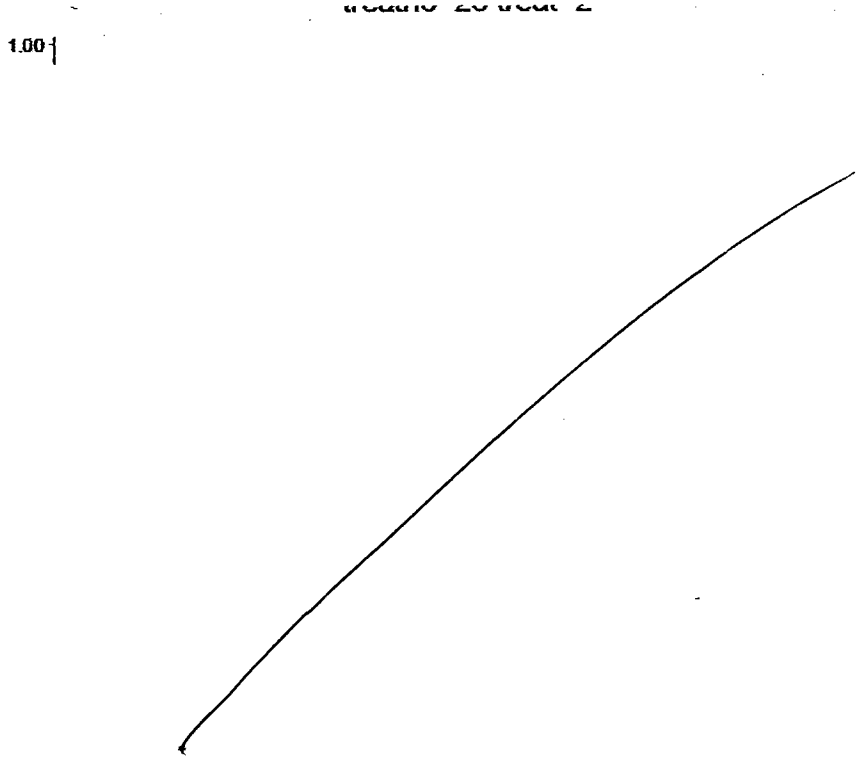
The sponsor conducted compartmental modeling on two different studies.

Compartmental modeling of Study SP 502:

Compartmental modeling was conducted by the sponsor from the data of Study SP 502 (single dose 3-way crossover BE study) to estimate the half life of rotigotine.

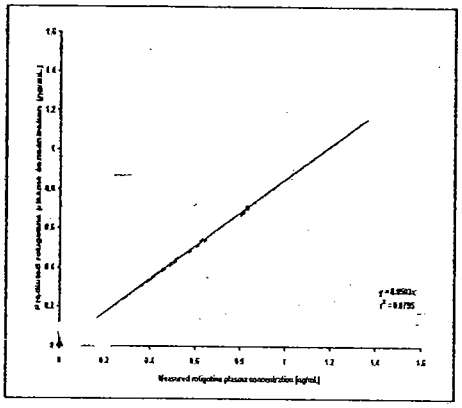
During the 3 different periods, blood samples for the analysis of rotigotine were taken predose and 1, 2, 4, 6, 8, 12, 15, 23, 24, 25, 26, 27, 28, 30, 32, 36, 40, and 48 hours post patch application. Samples taken 25 to 48 hours after application were samples after patch removal.
Limitation of the analysis: A 24-hour sampling period with 10 data points was available for this trial, plasma concentrations in the later part of the concentration time course were low, and therefore an adequate characterization of a second phase in the terminal part of the curve was not possible.
1 and 2 compartment models were tested.

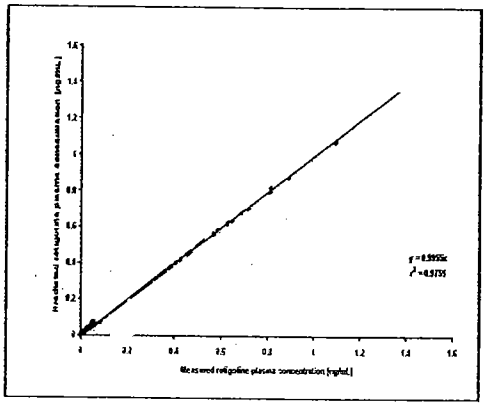
The figure presented below shows a representative example of an individual plasma concentration-time curve on a semilogarithmic scale.



The dots represent the measured plasma concentrations, the dashed line shows a simulation of the plasma concentration-time curve using the PK parameters obtained from the 1-compartment model, and the continuous line represents the result of the simulation of the plasma concentration-time curve using the PK parameters calculated with the 2-compartment model.

The correlation between the measured rotigotine plasma concentrations and the rotigotine plasma concentrations predicted by the 1- and 2-compartmental model are displayed in the figures below.





The coefficient of determination (r_2) for 1-compartmental model was 0.8795 and the slope of the regression line was 0.8503. The coefficient of determination (r_2) for 2-compartmental model was 0.9995 and the slope of the regression line was 0.9755.

These figures and regression show that the 2-compartment model is more appropriate for describing the plasma concentration-time course of rotigotine after patch removal.

The mean was 0.2918±0.1677 h^{-1} (arithmetic mean ± standard deviation) for α, 0.0325±0.0413 h^{-1} for β, and 0.0874±0.1543 h^{-1} for k_{21}. Because β was close to the condition of boundary (β>0) in half of the subjects, an additional evaluation of descriptive statistics for the PK parameters β and k_{21} was performed. Results are represented in Table 3. In this evaluation, β was 0.0650±0.0356 h^{-1} and k_{21} was 0.1652±0.1912 h^{-1}. Due to the different doses, C_0 was calculated separately for both groups with 0.470±0.138ng/mL in the group receiving 1 silicone patch, and 0.940±0.412ng/mL in the group receiving 2 patches.

The rate constant of transports corresponds to a $t_{1/2}$ of 2.4 hours for the α-phase and 21.3/10.7 hours (all subjects/subjects with β near to boundary excluded) for the β-phase ($t_{1/2}$=ln2/rate constant).

Conclusions:
After patch removal, the decline of rotigotine plasma concentrations can be described using a 2-compartment pharmacokinetic model. The first phase (α-phase) has a short half-life with approximately 2.4 hours in this evaluation and leads to a rapid decline in rotigotine plasma concentrations after patch removal. The biggest part of rotigotine

disappears in this α-phase. In the second phase (β-phase), the decline is slower, with a half-life of approximately 10 to 20 hours. The second phase could not be reliably calculated in this analysis.

Compartmental modeling of Study SP 628:

Study SP628 was a open, parallel-group, drug-drug interaction trial to evaluate pharmacokinetics of rotigotine TDS and levodopa/carbidopa in patients with idiopathic Restless Legs Syndrome. This study has been reviewed previously. This review summarizes the results of compartmental analysis only in order to determine the plasma half-life of rotigotine.

In this trial, the sampling period after removal of the rotigotine patch was 36 hours and included the collection of 7 blood samples (predose, 2, 4, 6, 12, 24, and 36 hours after patch removal). Most of the trials performed with rotigotine only had a sampling period of 24 hours after patch removal. Therefore, this trial was chosen to evaluate the appropriateness of a two-compartment model for the terminal concentration time course of rotigotine.

Limitation of analysis: With the total number of 7 samples collected with/after patch removal, the pharmacokinetic modeling has a limitation according to the precision of the results of the rate constants.

The coefficient of determination (r_2) is 0.966 and the factor for proportionality between the measured and the predicted concentration is 1.0109.

Nonlinear regression gave the following mean values: The mean of C_0 was 598±221pg/mL (arithmetic mean ± standard deviation), α was 0.2528±0.115/h, β was 0.04715±0.03674/h, and k_{21} was 0.1031±0.105/h. An additional evaluation of descriptive statistics for PK parameter β was performed by the sponsor, in which Subjects 10006, 10010, and 10015 were excluded because β reached the condition of boundary (β>0) in these subjects. In this additional analysis, β was 0.05422±0.034/h.

The rate constants of transports correspond to a $t_{1/2}$ of 2.74h for the α-phase and 14.7h or 12.8h (for all subjects or Subjects 10006, 10010, and 10015 excluded) for the β-phase.

Conclusions:
After patch removal, rotigotine plasma concentrations decreases bi-phasically with half-lives of about 3 hours (α-phase) and 13 hours (β-phase).

In Vitro Studies

Study 734: Investigation of human sulfotransferases involved in the metabolism of Rotigotine

The objective of this study was:
- to identify the sulfotransferase involved in the metabolism of SPM 962 in vitro
- to determine the kinetic parameter K_m and V_{max} of the reaction

The metabolism by the sulfotransferases SULT1A1*2, SULT1A2*1, SULT1A3, SULT1E and SULT2A1 were investigated in the study.

For the sulfotransferases identified to be capable to catalyze the sulfation of SPM 962, the kinetic parameter K_m (Michaelis Menten constant) and V_{max} (maximal velocity at saturation) were calculated together with the intrinsic clearance CL_{int} (V_{max}/K_m).

Sulfotransferase	K_m [µM]	V_{max} [pmol/min/mg protein]	CL_{int} [mL/min/mg protein]
SULT1A1*2	1.15	12951	11.26
SULT1A2*1	4.41	11326	2.57
SULT1A3	6.02	17225	2.86
SULT1E	0.78	2448	3.14

No significant (≤ 0.1 %) sulfation was observed in incubations with SULT2A1.

Conclusion:

The study indicates the involvement of the sulfotransferases SULT1A1*2, SULT1A2*1, SULT1A3 and SULT1E in the metabolism of SPM 962. The SULT1A family is known as the phenol sulfotransferase family. SULT1A3 catalyzes the sulfate conjugation of catecholamine and structurally related drugs and SULT1E conjugates estrogens and catecholestrogens. Based on K_m values and the calculated intrinsic clearance values, the SULT1A family is indicated to be an important rotigotine metabolizing enzyme family. As all K_m and intrinsic clearances values are approximately within the same order of magnitude, the clinical significance of polymorphism and potential enzyme inhibition by co-administered drugs on rotigotine metabolism seems unimportant when ignoring potential cofactor depletion issues, as several enzymes can take over the metabolism.

Study 743: Investigation of human UDP-glucuronosyltransferases involved in the metabolism of rotigotine

The objectives of this study were:
• to identify the UDP-glucuronosyltransferases involved in the metabolism of SPM 962 in vitro
• to determine the kinetic parameter K_m and V_{max} of the reaction

UDP-glucuronosyltransferases prepared from insect cells infected with a baculovirus containing the cDNA for a specific human UGT were used. Control microsomes were prepared from insect cells infected with a wild-type baculovirus.

Trifluoperazine (UGT1A4), eugenol (UGT2B17) and 7-hydroxy-4 trifluoromethylcoumarin (UGT1A8, UGT1A9, UGT2B4, UGT2B15) served as probe substrates. Quantification of the glucuronide conjugates was performed by HPLC analysis. For the UDP-glucuronosyltransferases identified to be capable to catalyze the glucuronidation of rotigotine, the following kinetic parameters K_m (Michaelis Menten constant) and V_{max} (maximal velocity at saturation) were calculated.

UDP-glucuronosyl-transferase	SPM 962 [µM]	K_m [µM]	V_{max} [pmol/min/mg protein]
UGT1A1	0.1 - 100	n.d.	n.d.
UGT1A3	0.1 - 100	n.d.	n.d.
UGT1A6	0.1 - 100	n.d.	n.d.
UGT1A7	0.1 - 100	n.d.	n.d.
UGT1A10	0.771 - 771.4	> 1000	82.5
UGT2B7	0.1 - 100	n.d.	n.d.

UDP-glucuronosyl-transferase	SPM 962 [µM]	K_m [µM]	V_{max} [pmol/min/mg protein]
UGT1A4	5 - 100	n.d.	n.d.
UGT1A8	5 - 100	n.r.	n.r.
UGT1A9	5 - 100	23.8	9966
UGT2B4	5 - 100	n.d.	n.d.
UGT2B15	5 - 100	18.2	2952
UGT2B17	5 - 100	n.d.	n.d.

n.d.: not detected

n.r.: calculation not reasonable

No glucuronidation of rotigotine was detected for the UDP-glucuronosyltransferases UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT2B4, UGT2B7 and UGT2B17. For the nonhepatic but gastrointestinal UDP-glucuronosyltransferases UGT1A8 and UGT1A10 rotigotine was found to have a low affinity and the K_m values are expected to be above 1000 µM.

Conclusion:
From the 12 UDP-glucuronosyltransferases tested, the experiments indicate that UGT1A9 and UGT2B15 are the enzymes responsible for the formation of the glucuronide conjugate metabolite of rotigotine.

Metabolism Update

The labeling information c

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/s/

Veneeta Tandon
1/30/2007 04:19:41 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
1/30/2007 04:21:54 PM
BIOPHARMACEUTICS

New Drug Application – Major Amendment
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-829
Type of Submission:	RS - Resubmission
Generic Name:	Rotigotine Transdermal System
Formulation:	Transdermal System
Strengths:	4.5 mg / 10 cm^2 to deliver 2 mg / 24 hours 9.0 mg / 20 cm^2 to deliver 4 mg / 24 hours 13.5 mg / 30 cm^2 to deliver 6 mg / 24 hours
Route:	Topical
Brand Names	Neupro®
Sponsor:	Schwarz Pharma

Submission Date(s):

000		**January 19, 2005**[1]
001	C	May 27, 2005
002	BZ	June 24, 2005
003	**BM**	**July 29, 2005**[1]
004	BC	August 9, 2005
005	BM	September 2, 2005
006	BM	September 9, 2005
007	**BM**	**September 15, 2005**[2]
008	AM	September 23, 2005
009	BC	September 29, 2005
010	BC	October 6, 2005
011	BM	October 31, 2005
012	BM	November 9, 2005
013	BM	December 15, 2005
014	BM	December 22, 2005
015	BC	January 5, 2006
016	BM	January 26, 2006
017	**BZ**	**January 30, 2006**[3]

Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

1 TABLE OF CONTENTS

[1] Contained information pertinent to OCPB and was reviewed
[2] PK and ECG data for study SP591 in Advanced Parkinson's Disease at Doses up to — Not requested or reviewed by OCPB
[3] Labeling submitted as a Microsoft Word Document

1.1 List of Tables

1.2 List of Figures

2 EXECUTIVE SUMMARY

2.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-829 submitted January 19, 2005 and amendments 003, 007, and 017 submitted July 29, 2005, September 15, 2005, and January 30, 2006.

OCPB finds this application acceptable provided that currently outstanding issues are adequately resolved, (i.e. agreement on dissolution and labeling).

2.2 Comments

Comments should be communicated to the sponsor as appropriate (see Section 2.2.2 Comments to the Sponsor and §2.2.2.1 Comments to be Communicated to the Sponsor Only upon Approval on page 14).

2.2.1 Comments to the Medical Division

2.2.1.1 Summary of Major Conclusions

The entire development program and submission was very poor. Consequently, reliable estimates of pharmacokinetic parameters cannot be assured. The concentration vs. time profile of rotigotine was very erratic with Cmaxs and Cmins potentially occurring at any time of the day, with typical peak-trough fluctuations of 2 fold. Typical concentrations at therapeutic doses of 13.5 mg and 18 mg patch content were in the 0.25 – 3 ng/ml range with concentrations occasionally reaching 15 – 16 ng/ml. Part of the variability was due to extensive depletion of drug from the patch so that delivery was not constant, and part was due to rotation among 6 application sites. Application to different sites commonly results in different bioavailability by site and this was shown for 3 of the sites, bioavailability from the other 3 sites was not examined. Although application site rotation is likely to result in significant interday variability and possibly intrasubject variability in response, Levodopa/Carbidopa intrasubject bioavailability and response is also highly variable and so high intrasubject variability with rotigotine might be acceptable.

The studies were not adequately designed to assess time invariance, and with transdermally applied irritating drugs such as rotigotine absorption can increase over time due to irritation. Due to the titration phase and extensive application site rotation this does not appear to be a major issue with rotigotine.

There is a question of linearity with dose, i.e. a less than proportional increase in concentration at the higher doses. This is supported by an apparent less than proportional increase in drug delivery with doses from different studies. A less than proportional increase in concentrations might explain the lack of difference in efficacy between the 13.5 mg and the 18.0 mg doses in the phase II dose ranging study, although this could also be due to lack of dose separation and normal variability.

The possible nonlinear drug delivery raises issues with specifying a nominal delivery rate, however using an average rate and making it directly proportional to drug content as the sponsor has done is probably the best solution, whereas other approaches might result in prescribing and dispensing issues. The appropriateness of substituting multiple smaller patches for a larger patch is presently not known, and should be advised against.

