Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm^2 / day	mcg / cm^2 / hr
								Form 4								
SP670	DDI Domperidone							Silicone patch CTF / TBM Form 4								
Clinical Pharmacology																
SP629																
SP673																
Pivotal Bioequivalence Study																
SP581	Pivotal BE		Healthy Male Vol		Fore axillary line of the chest		0		4.5 mg / 10 cm^2	1 / Day		2.41 ± 0.83 34.4 0.97 - 4.08 2.29	51.0 ± 17.6 34.4 20.5 - 86.3 48.5	28.2 ± 8.7 30.9 12.1 - 43.1 27.5	0.24 ± 0.08 (34.4) 0.10 - 0.41 [0.23]	9.6 ± 3.9 40.5 1.1 - 17.0 9.2
		Ref					3	Silicone patch 'Phase II' Form 3			Ref	2.02 ± 0.67 33.2 0.74 - 3.4 2.02	44.9 ± 14.9 33.2 16.5 - 75.6 44.9		0.20 ± 0.07 33.2 0.07 - 0.34 0.20	8.41 ± 2.80 33.2 3.1 - 14.17 8.43
		Test					30				Test	1.96 ± 0.69 35.2 1.0 - 3.83 1.89	43.6 ± 15.3 35.2 22.2 - 85.1 42.0		0.20 ± 0.07 35.2 0.1 - 0.38 0.19	8.18 ± 2.82 35.2 4.17 - 15.96 7.98
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																
SP534 Part 2																
SP535																
SP506																
SP540																
Population PK/PD Trial Reports																
SP512								Silicone patch CTF / TBM Form 4					No Data			
SP512 Part I													No Data			
SP513 Part I													No Data			
Uncontrolled Clinical Trials – Not Reviewed																
SP512 Part IId SP702								Silicone patch CTF / TBM Form 4					No Data			
SP513 Part IId SP716													No Data			
SP533																

Study No.	Study Description	Arm	Pop	Rx	Application Site	Duration of Application	N	Formulation	Strength	No. Patches	Applied Dose (mg)	Dose Delivered (mg)	% Depletion	Dose (mcg/kg)	Average Flux Rate	
															mg / cm^2 / day	mcg / cm^2 / hr
SP511																
SP650 Part Id																
SP650 Part IId (SP715)																
SP591																
SP666																
SP709d																

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

4 LABELING COMMENTS

A number of statements were made by the sponsor in the labeling that the studies performed by the sponsor did not provide any data to support. The basis of this information was unclear as there was no annotated labeling provided in the labeling section. Eventually this reviewer found a hypertext link to the annotated labeling under the summary section. This annotated labeling provided hypertext links to reference numbers from a bibliography list in the HpBio section with further links to image files of the articles.

This reviewer was thus able to confirm that there are at least literature citations for the information this reviewer has kept in the labeling, e.g. absolute bioavailability and mass balance data.

OCPB additions and deletions are marked in red.

Proposed deletions are marked by addition a ~~single line strikeout~~ to text to be deleted.

Proposed additions are marked by addition of a single underline to proposed additions.

39 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

5 APPENDICES

5.1 Appendix 1 - Study Designs

Table 103 Study Designs - List of Studies, Protocol Numbers, Study Dates, and Study Location

SP No.	Other Protocol #s.	Study Design	Study Title	Formulation	FPI	LPO	Country or Region(s)
Exploratory Proof of Concept Studies							
SP803	N-0923-001-2601	2 Phase, DB, PBO Ctrld, Seq RMD, Ph II, PK/PD Study in pxts with Hoehn & Yahr Stage II – IV Parkinson's Disease	A Pilot Evaluation of the Anti-Parkinson Efficacy and Safety of a New Dopaminergic Agonist in Parkinson Patients	IV	Dec 91	Mar 93	US
SP804	N-0923-002-001 WRA-006-002	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	A Pilot Evaluation of the Pharmacokinetics, Pharmacodynamics and Safety of a New Dopaminergic D_2 Agonist, N-0923 in Parkinsonian Patients	IV	Nov 92	Nov 93	US
SP805	N-0923-006-01	2 Phase DB, PBO Ctrld Seq RMD, Ph II, PK/PD Study in pxts with Hoehn & Yahr Stage III – IV Parkinson's Disease	The Activity of 7-Day N-0923 Continuous Intravenous Infusions in Patients with Stage III Through Stage IV Parkinson's Disease	IV	Oct 93	Nov 93	US
Formulation Development							
Mass Balance Studies							
SP610		OL, Rand, 2-Way XO, Absolute BA, metabolism and excretion study of ^{14}C-SPM 962 in healthy male volunteers	An open, randomized, two-way-cross-over study to evaluate absorption, metabolism and excretion of intravenously administered ^{14}C-SPM962 and transdermally applied SPM 962 in healthy young volunteers	IV Silicone patch 'Phase II' Form 3	4-dec-00	25-jan-01	Czech Republic

SP No.	Other Protocol #s.	Study Design	Study Title	Formulation	FPI	LPO	Country or Region(s)
SP606		OL SD Absorption and excretion of ^{14}C-SPM 962 in healthy volunteers	Absorption and excretion of radioactivity after single dermal application of [^{14}C]-SPM 962 in healthy human volunteers	Rotigotine 4.5 mg / 10 cm^2 (0.015 mg [^{14}C]-SPM 962)	5-Feb-01	9-Feb-01	Netherlands
PK Healthy Subject PK and Initial Tolerability Trial Reports							
SP503		OL, placebo run-in, un-rand, MD, S/T, PK study in healthy volunteers	Multiple dose pharmacokinetics and pharmacodynamics of SPM 962 and its metabolites during 14 day q.d. administration to 30 healthy male volunteers	Silicone patch 'Phase II' Form 3	25-Mar-99	22-May-99	Germany
Pivotal BE Study							
SP581		OL, SD 2-way X-over BE study of two different batches of Silicone patches in healthy volunteers	Bioequivalence evaluation of SPM 962 from two different silicone patches in 30 healthy male volunteers	Silicone patch CTF / TBM Form 4 Silicone patch 'Phase II' Form 3	03-Jul-00	9-Aug-00	Germany
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	An Open-Label, Multi-site, randomized trial of the pharmacokinetics and cardiac safety of rotigotine transdermal patch (18.0 mg) in subjects with early-stage, idiopathic Parkinson's Disease	Silicone patch CTF / TBM Form 4	23-Mar-04	28-Jun-04	United States, South Africa
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	Relative Bioavailability and Pharmacokinetics of SPM 962 after Transdermal Administration in Caucasian and Black Volunteers	Silicone patch 'Phase II' Form 3	16-Feb-01	10-Jun-01	France
SP717		OL, 2-arm parallel group SD PK & S/T study in healthy age and weight matched Japanese and Caucasian vols	Parallel group trial to evaluate the pharmacokinetics and safety/tolerability of single dose treatment with rotigotine CDS (10 cm^2/4.5 mg) in Japanese and Caucasian healthy subjects.	Silicone patch CTF / TBM Form 4	10-Oct-02	21-Dec-02	Germany
SP718		OL, 2-arm parallel group MRD PK & S/T study in healthy Japanese and Caucasian vols	Parallel group trial to evaluate the pharmacokinetics and safety/tolerability of repeated dose treatment with rotigotine CDS in three different dosages (5 cm^2/2.25 mg, 10 cm^2/4.5 mg, 20 cm^2/9 mg) in Japanese and Caucasian healthy subjects.	Silicone patch CTF / TBM Form 4	10-Dec-02	12-Mar-03	Germany
SP671		OL, 2-arm parallel group MD PK & S/T study in nl male vols and subjects with moderate hepatic impairment	Open, group-comparison trial to evaluate the influence of liver impairment on the pharmacokinetics and safety/tolerability of multiple dose treatment with rotigotine in hepatic impaired patients	Silicone patch CTF / TBM Form 4	Aug-02	May-03	Slovac Republic
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	Open, group-comparison investigation of pharmacokinetics, safety and tolerability of single dose transdermal treatment with rotigotine (10 cm^2 patch/4.5 mg) in patients with impaired renal function including patients requiring dialysis compared to healthy subjects.	Silicone patch CTF / TBM Form 4	18-Jun-03	16-Feb-04	Poland