No clear differences were observed for effects of race/ethnicity, (Black, Caucasian or Japanese), gender or age, however this could be due to poor study design. This is most significant for the effect of age as only 3 subjects were between 80 – 85 years of age and changes in the skin and drug absorption can become more pronounced at greater than 85 years of age. Increased absorption in the 'older' elderly might result in a greater incidence of nausea, vomiting and somnolence at the lower doses during the titration phase. With regards to maintanence dosing subjects are titrated to either a maximum labeled or

maximum tolerated dose.

Rotigotine is extensively metabolized. The primary oxidative enzymes involved appear to be CYP3A4, 1A2, and 2C19. CYP1A2 is induced by tobacco, and dietary polyaromatic hydrocarbons and indoles, found in grilled meats and fish and certain vegetables, and 2C19 is genetically polymorphic. There are significant gaps in our understanding of the metabolism, such as the enzymes involved in specific pathways, the activity and inhibition potential of certain metabolites, lack of identification of 20% of circulating species, and the metabolism and activity of cleavage products. Unless the chemistry reviewer or pharmacology reviewer indicate that any of the structures are worrisome, the low total dose and the concentrations achieved being in the single nanomolar range would strongly mitigate against the possibility of problems. (The chemistry and pharmacology reviewers also need to assess the risks from degradation products.) *In vitro* there was no signal for parent rotigotine to be either P450 inducer or inhibitor.

No interactions were detected *in vivo* with rotigotine and either carbidopa/levodopa or domperidone. For early Parkinson's Disease the studies were acceptable.

Moderate hepatic insufficiency, (Child-Pugh Class B), and moderate renal insufficiency did not affect rotigotine pharmacokinetics. However, exposure to total rotigotine, (i.e. rotigotine metabolites), increased as renal function decreased and in severe renal insufficiency, (i.e. ClCr < 30 ml/min) exposures were doubled.

The transdermal system performed very poorly. The degree of lift and incidence of detachment is clearly much, much worse than other approved once daily transdermal products.

Irritabilty with the rotigotine transdermal system was also significant with the majority of subjects in short term studies developing erythema and a significant percentage having edema, glazing, and itching. In one pivotal phase III study 8% of subjects dropped out due to skin reactions. There was also possible signal for sensitization.

Due to the intrasubject variability, and the issues with dermal tolerance and adhesion, and based on rotigotine's 6 – 8 hour half-life

Effects on ECGs were not covered by this review and the safety review should be consulted for conclusions regarding ECG effects.

The quality of the work performed was poor, resulting in uncertainty with regards to pharmacokinetic metrics, however there does not appear to be any other issues that need to be addressed that would necessitate redoing any of the *in vivo* studies submitted.

In conclusion, unless the medical and safety reviews reveal significant adverse events for which there may be additional concern due to the high intrasubject variability in exposures, there does not appear to be any indication from the pharmacokinetic and clinical pharmacology information available that would suggest any major issues or problems.

2.2.2 Comments to the Sponsor

2.2.2.1 Comments to be Communicated to the Sponsor

1) Supplemental Studies

2) Submission Quality

The quality of this submission was extremely poor.

Protocols and study reports were so poorly written that frequently it was difficult or impossible to ascertain with certainty the actual formulations, dosages, measurement, or sample timing. The sponsor's calculations of basic pharmacokinetic metrics such as Tlag, Tmax, Cmax, AUC and half-life were frequently incorrect or in some cases were not even provided. Summary statistics were also frequently not provided or were incorrect, and analyses for comparability of exposures were incorrect or not performed. For other studies raw data was not even provided, and in the QT study, neither the analyses nor the data for the primary ECG variables were provided.

Study designs were consistently so poor and incomplete that the studies don't adequately address the questions of interest. Factors such as insufficient samples and dosage, application site, duration of treatment, and sampling times were consistently so poor that results and conclusions from the studies cannot be relied on.

The electronic submission was extremely difficult to work with. Some studies didn't even have folders, and could only be reached by going to a cumulative list of studies in the summary section and reaching the study via a hyperlink. For other studies that did have folders the links sent you to a totally different study. Organization of the information in the study reports was inconsistent from study to study, for example PK data was variously reported under appendices, listings, tables, in different subsections in the clinical study report itself, in bioanalytical reports, or even in totally separate PK reports. In one case the reviewer had to drill down through 28 layers of links to be sent to another section, then had to drill down through another 30 layers to again be sent to another section. This was repeated 2 more times finally resulting in a statement that if the data are needed to please request it from the sponsor. Instead of descriptions of the results and tables in the study reports, the study reports frequently simply included links to a series of unidentified tables, i.e. table1... table14, clicking on these links brought you to data or summary tables without appropriate identifiers so it was impossible to tell if these tables were even associated with the study of interest.

2.2.2.2 Comments to be Communicated to the Sponsor Only upon Approval

2.2.2.2.1 Dissolution

Please adopt the following proposed dissolution method, specifications, and acceptance criteria for rotigotine transdermal systems as the regulatory method.

Table 1 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	

2.2.2.2.2 Labeling Comments

Labeling comments should be communicated to the sponsor as appropriate (see Section 4 on page 188).

2.3 Commitments to be Performed Prior to Approval

None.

2.4 Commitments to be Performed Post-Approval

None.

2.5 Summary of Clinical Pharmacology and Biopharmaceutics Findings

2.5.1 Introduction and Background

Rotigotine belongs to the group of non-ergolinic dopamine agonists. It is the levorotary enantiomer of an amino-tetraline compound and shows structural analogy to dopamine and apomorphine. It exhibits agonistic activity at all dopamine and some non-dopaminergic receptors. The rank order of affinities towards the different dopamine receptors is similar to that of dopamine. However, its affinities are much higher than those of dopamine. Thus, rotigotine resembles dopamine in respect to structure, receptor binding and functional activity.[4]

Mechanism of Action

The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is not known in detail. It is supposed to directly stimulate post-synaptic dopamine D1, D2 and D3 receptors within the caudate-putamen of the brain as suggested for dopamine agonists in general.[1]

Proposed Indication

The proposed indication for rotigotine is for the treatment of the signs and symptoms of early stage idiopathic Parkinson's disease.

Proposed Formulation and Strengths

Due to low bioavailability of rotigotine via the oral route and suitable physico-chemical properties for transdermal application, rotigotine has been developed for transdermal administration using patch technology.[1]

— strengths of rotigotine transdermal systems are proposed as shown in Table 2.

Table 2 Proposed To-be-marketed Strengths for Rotigotine Transdermal Systems

Rotigotine Content (mg)	Rotigotine TDS Surface Area (cm^2)	Proposed Nominal Delivery Rate (mg/day)
4.5	10	2.0
9.0	20	4.0
13.5	30	6.0

Proposed Dosage Regimen

The patch is applied once a day with rotation of the application sites with at least a 14 day interval between applications to the same spot. Proposed application sites include the front of the abdomen, thigh, hip, flank, shoulder, and upper arm.

The recommended starting dose is 4.5mg (10 cm^2) daily with the daily dosages increased in weekly increments of 4.5 mg (10 cm^2) up to —, based on the individual patient response. Proposed effective doses are 9.0 mg, 13.5 mg, or ~ mg per day.

[4] *Italicized text is taken from sponsor's submission.*

2.6 Pertinent Clinical Pharmacology and Biopharmaceutic Questions

What was the quality of this submission, and how did it affect the quality and reliability of this review?

The quality of this submission was extremely poor.

Protocols and study reports were so poorly written that frequently it was difficult or impossible to ascertain with certainty the actual formulations, dosages, measurement, or sample timing. The sponsor's calculations of basic pharmacokinetic metrics such as Tlag, Tmax, Cmax, AUC and half-life were frequently incorrect or in some cases were not even provided. Summary statistics were also frequently not provided or were incorrect, and inappropriate statistical analyses for bioequivalence were performed. For other studies raw data was not even provided, and in the QT study, neither the analyses nor the data for the primary ECG variables were provided.

Study designs were consistently so poor and incomplete that the studies don't adequately address the questions of interest. Factors such as insufficient samples and dosage, application site, duration of treatment, and sampling times were consistently so poor that results and conclusions from the studies cannot be relied on.

The electronic submission was extremely difficult to work with. Some studies didn't even have folders, and could only be reached by going to a cumulative list of studies in the summary section and reaching the study via a hyperlink. For other studies that did have folders the links sent you to a totally different study. Organization of the information in the study reports was inconsistent from study to study, for example PK data was variously reported under appendices, listings, tables, in different subsections in the clinical study report itself, in bioanalytical reports, or even in totally separate PK reports. In one case I had to drill down through 28 layers of links to be sent to another section, where I had to drill down through another 30 layers to again be sent to another section. This was repeated 2 more times finally resulting in a statement that if the data are needed to please request it from the sponsor. Instead of descriptions of the results and tables in the study reports, the study reports frequently simply included links to a series of unidentified tables, i.e. table1... table14, clicking on these links brought you to data or summary tables without appropriate identifiers so it was impossible to tell if these tables were even associated with the study of interest.

Due to the difficulty in reviewing this submission, the validity of the assays could not be reviewed.

Consequently, almost all conclusions reached in this review are tentative and the reliability of the conclusions reached cannot be assured.

What formulations were used in the pharmacokinetic, clinical pharmacology studies, and pivotal phase III studies?

Four formulations were investigated. The first two were development formulations,

The two later formulations were qualitatively/quantitatively identical silicone based formulations that differ only in their method of manufacture.

These formulations are variously referred to in the review as formulation 3 and 4, the Clinical-Trial-Formulation, (CTF), and the To-Be-Marketed formulation, (TBM), or by the sponsor as the 'phase II' and 'final' formulation.

The final TBM formulation was used in the pivotal phase III studies and in the multiple dose QT study, and a few other phase I studies of intrinsic or extrinsic factors. The CTF formulation was used in the phase II dose ranging study and most PK studies.

Are there any differences between the To-Be-Marketed, (TBM), and Clinical Trial Formulation, (CTF)?

The two formulations are qualitatively and quantitatively identical and differ only in the manufacturing methods used. Specifically the

Are the CTF and TBM formulation bioequivalent?

As the CTF and TBM formulations are qualitatively and quantitatively identical there is no need for this BE study. Yet a single dose bioequivalence study at the lowest dose of 4.5 mg / 10 cm^2 applied to the fore axillary line of the chest was performed. Although appropriate geometric means, geometric mean ratios, and 90% confidence interals were not calculated, comparison of summary statistics, (i.e. means standard deviations, ranges, medians), appears to indicate that these formulations perform similarly. However, the TBM formulation used was produced at — scale and has a much faster dissolution than any other CTF or TBM batch. Plus it's unclear if the site of application was studied in any other study. In any case this site was not explicitly stated as used in either the phase II dose ranging study or the pivotal phase III studies.

What is the general concentration time profile of rotigotine TDS and what are the potential clinical implications?

On single dosing typical lag times of 4 hours are seen as is expected with any transdermal formulation. A smaller fraction of subjects have lag times of 2 hours, although lag times of up to 12 hours have been seen. Maximum concentrations with single doses of 24 hours duration occur most frequently around 16 hours although ranges of 4 to 27 hours are observed. Thus on multiple dosing Tmaxs can occur at anytime although there is a peak incidence around 16 – 20 hours. Minimum concentrations also occur at almost anytime of the day although the distribution is opposite that of the Tmax with a peak incidence around 2 hours post dose.

Does rotigotine exhibit linear kinetics over the dosage range?

No adequate single or multiple dose studies of linearity were performed. However, several phase II and phase III studies did have limited PK sampling over the dose range of 4.5 mg to 18 mg, or in one phase III study, (SP512) to 13.5 mg.

In general it appears possibly linear to 13.5 mg with a plateau in exposure at 18 mg. However this could also be due to variability due to inadequeate sampling, etc. with linear PK to 18 mg.

To summarize:

Study	Description	PK Sampling	Comments
SP718	Ph I Rising MD Study	Extensive Sampling	Possibly linear from 2.25 mg to 9 mg
SP534 Pt II	Ph II Rising MD Study	C0, C2, C6, C12, C23 Days 1, 8, 15, 22	Appears to Plateau at 18 mg
SP535	Ph II Rising MD Study	Ibid.	Appears to Plateau at 18 mg
SP506	Ph II Fixed Dose Study	C24 at wks 4, 7, 11	Appears linear, although exposure at 13.5 mg is high and at 18 mg low
SP630	Ph II MD QT study	C24 during titration And C24 at 18 mg	Appears linear
SP512	Ph III Pivotal Efficacy Study with Titratable Doses	C24 during titration	Less than dose proportional increase. Possible plateau
SP513	Ph III Pivotal Efficacy Study with Titratable Doses	C24 during titration	Less than dose proportional increase. Possible plateau

What is rotigotine's multiple dose kinetics and does it exhibit time invariant kinetics?

Study SP503 was the only multiple dose study of sufficient duration to possibly detect time invariance. In this study of a 4.5 mg dose over 14 days the mean accumulation ratio was 1.54. Unfortunately, due to flip-flop kinetics and the lack of samples on intermediate days time invariance can't be assessed.

Based on 24 hour concentrations obtained at weeks 4, 7, and 11 in the phase II fixed dose study SP506, it does not appear that kinetics are time invariant after the initial 4 week titration period.However, due to the irritancy of rotigotine if the application site is not properly rotated, absorption and exposure could increase over time. However, based on the possible less than dose proportional increase with rising doses of the dose titration period induction and time invariance in the third week of treatment can't be ruled out. Although based on *in vitro* data it does appear unlikely.

What is the extent of exposure to rotigotine and what are the pertinent pharmacokinetic metrics?

At a dose of 18 mg daily typical Cmaxs are around 1.5 – 1.7 ng/ml, with most subjects having Cmaxs less than 3 ng/ml although an occasional subject will have a Cmax above 5 ng/ml, with Cmins around 0.5 – 0.8 ng/ml depending on the study. In study SP630 the typical Cmax:Cmin ratio is 2.5, although the distribution is log normal and the range is up to approximately 11 fold.

What is the bioavailability of rotigotine?

When radiolabeled rotigotine is administered in a patch approximately 50% of the drug content is delivered to the skin. If the skin is washed immediately after patch removal approximately 5% of the drug content can be recovered. Thus depending on if the skin is washed or not approximately 45% - 50% of the drug in the patch is absorbed.

Are there bioavailability differences by application site?

Study SP630 examined pharmacokinetics of rotigotine 18 mg upon multiple dosing in young and elderly men and women when applied to the 6 different proposed application sites. However due to insufficient numbers of subjects in each group and differing application sites on the day before sampling, no conclusions on the effect of applicaton site can be reached from this study. In contrast, SP626, a single dose BE study of 3 application sites showed that **none of the sites were bioequivalent**, and the exposure when applied to the arm was approximately 25% higher than when applied to the abdomen, and was approximately 40% higher when applied to the thigh compared to the abdomen.

Are there pharmacokinetics differences by gender?

Study SP630 examined pharmacokinetics of rotigotine 18 mg upon multiple dosing in young and elderly men and women when applied to the 6 different proposed application sites. However due to insufficient numbers of subjects in each group and differing application sites on the day before sampling, no conclusions on the effect of gender can be reached from this study. In contrast, study SP717 and SP718 in Caucasian and Japanese suggest that there may be higher exposures in women, which may possibly be due to weight.

Do rotigotine's pharmacokinetics change with age?

Study SP630 examined pharmacokinetics of rotigotine 18 mg upon multiple dosing in young and elderly men and women when applied to the 6 different proposed application sites. However due to insufficient numbers of subjects in each group and differing application sites on the day before sampling, no conclusions on the effect of age can be reached from this study. In addition, only 3 subjects were greater than 80 years of age and the old elderly, (i.e. > 85 years old), could have different skin characteristics resulting in differing absorption characteristics. However, when applied to the abdomen it appears that there may be increasing absorption with age.

What are the pharmacokinetic characteristics in children?

Rotigotine's pharmacokinetics has not been studied in children.

Are there pharmacokinetics differences by Race or Ethnicity?

There was no indication that the single dose pharmacokinetics of rotigotine differ between Blacks and Caucasians, or Japanese and Caucasians.

What are the population pharmacokinetics of rotigotine?

Population pharmacokinetics based on 24 hour concentrations was examined in the two pivotal phase III studies. Due to the highly variable absorption characteristics from the patch and the lack of appropriately timed samples the population pharmacokinetics cannot be considered reliable. In addition, the sponsor inappropriately fixed the lag time and absorption rate and excluded a large fraction of the samples due to their being greater than a certain percentage from previous values or from the mean. This also makes the population pharmacokinetic estimates suspect. As the data was not presented in an easily reconstituted format even description statistics were not calculated by the reviewer.

What is is metabolic profile of rotigotine?

Rotigotine is directly conjugated 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 any of the oxidative primary or secondary metabolites can potentially be conjugated to 5-O or 6-O sulfates or glucuronides.

The elimination of the despropyl-catechol and the thienyl-ethanol has not been described. However, the thienyl-ethanol could be oxidized, conjugated, and undergo S-oxidation.

How are Rotigotine and its' metabolites eliminated from the body?

After application of a radiolabeled rotigotine transdermal system 70% of the absorbed radiolabeled dose is recovered in urine and 20% is recovered in feces for an average recovery of 90%. No identification of eliminated species was performed in this study.

In the pivotal bioequivalence study urinary recovery over 48 hours of unconjugated rotigotine was 0.1%, 23% for total rotigitone, 5% for total despropyl rotigotine, and 2% for total desthienyl-rotigotine, with approximately 70% of the dose unaccounted for.

After IV dosing 22% of the dose is recovered the urine as rotigotine, 9% as rotigotine glucuronide, 13.5% as rotigotine sulfate, 1% as despropyl-rotigotine glucuronide, and 8% as despropyl-rotigotine sulfate, with another 23% of the dose recovered in feces as unidentified species. Thus the remaining 29% of the dose was unaccounted for, and the eliminated species was only identified for 54%of the dose.

Are there any stability problems with rotigotine, and if so are there any potential clinical issues?

Rotigotine is [redacted] This raises the question whether any of these are formed *in vivo* and if so if they are formed in sufficient quantities to cause problems as the [redacted] may be toxic and the [redacted] could also be potentially problematic.

What are the relative exposures to rotigotine metabolites relative to rotigotine?

Relative exposures to rotigotine and its' metabolites was determined from pooled plasma samples after IV administration of radiolabeled rotigotine. Relative Cmaxs and AUCs were similar for most measured metabolites. For rotigotine sulfate the exposure was approximately 3 fold higher, for Despropyl sulfate 20% higher, for total desthienyl conjugates, approximately 30 – 40% lower, and for rotigotine glucuronide approximately 20% to 44% lower. However, approximately 50% - 55% of the circulating radioactivity remains unidentified.

What is the receptor and transporter binding of rotigotine and its metabolites?

Except for binding to multiple dopamine receptors 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 of rotigotine. Of these only desthienyl-rotigotine appeared to inhibit D_3 and D_5 receptors at similar concentrations to rotigotine. However, the *in vivo* concentrations of desthienyl-rotigotine are below the level of quantitation, making the clinical significance of this metabolite uncertain.

What enzymes and transporters are involved in rotogotines disposition?

The primary isozymes responsible for rotigotine metabolism by appear to be CYP1A2 and 3A4 for both the despropyl and desthienyl metabolites, and 2C19 for these as well as for the catechol. Although these results are not totally consistent with the results of inhibition experiments performed with pooled human microsomes. Extrapolation of these observations to clinical dosing may not be appropriate as clinical doses are in the 3 – 30 nM/L range compared to 70 mM in the experiments. Thus metabolism by certain

isozymes may not be observed at the lower concentrations achieved clinically. No effects on pGP nor were binding to other transporters observed.

Clinically 1A2 is induced by tobacco, dietary indoles and polyaromatic hydrocarbons, and 2C19 is genetically polymorphic.

Does rotigotine induce or inhibit any of these or other disposition pathways?

There was no evidence of any induction or inhibition *in vitro*, for 1A2, 2C9, 2C19, 2D6, and 3A4.

What is rotigotine's protein binding and the effects of changes in protein binding?

Rotigotine is 89% protein bound to albumin at a concentration of 62.5 ng/ml. Thus no protein binding interactions are expected with albumin. However, rotigotine is cationic and no protein binding studies were performed with α1-acid glycoprotein.

What are the pharmacokinetic / pharmacodynamic characteristics of Rotigotine TDS?

Pharmacokinetics and Pharmacodynamics of rotigotine were examined in numerous studies. Unfortunately they were not examined in a rigorous manner.

Pilot intravenous studies seemed to indicate that pharmacologically active concentrations for Parkinson's Disease were in the range of 0.25 – 1.5 ng/ml. The phase II fixed dose study tends to support a concentration response relationship. Although there was a the lack of clinical difference between the 13.5 mg and the 18 mg doses in the phase II fixed dose ranging study this may or may not be due to reaching a plateau in the dose response instead it may be explainable by lack of separation in concentrations for these doses, although additional work would be needed to evaluate this.

Some data is evaluable to assess the relationships between rotigotine concentrations and somnolence, effects on dopamine dependent hormone concentrations, nausea and vomiting, and intraocular pressures. However, due to limited time these relationships could not be reviewed. If there is another review cycle these relationships may be examined.

Pharmacodynamic studies with continuous intravenous infusions indicate that diskinesias are due related to concentration and are not related to pulsatile delivery.

What was the PK/PD relationship of rotigotine to QTc?

In spite of performing a full PK profile at a steady-state dose of 18 mg, with simultaneous 12 ECG measurements, the sponsor did not report the results. Instead the sponsor only reported C24 concentrations and holter measurements from surrounding days. This raises the question of why the primary variables were not reported. Another QTc study with a positive control and using higher doses is currently being planned.

What is the effect of renal insufficiency on rotigotine?

There was no effect of any degree of renal impairment, (including ESRD), on rotigotine pharmacokinetics. With respect to total-rotigotine, with mild or moderate renal impairment, (ClCr 50 – 79 ml/min and 30 – 49 ml/ min respectively), there were no observable changes in pharmacokinetics. However, in severe renal impairment (ClCr < 30 ml/min) exposures doubled. The effect of renal impairment on other metabolites was not measured, although as known metabolites are formed via metabolism and are secondarily conjugated prior to renal elimination, it seems that with at least moderate renal function or better, (i.e. ClCr $\geq$ 30 ml/min), no dosage adjustment is indicated. With more severe renal impairment the effects of accumulation of conjugates cannot be predicted.

What is the effect of hepatic insufficiency on rotigotine?

In subjects with moderate hepatic impairment, (Child-Pugh Class B), there were no observable changes in rotigotine pharmacokinetics compared to healthy volunteers. However, nonrenal clearance of rotigotine conjugates was decreased and exposures to these conjugates were increased by approximately 40%, effects on other metabolites were not examined. The clinical implications of these changes are unknown.

What are the results of the drug / drug interactions studies?

Three drug /drug interaction studies were performed:

- Rotigotine 9 mg / 20 cm^2 and Cimetidine 400 mg q12h
- Rotigotine 9 mg / 20 cm^2 and Carbidopa / Levodopa 50/200 qd
- Rotigotine 4.5 mg / 10 cm^2 and Domperidone 10 mg tid

There was no evidence of an effect of this regimen of cimetidine on rotigotine pharmacokinetics and interactions at higher rotigotine doses would be even less likely. Although the effect on cimetidine was not examined cimetidine is largely renally eliminated and has a very high therapeutic index so clinically significant effects on cimetidine are not expected.

No interaction was detected between rotigotine and either carbidopa and levodopa. However the dose of rotigotine was low and would not adequately 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 we cannot extrapolate these conclusions to doses of CD/LD used in, or doses of rotigotine that might be used in Advanced Parkinson's Disease. In addition, at these doses carbidopa is considered subtherapeutic and the AE profile observed in this study is unlikely to reflect the situation in clinical practice.

There was no evidence of an effect of domperidone on rotigotine. Unfortunately the domperidone dose was below the maximum recommended dose of 20 mg q4h for nausea and vomiting in Parkinson's Disease. However, as both drugs were used at ¼ of their maximum daily dosage (MDD), no interaction is expected when both drugs are used at their MDD. Even if an interaction would occur at the 4.5 mg dose, exposures might still be below that achieved with an 18 mg dose. It is noteworthy that one subject experienced syncope during the study.

What are the adhesion characteristics of Rotigotine TDS?

Formal dedicated adhesion studies with the rotigotine patch were not performed. A number of studies did assess adhesion however most of these studies did not use a sensitive adhesion scale, and evaluated adhesion under ideal conditions, i.e. the smallest patch size, short duration, and possibly inpatient studies.

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), [redacted], 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%-10% of patches and greater than 25% lift in about 5% 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.

What are the effects of bathing, exercise, clothing, skin treatments, etc. on the adhesion characteristics of Rotigotine TDS?

The effects of bathing, exercise, tight clothing, skin treatments, and other factors on the adhesion of rotigotine TDS was not examined, however, due to the poor adhesive properties observed a conservative approach should be taken with any factor that might adversely affect adhesion.

What is the dermal tolerability and sensitization potential of Rotigotine TDS?

Two studies SP629 and SP673 examined the sensitizing potential of tiny 2.5 cm^2 and 5 cm^2 patches. When 5 cm^2 patches were applied repeatedly to the same site for 3 weeks the degree of irritancy approached the same levels as seen with a positive control and significant erythema and even edema was observed. When the 2.5 cm^2 patch was applied three times weekly for 3 weeks followed by a rechallenge period, 5% of placebo group exhibited sensitization, and 6.8% of the rotigotine group exhibitied sensitization. This may indicate that the patch excipients are sensitizing possibly in addition to the API and sensitization may be more common when the larger therapeutically used patch sizes are used.

With the largest patch 18 mg / 40 cm^2 administered . 42.5% of applications developed erythema over 6 days, and 0.4% exhibited edema and papules. Approximately 20% developed glazing, and 0.4% also had cracked skin in addition to glazing, 12.3% also experience other site reactions, primarily consisting of itching. In the pivotal phase III study SP513 that went up to a dose of 18 mg 8% of subjects discontinued treatment due to dermal site reactions.

With single applications of the 4.5 mg / 10 cm^2 patch 50% to 100% of subjects experienced slight redness, 18% -43% experienced marginal edema, and 5% - 33% experienced slight edema, i.e elevated skin.

In conclusion this appears to be a product that produces significant irritation and may potentially be sensitizing.

What is the rotigotine transdermal delivery rate from Rotigotine TDS?

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 delivery rates 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. 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, (44.4% of labeled content).

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.

What other factors might effect bioavailability and rate of drug delivery?

Although the influence of other factors such as inflamed skin, and heat application on the bioavailability of rotigotine was not examined these factors typically increase absorption rate and bioavailability from transdermal systems up to several fold. Certain skin treatments containing permeation enhancers might also affect absorption. In addition, Consequently, labeling should

Are the proposed dissolution method, specifications, and acceptance criteria acceptable?

The proposed dissolution method, is acceptable, however the specifications and acceptance criteria need to be modified.

The sponsor's proposed specifications were in milligrams rather than percent of the labeled content, and were unacceptably wide. The acceptance criteria were not sufficiently specific as they did not reference the specific edition of the USP/NF.

For the To-Be-Marketed product the dissolution at each time point was very tight with coefficients of variation typically <1%. Consequently, the typical specification range of ± — may be excessively wide and may not detect changes in the manufacturing process or clinically significant changes in dissolution. However, the differences in mean dissolution between the CTF batch and the pilot TBM batch used in the pivotal BE study was 21.5% at 0.5 hours, and 28.8% different at 1 hour,

APPEARS THIS WAY
ON ORIGINAL

2.7 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Date**

Senior Reviewer
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

Raman Baweja, Ph.D. **Date**

Team Leader
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Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Meeting:

Date:	Tuesday, February 21, 2006
Time:	2:30 PM – 3:30 PM
Location:	White Oak Building 21 Room 1539
Level:	Required Inter-Divisional
Attendees:	KavanaghR, BawejaR, RahmanA, MehtaM, HuntJ, SelenA, LazorJ, HuangS, SahajwallaC, KatzR, FeeneyJ, StoneM, KapcalaL, ColangeloP, ReynoldsK, ZhengJ, ChilukuriD

CC: NDA 21-829 edr
HFD-120 (KatzR, FeeneyJ, RancoosinJ, StoneM, KapcalaL, WhealousT, FriedL, RoneyP, ClaffeyD)
HFD-860 (KavanaghR, YasudaS, TandonV, UppoorR, BawejaR, MehtaM)

3 DETAILED REVIEW

3.1 Chemistry

3.1.1 Drug Substance

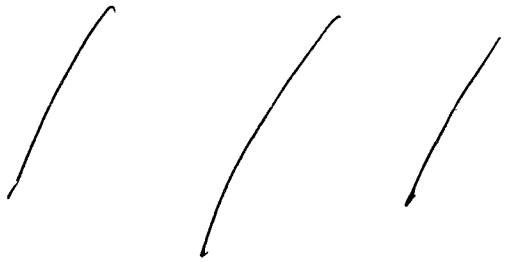
3.1.1.1 Description

Rotigotine is the levorotary S-(-) enantiomer of an amino-tetraline compound.

3.1.1.2 Structural Formula

Rotigotine has the following structural formula, (see Figure 1):

Figure 1



3.1.1.3 Molecular Formula

The molecular formula is: $C_{19}H_{25}NOS$

3.1.1.4 Molecular Mass

The molecular mass is: 315.48

3.1.1.5 Manufacturer – Drug Substance

3.1.1.6 Nomenclature

3.1.1.6.1 Non-Proprietary Names

International Non-Proprietary Name (INN): Rotigotine
United Stated Adopted Name (USAN): Rotigotine

3.1.1.6.2 Chemical Names

(6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol (IUPAC)
(S)-6-[propyl(2-thiophen-2-yl-ethyl)-amino]-5,6,7,8-tetrahydro-naphthalen-1-ol
(S)-(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthalenol

3.1.1.6.3 CAS Registry Number

[99755-59-6]

3.1.1.6.4 Sponsor's Laboratory Codes

SPM 962
N-0923

3.1.1.7 Physico-chemical Properties

3.1.1.7.1 Appearance

Rotigotine is a white to off-white powder.

3.1.1.7.2 Crystalline Structure and Polymorphism

[redacted]

3.1.1.7.3 pKa

pKa's based on titration in water / methanol solution is shown below:

pKa 1 (acidic phenolic hydroxy group) = [redacted]
pKa 2 (basic amino group) = [redacted]

1 Page(s) Withheld

√ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

3.1.1.7.5 Physical / Chemical Stability

Proposed degradation pathways are shown in Figure 2. This raises the question whether any of these are formed *in vivo* and if so in sufficient quantities to cause problems as the [redacted] may be toxic and the [redacted] could also be potentiall problematic.

Figure 2 Degradation Pathways

3.1.2 Drug Product

3.1.2.1 Description

Rotigotine patch is a matrix-type transdermal system consisting of the following three main components:

1. Backing Film (BF): Flexible beige to light brown color
2. Silicone Drug Matrix (DM): Self adhesive, drug-loaded
3. Protective foil (PF): Release liner

3.1.2.2 Strengths

The composition per patch unit area is identical for all dose strengths, (0.45 mg / cm^2). Thus the strength is determined by the patch size.

The strengths proposed for marketing are shown in Table 6.

Table 6 Proposed To-Be-Marketed Strengths

Rotigotine Content (mg Free Base)	Patch Size (cm^2)
4.5	10
9.0	20
13.5	30

3.1.2.3 Qualitative / Quantitative Composition

The following table, (Table 7), describes the quantitative composition of the patches.

Table 7 Qualitative / Quantitative Composition of Pivotal Clinical Trial / To-Be-Marketed (CTF/TBM) Formulation

Component Material	Weight (mg)[b] (10 cm²)	(20 cm²)	(30 cm²)	—	% (w/w)	Function	Reference to standards
Rotigotine	4.50	9.00	13.50	—	—	Active ingredient	In-house standard
Silicone adhesive							
Povidone							USP
Sodium metabisulfite							USP/NF
Ascorbyl palmitate							USP/NF
Vitamin E							USP
Backing foil aluminized, color coated							
	—	—	—	—	—		
	—	—	—	—	—		
	—	—	—	—	—		
	—	—	—	—	—		
Total Weight	50.0	100.0	150.0		100.0	—	—

3.1.3 Primary Packaging

3.1.3.1 Backing Film

The backing film is a flexible foil composed of , polyester) , aluminized and color coated. The sequence of the layers and the corresponding manufacturers of each part are shown in Table 8:

Table 8 Component Layers of Backing Film

Layer	Supplier	DMF

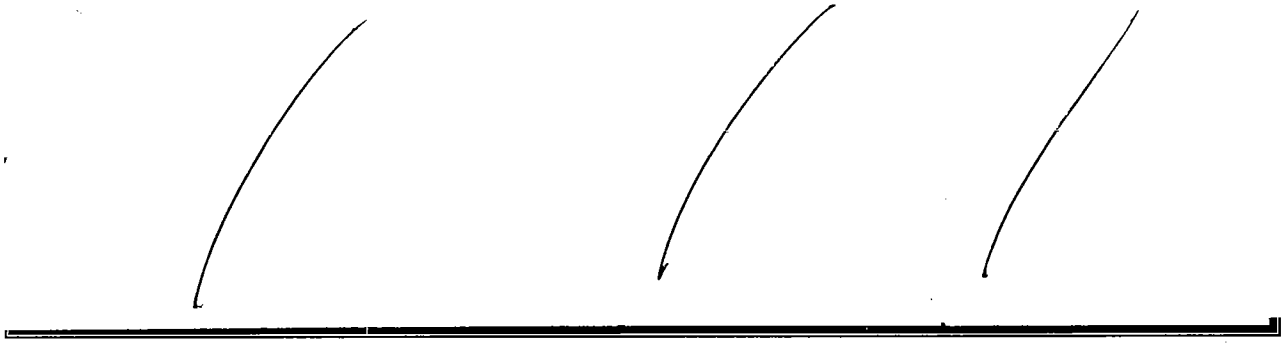
3.1.3.2 Protective foil (release liner)

The protective foil covers the drug containing matrix and is removed prior to application. It is composed of a transparent polyester foil and is coated with a fluoropolymer on the side that comes into contact with the matrix.