SP No.	Other Protocol #s.	Study Design	Study Title	Formulation	FPI	LPO	Country or Region(s)
Extrinsic Factors							
SP626		OL, SD, 3-way X-over rel. BA study of various application sites in healthy male vols	Influence of the Application Site of on the Absorption of SPM962 in Healthy Subjects	Silicone patch 'Phase II' Form 3	23-Nov-00	18-Dec-00	Germany
SP627		OL, MD, Rand 2-way X-over PK DDI study of rotigotine TDS in the presence and absence of cimetidine in healthy volunteers	Influence of cimetidine comedication on the pharmacokinetic of SPM 962 in 12 healthy subjects	Silicone patch 'Phase II' Form 3	22-Mar-01	27-Apr-01	Germany
SP628		OL, 2-arm, parallel-group, MD PK DDI study of of rotigotine CDS and levodopa/carbidopa in patients with idiopathic RLS	Open, parallel-group, drug-drug interaction trial to evaluate pharmacokinetics of rotigotine CDS and levodopa/carbidopa in patients with idiopathic Restless Legs Syndrome	Silicone patch CTF / TBM Form 4	15-Oct-02	16-Apr-03	Germany
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	Open, randomized, two-fold crossover trial to evaluate the influence of domperidone on the pharmacokinetics and safety/tolerability of multiple dose treatment of rotigotine in young healthy male subjects	Silicone patch CTF / TBM Form 4	17-Dec-01	16-Feb-02	France
Clinical Pharmacology Studies							
SP629		Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites) in healthy volunteers No PK	Single-site, placebo-controlled investigation of cumulative skin irritation after repetitive administration of rotigotine transdermal patch (2.5cm^2/1.125mg) to the same skin site in comparison to multiple administration of rotigotine transdermal patch (2.5cm^2/1.125mg) to daily rotating skin sites in healthy subjects	Silicone patch CTF / TBM Form 4	15-Sep-03	10-Mar-04	Germany
SP673		Sensitization potential in healthy volunteers No PK	Two-Site, placebo-controlled investigation of skin sensitization after repeated administration of rotigotine transdermal patch (2.5cm^2/1.125mg) in healthy subjects	Silicone patch CTF / TBM Form 4	08-Oct-03	09-Feb-04	Germany
Phase II Studies							
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	A single center, double-blind, placebo controlled, parallel group, dose-ranging study to assess the safety and tolerability of transdermal doses of SPM 962 in subjects with early stage Parkinson's disease	Silicone patch 'Phase II' Form 3	13-Apr-99	19-Jul-2000	US
SP534 Part 2		Evaluate safety and tolerability of dose escalation	Part II includes a titration scheme due to intolerability in part 1	Silicone patch 'Phase II' Form 3	17-Aug-99	01-Dec-99	US
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	A Single Center, Double-Blind, Placebo Controlled, Dose Escalation Study to Assess the Safety and Tolerability of Transdermal Doses of SPM 962 in Subjects with Early Stage Parkinson's Disease	Silicone patch 'Phase II' Form 3	09-Nov-99	25-Jan-01	US

SP No.	Other Protocol #s.	Study Design	Study Title	Formulation	FPI	LPO	Country or Region(s)
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)	A Multi-site, Single-blind, Dose Escalation Trial to Potential Benefits the Safety Limitations of Transdermal Doses of SPM 962 in Subjects with Early IdiopathicParkinson's Disease	Silicone patch 'Phase II' Form 3	19-Jul-99	20-Oct-99	Europe, South Africa
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	A Multi-Center, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Dose-Ranging Study to Assess the Efficacy, Safety and Tolerability of Escalating Transdermal Doses of SPM 962 in Subjects with Early Stage Parkinson's Disease	Silicone patch 'Phase II' Form 3	15-Nov-99	16-Nov-00	Canada, Europe, India, South Africa, Ukraine, US
Phase III Safety & Efficacy 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	A multi-center, multinational, phase III, randomized, double-blind, placebo controlled trial, of the efficacy and safety of the rotigotine patch in subjects with early-stage, idiopathic Parkinson's disease (Part 1), (the open-label extension portion of this trial [Part 2] will be reported separately).	Silicone patch CTF / TBM Form 4	20-Nov-01	16-Apr-03	Canada, US
SP512		Pop PK	Pharmacokinetics of Total Rotigotine in Patients with Early-Stage Idiopathic Parkinson's Disease	ibid	ibid	ibid	
SP513 Part I		Ph III, Rand, DB, PBO & roprinirole 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	A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and ropinirole-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic Parkinson's disease (Part I), (the open-label extension portion of this trial [Part II] will be reported separately).	Silicone patch CTF / TBM Form 4	31-Jan-02	09-Sep-03	Europe, Israel, New Zealand, South Africa, Switzerland Australia 21 countries
Phase III Open Label Safety Extension Studies							
SP512 Part IId (SP702)		Evaluate long-term safety Retritrated over 3 weeks	A multi-center, multinational, Phase 3, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage, idiopathic Parkinson's disease (Part I), and an open-label extension to assess the safety of long-term treatment of rotigotine CDS (Part II).	Silicone patch CTF / TBM Form 4	28-Jun-02	Ongoing	Canada, US
SP513 Part IId (SP716)		Evaluate long-term safety	A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and ropinirole-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic Parkinson's disease (Part I) I], and an open-label extension to assess the safety of long-term treatment of rotigotine CDS (Part II).	Silicone patch CTF / TBM Form 4	16-Oct-02	Ongoing	Europe, Israel, New Zealand, South Africa, Switzerland Australia
Other Trial Reports	The following studies were conducted for other indications						
SP533		Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease	A single center, double-blind, dose-escalation study to assess the efficacy, safety, and tolerability of transdermal doses of N-0923 (rotigotine) in subjects with advanced-stage Parkinson's disease (SP533)				US

SP No.	Other Protocol #s.	Study Design	Study Title	Formulation	FPI	LPO	Country or Region(s)
SP511		Assess dose groups of rotigotine in subjects with advanced Parkinson's disease	Multicenter, double-blind, randomized, placebo-controlled, 4-arm, parallel-group trial of SPM 962 TDS in subjects with advanced stage idiopathic Parkinson's disease.				Europe, South Africa, United Kingdom
SP650 Part Id		Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease	A multi-center, multinational, phase III, randomized, double-blind, parallel group, placebo controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part I) and open-label extension to assess the safety of long-term treatment of rotigotine CDS (Part II)				Canada, US
SP650 Part IId (SP715)		Evaluate long-term safety in subjects with advanced Parkinson's disease	SP650: A multi-center, multinational, phase III, randomized, double-blind, parallel group, placebo controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part I) and open-label extension to assess the safety of long-term treatment of rotigotine CDS (Part II)				Canada, US
SP591		Evaluate safety and tolerability in subjects with advanced Parkinson's disease	Parallel, open-label, dose-escalation trial to assess the individual maximal achievable dose (MAD) with two titration schemes for transdermal doses of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease				Europe, Croatia
SP666		Evaluate dose-response relationship, safety and tolerability in subjects with RLS	Multicenter, double-blind, randomized, placebo-controlled, four-arm, parallel-group trial of rotigotine CDS in patients with idiopathic Restless legs Syndrome (Phase IIa)				Germany
SP709d		Evaluate safety and efficacy of rotigotine in subjects with RLS	Multi-center, double-blind, randomized, placebo controlled, six-arm, parallel-group, dose finding trial to determine efficacy, safety, and tolerability of five different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome				Europe

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

Table 104 Study Designs - Inclusion Criteria by Study

Study No.	Age & Dx of PD	Sex	Age (yo)	Race	Weight Met Wt Tables[a]	Tob[b]	EtOH Breath Test	Urine Drug Screen
Initial Exploratory PK/PD Proof of Concept Studies								
SP803	Mild to mod PD	M/F ncbp	Legal age	—	—	—	—	—
SP804	Mild to mod PD H&Y	M/F	Adults	Any		NS		
SP805	PD H&Y III – IV		Adults			NS		
Formulation Development								
Mass Balance								
SP610	Healthy Vols	M	18 – 50	Caucasian	± 15% IBWt	< 0.5 PPD		
SP606	Healthy Vols	M	18 – 45	Caucasian	BMI ≤ 28			
Healthy Subject PK and Initial Tolerability Trial Reports								
SP503	Healthy Vols	M	18 – 50	Caucasian	BMI < 30	—	—	—
Intrinsic Factors								
SP630	idiopathic Parkinson's H&Y St ≤III &	M & F	≥18 yo				+	+
SP596	Healthy Vols Age, Wt & BMI matched	M	18-50 Age matched +/ 2 yrs	Caucasian Black	± 15% matched to ± 5% BMI	≤0.25 PPD	+ Hx Drug abuse w/i 2 yrs	+ Hx Drug abuse w/i 2 yrs
SP671	Healthy and Hepatic Impaired Child-Pugh B	M	18-65 yo Age matched +/ 5 yrs	Caucasian	Wt matched ± 5% 20-34 kg/m2 matched to ± 5% BMI	≤1 PPD	+ Hx Drug abuse w/i 6 mo	+ Hx Drug abuse w/i 6 mo
SP672	Measured Clcr	M/F	18-75 yo	Caucasian	18-34 kg/m2	≤0.25	+ Hx Drug abuse w/i 5 yr	+ Hx Drug abuse w/i 5 yr