3.1.3.3 Pouch

Each patch is sealed within a pouch (sachet). and are shown in Table 9.

Table 9 Composition of Pouches Used for Primary Packaging



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3.1.4 Physicochemical Characteristics

3.1.4.1 Dissolution

See §3.9.2 on page 174.

3.1.4.2 Stability

Rotigotine is [redacted] during long term storage.

The primary packaged product must be stored at room temperature.

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3.1.5 Clinical Trial Formulations

3.1.5.1 Intravenous Formulations

In the I.V. studies N-0923/001-2601, 002-01, and 006-01 performed by [redacted] a solution of [redacted] in sterile water for injection was used.

The solution was supplied in 5 ml ampoules.

3.1.5.2 Transdermal Patch Formulations

3.1.5.2.1 Overview of Development Formulations

Four patch formulations were used during the clinical development program, (i.e. phase I to III studies), see Table 16.

Table 16 Summary of Transdermal Formulations Used in Clinical Trials

OCPB Formulation Code	Sponsor's Code / terminology	API	Adhesive	Use	Comment
Formulation 1	Prototype [redacted]			Used in 2 formulation development studies	
Formulation 2	Prototype [redacted]			Used in 2 formulation development studies	
Formulation 3	'phase II' formulation	Rotigotine	Silicone	Used in SD PK, MD PK, and initial phase II study	Compositionally identical. only difference from formulation 3 is the change in the manufacturing process
Formulation 4 CTF/TBM	'phase III' or 'Final' formulation	Rotigotine	Silicone	Used in all other phase I, II, and III studies.	

The silicone 'phase II' formulation (formulation 3) was chosen for further development based on the *in vivo* data of study SP502 (see Table 21 Summary of Rotigotine TDS Study Designs on page 48).

The final pivotal clinical trial / to-be-marketed (CTF/TBM) formulation, (formulation 4) is compositionally identical to formulation 3. The differences between these formulations are due to changes in the manufacturing process.

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3.1.5.2.1.3 *Formulation 3 – Phase II Formulation*

The studies SP502, SP503, SP506, SP511, SP540, and SP591 were performed with the following patch formulation:

Table 19 Formulation 3 - (Sponsor's Phase 2-Formulation)

Name of Ingredient	mg / 10 cm² patch	mg / 20 cm² patch
Rotigotine	4.50	9.00
Silicone adhesive		
Povidone		
Sodium metabisulfite		
Ascorbyl palmitate		
(vitamin E, DL-α-Tocopherol)		

3.1.5.2.1.4 *Formulation 4 – Final (CTF/TBM) Formulation*

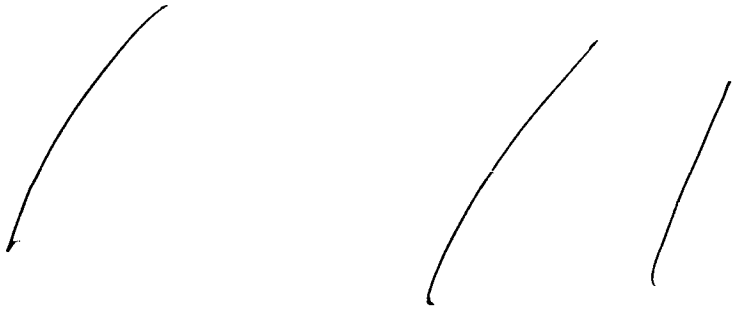
As mentioned previously the qualitative/quantitative composition is identical to formulation 3 shown in Table 19 above.

The qualitative / quantitative composition for all 4 proposed strengths along with the function of each ingredient, the reference standard, and the % composition for this formulation may be found in Table 7 on Page 32.

The production process uses a

The final manufacturing process of rotigotine patch can be divided into the steps below and are partially outlined in Figure 3,

3.1.5.2.1.5 *Differences in the Manufacturing Process between Formulation 3 – ('Phase II' Formulation) and Formulation 4 – Final (CTF/TBM) Formulation*



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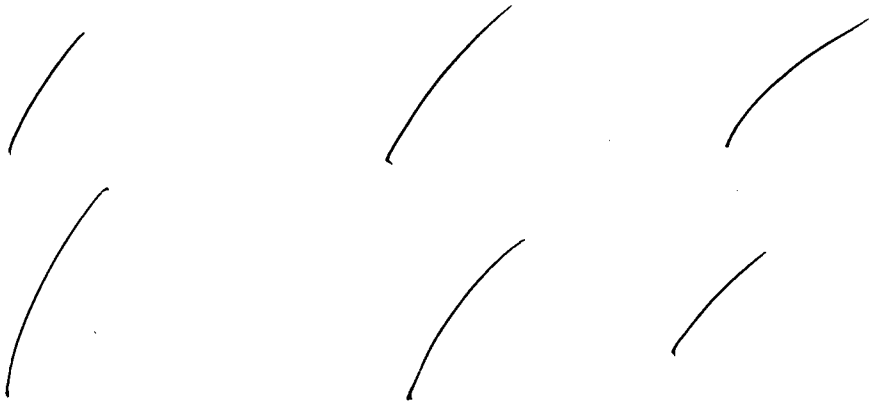

According to the sponsor:

"The pharmaceutical quality of patches produced according to both procedures is comparable. A slight difference was only observed in the 3 hours dissolution test (see section P.2.2 Pharmaceutical Development - Drug Product). Batches manufactured on a technical scale according to both procedures were compared in a bioequivalence study and found to be bioequivalent (see section P.2.2 Pharmaceutical Development - Drug Product). Therefore patches manufactured according to the improved phase 3 and final procedure and patches manufactured according to the — . phase 2 procedure are equivalent and adequately characterized."

3.1.6 Batches Used in Clinical Trials

An overview of selected batches used in clinical trials performed by Schwarz is given in Table 100 on page 179 at the end of section §3.9.2 Dissolution. The batches were either packaged in — pouches

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3.2 Clinical Studies

Organizing a logical presentation of the sponsor's clinical studies was exceptionally difficult.

A number of studies were labeled with multiple different study numbers, especially the early studies. Many studies had multiple parts which really could be considered totally separate studies. In addition a number of studies had multiple amendments, which for a number of studies were total redesigns that were undertaken in the middle of conducting the studies. Formulation, dosage, application site, undertaking multiple objectives in a single study, and [redacted] added to the complexity in trying to understand and construct a logical organization. In addition, there were a number of integrated study reports of multiple studies, (e.g. drug delivery, Pop PK, and cardiac PK/PD), that also were included in the submission.

Table 21 on the following pages attempts to present a logical overview of the clinical studies and should be referred to frequently when reading this review.

This table groups studies by their major objectives as follows:

- Initial Exploratory PK/PD Proof of Concept Studies
- Formulation Development
- Mass Balance Studies
- Initial SD PK with Final Patch Composition
- Intrinsic Factors
- Extrinsic Factors
- Clinical Pharmacology Studies
- Pivotal Bioequivalence Study
- Phase II Patient PD and PK/PD
- Pivotal Phase III Efficacy and Population PK Studies
- Phase III Long Term Safety Studies
- Other Trial Reports – Restless Legs Syndrome and Advanced Parkinson's Disease

The table gives the 'SP coded study number' and a brief description of the study design but the major focus is on the formulation composition, API, total daily dosage, dosage strengths used, dosing, application site, 'frequency' of administration, and duration of treatment.

Colored text is used in Table 21 to highlight various aspects of the information presented in the table.

Green text is used to indicate use of the initial prototype formulation that was used in only 2 studies.

Royal Blue text is used to indicate use of an [redacted]ased formulation that was used in only 3 studies.

Orange text is used to indicate use the 'Phase II' formulation. This formulation is compositionally identical to the final to-be-marketed (TBM) formulation. It only differs from the TBM formulation in the manufacturing methods used. The 'Phase II' formulation was used in 4 studies: a SD PK/BA study, a MD PK study, a phase II trial, and a pilot study in advance Parkinson's Disease.

Red text is primarily used to indicate the final clinical trial / to-be-marketed formulation. (CTF/TBM). It is also used to highlight aspects of the study that are consistent with the proposed dosage and administration.

Pink text is used to indicate CTF/TBM patches using radiolabeled rotigotine.

Purple text is used to highlight especially noteworthy aspects of the protocol.

Light Blue text is used to indicate formulation dosages, or dosage and administration, that is different than those proposed for mild to moderate Parkinson's Disease, e.g. these may be more appropriate for Restless Legs Syndrome or Advanced Parkinson's Disease. Or that may not be directly applicable to clinical use.

Light Green background is used to highlight pivotal BE, Phase II, and Phase III efficacy studies. Population PK may have also been performed for some of these studies.

Taken together the information in Table 21 summarizes much of the applicability of the studies to actual clinical usage.

In addition, to Table 21 there are a number of similarly laid out tables in this review, particularly in the appendix that were created to help understand the and compare the various studies and their designs. Although these tables are included in the review for completeness, some of the tables may not be complete, there may be mistakes, and footnotes from the sponsor may have been left in that are not applicable to these tables. These tables should be identifiable as they deal primarily with study designs.

Table 21 Summary of Rotigotine TDS Study Designs

Study Design & Dosage Regimen Table												
Study No.	Study Design	Rx Arm	Formulation*	API	TDD (nominal)	Strengths	Dosing	Application Site / Route	Frequency	Duration of Treatment	Washout (WO)	Comments
Initial Exploratory PK/PD Proof of Concept Studies												
SP803	2 Phase, DB, PBO Ctrld, Seq RMD, Ph II, PK/PD Study in pxts with Hoehn & Yahr Stage II – IV Parkinson's Disease	Phase A	IV 1 mg/ml in SWI (3 ml) secondarily diluted in D_5W 100 – 500 ml				Initial: QD or BID RD of 1 – 300 mcg/kg in 50 ml D5W / 10 min (6-1800 mcg/kg/hr) x up to 14 days Amend II: BID RD of 1, 2, 4, 8, 16, 24, 32, 42, 56, 78 mcg/kg for 1st subject. BID RD of 1, 2, 4, 8, 16, 32 mcg/kg bid then qd RD, dosages TBD Amend IV: Phase B 1st with Phase A optional due to AEs with rapid infusions			Interperiod WO 7 days On LD/CD until day before Rx. Must agree to be off Rx for up to 2 wks for each phase.	Amend II: to be infused while supine due to ↓BP Amend III: Do not need to be supine for Phase B:
		Phase B					Initial: RD 80 – 400 mcg/kg in 100 ml D_5W / 4 hr (20 – 100 mcg/kg/hr) qd until MTD achieved, dosing to increase over 2 weeks Amend II: Duration based on modeling from phase A and will be max of 6 x t1/2 or 4 hrs Amend IV: Phase B to be administered first then Phase A Optional due to AEs					
SP804	2 Phase DB, PBO Ctrld Seq RMD, Ph II, PK/PD Study in pxts with mild to moderate Hoehn & Yahr Stage II-IV Parkinson's Disease	Day 1	IV 1 mg/ml in SWI (3 ml) secondarily diluted in D_5W 100 – 500 ml				0.5, 1, 2, 4, 6, 8, 10 mg/kg / 0.5 hr sequentially until MTD (1-20 mcg/kg/hr) 1 hr WO then active dose repeated			1.5 days except with selegiline (MAOI)	MDD 31.5 mcg/kg bur & 10 Max allowed is 75 mcg/kg/day
		Day 2					LD: Active and best tolerated dose from day 1 over 30 min MD: CIVI at 35% dose x 4 hr rate may be inc to maintain effect					Calc max dose per protocol 38 mcg/kg, but MDD allowed is 75 mcg/kg
SP805	2 Phase DB, PBO Ctrld Seq RMD, Ph II, PK/PD Study in pxts with Hoehn & Yahr Stage III – IV Parkinson's Disease	A	Rotigotine / 'optimal dose' IV 1 mg/ml in SWI (3 ml) secondarily diluted in D_5W 100 – 500 ml				1, 2, 4, 6, 8, 12, 15 mcg/kg / 0.5 hr sequentially until MTD. (2 - 30 mcg/kg/hr)			0.5 days	MD 30 mcg/kg/hr	
		B					Then CIVI at 35% MTD then titrated at investigator's discretion to optimize. x 7 days Max rate 30 mcg/kg/hr					
Formulation Development												

Study Design & Dosage Regimen Table

Study No.	Study Design	Rx Arm	Formulation[a]	API	TDD (nominal)	Strengths	Dosing	Application Site / Route	Frequency	Duration of Treatment	Washout (WO)	Comments
Mass Balance Studies												
SP610	OL, Rand, 2-Way XO, Absolute BA, metabolism and excretion study of ^{14}C-SPM 962 in healthy male volunteers		IV	[^{14}C]-SPM 962 & (0.6 mg or each) SA ~50%	1.2 mg	1.2 mg / 480 ml 0.9% NaCl	1.2 mg / 12 hr	IV site not mentioned	SD	12 hours	2 wk IP WO	0.1 mg / 40 ml / hr
			Silicone patch CTF / Phase II Form 3	Rotigotine	4.5 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	Upper abdomen below lowest rib	SD	24 hours		
SP606	OL SD Absorption and excretion of ^{14}C-SPM 962 in healthy volunteers			Rotigotine 4.5 mg / 10 cm^2 (0.015 mg [^{14}C]-SPM 962)	4.5 mg	4.5 mg / 10 cm^2 (0.015 mg [^{14}C]-SPM 962)	1 x 4.5 mg / 10 cm^2	Contralateral Forearm	SD	24 hours		
Healthy Subject PK and Initial Tolerability Trial Reports												
	See SP 581 pivotal BE study below											
SP503	OL, placebo run-in, un-rand, MD, S/T, PK study in healthy volunteers		Silicone patch CTF / Phase II Form 3	Rotigotine	PBO 4.5 mg	0 mg / 10 cm^2 4.5 mg / 10 cm^2	1 x 0 mg / 10 cm^2 1 x 4.5 mg / 10 cm^2	Alternating sides of the medio-axillar region of the trunk	MD	24 hours x 2 days 24 hours x 14 days		
Intrinsic Factors												
SP630	OL, MD, rand, PK/PD (ECG) study of an 18 mg dose in pxts with early stage idiopathic Parkinson's dz N.B. This is a M/F and young vs. Elderly study in 24/24 M/F and 24/24 Yng/Eld		?	Rotigotine	PBO 4.5 mg 9.0 mg 13.5 mg 18.0 mg	PBO 4.5 mg / 10 cm^2 9.0 mg / 20 cm^2 13.5 mg/ 30 cm^2	PBO 1 x 4.5 mg / 10 cm^2 1 x 9.0 mg / 20 cm^2 1 x 13.5 mg / 30 cm^2 2 x 9 mg /20 cm^2	6 Rotating sites on the skin of subjects abdomen, flank, upper arm, shoulder, thigh, hip	MD	4.5mg qd x 6 days 9.0 mg qd x 6 days 13.5 mg qd x 6 days 18.0 mg qd x 12 days 13.5 mg qd x 2 days 9.0 mg qd x 2 days 4.5mg qd x 2 days		
SP596	OL, SD, 2-arm parallel design PK study to Evaluate relative BA and PK in healthy age and weight matched male Caucasian and Black subjects		Silicone patch CTF / Phase II Form 3	Rotigotine	4.5mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	Ventral Corpus (Abdomen)	SD	24 hours		
SP717	OL, 2-arm parallel group SD PK & S/T study in healthy age and weight matched Japanese and Caucasian vols		Silicone patch CTF / TBM Form 4	Rotigotine	4.5 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	ventral/lateral abdomen.	SD	24 hours		
SP718	OL, 2-arm parallel group MRD PK & S/T study in healthy Japanese and Caucasian vols		Silicone patch CTF / TBM Form 4	Rotigotine	2.25 mg 4.5 mg 9.0 mg	2.25 mg / 5 cm^2 4.5 mg / 10 cm^2 9.0 mg / 20 cm^2	1 x 2.25 mg / 5 cm^2 1 x 4.5 mg / 10 cm^2 1 x 9.0 mg / 20 cm^2	ventral/lateral abdomen	MD	2.25 mg / 5 cm^2 x 3 days 4.5mg / 10 cm^2 x 3 days 9.0mg / 20 cm^2 x 3 days		
SP671	OL, 2-arm parallel group MD PK & S/T study in nl male vols and		Silicone patch CTF / TBM	Rotigotine	4.5 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	Fore axillary line of the side of the	MD	3 days		Started in 1 country then