Study No.	Age & Dx of PD	Sex	Age (yo)	Race	Weight Met Wt Tables[a]	Tob[b]	EtOH Breath Test	Urine Drug Screen
	Healthy Clcr ≥80 ml/min and Renal Impaired Clcr ≥50 < 80 ml/min Clcr ≥30 < 50 ml/min Clcr > 80 ml/min Clcr > 80 ml/min Clcr <30 ml/min and not needing dialysis (4 20-30 & 4 15-20) < 15 ml/min & dialysis x 4 mo	Gender Matched Grp 1 & 4 matched Grp 2,3, & 5 matched	age matches (mean ± 10 yr) Grp 1 & 4 matched Grp 2,3, & 5 matched			PPD		
SP717	Healthy Vols Caucasian & Japanese (both parents japanese and left japan ≤10yrs ago)	M/F	20-45 Age matched ± 5 yrs	Match age, gender, wt	18-28 kg/m2 matched to ±10% BMI	≤0.25	X Hx	X Hx
SP718	Healthy Vols Caucasian & Japanese (both parents Japanese and left Japan ≤10yrs ago)	M/F	20-30	Caucasian & Japanese	18-25 kg/m2	≤0.25	X	X
Extrinsic Factors								
SP626	Healthy Vols	M	18-50	Caucasian	± 15%	≤0.25 PPD	+ Hx w/i 2 yrs	+ Hx w/i 2 yrs
SP627	Healthy Vol	M	18-45		19-30 kg/m2	NS	+ Hx w/i 6 mo	+ Hx w/i 6 mo
SP628	Idiopathic RLS on CD/LD 25/100 bid x 1 mo	M/F ncbp	45-70	Caucasian	19-30 kg/m2	≤0.25 PPD	+ Hx w/i 5 yrs	+ Hx w/i 5 yrs
SP670	Healthy Vols	M	18-45	Caucasian	20-28 kg/m2	≤0.25 PPD	+ Hx w/i 6 mo	+ Hx w/i 6 mo
Clinical Pharmacology Studies								
SP629	Healthy Vols	M/F	18-60 yo	Caucasian	18-30 kg/m2	≤0.25 PPD	+ Hx w/i 5 yrs	+ Hx w/i 5 yrs
SP673	Come back to							
Pivotal Bioequivalence Study								
SP581	Healthy Vols	M	18 – 50	Caucasian	± 15% IBWt	<0.25 PPD	Neg	Neg
Patient PD and PK/PD								

Study No.	Age & Dx of PD	Sex	Age (yo)	Race	Weight Met Wt Tables[a]	Tob[b]	EtOH Breath Test	Urine Drug Screen
SP534 Part 1	PD < 5yr H&Y ≤III MMSE ≥26	M/F	≥ 30	—	—	—	+ Hx	+Hx
SP534 Part 2				—	—	—		
SP535	PD < 5yr H&Y ≤III MMSE ≥26	M/F	≥ 30	—	—	—	+ Hx	+Hx
SP506	PD H&Y ≤3 MMSE ≥ 24	M/F	≥ 30				+ Hx w/i 5 yrs	+Hx w/i 5 yrs
SP540	Idio PD < 5 yr H&Y St I-III	M/F	> 30	—	—	—	+ Hx	+Hx
Population PK/PD Trial Reports								
SP512	Phase III study Pop PK report							
SP512 Part I	Idio PD < 5 yr H&Y St I-III MMSE ≥ 25 UPDRS – III ≥ 10 Stable doses of drugs	M/F	≥ 30	—	—	—	+ Hx w/i 5 yrs	+Hx w/i 5 yrs
SP513 Part I	Idio PD < 5 yr H&Y St ≤ III MMSE ≥ 25 UPDRS – III ≥ 10 Stable doses of drugs	M/F	≥ 30	—	—	—	+ Hx w/i 5 yrs	+Hx w/i 5 yrs
Uncontrolled Clinical Trials								
SP512 Part IId (SP702)								
SP513 Part IId SP716								
Other Trial Reports – Not Reviewed								

Study No.	Age & Dx of PD	Sex	Age (yo)	Race	Weight Met Wt Tables[a]	Tob[b]	EtOH Breath Test	Urine Drug Screen
SP533								
SP511								
SP650 Part Id								
SP650 Part IId (SP715)								
SP591								
SP666								
SP709d								

Table 105 Study Designs - Exclusion Criteria

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucome	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
	Initial Exploratory PK/PD Proof of Concept Studies																
SP803	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	'Any other clinically significant systemic disease' Subjects using agents that can have a substantial effect on dopaminergic agents included at discretion of investigator, (e.g. antipsychotics, anti-muscarinics, antihypertensives).
SP804	Atrial or Ven arrhytmis				X							X					
SP805	Atrial or Ven arrhytmis				X			hypotension				X					
	Formulation Development																
	Mass Balance Studies																
SP610	nl	4 – 6 units of EtOh /day	Unusual Diet	> 600 mg Caffeine /day	"		" or S/P MI		HIV or HBsAG +			X	X				
SP606		EtOH > 28 units / week											Dermal in application area			Drug hyper sens to DA agonists	
	Healthy Subject PK and Initial Tolerability Trial Reports																
SP503	QTc > 440 mSec								+								
	Pivotal Bioequivalence Study																
SP581		Sub Abuse	X	X	X				HIV ½ or HBsAG	X		X				Hyper to drug	

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucome	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
									+								
	Intrinsic Factors																
SP630	Conduction abno. QRS > 110 ms PR > 240 ms OTc > 480 ms or cardiac dys +	Hx Drug or EtOh Abuse					or MI wi 12 mo	Hx of symptomation hypotension Hepatic dysfsn > 2x ULN	HIV ½ Ab or HBsAG + HBcAb HCV-Ab			On stable dose of AntiACh or MAOI-B MAO-A exc		Hx or activeS kin Dz		Hypersens to adhesive or transdermal;s	
SP596	SBP < 105 HR <50 bpm QTc > 450	>40 gm/day	Unusal	> 600 mg/day	X				HIV ½Ab or HBsAG HCV-Ab	Narrow Angle Glauc		MAOI Hep inducers inhibs	Ibid	ibid			
SP671																	
SP672																	
SP717	HR<50>100 SBP <100 > 145 DBP <60 >95 WTC > 430 M 450 F QRS > 120 2nd or 3rd o AV block	40 gm	Unsual diet	> 600	x	Hx			HIV ½Ab or HBsAG HCV-Ab			MAOI	X			X	
SP718	ibid	20 g	"	> 600						X		x	x				
	Extrinsic Factors																
SP626		>40 gm/day	X			X	X sp MI		HIV ½Ab or HBsAG HCV-Ab	X		MAOI induc inhi				+	
SP627																	
SP628																	
SP670																	
	Clinical Pharmacology Studies																
SP629																	
SP673																	
	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,																

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucome	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
	and SP591 – Advanced PD).																
SP534 Part 1																	
SP534 Part 2	QTc > 500 msec 2ndor or 3rd deg blk or SSS CHF NYHC III or IV							Hypor or DBP < 85 SBP D⇓30				MAOi-A				X	
SP535	QTc > 500 msec 2ndor or 3rd deg blk or SSS CHF NYHC III or IV							Hypor or DBP < 85 SBP D⇓30				MAOI-A				X	
SP506	QTc ≥ 500 mSec BBB 2nd 3rd AV blockl SSS NYHC II or IV MI wi 12 mo						Hx V-Tach	Hypor or DBP < 85 SBP D⇓30						Hx syncope		X	
SP540	2ndor or 3rd deg blk or SSS CHF NYHC III or IV				X		X & angina					MAOI-A		Hx MI		x	
	Population PK/PD Trial Reports																
SP512																	
SP512 Part I																	
SP513 Part I																	
	Uncontrolled Clinical Trials																
SP512 Part IId (SP702)																	
SP513 Part IId SP716																	
	Other Trial Reports																
SP533																	
SP511																	
SP650 Part Id																	
SP650																	

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucome	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
Part IId (SP715)																	
SP591																	
SP666																	
SP709d																	

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

Table 106 Study Designs - Exclusion Criteria

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucoma	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
Initial Exploratory PK/PD Proof of Concept Studies																	
SP803	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	'Any other clinically significant systemic disease' Subjects using agents that can have a substantial effect on dopaminergic agents included at discretion of investigator, (e.g. antipsychotics, anti-muscarinics, antihypertensives).
SP804	Atrial or Ven arrhytmis				X							X					
SP805	Atrial or Ven arrhytmis				X			hypotension				X					
Formulation Development																	
Mass Balance Studies																	
SP610	nl	4 – 6 units of EtOh /day	Unusual Diet	> 600 mg Caffeine /day	"		" or S/P MI		HIV or HBsAG +			X	X				
SP606		EtOH > 28 units / week											Dermal in application area			Drug hyper sens to DA agonists	
Healthy Subject PK and Initial Tolerability Trial Reports																	
SP503	QTc > 440 mSec								+								
Pivotal Bioequivalence Study																	
SP581		Sub Abuse	X	X	X				HIV ½ or HBsAG +	X		X				Hyper to drug	
Intrinsic Factors																	
SP630	Conduction abno. QRS > 110 ms PR > 240 ms QTc > 480 ms or cardiac dys +	Hx Drug or EtOh Abuse					or MI wi 12 mo	Hx of symptomation hypotension Hepatic dysfsn > 2x	HIV ½ Ab or HBsAG + HBcAb HCV-Ab			On stable dose of AntiACh or MAOI-B MAO-A exc		Hx or activeS kin Dz		Hypersens to adhesive or transdermal;s	

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucoma	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
								ULN									
SP596	SBP < 105 HR <50 bpm QTc > 450	>40 gm/day	Unusual	> 600 mg/day	X	Hx of	Present sinus, atrial, pr ventricular arrhythmias or S?P MI		HIV ½Ab or HBsAG HCV-Ab	Narrow Angle Glauc		MAOI Hep inducers inhibs Anitemetics, antiHTN	Ibid	ibid		Drug Hypersensitibit y or suspected sensivity to dopaminergic agonists Contrindication s against sympathomimet ics	
SP717	HR<50 >100 SBP <100 >145 DBP <60 >95 QTc > 430 M >450 F QRS > 120 2nd or 3rd o AV block	>40 gm / day	Unsual diet	> 600	x	X	X		HIV ½Ab or HBsAG HCV-Ab			MAOI COMPT	X	X		X Clinically relevant allergies Hypersensitity to any component	
SP718	ibid	>20 gm / day	X	> 600	X	X	X		HIV ½Ab or HBsAG HCV-Ab	X		X	X	X		Clinically relevant allergies Hypersensitity	
SP671	SBP <100 or >150 DBP <60 >95 HR <50 bpm >100 QRS>120 mSec QTc > 430 mSec	>40 gm/day >20 for Hepatic Subj	Unusual	> 600 mg/day	X	X	2nd or 3rd o AV blk		HIV ½Ab or HBsAG HCV-Ab					X		Hypersensitity to any component	Hep ClCr < 50 ml/min Cirrhosis due to autoimmume dz
SP672	QRS > 120 QTc > 430 M > 450 F				X	X	Multiple multi-focal Vent ec beats Hsx Arr NYHA 3 or 4 Hx MI		HIV ½Ab or HBsAG HCV-Ab	Narrow or wide X		3 mon		X		Clinically relevant allergiesHs skin hyper sens	
Extrinsic Factors																	
SP626		>40 gm/day	X	X	X	X	X sp MI		HIV ½Ab or HBsAG HCV-Ab	X		MAOI induc inhi				+	
SP627		>40 gm/day	Vegetaria n of Vegan	X	SZR		Present sinus, atrial, pr ventricular arrhythmias or S?P MI		HIV ½Ab or HBsAG HCV-Ab	x		ibid				X	
SP628	2nd or3rd AV blk QRS >120	>40 gm/day	X	X	X	X	X	SBP <100 >160	HIV ½Ab or HBsAG	X				X		X	

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucoma	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
	QTc >430 M >450F							DBP <60 >100 HR <50 >100	HCV-Ab								
SP670	2nd or3rd AV blk QRS >120 QTc >430 M >450F		X Vegetarian of Vegan		X	X	X	SBP <100 >150 DBP <60 >95 HR <50 >100	HIV ½Ab or HBsAG HCV-Ab			X		X		Clinically Relevant Allergry	
Clinical Pharmacology Studies																	
SP629	2nd or3rd AV blk QRS >120 QTc >430 M >450F	>20 gm/day			X	X		SBP <100 >145 DBP <60 >95 HR <50 >100	HIV ½Ab or HBsAG HCV-Ab	X		X		X		X	
SP673																	
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	QTc > 500 msec 2ndor or 3rd deg blk or SSS CHF NYHC III or						S/P MI									X	Prior or concurrent therapy with a dopamine agonist 2. Concurrent therapy with carbidopa/levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy). History of pallidotomy, thalamotomy, deep brain stimulation or fetal brain transplant.
SP534 Part 2	QTc > 500 msec 2ndor or 3rd deg blk or SSS CHF NYHC III or IV							Hypor or DBP < 85 SBP DU30				MAOi-A				X	
SP535	QTc > 500 msec 2ndor or 3rd deg blk or SSS CHF NYHC III or IV							Hypor or DBP < 85 SBP DU30				MAOI-A				X	Prior or concurrent therapy with a dopamine agonist within 28 days 2. Concurrent therapy with carbidopa/levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy). History of pallidotomy, thalamotomy, deep brain stimulation or fetal brain transplant.
SP506	QTc ≥ 500 mSec BBB 2nd 3rd AV block SSS NYHC II or IV MI wi 12 mo						Hx V-Tach Hx unexplained syncope	Hypor or DBP < 85 SBP DU30				MAOI		Hx syncope		X	Prior or concurrent therapy with a dopamine agonist within 28 days Concurrent therapy with carbidopa/levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy).

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucoma	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
																	History of pallidotomy, thalamotomy, deep brain stimulation or fetal brain transplant.
SP540	2nd or or 3rd deg blk or SSS CHF NYHC III or IV				X	Hx w/I 12 mo	X & angina	Hypor or SBP < 100 SBP D⇩20				MAOI-A		Hx MI		x	Prior or concurrent therapy with a dopamine agonist within 28 days. Concurrent therapy with levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy).
Population PK/PD Trial Reports																	
SP512	QTc > 500 visit 1 or visit 2 QTc >450 M >470 F				X		Hx or S/P MI	Orthod Hypo or SBP < 105 SBP D⇩20 DBP D⇩10				MAOI - A		X recent		X	Prior or concurrent therapy with a dopamine agonist within 28 days. Concurrent therapy with levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy).
SP512 Part I																	
SP513 Part I	QTc > 500 visit 1 or visit 2 QTc >450 M >470 F			X	Hx or TIA		Any Cardiac	Orthod Hypo or SBP < 105 SBP D⇩20 DBP D⇩10				MAOI - A		X recent		X	Prior or concurrent therapy with a dopamine agonist within 28 days. Concurrent therapy with levodopa Presence of atypical Parkinson's syndromes due to drugs (e.g., metoclopramide, flunarazine), metabolic identified neurogenetic disorders (e.g., Wilson's disease), encephalitis, or degenerative disease (e.g., progressive supranuclear palsy). History of pallidotomy, thalamotomy, deep brain stimulation or fetal brain transplant.
Uncontrolled Clinical Trials																	
SP512 Part IId (SP702)																	
SP513 Part IId SP716																	
Other Trial Reports																	
SP533																	
SP511																	
SP650 Part Id																	
SP650 Part IId (SP715)																	
SP591																	

Study No.	12 lead ECG	EtOH >28 units / week	Unusual Diet	> 600 mg Caffeine / day	Neuro / Psych	Active Malig	Hx arrhythmias	Hypotension	HIV or HBsAG +	Narrow Angle Glaucoma	α blkers Ca antags	MAOIs or hepatic inhibitors w/i 30 days	Dermal problems in application area	Hx of Skin Dz		Drug Hyper-sensitivity or allergy	Comments
SP666																	
SP709d																	

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

Table 107 Study Designs - Concomitant Medications

Study No	Age & Dx of PD	CD/LD	Ergolines	MAOIs	Needed Systemic Meds with no expected DDI	CD/LD			
	Initial Exploratory PK/PD Proof of Concept Studies	No WO	1 week	2 wks	May be used	May be used when medically indicated	Domperidone for NV		
SP803	Mild to mod PD								
SP804	Mild to mod PD H&Y								
SP805	PD H&Y III – IV								
	Formulation Development								
	H ealthy Subject PK and Initial Tolerability Trial Reports								
SP503	Healthy Vols								
	Pivotal Bioequivalence Study								
SP581	Healthy Vols								
	Intrinsic Factors								
SP630	idiopathic Parkinson's H&Y St ≤III &								
SP596	Healthy Vols Age, Wt & BMI matched								
SP671									
SP672									
SP717	Healthy Vols								
SP718	Healthy Vols								
	Extrinsic Factors								
SP626	Healthy Vols								
SP627									
SP628									
SP670									
	Clinical Pharmacology Studies								
SP629	Come back to								
SP673	Come back to								
	Patient PD and PK/PD								
SP534 Part 1	PD < 5yr H&Y ≤III MMSE ≥26	Exclusion Criteria					Subjects receiving deprenyl, anticholinergic agents (i.e. Cogentin, Artane, Parsitan (Parsidol), Kemadrin, Akineton), or amantadine must be on a stable dose for at least 28 days prior to trial entry		
SP534 Part 2									
SP535	PD < 5yr								

Study No.	Age & Dx of PD	CD/LD	Ergolines	MAOIs	Needed Systemic Meds with no expected DDI	CD/LD			
	H&Y ≤III MMSE ≥26								
SP506	PD H&Y ≤3 MMSE ≥ 24								
SP540	Idio PD < 5 yr H&Y St I-III								
	Population PK/PD Trial Reports								
SP512	Phase III stuidy PK report								
SP512 Part I									
SP513 Part I									
	Uncontrolled Clinical Trials								
SP512 Part IId (SP702)									
SP513 Part IId SP716									
	Other Trial Reports								
SP533									
SP511									
SP650 Part Id									
SP650 Part IId (SP715)									
SP591									
SP666									
SP709d									