Study Design & Dosage Regimen Table												
Study No.	Study Design	Rx Arm	Formulation*	API	TDD (nominal)	Strengths	Dosing	Application Site / Route	Frequency	Duration of Treatment	Washout (WO)	Comments
	subjects with moderate hepatic impairment		Form 4					abdomen				switched due to irregularities
SP672	OL 5-arm parallel group SD PK& S/T study in nl male & female vols and subjects with mild, moderate, severe, or End Stage Renal Disease (<15 ml/min) n = 8 per grp		Silicone patch CTF / TBM Form 4	Rotigotine	4.5 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	ventral/lateral abdomen. areas	SD	24 hours		
SP626	OL, SD, 3-way X-over rel. BA study of various application sites in healthy male vols	A B C	Silicone patch Phase II Form 3	Rotigotine	4.5 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	A Ventral Abdomen B Ventral Upper Arm C Ventral / lateral upper leg	SD	24 hours	7 days	
Extrinsic Factors												
SP627	OL, MD, Rand 2-way X-over PK DDI study of rotigotine TDS in the presence and absence of cimetidine in healthy volunteers	A B	Silicone patch Phase II Form 3	Rotigotine Rotigotine & Cimetidine	4.5 mg 9.0 mg 4.5 mg 9.0 mg 800 mg	4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2 2 x 4.5 mg / 10 cm^2 1 x 4.5 mg / 10 cm^2 2 x 4.5 mg / 10 cm^2	ventral abdomen	MD	4.5 mg x 2 days 2 x 4.5 mg (9 mg) x 4 days 4.5 mg x 2 days 2 x 4.5mg (9 mg) x 4 days & cimetidine 400 mg q 12h x 7 days		IP WO ?
SP628	OL, 2-arm, parallel-group, MD PK DDI study of of rotigotine CDS and levodopa/carbidopa in patients with idiopathic RLS	A B	Silicone patch CTF / TBM Form 4	Rotigotine & CD/LD 25/100	4.5 mg 9.0 mg	4.5 mg / 10 cm^2 9.0 mg / 20 cm^2	1 x 4.5 mg / 10 cm^2 1 x 9.0 mg / 20 cm^2	Alternating sides ventral abdomen	MD	Grp A Days 1 - 3:4.5 mg / 10 cm^2 qd Days 4 - 9:9.0 mg / 20 cm^2 qd Days 7 - 12:CB/LD 25/100 B Grp B Days 1 - 8: CB/LD 25/10 Days 3- 5: 4.5 mg / 10 c Days 6 - 11: 9.0 mg / 20 c		IP WO ?
SP670	OL, MD, Rand 2-way X-over PK DDI study of rotigotine TDS in the presence and absence of domperidone in young healthy male volunteers	A B	Silicone patch CTF / TBM Form 4	Rotigotine Rotigotine & Domperidone po	4.5 mg 4.5 mg 30 mg	4.5mg / 10 cm^2	1 x 4.5 mg / 10 cm^2	fore axillary line of the side of the abdomen.	MD	4.5 mg qd x 4 day 4.5 mg qd x 4 days +domperidone 10 mg tid x 5 days	7 days	
Clinical Pharmacology Studies												
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites) in healthy volunteers No PK		Silicone patch CTF / TBM Form 4	Rotigotine	0 mg 1.125 mg	0 mg / 2.5 cm^2 1.125 mg / 2.5 cm^2	1 x 2.5 cm^2 PBO patch qd to the same site x 21 days 1 x 1.125 mg / 2.5 cm^2qd to the same site x 21 days 1 x 1.125 mg / 2.5 cm^2qd to rotating sites x 21 days 200 µl 0.9% NaCl in 2.5 cm^2 chamber x 21 days (- ctrl) 200 µl 0.1% SLS in 2.5 cm^2 chamber x 21 days (+ ctrl)		MD (23+/- 1 hours)	21 days		+ and - controls of SLS 0.1% and 0.9% NaCl are each applied to same site each day
SP673	Sensitization potential in healthy volunteers No PK		Silicone patch CTF / TBM Form 4	Rotigotine/	0 mg 1.125 mg	0 mg / 2.5 cm^2 1.125 mg / 2.5 cm^2	1 x 2.5 cm^2 PBO patch qd to the same site x 21 days 1 x 1.125 mg / 2.5 cm^2qd to the same site x 21 days 1 x 1.125 mg / 2.5 cm^2 x 48 hours		MD SD x 48 hr	3 weeks 48 hours	14 day IP WO	Sensitization phase, followed by WO (rest) phase, followed by rechallenge
Pivotal Bioequivalence Study												
SP581	OL, SD 2-way X-over BE study of two different batches of Silicone patches in healthy volunteers		Silicone patch CTF / TBM Form 4 Silicone patch Phase II	Rotigotine	4.5 mg	Test: 4.5 mg / 10 cm^2 NDO754 Ref: 4.5 mg / 10 cm^2	1 x 4.5 mg / 10 cm^2 1 x 4.5 mg / 10 cm^2	Fore axillary line of the chest	SD	24 hours	7 day IP WO	T: WE11249 7/31/00 4//14/00'Final' R: WE11114 12/31/01 1/22/00 'Phase III'

Study Design & Dosage Regimen Table												
Study No.	Study Design	Rx Arm	Formulation[a]	API	TDD (nominal)	Strengths	Dosing	Application Site / Route	Frequency	Duration of Treatment	Washout (WO)	Comments
			Form 3			NDA51						QQ same Process different
Patient PD and PK/PD												
Patient PK and Initial Tolerability Trial Reports by Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, (SP533, and SP591 – Advanced PD).												
SP534 Part 1	Ph II, DB, PBO Ctrld, 4-Arm Parallel Group Fixed Dose, Dose Ranging PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease Doesn't appear to be truly blinded as dose assignment and doses are sequential		Silicone patch Phase II Form 3	Rotigotine	9 mg 18 mg 27 mg 36 mg	9 mg / 20 cm²	9 mg (1 x 20 cm²) or PBO 18 mg (2 x 20 cm²) or PBO 27 mg (3 x 20 cm²) or PBO 36 mg (4 x 20 cm²) or PBO	upper abdomen (above the umbilicus)	MD	PBO run in: 1 wk Patch Tolerance: 4 days on then 3 days off Maintanence: 3 weeks FU: 4 weeks Each arm will have subjs 5:1 Active:PBO		Dosage doesn't make sense unless there're different Inconsistent some say 10 cm² some say 20 cm² some say higher dose some say lower conc's
SP534 Part 2	Evaluate safety and tolerability of dose escalation		Silicone patch Phase II Form 3	Ibid.	Ibid.	Ibid.	Ibid.		MD			
SP535	Ph II, Rand DB, PBO Ctrld 2-Arm RMD Dose escalation PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease		Silicone patch Phase II Form 3	Rotigotine	4.5 mg 9.0 mg 13.5 mg 18 mg	0 mg / 10 cm² 0 mg / 20 cm² 4.5 mg / 10 cm² 9 mg / 20 cm²	4.5 mg (1 x 4.5 mg / 10 cm² + 2 x 20 cm² PBO) 9.0 mg (1 x 10 cm² PBO + 1 x 20 cm² PBO + 1 x 9.0 mg / 20 cm²) 13.5 mg (1 x 4.5 mg / 10 cm² + 1 x 9.0 mg / 20 cm² + 1 x 20 cm² PBO) 18.0 mg (1 x 10 cm² PBO + 2 x 9.0 mg / 20 cm²) (3 patches total each week: 1 x 10 cm² & 2 x 20 cm²)	upper abdomen (above the umbilicus) alternating sides	MD	Day -7 to 1: Placebo qd Day 1–7: 4.5 mg (10 cm²) qd Day 8–14: 9.0 mg (20 cm²) qd Day 15–21: 13.5 mg (30 cm²) qd Day 22–28: 18.0 mg (40 cm²) qd		Subjects 4:1 Drug: PBO
SP540	Single Blind, uncontrolled, fixed escalating dose Phase II Exploratory Safety and Efficacy Study To explore a slower titration scheme (4.5 mg qweek instead of qod)		Silicone patch Phase II Form 3	Rotigotine maximum tolerated dose up to 18.0 mg / Silicone patch	4.5 mg 9.0 mg 13.5 mg 18 mg	4.5 mg / 10 cm² 9.0 mg / 20 cm²	4.5 mg (1 x 4.5 mg / 10 cm²) 9.0 mg (1 x 9.0 mg/ 20 cm²) 13.5 mg (1 x 4.5 mg / 10 cm² & 1 x 9.0 mg / 20 cm²) 18.0 mg (2 x 9.0 mg / 20 cm²)	Upper abdomen	MD	Increase by 4.5 mg weekly Total Duration: 28 days		
SP506	Ph II, Rand, DB, PBO Ctrld 12 week 2-Arm RMD Dose escalation PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease		Silicone patch Phase II Form 3	Rotigotine	4.5 mg 9.0 mg 13.5 mg 18 mg	0 mg / 10 cm² 4.5 mg / 10 cm²	4.5 mg (1 x 4.5 mg / 10 cm² + 3 x 10 cm² PBO) 9.0 mg (2 x 4.5 mg / 10 cm² + 2 x 10 cm² PBO) 13.5 mg (3 x 4.5 mg / 10 cm² + 1 x 10 cm² PBO) 18 mg (4 x 4.5 mg / 10 cm²)	**upper abdomen (above the umbilicus)**	MD	4 week dose esc. to a randomized target dose of 4.5, 9.0, 13.5, or 18.0 mg rotigotine or placebo, then 7 weeks maintenance, followed by 1 week de-escalation and 2 wk FU for 12 wks total		
Pivotal Phase III Efficacy and Population PK Studies												
SP512 Part I	Ph III, Rand, DB, PBO Ctrl 2-Arm parallel grp, Titrated Dose Efficacy & safety trial PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease Evaluate efficacy, safety, and PK compared to placebo		Silicone patch CTF / TSM Form 4	Rotigotine	4.5 mg 9.0 mg 13.5 mg	PBO 4.5 mg / 10 cm² 9.0 mg / 20 cm² 13.5 mg / 30 cm²	PBO 1 x 4.5 mg / 10 cm² 1 x 9.0 mg / 20 cm² 1 x 13.5 mg / 30 cm²	Right or left side of following areas: upper or lower abdomen (above the umbilicus), thigh, hip, flank, shoulder, and / or upper arm	MD	Initial dose of 4.5mg/day with weekly increases of 4.5mg/day to a maximum target dose of 13.5mg/day. Then 24 wks Maint phase Rx 27 weeks Upon w/d decescalated dose by 10 ^{cm2} q2days		

Study Design & Dosage Regimen Table												
Study No.	**Study Design**	**Rx Arm**	**Formulation[a]**	**API**	**TDD (nominal)**	**Strengths**	**Dosing**	**Application Site / Route**	**Frequency**	**Duration of Treatment**	**Washout (WO)**	**Comments**
SP813 Part I	Ph III, Rand, DB, PBO & ropinirole Ctrld Double Dummy 3-Arm parallel grp. Titrated Dose Efficacy & safety trial PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease Evaluate efficacy safety, and PK of rotigotine compared to placebo and ropinirole	B	Silicone patch CTF / TBM Form 4	Rotigotine	4.5 mg 9.0 mg 13.5 mg 18 mg	4.5 mg / 10 cm^2 9.0 mg / 20 cm^2 13.5 mg / 30 cm^2	1 x 4.5 mg / 10 cm^2 1 x 9.0 mg / 20 cm^2 1 x 13.5 mg / 30 cm^2 2 x 9.0 mg / 20 cm^2	Right or left side of following areas upper or lower abdomen (above the umbilicus), thigh, hip, flank, shoulder, and / or upper arm	MD	Dose esc up to 13 weeks. maint 24 weeks 12 day deescalation. (Total duration 39 weeks)		Arm A is PBO
		C	Roprinirole	Ropinirole encapsulated tablets	0.75 mg - 24 mg per day	Capsule strengths: 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg and 5.0 mg	Ropinirole doses included: 0.75, 1.5, 2.25, 3.0, 4.5, 6.0, 7.5, 9.0, 12.0, 15.0, 18.0, 21.0 or 24.0 mg / day In 3 divided doses with meals (0.25 mg – 8 mg / dose)					
Uncontrolled Clinical Trials (Phase III Long Term Safety)												
SP812 Part IId (SP702)	Evaluate long-term safety Retritrated over 3 weeks		Silicone patch CTF / TBM Form 4	Rotigotine	Year 1: up to 18 mg; Years 2-4: up to 36.0mg	4.5 mg / 10 cm^2 9.0 mg / 20 cm^2 13.5 mg / 30 cm^2 18.0 mg / 40 cm^2	4.5 mg (1 x 4.5 mg / 10 cm^2) 9.0 mg (1 x 9.0 mg / 20 cm^2) 13.5 mg (1 x 13.5 mg / 30 cm^2) 18 mg (1 x 18 mg / 40 cm^2 or 2 x 9 mg / 20 cm^2) 22.5 mg (1 x 9 mg / 20 cm^2 + 1 x 13.5 mg / 30 cm^2) 27 mg (2 x 13.5 mg / 30 cm^2) 31.5 mg (13.5 mg / 30 cm^2+ 18 mg / 40 cm^2) 36.0 mg (2 x 18.0 mg / 40 cm^2)		MD	up to 4 years		Higher doses allowed for worsening disease
SP813 Part IId (SP716)	Evaluate long-term safety		Silicone patch CTF / TBM Form 4	ibid	ibid	Idid.	ibid		MD	up to 4 years		Higher doses allowed for worsening disease
Other Trial Reports – Restless Legs Syndrome and Advanced Parkinson's Disease												
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease			Rotigotine	9.0 mg to —				MD	28 days		
SP511	Assess dose groups of rotigotine in subjects with advanced Parkinson's disease		Silicone patch Phase II Form 3	Rotigotine	9.0mg, 18.0mg, 27.0 mg				MD	3 months		
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease		Silicone patch CTF / TBM Form 4	Rotigotine	18.0 mg and 27.0 mg				MD	up to 38 weeks		
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's disease		Silicone patch CTF / TBM Form 4	Rotigotine	Up to 27.0 mg				MD	Up to 4 years		
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease		Silicone patch Phase II Form 3	Rotigotine	Up to —				MD	12 weeks		
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS			Rotigotine	1.125mg, 2.25 mg, 4.5 mg				MD	1 week		
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS			Rotigotine	1.125 mg, 2.25 mg, 4.5 mg,				MD	7 weeks		

Study Design & Dosage Regimen Table												
Study No.	Study Design	Rx Arm	Formulation[a]	API	TDD (nominal)	Strengths	Dosing	Application Site / Route	Frequency	Duration of Treatment	Washout (WO)	Comments
		[redacted]			6.75 mg,							

a Formulation 3 and Formulation 4 have the same qualitative / quantitative composition and only differ in there method of manufacture. (See §3.1.5.2.1.5for details)

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Additional information on study designs may be found in Appendix 1 - Study D.

This appendix includes the following tables:

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3.3 Submission Amendments

Table 22 Summary of Amendments to NDA

Submission Number	Letter Date	EDR Date	Submission Code	Description
001	5/25/05	5/27/05	C	Labeling Pharm Tox CRFs 120 day safety update
002	6/23/05	6/24/05	BZ	Labeling Drug Sub Clin Response to Requests for Data Anal 512 and 513
003	7/29/05	7/29/05	BM	Response to OCPB request for data files for clinical studies.
004	8/9/05	8/9/05	BC	Response to CMC Request re: Impurities in Drug Substance
005	9/2/05	9/2/05	BM	? Delete AEs
006	9/6/05	9/9/05	BM	Response to Req re: incomplete information re: 120 day safety update
007	**9/13/05**	**9/15/05**	**BM**	**Response to Req PK/PD Data for ECG Study SP591 Response to Req re: SAS Codes**
008	9/23/05	9/23/05	AM	Additional infor re: req for safety infor.
009	9/29/05	9/29/05	BC	Response to CMC Req.
010		10/6/05	BC	Response to CMC Req re: Drug Product
011		10/31/05	BM	Response to Req re: Database for possible Malignant Melanomas
012		11/9/05	BM	Response to Req re: Subgroup Analysis by Age in Pivotal Phase III Studies
013		12/15/05	BM	Response to Req re: Treatment Emergent Malignancies
014		12/22/05	BM	Response to Req re: AEs & Dose Response
015		1/5/06	BC	Response to Req re: stability data
016		1/26/06	BM	Response to Req re: compulsive behaviors
017		1/30/06	BZ	Labeling as Word Document

3.4 Submission Quality

The following is a list of comments reflecting the submission quality made while conducting the review.