Table 108 Study Designs - Patch Application

Study	Trial Objective(s)	Product(s)/ Regimen/Route	Application Site/Route	Hair	Prep of Area	Applied by whom	Washing	Activity	Skin Care Lotions etc.	Tape	Clothing	Comments	Batch	Lot	Date Made		
Initial Exploratory PK/PD Proof of Concept Studies																	
SP803	Evaluate safety and efficacy	Rotigotine/ maximum tolerated dose/ intravenous															
SP804	Evaluate safety and efficacy	Rotigotine/ maximum tolerated dose/ intravenous															
SP805	Evaluate safety and efficacy	Rotigotine/ optimal dose/ intravenous															
Formulation Development																	
Mass Balance																	
SP610	Absorption, metabolism and excretion of 14C-SPM 962 in healthy volunteers	Rotigotine/ 1.2mg and 4.5mg/ infusion solution and silicone patch	IV site not mentioned Upper abdomen below lowest rib	Hair free or removed by electric razor	Wash with H2O 0.5 hr prior & air dry			No. In Bed. Full clothing. RT moderate	No med soaps, lotions. shampoos, creams, oints.	Allowed if nonocclusive							
SP606	Absorption and excretion of 14C-SPM 962 in healthy volunteers	Rotigotine/ 4.5mg/ silicone patch	Volar aspect of Forearm														
Healthy Subject PK and Initial Tolerability Trial Reports																	
SP503	Evaluate PK, safety and tolerability in healthy volunteers	Rotigotine/ 4.5mg/ silicone patch	Right and left side of trunk alternatively Medio-axillar region	Hairless area													
Intrinsic Factors Ventral Corpus (Abdomen)																	
SP630	Define PK with rotating patch application sites, evaluate ECG effects, safety and tolerability	Rotigotine/ 4.5mg, 9.0mg, 13.5mg (once daily for 6 days each), 18.0mg (once daily for 12 days) silicone patch					No Baths, swimming, sauna. Shower allowed but no water on patch.	No heavy physical exertion	No soaps, creams, or lotions.	Hypoallergenic Tape or Tegoderm	Full	No natural or artificial sunlight exposure Do Not rub.					

Study	Trial Objective(s)	Product(s)/ Regimen/Route	Application Site/Route	Hair	Prep of Area	Applied by whom	Washing	Activity	Skin Care Lotions etc.	Tape	Clothing	Comments	Batch	Lot	Date Made		
SP596	Evaluate the relative BA and PK in Caucasian vs. Black subjects	Rotigotine/ 4.5mg/ silicone patch	A Fore axillary line of Ventral Abdomen B Ventral Upper Arm C Ventral / lateral upperleg		Clean & Dry with lukewarm soap-suds air dry wo strong rubbing	Pressed on by physicians for 30 sec		No physical exertion Must be Sitting/lying	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing					
SP671	Evaluate PK, safety and tolerability in subjects with impaired hepatic function	Rotigotine/ 4.5mg/ silicone patch	ventral/lateral abdomen. Fore axillary line sides will be switched with each application	Hairly area must be shaved 3 days prior	Clean & Dry with lukewarm soap-suds air dry wo strong rubbing & allowed to air dry			No physical exertion Must be Sitting/lying Must stay supine for 2 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing	Room Temp such that No shivering or sweating	Avoid waist			
SP672	Evaluate PK, safety and tolerability in subjects with impaired renal function	Rotigotine/ 4.5mg/ silicone patch	ventral/lateral abdomen.	Hairless not shaved	Clean & Dry with lukewarm soap-suds air dry wo strong rubbing & allowed to air dry	Pressed on for 30 sec	Day 1 the subjects will be allowed to shower 30 minutes prior to patch application and on Day 2 between 1 and ½ hour before patch removal.	No heavy exertion Must stay supine for 2 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing	Room Temp such that No shivering or sweating	Avoid waistline			
SP717	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects	Rotigotine/ 4.5mg/ silicone patch	ventral/lateral abdomen					No heavy exertion Must stay supine for 2 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Adequate	No rubbing	Room Temp such that No shivering or sweating				
SP718	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects	Rotigotine/ 2.25mg, 4.5mg, 9.0mg (once daily over 3 days each)/ silicone patch	ventral/lateral abdomen		Clean & Dry with lukewarm doap subs air dry wo strong rubbing		Shower 1 – 1.5 hr a removal Except for days with PK sampling	No heavy exertion Must stay supine for 2 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing	Room Temp such that No shivering or sweating				
Extrinsic Factor ventral abdomen																	
SP626	Investigate influence of application site on the bioavailability of rotigotine	Rotigotine/ 4.5mg/ silicone patch	A Fore axillary line of Ventral Abdomen B Ventral Upper Arm C Ventral / lateral upperleg		Clean & Dry with lukewarm soap subs air dry wo strong rubbing			No exertion Sittin lying Must stay supine for 4 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing	Room Temp such that No shivering or sweating				
SP627	Evaluate influence of cimetidine on PK of rotigotine in healthy volunteers	Rotigotine/ 4.5mg (once daily over 2 days, 9.0mg (once daily over 4 days)/ silicone patch Cimetidine/800mg/ oral	fore axillary line of the side of the abdomen.		Clean & Dry with lukewarm doap subs air dry wo strong rubbing		Shower 1 – 1.5 hr a removal Must sit or lie in bed.	No exertion	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		Full	No rubbing	Room Temp such that No shivering or sweating				
SP628	Evaluate PK of rotigotine and levodopa/ carbidopa in subjects with RLS	Rotigotine/ 4.5mg (3 days), 9.0mg (6 days)/ silicone patch Levodopa/ 200mg carbidopa/ 50mg/ oral	Ventral / lateral Abdomen Alternating sides		Clean & Dry with lukewarm soap subs air dry wo strong rubbin		Shower 1 – 1.5 hr a removal except PK days	No heavy exertion Must stay supine for 2 hr after application	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)		full	No rubbing					
SP670	Evaluate influence of domperidone on PK, safety and tolerability of rotigotine in healthy volunteers	Rotigotine/ 4.5mg/ silicone patch Domperidone/ 30mg/ oral	fore axillary line of the side of the abdomen. alternating sides	Hairly area must be shaved 3 days prior	Clean & Dry with lukewarm			No exertion Sitting lying No heavy exertion	No crms lotion or like medicated soaps, lotions,		full	No rubbing					

Study	Trial Objective(s)	Product(s)/ Regimen/Route	Application Site/Route	Hair	Prep of Area	Applied by whom	Washing	Activity	Skin Care Lotions etc.	Tape	Clothing	Comments	Batch	Lot	Date Made		
					soap subs air dry wo strong rubbin			Must stay supine for 2 hr after application	shampoos (e.g. w SLS)								
Alternating sides of medio-axillar region of the trunk																	
SP502	Comparative BA of [redacted] vs. silicone patches in healthy volunteers	Rotigotine/ 9.0mg (silicone) or [redacted] silicone or [redacted] patch	Fore axillary line of the chest														
Clinical Pharmacology																	
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites)	Rotigotine/ 1.125mg up to 2.25mg/ silicone patch	One paraspinal side: 3 cm between Rotigotine 1.125 mg/2.5 cm2 PBO 2.5 cm2 SLS 0.1% (high irritancy ctrl) 0.9% NaCl (low irritancy ctrl) Opposite paraspinal side: Rotigotine 1.125 mg/2.5 cm2 to 21 separate sites 1 cm between 200 □l	Hairless not shaved Bland, free of acne, tattoos, scars and folliculitre and Naevi		30 seconds		No heavy exertion	No crms lotion or like medicated soaps, lotions, shampoos (e.g. w SLS)	If > 20% lift may use tegoderm	full	No rubbing	Room Temp such that No shivering or sweating	Avoid waist bra			
SP673	Sensitization potential in healthy volunteers	Rotigotine/ 1.125mg/ silicone patch	Come Back to														
Pivotal Bioequivalence Study																	
SP581	BE evaluation of rotigotine from two different batches of silicone patches in healthy volunteers	Rotigotine/ 4.5mg/ silicone patch	Alternating sides of the fore axillary line of side of chest medio-axillar region of the trunk		Wash with H2O & soap prior & air dry Clean & Dry			No. In Bed. Full clothing. RT moderate	No med soaps, lotions, shampoos, creams, oints.,			No rubbing of patch.					
	Patient PK and Initial Tolerability Trial Reportsb b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.		Ventral Forearm				Not allowed										
	Population PK Trial Reportsc Population PK analyses were done in SP512 Part 1) and SP513 Part 1) which appear under "Controlled Clinical Trials."																
Patient PD and PK/PD Trial Reports																	
	Efficacy and Safety Trials																
SP534 Part 1	Evaluate safety and tolerability of fixed doses	Rotigotine/ 9.0mg and 13.5mg/ silicone patch	upper abdomen (above the umbilicus) alternating sides		Healthy dry intact area												
SP534 Part 2	Evaluate safety and tolerability of dose escalation	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	upper abdomen (above the umbilicus)		Healthy dry intact area	Pxt											
SP535	Evaluate safety and tolerability	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	upper abdomen (above the umbilicus). Flank if needed alternating sides		Healthy dry intact area Wash with soap & water and dry							Press for 30 sec				Removal wash with soap and watter	
SP506	Evaluate efficacy, safety and tolerability	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	following right or left side body parts: upper or lower abdomen (above the umbilicus), flank if necessary			Pxt	Normal soap and dry			Hypo-allergenic tape supplied		Press for 20 to 30 sec.					

Study	Trial Objective(s)	Product(s)/ Regimen/Route	Application Site/Route	Hair	Prep of Area	Applied by whom	Washing	Activity	Skin Care Lotions etc.	Tape	Clothing	Comments	Batch	Lot	Date Made		
SP540	Evaluate efficacy and safety	Rotigotine/ maximum tolerated dose up to 18.0mg/ silicone patch															
Population PK/PD Trial Reports																	
SP512	Evaluate PK	Rotigotine/ 4.5mg, 9.0mg, 13.5mg/ silicone patch	6 Rotating sites on the skin of subjects alternating sides and alt upper and lower body upper abdomen, lower abdomen, flank, shoulder and/or upper arm, thigh, hip 14 days between applications to same site	Avoid	Healthy dry intact area	20-30 seconds	that it is acceptable for them to shower, swim etc whilst wearing the patches. However, excessive bathing should be avoided					Following removal of patches, subjects should be instructed to wash the skin, with warm water, to remove any adhesive residue. If this is not sufficient to remove all adhesive from the skin, baby oil or a mild detergent can be used. Acetone or rubbing alcohol should not be used for this purpose.				If irrit > 3 days contact investigator	
SP512 Part I	Evaluate efficacy, safety, and PK compared to placebo	Rotigotine/ 4.5mg, 9.0mg, 13.5mg/ silicone patch	6 Rotating sites on the skin of subjects alternating sides and alt upper and lower body upper abdomen, lower abdomen, flank, shoulder and/or upper arm, thigh, hip 14 days between applications to same site				Showering or swimming is allowed excessive bathing should be avoided.					Following removal of patches, subjects should be instructed to wash the skin, with warm water, to remove any adhesive residue. If this is not sufficient to remove all adhesive from the skin, baby oil or a mild detergent can be used. Acetone or rubbing alcohol should not be used for this purpose.					
SP513 Part I	Evaluate efficacy safety, and PK of rotigotine compared to placebo and ropinirole	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch Ropinirole/ 0.75-24.0mg/ oral	6 Rotating sites on the skin of subjects alternating sides and alt upper and lower body upper abdomen, lower abdomen, flank, shoulder and/or upper arm, thigh, hip 14 days between applications to same site	Avoid Shave at least 3 days prior	Healthy dry intact area	20-30 seconds						Following removal of patches, subjects should be instructed to wash the skin, with warm water, to remove any adhesive residue. If this is not sufficient to remove all adhesive from the skin, baby oil or a mild detergent can be used. Acetone or rubbing alcohol should not be used for this purpose.					
Uncontrolled Clinical Trials																	
SP512 Part IId (SP702)	Evaluate long-term safety	Rotigotine/ Year 1=up to 13.5mg, Years 2-4=up to 36.0mg/ silicone patch															
SP513 Part IId	Evaluate long-term safety	Rotigotine/ Year 1=up to 18.0mg, Years 2-4=up to															

Study	Trial Objective(s)	Product(s)/ Regimen/Route	Application Site/Route	Hair	Prep of Area	Applied by whom	Washing	Activity	Skin Care Lotions etc.	Tape	Clothing	Comments	Batch	Lot	Date Made		
(SP716)		36.0mg/ silicone patch															
Other Trial Reports																	
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease	Rotigotine/ 9.0mg to [redacted]															
SP511	Assess dose groups of rotigotine in subjects with advanced Parkinson's disease	Rotigotine/ 9.0mg, 18.0mg, 27.0mg/															
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease	Rotigotine/ 18.0mg and 27.0mg/ silicone patch															
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's disease	Rotigotine/ up to 27.0mg/ silicone patch															
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease	Rotigotine/ up to [redacted] silicone patch															
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS	Rotigotine/ 1.125mg, 2.25mg, 4.5mg/ silicone patch															
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS	Rotigotine/ 1.1.25mg, 2.25mg, 4.5mg, 6.75mg [redacted] silicone patch															

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

Table 109 Study Designs - PK Sampling

	Product(s)/ Regimena/Route	Rx Arm	Plasma		Total	Sampling Site	Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal						
Initial Exploratory PK/PD Proof of Concept Studies										
SP803	Rotigotine/ maximum tolerated dose/ intravenous	A	A: Initial: Amend I: At or near max anticipated dose Pre, 2 and 5 min into infusion Amend III only at a single dose at or near max	A: Initial: At or near max anticipated dose 0, 30, 60, 90, 120, 180, 240, 300 min post infusion Amend I: then 0, 30, 60, 90, 120, 180, 240, 300 min post infusion Amend II: only thru 180 min post infusion but at 2 separate doses at or near max dose. Amend III only at a single dose at or near max						
		B	B: At or near max anticipated dose Amend I: At or near max anticipated dose 0, 15, 30, 60, 120, 180 min into infusion Amend II Only at a single dose level but time points may change based on t1/2 from phase A	B: At or near max anticipated dose Amend I: At or near max anticipated dose 0, 2, 5, 10, 20, 30, 60, 90, 120, 180 min post infusion Amend II Only at a single dose level but time points may change based on t1/2 from phase A						
SP804	Rotigotine/ maximum tolerated dose/ intravenous	Day 1	0, 0.25, 0.5 hr during last infusion.	10, 20, 40, 60, 90, 120, 150, 180, 240 post						
		Day 2	0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 during infusion	10, 20, 40, 60, 90, 120, 150, 180, 240 post						
SP805	Rotigotine/ optimal dose/ intravenous		End of dose escalation before CIVI then q 1h during CIVI until 5 PM and when changing infusion rate Day 2 – 7 q 4 hr and prior to changing rate							
Formulation Development										

	Product(s)/ Regimena/Route	Rx Arm	Plasma				Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal	Total	Sampling Site				
Mass Balance										
SP610	Rotigotine/ 1.2mg and 4.5mg/ infusion solution and silicone patch		0, 1, 2, 4, 6, 8, 10,12, 16, 20, 24 IV 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12	1, 2, 4, 8, 12, 24 hrs 2, 4, 8, 12, 18, 24, 36, 60, 84, 108, 132, 156, 180, 204	48 216	Contralateral arm	0-48 0-216	0-216		
SP606	Rotigotine/ 4.5mg/ silicone patch		0, 2, 4, 6. 8, 12, 24	24, 48, 72	96	Contralateral arm	0-96 hrs	0-96 hrs	0 post removal wipe 10 x with 5% SLS cotton wool rolls	16 @ 96 hours
SP503	Rotigotine/ 4.5mg/ silicone patch		Day 1: 0,1,2,4,6,12,24 Day 2-12: 48,72,96,120,144,168,192,216,240,264,288 Day 13: 312,316,320,324,336 0, 4, 8, 12, 24	Day 14: 0, 1, 2, 3, 4, 6, 8, 14, 24, 36, 48						
Intrinsic Factors										
SP630	Rotigotine/ 4.5mg, 9.0mg, 13.5mg (once daily for 6 days each), 18.0mg (once daily for 12 days) silicone patch		Day 6, 13, 19: pre Day 25, 26, 28 & 29: 0.5 pre and 4, 8, 12 h post Day 27 & 30: Pre, 1, 2, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, and 23.5 hours after patch application				Day 27 & 30: 0-24 hours			
SP596	Rotigotine/ 4.5mg/ silicone patch		0, 1, 2, 4, 6, 8, 10, 12, 15, 23, 24, 25, 26, 27, 28, 30, 36, 48	0, 1, 2, 3, 4, 6, 12, 24						
SP717	Rotigotine/ 4.5mg/ silicone patch		predose, 1, 2, 4, 8, 12, 16, 24, 25, 26, 28, 30, 33, 36, 48 and 60 hours after administration	0, 1, 2, 4, 6, 9, 12, 24 and 36 hours			predose, 0-24 h, 24-48 h, 48-60 h			
SP718	Rotigotine/ 2.25mg, 4.5mg, 9.0mg (once		day 1 predose (days 3 and 6) 0, 1, 2, 4, 8, 12, 16, 24 hours	Days 10-11 0, 1, 2, 4, 6, 9, 12, and 24 hours						