Can't find protocol numbers, sometimes one set of numbers is used for a protocol and other times a dfferent numbering system is used for the same protocol.

Hyperlinks take you to the wrong place. It's unclear if this is due to the FDA or the sponsor.

Formulation differences are unclear.

Scanned images provided instead of alphanumeric data.

There are multiple places & numbers for protocols especially for the Phase III studies so it's difficult to know if you've already reviewed something or missed it.

Labeling was provided with line numbering that couldn't be removed making editing difficult

No subanalysis of subjects by gender was performed when the data was available.

No information was provided on isomeric interconversion.

Half-lives were reported as 1 hour while the semilog plots revealed half-lives of 7 – 8 hours.

Early PK PD study protocols were so poorly written that dosage mistakes are highly probable.

Descriptions of dosing were inconsistent within protocols such that dosing could not be determined. This was repeatedly noted in various protocols.

Studies were not performed with the highest strength patch.

More than one study is refered to as protocol 0923-002, i.e. both studies SP800 and SP804.

For study SP800 the inclusion criteria is subjects from study SP804.

Intravenous studies SP803 and SP804 performed at the NIH in Chevy Chase, MD were especially poor. For example there were multiple protocol amendments before starting the protocol. Monitoring was not specified in the protocol. Then in the clinical study report it was reported as every 2 minutes.

The protocol summary for SP804 is the same as for SP803. The wrong drug is stated in the CRF ie loading dose is stated with buprenox rather than rotigotine. The IV bag is not blinded and the dose escalation is improper such that the protocol isn't actually blinded. In addition no dyskinesia scale was included in the protocol even though one objective is to evaluate dyskinesias.

Figures are illegible as scanned. Spelling mistakes were common in the protocol, e.g. DEW for D_5W.
Multiple dose admininistration is not blinded, only the rater is blinded.'
Study 803 presents data as image files of Excel spreadsheets.

The sponsor's definition of lag time is incorrect and gives a bias of approximately 2 hours shorter than the true lag time.

Assay method vaiidation is frequently incorrect as they threw out outliers and didn't provide raw data.

Assay method KA355 II for total rotigotine inappropriately threw out outliers.When outliers are included the variability is excessive.

Assay method KA-355-III Validation Study Report: Simultaneous Determination of Despropyl- and Desthienyl-SPM 962 in Human Urine by LC-MS/MS
ibid - many outliers CV goes from 30% - 40% to 50% to 100%.

Assay report MA036 / I (free rotigotine) incorrect calculation of bias and precision

Can't open folder for the urine enantiomer bioanalytic feasibility study

In the FDA review in the edr for phase III studies almost no links work except to the legacy report. Adobe acrobat tree links do not work, thus you have to go back to the table of contents.

Sponsor threw out a large fraction of PK data from the Phase III pop PK analysis as it would show the true variability.

Click on a link in Adobe Acrobat file and the tree structure closes and all folders collapse.

Some links open to acrobat files with tree structure. Some don't have a tree structure.

Not all drug product batches were listed for all studies.

QT data was not provided.

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

When open a file or click on link to a different section of the studies, the computer doesn't do anything for several seconds. Then it goes back to the edr. This has happened repeatedly.

The following list of comments was sorted by protocol. In some cases this illustrates how finding the way to get to study reports was by luck and varied on different attempts on different days.

SP503 had to drill down 19 levels to find information to go to another section then back up and down again, then repeated multiple times.

For SP 503 the mean, minimum, maximum and median were correctly calculated, but the Standard Deviation was approximately 30% off in every case even after checking for correct transcription of data.

SP503 for Tmax and Cmax on Day 14 the sponsor inappropriately excluded 0 hr data. Also there was no 18 hr sample, therefore can't identify the true Tmax and Cmax when Tmax occurs between 12- 24 hours. Pages are not labeled with Protocol Number, Page number etc... When printed can't figure out what protocol it belongs to.

SP506 Acrobat keeps closing when click on hyperlinks to go to another section.

SP506 also under link to study SP512

SP506 baseline UPDRS not reported so can't do PK/PD for change from baseline.

SP506 PK report was found under the informed consent subfolder.

Data listings for JMP files for SP506 instead contains data listing for SP512

SP506 under link to SP535

SP512 has no link directly to study report.

SP512 part II CRF for Subj 13001 found under Synopsis, Synopsis for SP513 Part II found under CRF folder for site 034. Study report can only be reached via from synopsis.

SP512 part II no link to study. There is a subfolder to study SP513 Part II but the link doesn't work. Only link to study page works to SP513 at II.

SP512 To get to SP512 part II have to go to list of studies.

Links to phase II and III trials bring you to the wrong studies.

Synopsis folder under the pivotal efficacy study SP512 only has a link to documentation of audits performed. Audit subfolder has link to a CRF. Same with the Randomization folder, and randomization link is under the investigator signature page link, list of sites folder has link to bioanalytic report. Consent Form has link to pop pk, Sample CRF, links to interlab standards, protocol link to statistical methods, and study report folder to investigator's signature page and bioanalysitic report. Individual data list subfolder has links to data listings for study 513.

SP513 has same link problems. Links tor individual subject data listing goes to studySP 512.

SAS transport files for pop PK data sometimes lists the study id factor as SP513 and sometimes as 513.

SP513 lacks many aspects from other studies e.g. sample handling.

SP513 part II CRFs contains data files and a study report for study SP540, although the link to it doesn't open. A link to a 'title page' in a different CRF folder does open SP540 but not SP513 part II.

SP513 part II no link to study.

SP515 – Study in Advanced Parkinsonism

SP534 – Part I CSR found. Reached when click on study report for study SP805.

SP534 Part I no link under folder. Have to go to list of studies at front of clinical study section.

SP534 Part I PK not in CSR but found in separate PK Study Report in appendices. Protocol amendment for SP534 Part I are actually the rewritten protocol SP534 Part II. In protocol to find PK refers to appendix.

SP534 part II (2) under link to SP534 part I (1)

SP534 Study SP 534 PK under Additional Appended Reports under Appendices

SP535 bioanalytical reports were found under case report form subfolders.

For studies such as SP535 when you click on the link under study synopsis subfolder it instead brings you to a single page file containing the investigator's signature page. You then need to open the tree structure for the whole study report to find the file that contains the synopsis.

SP535 is under link to SP534 part II (2), but if you click on signature page link under SP535 link it does open SP535.

Folder for SP535 has a subfolder for study SP506. However link under this subfolder doesn't work

SP540 completed in 1999. Only link in edr is under 120 day safety update, but this is only to AE data table. Could only find study report because the list of studies had a link to it.

SP540 folder only contains an AE data file.

Formulations used in study SP540 are inconsistent between tables and text.

SP581 sponsor excluded some values when they calculated summary statistics for an unknown reason. Sponsor claimed this was due to patch adhesion, but measured plasma concentrations don't seem to indicate a problem. When I calc ulated the kels the elimination rate constant was in most cases a good to very good fit. However, t1/2 was sometimes much longer and sometimes much shorter than indicated by the sponsor. Mean AUCinf decreased but the 2 groups' means were much closer

Folder to SP710 under Efficacy and Safety Studies opens subfolders to 7 new studies none or which are SP710

In study SP610's report there's one table with radioactivity PK metrics in the study report, but it doesn't indicate the treatment, i.e. IV or TDS and there's no information on metabolite or BA. Have to go to the appendix.

SP799 Confidence interval miscalc ulated and off by factor of 10.

SP803 No pk metrics reported in appendicies only raw data even though claimed in study report with units given. Raw data disorganized would take too much work to sort it out.

SP804 AUC ng.ml.min appears to have been calculated by multiplying ng/ml/hr *60 instead of dividing by 60.

SP804 PK metric miscalculated. Sponsor's valued don't match mine based on raw data include AUC CI etc. PK equations inoorrect, ie AUCinf = AUCt + Cplast/Cp.

Table 23 Example of a Search for PK Data in One Study

Levels										Comments
1	2	3	4	5	6	7	8	9	10	
		eCTD FDA Levels					*NDA Levels per FDA guidance*			
1	2	3	4	5	6	**1**	2	**3**	**4**	
						eCTD Section	Topic	SubTopic	Study Itself	
Intranet - Internet Explorer										
	EDR									
		NDA no.								
			View with FDAreview							
				FDA						
					Submission No					
						Clinical Study Reports				
							Reports of Human Pharmacokinetic Studies			
								Healthy Subject PK and Initial Tolerability Study Reports		
									MD Study Specialized Safety / Tolerability Studies	
							Reports of Biopharmaceutic Studies			
								Bioavailability Studies		
									Rotgotine TDS ADME Study	**Only total Radioactivity provided**
									Absolute BA and IV ADME Study	

Cumulative Number of Levels										
10	11	12	13	14	15	16	17	18	19	
NDA Level						Levels within Study Report				
4	1	2	3	4	5	6	7	8	9	**Comments**
Study itself										
Absolute BA & IV ADME Study										**Description of Contents or Sponsor's Instructions**
	Legacy Study Report									
		Title Page								
			List of Sections							
			Section 13 Tables and Figures.							
				13.1.10 Pharmacokinetic Data						
					PK metrics and data should be here or description with hyperlink to data and PK metrics					See Chapter 9.
			Section 9 Pharmacokinetic Results							Whole blood and plasma radioactivity ng equivalent and recovery information, however no route of administration information. 'See Appendix 14.1.15 for Pharmacokinetics.'

14 Appendices
14.1 Trial Information
14.1.15 Pharmacokinetic Reports
2 Pharmacokinetics — Describes PK metrics that are to be reported
Gives only mean data for only some of the metabolites with no other statistics

3 Pharmacokinetic Results - IV
4 Pharmacokinetic Results - TDS
4.2 Pharmacokinetic Results in Plasma — For Raw Data refer to analytical report'

5 Kinetica Reports — Calculation of mean PK metrics based on naïve pooled concentration vs. time data

14 Appendices
14.1 Trial Information
14.1.13 Bioanalytical Reports - part(s)
Analytical Report (Mass Balance)
3 Results
3.2 Assay Performance
3.2.7 Concentrations in Study Samples — Listing of dpms in each sample

14 Appendices
14.1 Trial Information
14.1.13 Bioanalytical Reports - part(s)
KA397-I Analytical Report - SPM 962 in Human Plasma (SP610)
5 Results
5.1 Study Samples — See Appendix 1
Appendix I Subject Samples Results — Raw Data only pg/ml
N.B. Some Appendices hundreds of pages long and need to be scrolled through to find data.

KA397-II Analytical Report - Unconjugated SPM 962 in Urine (SP610) — All data in this Report provided as image files.
KA397-III Analytical Report - Desalkylmetabolites in Urine free (SP610)
KA397-IV Analytical Report - Desalkylmetabolites in Urine (Total) (SP610)
KA397-V Analytical Report SPM 962 in Urine (Total) (SP610)
Bioanalytical Report (Identification of metabolites)

3.5 Pharmacodynamics

3.5.1 Exploratory Pharmacodynamics

3.5.1.1 Phase I – Proof of Concept IV PD and PK/PD Studies

The initial clinical studies with rotigotine were 3 proof-of-concept and dosing ranging studies conducted with intravenously administered rotigotine in patients with mild to severe Parkinson's Disease. A general outline of the study designs are shown in Table 24.

Table 24 Overview of Study Designs for Intravenous Proof-of-Concept / Dose Ranging Studies

SP #	Original Study Number	Subjects	Phase	Dosage
SP803	N-0923-001-2601	Male and Female Patients with mild to Severe Parkinson's Disease (H&Y Stages II – IV)	A	Single rising dose IV infusions administered over 10 minutes with two dosages administered daily for up to 14 days. Start at 1 mcg/kg doubling each dose.
			B	4 hour infusion or up to 6 x t ½ Range 80 – 400 minutes
SP804	N-0923-002-01	Elderly Male and Female Pxts with Parkinson's Disease	A	Single rising dose IV infusions of 0.5 - 10 mcg/kg infused over 30 minutes with dose increases each half hour until an active and tolerated dose is achieved. This is followed by a 1 hour washout then the 'active and tolerated' dose is repeated.
			B	The 'active and tolerated dose from phase A is given as a LD over 30 minutes followed by a MD at 35% of the infusion rate of the LD for 4 hours.
SP805	N-0923-006-01	Male and Female Patients with moderate to severe Parkinson's Disease (H&Y Stages III – IV)	A	Single rising dose IV infusions of 1 - 15 mcg/kg infused over 30 minutes with dose increases each half hour until a maximally tolerated dose is achieved.
			B	CIVI at 35% MTD then titrated at investigator's discretion to optimal effect for a total duration of 7 days. Max rate is 30 mcg/kg/hr

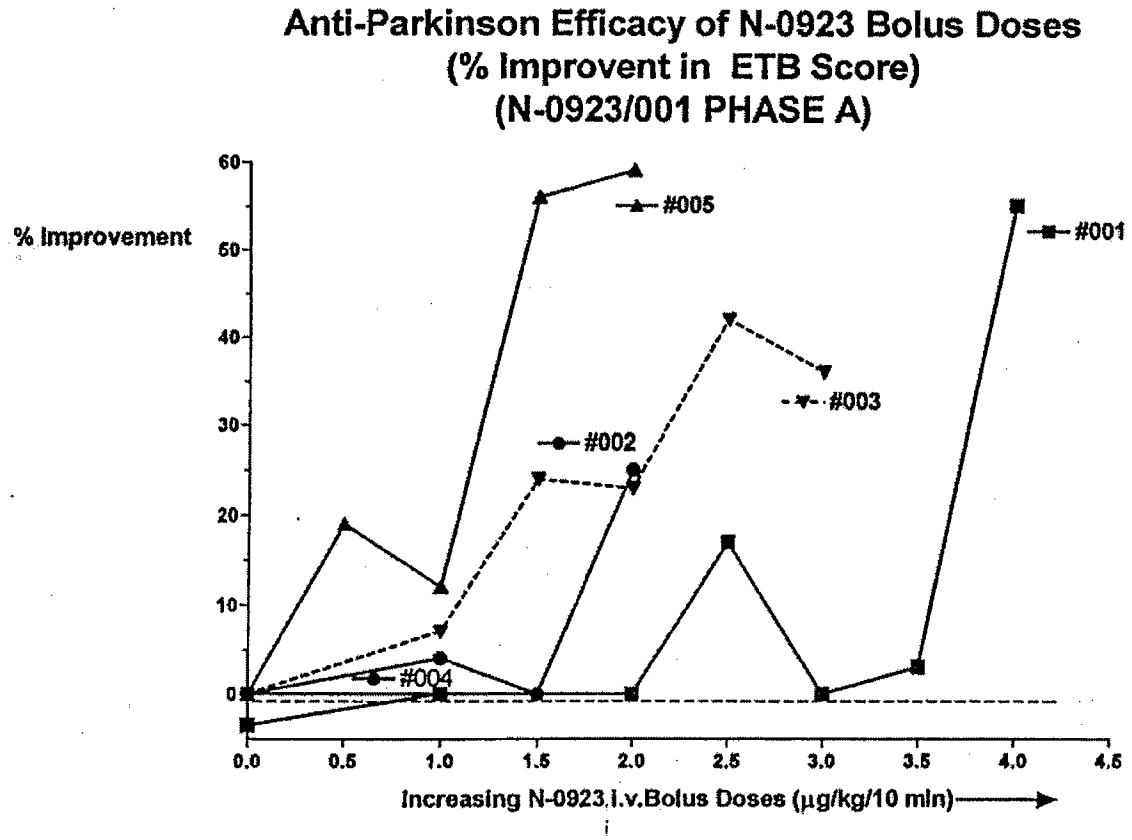
3.5.1.1.1 Study SP803

3.5.1.1.1.1 Study SP803 – Part A – 10 minute IV Infusion Dose vs. % Improvement in Modified Columbia Rating Scale

Study SP803 was the initial proof of concept study.

Figure 5 shows the % improvement in the Modified Columbia Rating Scale Score for Parkinson's Disease, (MCRS), by dosage rate in 4 patients given a 10 minute infusion in part A of study SP803.

Figure 5 10 minute IV Infusion Dose vs. % Improvement in Modified Columbia Rating Scale



From Figure 5 dosage rates required for a therapeutic effect varied from approximately 1 mcg/kg to 4 mcg/kg over 10 minutes.

Table 25 shows this range of infusion rates in varying units along with extended daily doses for a typical 75 kg adult. However, it should be remembered that steady-state could not have been reached in 10 minutes so the total daily dose is likely to be much less, and since the MCRS was measured after the infusion was terminated concentrations would be decreasing giving another reason to suppose the actual daily dose will be lower. Subject number 1 who received the 4 mcg/kg dose was the highest weight subject at 77 kg his extended dose would be 44.4 mg per day.