	Product(s)/ Regimena/Route	Rx Arm	Plasma				Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal	Total	Sampling Site				
	daily over 3 days each)/ silicone patch		(days 9-11) 0, 1, 2, 4, 8, 12, 16, 24, 25, 26, 28, 30, 33, 36 and 48 hours after administration							
SP671	Rotigotine/ 4.5mg/ silicone patch		0, 1, 2, 4, 6, 8, 10, 12, 23.5, 24, 26, 28, 30, 36, 48, 60, 72 h	0, 2, 4, 6, 12, 24, 36, 48h			Pre-dose 0-12,12-24,24-48,48-72			
SP672	Rotigotine/ 4.5mg/ silicone patch	Grp 1-4 Grp 5	0, 1, 2, 4, 8, 12, 16, 23.5, 24, 26, 28, 30, 36, 48, 60h 0, 6, 12,22 (prior to dialysis), 24 (total & free), 26 (art + venous), 28, 30, 36, 48,60	0, 2, 4, 6, 12, 24, 36h			Pre-dose 0-4, 4-8, 8-12, 12,12-24, 24-36, 36-48, 48-72			
Extrinsic Factor										
SP626	Rotigotine/ 4.5mg/ silicone patch		0, 1, 2, 4, 6, 8, 10, 12, 15, 23, 24, 25, 26, 27, 28, 30, 36, 48	0, 1, 2, 3, 4, 6, 12, 24						
SP627	Rotigotine/ 4.5mg (once daily over 2 days, 9.0mg (once daily over 4 days)/ silicone patch Cimetidine/800mg/ oral		Day 1: 0 Day 6 & 19: 0, 1, 2, 4, 8, 12, 23.5, 24, 25, 26, 28, 30, 32, 36, 40, 48	Day 7 and 20: 0, 1, 2, 4, 6, 8, 12, 16, 24			Day 1 -2-0 Day 6 and 19: 0-12,12-24			
SP628	Rotigotine/ 4.5mg (3 days), 9.0mg (6 days)/ silicone patch Levodopa/ 200mg carbidopa/ 50mg/ oral	Rotigotine	0, 1, 2, 4, 8, 12, 16, 24	0, 2, 4 ,6, 12, 24, 36			Day 8 pr 8 and days 9-11 or 11-13 0-24hr			
		CD/LD Fasted	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12							
SP670	Rotigotine/ 4.5mg/ silicone patch Domperidone/ 30mg/ oral	Domperidone Fasted	Day 1: 0 Day 4: 0, 1, 2, 4, 8, 12, 23.5, 24, 26, 28, 30, 36, 48 Extra on day 4	0, 2, 4, 6, 12, 24	28		Day 4: 0-12, 12-24			
Clinical Pharmacology										
SP629	Rotigotine/ 1.125mg up to 2.25mg/ silicone patch		Come back to							
SP673	Rotigotine/ 1.125mg/ silicone patch		Come back to							

	Product(s)/ Regimena/Route	Rx Arm	Plasma				Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal	Total	Sampling Site				
Pivotal Bioequivalence Studies										
SP581	Rotigotine/ 4.5mg/ silicone patch		0, 1, 2, 4, 6, 8, 12, 15, 23, 24	1, 2, 3, 4, 6, 8, 16, 24	48		0-48			
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	Rotigotine/ 9.0mg and 13.5mg/ silicone patch		Day 1: Pre, 2, 4, 6 Days 2-4 & 8, 15, 22,: Pre	Day 5: 0, 2, 4, 6 Day 29: 0, 1,2,4,8,12						
SP534 Part 2	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch		Day 1: pre, 2, 6, 12, 23 hrs post Days 8, 15, 22 (first day of new dose): 0, 2, 6, 12, 23 hrs post	Days 29, 0, 2,4,6 post						
SP535	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch		Days 1, pre Days 8, 15, 22, 29: 24 hr							
SP506	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch		Days: 28, 49, 77: 24 hr							
SP540	Rotigotine/ maximum tolerated dose up to 18.0mg/ silicone patch		Days ½, 8/9, 15/16, 22/23, 27/28: 23, 23.5 hrs	1,2,4,8 MP1, MP2, MP11, MP 12 this is according to appendix						
	Healthy Subject PK and Initial Tolerability Trial Reports		0, 1, 2, 4, 6, 12, 24 and q24 hrs x 11 days (hrs 48 – 288 Days 3 – 13) then 0, 4, 8, 12, and 24 on day 14 the last day of patch wear,	1, 2, 3, 6, 8, 14, 24, 36, 48						
Patient PK and Initial Tolerability Trial Reportsb b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.										
SP512	Rotigotine/ 4.5mg, 9.0mg, 13.5mg/ silicone patch									
Population PK Trial Reportsc Population PK analyses were done in SP512 Part 1) and SP513 Part 1) which appear under "Controlled Clinical Trials."										
Patient PD and PK										

	Product(s)/ Regimena/Route	Rx Arm	Plasma				Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal	Total	Sampling Site				
/PD Trial Reports										
Efficacy and Safety Trials										
Pop PK/PD Trial Reports										
SP512 Part I	Rotigotine/ 4.5mg, 9.0mg, 13.5mg/ silicone patch		Days: 1, 16, 72, 100, 128, 174, 213 Week: 1,2,3,4,12,20,28,32,w/d							
SP513 Part I	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch Ropinirole/ 0.75-24.0mg/ oral		Day 1, 8, 15, 22, 29, 43, 57, 71, 85, Week 0,1,2,3,4,6,8,10,12,13,17,21,24,29,33,37,41,w/d							
	Uncontrolled Clinical Trials									
SP512 Part IId SP702	Rotigotine/ Year 1=up to 13.5mg, Years 2-4=up to 36.0mg/ silicone patch		End of Week: 2,3,4,8,16,28,40,52,Dose Changes, End of Rx, 4 wks post d/c Prior to patch change and 1 to 4 hours after							
SP513 Part IId SP716	Rotigotine/ Year 1=up to 18.0mg, Years 2-4=up to 36.0mg/ silicone patch		Week 1,2,3,4,5,6,7,8,9,10,q12 thru 24 mo EoRx/wd. 4 wk fu							
Other Trial Reports										
SP511	SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease	Rotigotine/ 9.0mg to							
SP650 Part Id	Rotigotine/ 18.0mg and 27.0mg/ silicone patch									

	Product(s)/ Regimena/Route	Rx Arm	Plasma				Urine	Feces	Skin Wash	Skin Stipping
			During Rx	Post Removal	Total	Sampling Site				
SP650 Part IId (SP715)	Rotigotine/ up to 27.0mg/ silicone patch									
SP591	Rotigotine/ up to [redacted] silicone patch									
SP666	Rotigotine/ 1.125mg, 2.25mg, 4.5mg/ silicone patch									
SP709d	Rotigotine/ 1.1.25mg, 2.25mg, 4.5mg, 6.75mg [redacted] silicone patch									

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

Table 110 Study Designs - PD Measurements

Study No.	Trial Objective(s)	Rx Arm	Clinical Measures: PD, Sleep, etc.	Others: Chemistry, etc.	Comments
Initial Exploratory PK/PD Proof of Concept Studies					
SP803	IV PK/PD	A	A: Modified Columbia Scale performed frequently post infusion for at least 30 min or until activity dissipated at q-dose level (per protocol) Q 2 min (per study report) Analysis Post vs. Pre	A: Prolactin at or near max anticipated dose 0, 30, 60, 90, 120, 180, 240, 300 min post infusion	A: IOPs at or near max anticipated dose Amend II: IOP optional
SP803	IV PK/PD	B	Modified Columbia Scale evaluated at each dose level	B: Prolactin at or near max anticipated dose no times given in text	B: IOPs ibid Amend II: IOPs optional
SP804	IV PK PD	Day 1:	MCRS Q 15 min until end of dosing or until abated Over axis and 4 extremities as well as for gait dyskinesia sep		Domperidone administered propylactically
		Day 2:	MCRS Q 30 min until end of dosing or until abated		
SP805			Day -1 q 4 h Day 1 q 30 min Then q 1 hr until 5 pM during CIVI Days 2 – 7 q 4 h until 5 pM	Aldosterone q AM Da 7 24g urine electrolites	
Formulation Development					
SP799	Evaulate safety and PK in healthy volunteers				VS times same as PK Holter vs. 12 lead stated in diff places in protocol confusing
SP800	Define PK and evaluate safety		Baseline, Pre, 1, 2, 4, 6, 8, 12, 24, 30, 31, 32, 33, 34, 36 Videotape Baseline , Pre, 8, 12, 24 MCRS		
SP801	Define PK and safety in healthy volunteers		None		Prochlorperazine 5-10 mg IM PRN
SP802	Define PK, dose response, evaluate efficacy and safety in subjects with advanced Parkinson's disease				
SP502	Comparative BA of [redacted] vs. silicone patches in healthy volunteers				
Mass Balance Studies					
SP610	Absorption, metabolism and excretion of 14C-SPM 962 in healthy volunteers	Patch			
SP606	Absorption and excretion of 14C-SPM 962 in healthy volunteers				

Study No.	Trial Objective(s)	Rx Arm	Clinical Measures: PD, Sleep, etc.	Others: Chemistry, etc.	Comments
Healthy Subject PK and Initial Tolerability Trial Reports					
SP503	Evaluate PK, safety and tolerability in healthy volunteers			Prolactin, HGH, LH-FSH, TSH, Aldosterone -26,-20,-12,-6,-4,-2, Day 1: 1, 2, 3, 4 hrs Last Day(day 14): 18, 20, 22 4 and 12 hrs post removal of last patch	
Intrinsic Factors					
SP630	Define PK with rotating patch application sites, evaluate ECG effects, safety and tolerability		Epworth sleepiness scale		
SP596	Evaluate the relative BA and PK in Caucasian vs. Black subjects				
SP671	Evaluate PK, safety and tolerability in subjects with impaired hepatic function				
SP672	Evaluate PK, safety and tolerability in subjects with impaired renal function				
SP717	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects				
SP718	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects				Labs predose day 1, days 3, 6, 9 ,11 and follow-up
Extrinsic Factors					
SP626	Investigate influence of application site on the bioavailability of rotigotine				
SP627	Evaluate influence of cimetidine on PK of rotigotine in healthy volunteers				
SP628	Evaluate PK of rotigotine and levodopa/ carbidopa in subjects with RLS				
SP670	Evaluate influence of domperidone on PK, safety and tolerability of rotigotine in healthy volunteers				
Clinical Pharmacology Studies					
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites)				
SP673	Sensitization potential in healthy volunteers				