Table 25 Extended Infusion Rates and Daily Doses based on 10 minute IV Infusions

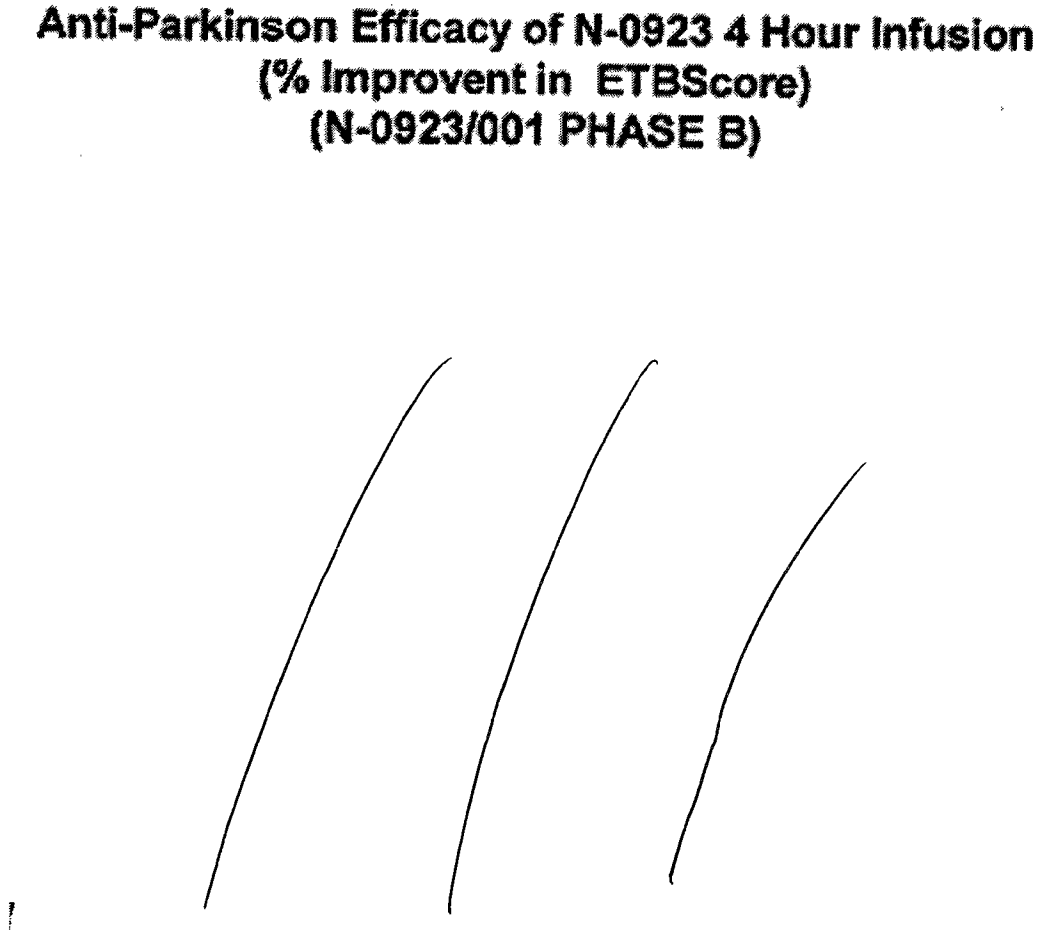
Infusion Rates				Extended Daily Dose for a 75 kg Adult (mg)[a]
mcg / kg/ 10 minutes	mcg / kg / hr	mcg / kg / 24 hours	mg / hr / 75 kg Adult	
1.0	6	144	0.45	10.8
4.0	24	576	1.8	43.2

a based on 10 minute infusions; true daily dosages are likely much lower.

3.5.1.1.1.2 Study SP803 – Part B – 4 Hour IV Infusion Dose vs. % Improvement in Modified Columbia Rating Scale

Figure 6 shows the % improvement in the Modified Columbia Rating Scale Score for Parkinson's Disease, (MCRS), by dosage rate in 7 patients given a 1 to 4 hours infusion in part B of study SP803.

Figure 6 Continuous IV Infusion Infusion Rate vs. % Improvement in Modified Columbia Rating Scale



From Figure 6 dosage rates required for a therapeutic effect varied from approximately 1 to 6 mcg/kg/hr, which is approximately ¼ to 1/6 of the extended dose rate from the 10 minute infusion in part A as shown in Table 25.

Table 26 shows this range of infusion rates in varying units along with extended daily doses for a typical 75 kg adult. As indicated in the previous section the new extended daily dose is lower. However, even with a 4 hour infusion steady state would not have been achieved and the true daily dose is likely to be even lower.

Table 26 Extended Infusion Rates and Daily Doses based on 10 minute IV Infusions

Infusion Rates			Extended Daily Dose for a 75 kg Adult (mg)[a]
mcg / kg / hr	mcg / kg / 24 hours	mcg / hr / 75 kg Adult	
1	24	75	1.8
6	144	450	10.8

a based on 1 – 4 hour infusions; true daily dosages are likely much lower.

Table 27 on the following page shows the pharmacokinetic metrics for 3 of the subject in part B of study 803.

In addition, Figure 7 of the concentration vs. time profiles when compared with the efficacy data in Figure 6 indicate that effective concentrations are in the range of approximately 250 – 1500 pg/ ml, (0.25 – 1.5 ng/ml), and when subject 5 who appears sensitive to drug effects is excluded the other 3 subjects had effective concentrations around 1 ng/ml.

It should be noted that the sponsor's calculated half-lives in Table 27 are around 2 hours, however inspection of semi-log plots shown in Figure 8 indicate the half-lives are much longer, and are more likely in a range of 7 – 8 hours.

Efficacy data by dose are shown for part B for a single subject, subject 10, in Figure 9. The sequence of plots not only shows a dose response for effect on MCRS in this individual, but also a dose response for a dyskinesia score at the 4 highest doses. Subjects 11 and 12 but no other subjects experienced dyskinesiae. This possibly indicates a narrow therapeutic window.

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Table 27 Sponsor's Calculated PK Metrics for Rotigotine when given over a 1 – 4 hour infusion - Study SP803 Part B

Subj	Age	Sex	Weight (kg)	H & Y Stage	Dose				Tmax (hrs)	Cmax (pg/ml)	AUCt (pg/ml x hr^{-1})	AUCinf		% extrap	t1/2 (hrs)	Cl		Vd	
					mcg/kg / hr	mcg/kg / 4 hrs	mcg	mg/24 hr				pg/ml x hr^{-1}	ng/ml x hr^{-1}			L/hr	L/hr/kg	L	L/kg
5	64	F	58.3	IV	1.25	5	291.5	1.75	3		1157.0	1304.2	1.304	11.3	2.02	22.4	0.38	20.5	0.35
10	57	M	72.7	II	6	24	1744.8	10.47	2		3508.3	3694.2	3.694	5.0	1.94	47.2	0.65	37.5	0.52
11	56	M	57.4	IV	7	28	1607.2	9.64	2		3327.5	3735.5	3.735	10.9	1.88	43.0	0.75	30.5	0.53
12	75	M	71.4	II	5	20	1428	8.57	—	—	—	—	—	—	—	—	—	—	—
	59.0 ± 4.4 (7.4) 56 - 64 [57]		62.8 ± 8.6 (13.7) 57.4 - 72.7 [58.3]		4.8 ± 3.1 (64.7) 1.25 - 7 [6]	19 ± 12.3 (64.7) 5 - 28 [24]	1214 ± 802 (66.1) 292 - 1745 [1607]	7.29 ± 4.81 (66.1) 1.75 - 10.47 [9.64]	2.3 ± 0.6 (24.7) 2 - 3 [2]	906 ± 547 (60.4) 298 - 1360 [1060]	2664 ± 1308 (49.1) 1157 - 3508 [3327]	2911 ± 1392 (47.8) 1304 - 3735 [3694]	2.9 ± 1.39 (47.8) 1.3 – 3.74 [3.69]	9.1 ± 3.5 (38.7) 5.0 - 11.3 [10.9]	1.9 ± 0.1 (3.7) 1.9 - 2.0 [1.9]	37.5 ± 13.3 (35.5) 22.4 - 47.2 [43.0]	0.6 ± 0.19 (31.9) 0.38 - 0.75 [0.65]	29.5 ± 8.6 (29.1) 20.5 - 37.5 [30.5]	0.47 ± 0.10 (21.5) 0.35 - 0.53 [0.52]

a n = 3 with PK data

Figure 7 Rotigotine Concentration vs Time Profiles when given as a 1 to 4 hour CIVI – Study SP803 – Part B

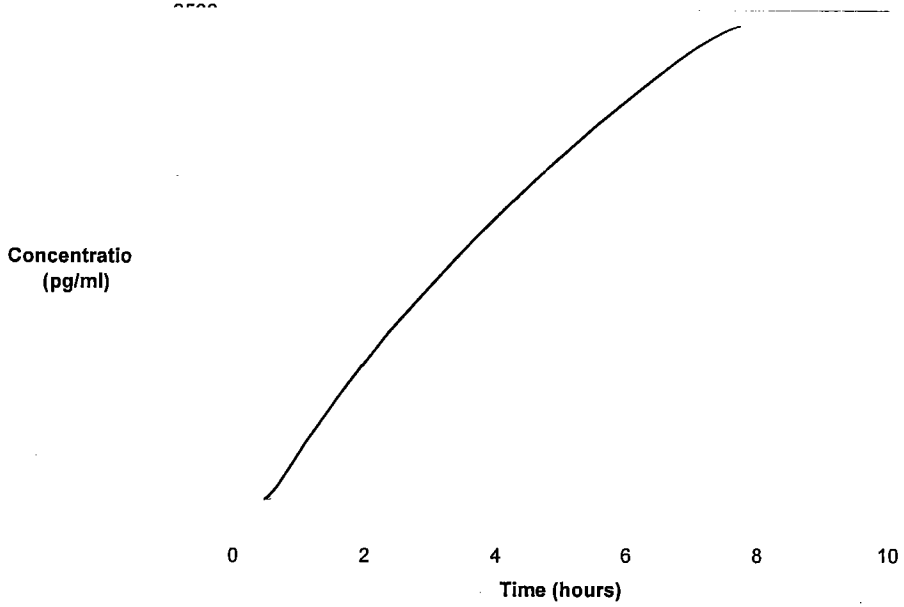
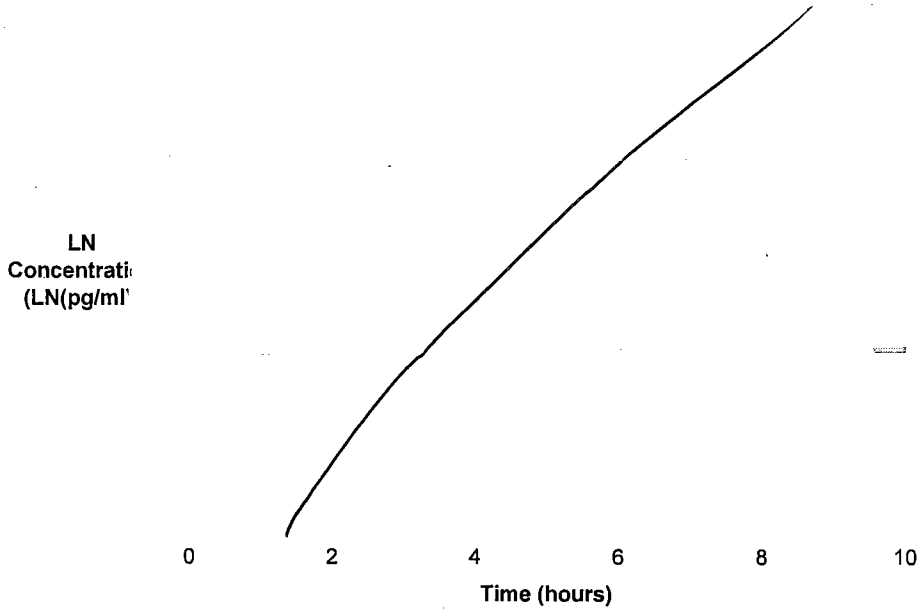


Figure 8 Rotigotine Semi-log Concentration vs Time Profiles when given as a 1 to 4 hour CIVI – Study SP803 – Part B



6 Page(s) Withheld

1 Trade Secret / Confidential

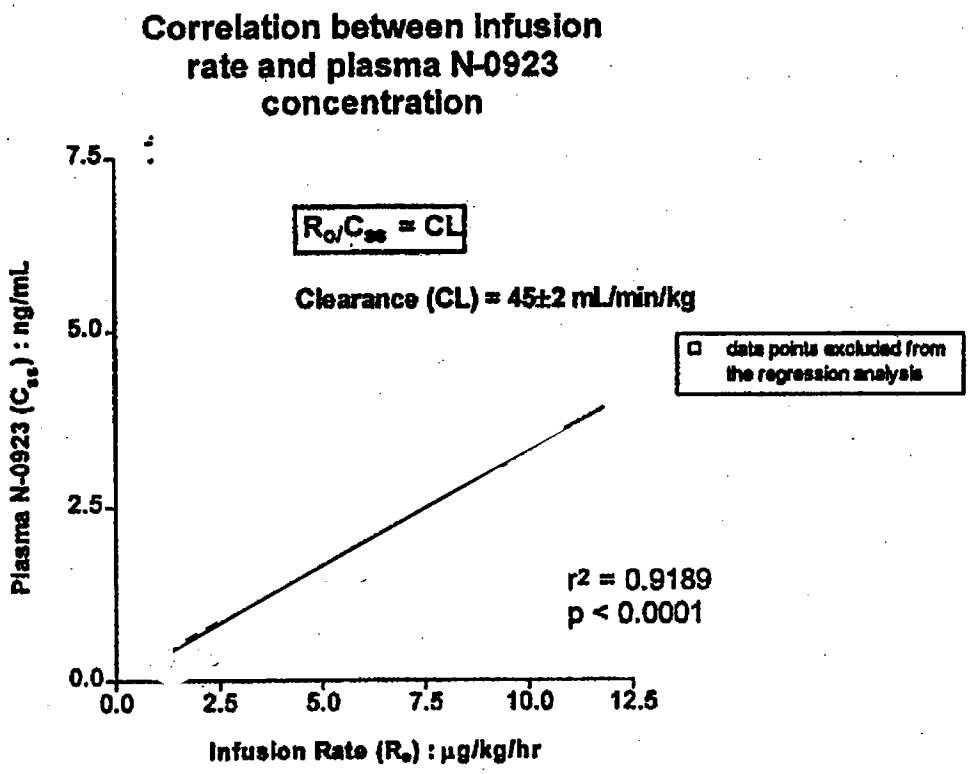
_____ Draft Labeling

_____ Deliberative Process

Figure 15 shows the sponsor's estimate of systemic clearance based on continuous IV infusion rates in study 805. This clearance estimate is somewhat suspect as it's likely that infusions were not at steady state and also as several outlying data points were excluded from the analysis. These 'outliers' would conceivably have low clearances and exceptionally high exposures. This data is from subjects 2 6 and 10 who had uncommonly short infusion durations. It's conceivable that the short infusion durations could be due to a lack of tolerability to the drug, although inspection of the AE data does not reveal anything unusual about subjects 6 or 10. Subject 2 did have a number of ECG findings, (see Figure 12).

Exclusion of outliers for no appropriate reason other than they're statistical outliers was a common theme throughout this submission.

Figure 15 Sponsor's Estimate of Rotigotine Systemic Clearance - Study SP805



3.5.2 Phase II Dose Titration Studies

3.5.2.1 Overview

Five phase II pilot efficacy studies in early Parkinson's Disease were conducted and are shown in Table 30. These include studies SP534 Part I, SP534 Part II, SP535, SP540, and SP506. The first 4 studies will each be discussed briefly as they were used as the basis for the dose titration scheme, which has bearing on the QT study design.

Study SP506 is a large fixed dose efficacy study with PK/PD information and will be discussed in the Pop PK section, §3.5.3 on page 82, along with the pivotal phase III efficacy studies SP512 and SP513.

3.5.2.2 Study SP534 Part I

Study SP534 was a sequential multiple rising dose study initially designed to evaluate whether a range of fixed doses of rotigotine could be administered without the need for a titration period. It was begun in April of 1999. Doses of 3 groups of 4 subjects were to receive rotigotine 9 mg, 13.5 mg, or 18 mg patches for 3 weeks. Each dosage level was administered sequentially with the completion of dosing of one dosage level before beginning administration to the next dosage level group.

Five subjects received the 9 mg dosage and 3 subjects received the 13.5 mg dosage before the study was stopped due to intolerable nausea and vomiting. The incidence of nausea and vomiting for each dosage group is shown in Table 28.

Table 28 Incidence of Nausea and Vomiting in Study SP534 Part I

Dose Level	Nausea	Vomiting	No of Subject with either Nausea or Vomiting
Placebo	—	1/5	1
9 mg	2/5	1/5	2
13.5 mg	3/5	1/5	3

The sponsor claims that employing a dose titration period may allow patients to acclimate to the effects of rotigotine on the chemoreceptor trigger zone and allow more subjects to reach higher doses. Although this is not clear from the data reviewed whether this is true or not.

Table 31 on page 77 shows all Treatment Emergent Adverse Events in Study SP534 Part I for each subject along with maximum concentrations and when they occurred.
What's clear from the PK data is that two subjects with experienced vomiting had especially high concentrations >0.7 ng/ml within several hours of applying the first patch. Other subjects achieved similar concentrations but until after several days of dosing.

3.5.2.3 Study SP534 Part II

After the 13.5 mg dosage group, a new trial design was implemented in Protocol Amendment 2 which changed the dosing schedule from a fixed dose design to using an escalating dose titration period, and this design was named SP534 Part II.

The titration period was begun with a lower dose, (4.5 mg / 10 cm^2), with titration steps of 4.5 mg at weekly intervals. This study design was implemented in August of 1999 with 8 subjects.

Table 32 on 79 shows a summary of treatment emergent adverse events by dose level in Study SP535 Part II. No vomiting was observed at the 18 mg dose level 2 subjects had GI complaints and 3-4 subjects had heart rated and rhythm disorders.

3.5.2.4 Study SP533

Although not reviewed, in May of 1999 between the conduct of SP 534 Part I and Part II the sponsor implemented a study in 10 patients with **Advanced Parkinson's Disease**, (Study SP533), using dosages of **9 mg to 36 mg** with titration steps **of 4.5 mg every 2 – 3 days**. It may be that data from this study might support the sponsor's contention that a slower titration schedule improves tolerability.

3.5.2.5 Study SP535

Study SP 535 was another small dose titration study in 8 subjects that used a beginning dose of 4.5 mg, with titration steps of 4.5 mg at weekly intervals up to 18 mg. No clear pattern of treatment emergent AEs with dose was observed, (see Table 33 on page 80), although subject number 710 was discontinued after achieving a dose of 18 mg due to a pattern of leukocytopenia and thrombocytopenia. However, hematology values from when rotigotine was discontinued indicate either that the leukopenia and thrombocytopenia was beginning to resolve or quickly resolved on discontinuation, (see Table 29 below).

Table 29 White Blood Cell and Platelet Counts in Subject 710 from Study SP535 by Treatment Day and Rotigotine Dose

Day	Day -6	Day 1	Day 8	Day 15	Day 17
Dose	Baseline	4.5 mg	9 mg	13.5 mg	13.5 mg
WBC	5.6	4.4	4.3	3.8	6.1
Plts	165	161	135	111	175
Comments					patch removed @ 5:30 PM

3.5.2.6 Study SP540

Study SP540 was a similar in design to studies SP534 Part II, and SP535, beginning with a dose of 4.5 mg and titrating up in weekly steps of 4.5 mg to a top dose of 18 mg. The primary difference is that study SP540 enrolled 31 subjects. One subject was discontinued the first week due to noncompliance and one subject was discontinued at a dose of 13.5 mg due to ventricular extrasystoles. Although incidence of nauseas or vomiting doesn't change much with dose, the severity of nausea does appear that it might be increasing with dose, (see Table 34 Treatment Emergent Adverse Events by Dose Level in Study SP540 on page 81).

Table 30 Summary of Study Designs and Dosing for Phase II Pilot Efficacy Studies

Study No.	Study Design	Arm	N Planned Rx/PBO	Dosing: Run in	Week 1	Week 2	Week 3	Week 4	Maint	Deescalation	Comments
SP534 Part 1	Ph II, DB, PBO Ctrld, Sequential 4-Arm Parallel Group Fixed Dose, Dose Ranging PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease	A	4/2	PBO Days -7 to -4 WO Days -3 to -1	9 mg or PBO				—	—	Doesn't appear to be truly blinded as dose assignment and doses are sequential
		B	4/2		18 mg or PBO				—	—	
		C	4/2		27 mg or PBO				—	—	
		D	4/2		36 mg or PBO				—	—	
SP534 Part 2	Ph II, Rand DB, PBO Ctrld 2-Arm Rising MD Dose PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease	—	10/2	PBO Days -7 to -1	9 mg or PBO	18 mg or PBO	27 mg or PBO	36 mg or PBO	—	—	Appears to be an identical design to study SP535
SP535	Ph II, Rand DB, PBO Ctrld 2-Arm Rising MD Dose escalation PK/PD S/T Study in pxts with 'early stage' Parkinson's Disease	—	10/2	PBO	4.5 mg	9.0 mg	13.5 mg	18.0 mg	—	—	(3 patches total each week: 1 x 10 cm^2 & 2 x 20 cm^2)
SP540	Ph II Non-Rand Single Blind, uncontrolled, fixed Rising MD Exploratory Safety and Efficacy Study To explore a slower titration scheme (4.5 mg qweek instead of qod)	—	31	Day –1 PBO Training	4.5 mg	9.0 mg	13.5 mg	18.0 mg	—	—	No PBO qod escalation appears to be done in advanced PD study that was not reviewed. Different In one location it states that single patches are used to make the total dose and in other locations multiple patches are used.
SP506	Ph II, Rand, DB, PBO Ctrld 12 week 5-Arm RMD Dose escalation and Fixed Treatment Dose PK/PD S/T, pilot efficacy Study in pxts with 'early stage' Parkinson's Disease			1 week	4 weeks				7 weeks	1 week	
		A	45	4 – 7 Day PBO Run in	4.5 mg				4.5 mg	Dose decreased qod	
		B	45		4.5 mg	9.0 mg			9.0 mg		
		C	45			9.0 mg	13.5 mg	13.5 mg	13.5 mg		
		D	45					18.0 mg	18.0 mg		
		E	45		PBO	PBO	PBO	PBO	PBO		

Table 31 Treatment Emergent Adverse Events in Study SP534 Part I

Rx Group:	Subject Number	Sex	Age (yrs)	Race	Weight (kg)	Body System	Preferred Term	Investigator Entry	Study Period,	DC	Cmax	Tmax
9.0 mg	101/501	Male	64	Caucasian	126	APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	DEFINITE ERYTHEMA AT PATCH REMOVAL SITE	Patch Tolerance		0.85	6
						Body as a whole	MALAISE					
						CARDIOVASCULAR DISORDERS	ARTERIAL BLOOD PRESS URE DECREASED	DECREASED BLOOD PRESSURE				
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
						GI	Nausea	Nausea				
							Vomiting	Vomiting				
						Psych	Sleepiness	Sleepiness				
						Resp	SOB					
						Skin	Diaphoresis	Diaphoresis				
	102/502	Male	74	Caucasian	67	APPLICATION SITE DISORDERS	APPLICATION SITE REA CTION	DEFINITE ERYTHEMA AT PATCH SITE			0.52	72
								Itching at patch site				
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
							TINGLING SKIN	LIPS TINGLING				
						GI	Nausea	Nausea				
						Neoplasms	Neoplasm NOS	Growth on Right Ear Removed				
						Psych	Sleepiness	Sleepiness				
						Vascular (Extra-cardiac) Disorders	Skin Flushed	Flushed				
	104/504	Male	78	Caucasian	78	APPLICATION SITE DISORDERS	APPLICATION SITE REA CTION	Minimal ERYTHEMA AT PATCH REMOVAL SITE			0.36	48
						CENTR & PERIPH NERV SYST DISORDERS	Marked Restlessness	Restlessness				
						Psych	Dreaming Abnormal	Vivid Dreaming				
	105/505	Female	74	Caucasian	95	APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	DEFINITE ERYTHEMA AT PATCH REMOVAL SITE			0.22	72
						Musculoskeletal	Arthritis Aggravated	Increased Arthritis Pain				
						BODY AS A WHOLE -GENERAL DISORDERS	FATIGUE	LACK OF ENERGY				
							FATIGUE	DECREASED ENERGY	Post-Treatment			
						CNS	BEWILDERMENT	UNSTEADINESS	Post-Treatment			
							DIZZINESS	DIZZINESS	Post-Treatment			
						PSYCHIATRIC DISORDERS	Thinking Slow	SLOWNESS	Post-Treatment			
	106/506	Female	69	Caucasian	64	APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	DEFINITE ERYTHEMA AT PATCH REMOVAL SITE			0.58	96
						BODY AS A WHOLE -GENERAL DISORDERS	FATIGUE	DECREASED ENERGY				
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
						GI	Abdominal Pain	Mid Abdominal Tenderness				
							Appetite Decreased	Loss of Appetite				
13.5 mg	107/507	Male	74	Caucasian	92	BODY AS A WHOLE -GENERAL DISORDERS	CRAMP ABDOMINAL	STOMACH CRAMPS			0.34	96
						VASCULAR (EXTRACARDIAC DISORDERS)	VASCULAR DISORDER	SIGNIFICANT ISCHEMIA				
						NOT CODABLE	NOT CODABLE	FALL	Post-Treatment			
						NOT CODABLE	NOT CODABLE	Abrasions Arms & Legs	Post-Treatment			
	109/508	Male	62	Caucasian	79	APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	DEFINITE ERYTHEMA AT PATCH REMOVAL SITE		DC	0.79	24
								MINIMAL ERYTHEMA AT PATCH REMOVAL SITE			0.73	9
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
						GI	Vomiting	Vomiting				
						GI Liver and Biliary	SGOT Inc	Elevated SGOT				
						SKIN AND APPENDAGES DISORDERS	DIAPHORESIS	DIAPHORESIS				
							Sweating Increased	SWEATY PALMS				
						GI	Nausea	Nausea				
	110/509	Male	72	Caucasian	82	APPLICATION SITE DISORDERS	APPLICATION SITE REA CTION	MINIMAL ERYTHEMA AT PATCH REMOVAL SITE			0.27	96
						SKIN AND APPENDAGES DISORDERS	DIAPHORESIS	DIAPHORESIS				
						NOT CODABLE	NOT CODABLE	EXCESS SALIVA				

Rx Group:	Subject Number	Sex	Age (yrs)	Race	Weight (kg)	Body System	Preferred Term	Investigator Entry	Study Period,	DC	Cmax	Tmax
13.5 mg	112/511	Male	83	Caucasian	102	APPLICATION SITE DISORDERS	APPLICATION SITE REA CTION	MINIMAL ERYTHEMA AT PATCH REMOVAL SITE		DC	0.5	72
						CARDIOVASCULAR DISORDERS GENERAL	HYPERTENSION	HYPERTENSION				
						CENTR & PERIPH NERV SYST DISORDER	DIZZINESS	DIZZINESS				
						GASTRO-INTESTIN AL SYSTEM DISORDERS	NAUSEA	NAUSEA				
						MUSCULO-SKELETAL SYSTEM DISORDERS	MUSCLE WEAKNESS	LEG WEAKNESS				
						PSYCHIATRIC DISORDERS	SOMNOLENCE	INCREASED SLEEPINESS				
	113/512	Male	65	Caucasian	82	APPLICATION SITE DISORDERS	APPLICATION SITE REACTION	MINIMAL ERYTHEMA AT PATCH REMOVAL SITE			0.8	48
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
						GASTRO-INTESTINAL SYSTEM DISORDERS	GASTROESOPHAGEAL REFLUX	ESOPHAGEAL REFLUX				
							NAUSEA	NAUSEA				
						MUSCULO-SKELETA L SYSTEM DISORDERS	BACK PAIN	BACK PAIN				
						PSYCHIATRIC DISORDERS	IRRITABILITY	IRRITABILITY				
							SOMNOLENCE	INCREASED SLEEPINESS				
						SKIN AND APPENDAGES DISORDERS	DIAPHORESIS	DIAPHORESIS				
						VISION DISORDERS	EYE PAIN	PAIN POST BILATERAL EYELID SURGERY				
PBO	103/503	Male	67	Caucasian	81	APPLICATION SITE DISORDERS CTION	APPLICATION SITE REACTION	MINIMAL ERYTHEMA AT PATCH REMOVAL SITE			—	
						CENTR & PERIPH NERV SYST DISORDERS	GAIT DISORDER	STOOPED GAIT	Post-Treatment			
						HEART RATE AND RHYTHM DISORDERS	TACHYCARDIA ATRIAL	INTERMITTENT ATRIAL TACHYCARDIA				
	111/510	Male	45	Other	92	APPLICATION SITE DISORDERS	APPLICATION SITE REA CTION	MINIMAL ERYTHEMA AT PATCH REMOVAL SITE			—	
						CENTR & PERIPH NERV SYST DISORDERS	HEADACHE	HEADACHE				
						GASTRO-INTESTIN AL SYSTEM DISORDERS	TOOTH ACHE	PAIN FROM TOOTH EXTRACTION				
							VOMITING	VOMITING				

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Table 32 Treatment Emergent Adverse Events by Dose Level in Study SP535 Part II (n = 8)

Body System	Preferred Term	Percent (%)				
		Dose Level (mg)				Total
		4.5	9	13.5	18.0	
Percent of subjects with at least one adverse event		62.5	75	75	71.4	100
APPLICATION SITE DISORDERS	Any	5	5	12.5	42.9	100
	APPLICATION SITE REACTION	5	5	12.5	42.9	100
SKIN AND APPENDAGES DISORDERS	Any			12.5		12.5
	DERMATITIS			12.5		12.5
GASTRO-INTESTINAL SYSTEM DISORDERS	Any		12.5	25		37.5
	NAUSEA		12.5	12.5		25
	CONSTIPATION			12.5		12.5
	DIARRHOEA		12.5			12.5
AUTONOMIC NERVOUS SYSTEM DISORDERS	Any	25.		12.5		37.5
	APPETITE INCREASED	12.5				12.5
	SINUS BRADYCARDIA			12.5		12.5
	SINUS TACHYCARDIA	12.5				12.5
HEART RATE AND RHYTHM DISORDERS	Any		12.5	37.5		37.5
	BIGEMINY		12.5	25		25
	PALPITATION			12.5		12.5
CARDIOVASCULAR DISORDERS, GENERAL	Any	12.5		12.5		25
	HYPERTENSION			12.5		12.5
	HYPOTENSION ORTHOSTATIC	12.5				12.5
CENTR & PERIPH NERV SYST DISORDERS	Any	12.5		12.5		25
	DIZZINESS	12.5				12.5
	HEADACHE			12.5		12.5
PSYCHIATRIC DISORDERS	Any	12.5		12.5	28.6	25
	INSOMNIA					25
	DREAMING ABNORMAL			12.5		12.5
	SLEEP DISTURBED	12.5				12.5
BODY AS A WHOLE - GENERAL DISORDERS	Any		12.5			12.5
	FATIGUE		12.5			12.5
METABOLIC AND NUTRITIONAL DISORDERS	Any			12.5		12.5
	WEIGHT INCREASE			12.5		12.5
RESPIRATORY SYSTEM DISORDERS	Any	12.5				12.5
	THROAT SORE	12.5				12.5

Table 33 Treatment Emergent Adverse Events by Dose Level in Study SP535 (n = 8)

Body System	Preferred Term	Dose Level (mg)			
		4.5	9	13.5	18.0
N		8	8	7	7
APPLICATION SITE DISORDERS	Any				
	APPLICATION SITE REACTION	4	3	2	1
SKIN AND APPENDAGES DISORDERS	Any				
	DERMATITIS			1	
GASTRO-INTESTINAL SYSTEM DISORDERS	Any		2	2	
	NAUSEA		1	1	
	CONSTIPATION			1	
	DIARRHOEA		1		
AUTONOMIC NERVOUS SYSTEM DISORDERS	Any	3	2	2	
	APPETITE INCREASED	1			
	Dry Mouth	1			
	SINUS BRADYCARDIA		1	1	
	SINUS TACHYCARDIA	1	1	1	
HEART RATE AND RHYTHM DISORDERS	Any		1	2	
	ATRIAL BIGEMINY			1	
	Ventricular BIGEMINY		1		
	PALPITATION			1	
CARDIOVASCULAR DISORDERS, GENERAL	Any	1		1	
	HYPERTENSION			1	
	HYPOTENSION ORTHOSTATIC	1			
CENTR & PERIPH NERV SYST DISORDERS	Any	2	1	1	
	DIZZINESS	1			
	HEADACHE			1	
	Paresthesia	1	1		
PSYCHIATRIC DISORDERS	Any	2		1	3
	INSOMNIA	2		1	3
	DREAMING ABNORMAL			1	
	SLEEP DISTURBED				
BODY AS A WHOLE - GENERAL DISORDERS	Any		1		
	FATIGUE		1		
METABOLIC AND NUTRITIONAL DISORDERS	Any			1	
	WEIGHT INCREASE			1	
RESPIRATORY SYSTEM DISORDERS	Any	1		1	
	Flu Like Syndrome			1	
	THROAT SORE	1			