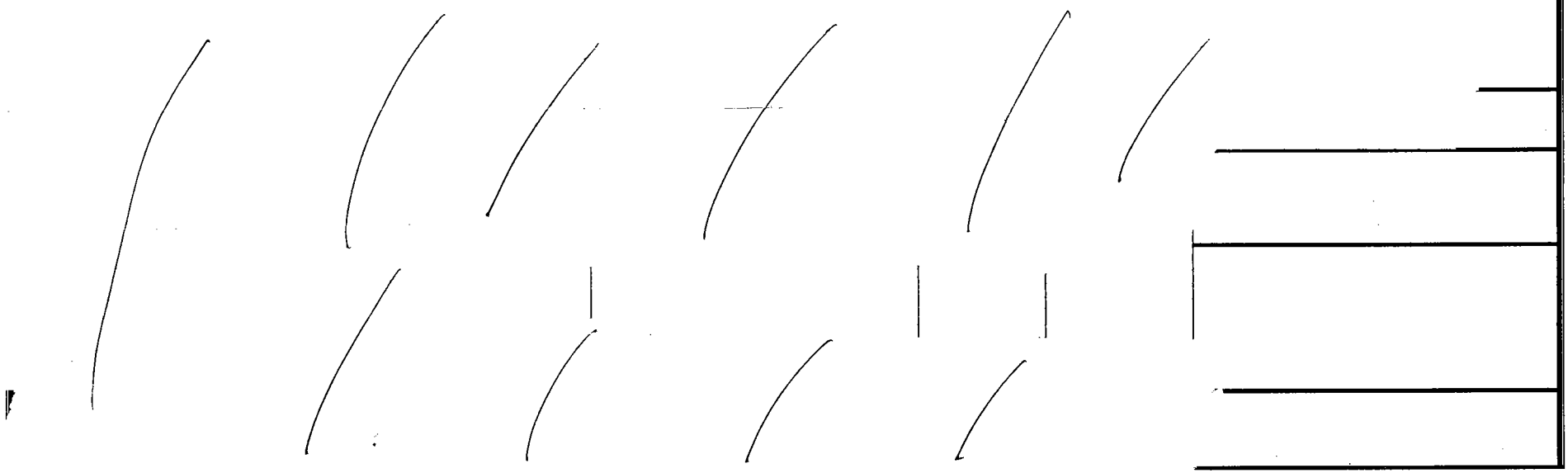
Study No.	Trial Objective(s)	Rx Arm	Clinical Measures: PD, Sleep, etc.	Others: Chemistry, etc.	Comments
	Patient PK and Initial Tolerability Trial Reportsb b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.				
Pivotal Bioequivalence Studies					
SP581	BE evaluation of rotigotine from two different batches of silicone patches in healthy volunteers				
Population PK Trial Reportsc Population PK analyses were done in SP512 Part 1] and SP513 Part 1] which appear under "Controlled Clinical Trials."					
Patient PD and PK/PD Trial Reports					
SP534 Part 1	Evaluate safety and tolerability of fixed doses				
SP534 Part 2	Evaluate safety and tolerability of dose escalation		H&Y UPDRS Day 1 & 29		
SP535	Evaluate safety and tolerability			Prolactin Days 1 8,15,22,29:– 1, -0.5, 23, 23.5	
SP506	Evaluate efficacy, safety and tolerability		UPDRS: Days 0, 14, 28, 49, 77, 98 H&Y Days: 0, 28 ,77		
SP540	Evaluate efficacy and safety		UPDRS III, H&Y Days ½, 8/9, 15/16, 22/23, 27/28:		
	Population PK/PD Trial Reports				
SP512 Part I	Evaluate efficacy, safety, and PK compared to placebo		CGI: 1,8,15, 16, 100, 174, 213 UPDRS 1,8,15,16, 44, 72, 100, 128, 156, 174, 213 H&Y: 1, 174	Prolactin Days: 1, 16, 72, 100, 128, 174, 213	Epworth Sleepiness Scale 1, 16, 100, 174 Euroqol EQ-5D 1, 174
SP513 Part I	Evaluate efficacy safety, and PK of rotigotine compared to placebo and ropinirole,	?	CGI: Week 0,1,2,3,4,6,8,10,12,13,25,37,41, w/d UPDRS (II-IV) Day 1, 8, 15, 22, 29, 43, 57, 71, 85, Week 0,1,2,3,4,6,8,10,12,13,17,21,24,29,33,37,41,w/d H&Y: Pre, Week: 37, WD	Prolactin Week: 1, 4, 12, 20, 28, 32	Epworth Sleepiness Scale: Week 0,13,25,37w/d Euroqol EQ-5D: Week 0, 37,w/d
Uncontrolled Clinical Trials					
SP512 Part IId SP702	Evaluate long-term safety		CGI: Week 2,3,4,8, 16,28,40,52 q12, EoRx/wd. 4 wk fu UPDRS (II-IV) Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd. 4 wk fu Motor Complication Assessment: Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd 4 wk fu H&Y: 8, 10, q12, EoRx/wd		Epworth Sleepiness Scale Week: 4,28,52 q12, w/d Euroqol EQ-5D Week 4, 52, q12, EoRx/wd
SP513	Evaluate long-term safety		CGI: Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd. 4 wk fu		Epworth Sleepiness Scale Week: 5,8,10,q12,

Study No.	Trial Objective(s)	Rx Arm	Clinical Measures: PD, Sleep, etc.	Others: Chemistry, etc.	Comments
Part IId SP716			UPDRS (II-IV) Week 1,2,3,4,8, 16,28,40,52 q12, EoRx/wd. 4 wk fu Motor Complication Assessment: Week 1,2,3,4,8,16,28,40,52 q12, EoRx/wd 4 wk fu H&Y: 8, 10, q12, EoRx/wd		EoRx/wd Euroqol EQ-5D 5,10,q12, EoRx/wd
Other Trial Reports					
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease				
SP511	Assess dose groups of rotigotine in subjects with advanced Parkinson's disease				
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease				
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's disease				
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease				
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS				
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS				

a Daily dose, unless otherwise specified.
b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.
c Population PK analyses were done in SP512 (Part 1) and SP513 (Part 1) which appear under "Controlled Clinical Trials."
d Report includes data available as of 31 Dec 2003.
e The protocol and clinical trial report for SP540 refers to the trial as a single-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.
f The protocol and clinical trial report for SP533 refer to the trial as a double-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.
• 24, -23, -22, -20, -18, -12, 0, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 4, 8, 12, 24, 1, 2, 3, 4, 6, 8, 14, 24, 36, 48

Table 111 Study Designs - Safety Monitoring

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
Initial Exploratory PK/PD Proof of Concept Studies							
SP803	IV PK/PD	A	Not explicit. Appears likely spontaneous reports of observed.	HR BP same times as PD measures		~3x / wk	Dromperidone prophylactically for N/V Amend II: to Rx N/V as goal is to determine dose causing N/V
		B	Ibid	Amend III: Not every 2 min but q 30 min during infusion.		ibid	
SP804		Day 1	Spontaneous Reports or observed.	q 15 min until end of dosing or until abated	24 hr holter	Screen Day 1 , 2, post	
		Day 2	Spontaneous Reports or observed.	q 30 min until end of dosing or until abated	24 hr holter		
SP805			Q 4hr until 5 PM	Q 4 hr			
Formulation Development							



Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
Mass Balance							
SP610	Absorption, metabolism and excretion of 14C-SPM 962 in healthy volunteers	Patch	Pre, 3, 12, Day 2	Pre, 3, 12	At Patch removal	Pre, Post Drug, FU	
SP606	Absorption and excretion of 14C-SPM 962 in healthy volunteers		Protocol refers to CRF but CRF does not have specific times for assessments.	Screen, Pre, Post, FU		Post	
		IV	Pre, 3, 12, once qd up to 9 days post dose	Pre, 3, 12 supine	At end of infusion	Pre, Post drug, FU	
Healthy Subject PK and Initial Tolerability Trial Reports							
SP503	Evaluate PK, safety and tolerability in healthy volunteers		Prestudy, Q12 hr x 3 days, then q24 hrs until 3 days after last patch	HR BP Day -1:-24, -23, -22, -20, -18, -12 Day 1: 0, 1, 2, 4, 6, 12, 24 Days 3-13: q 24 h Day 14: 0, 4, 8, 12, 24 Post Removal:1, 2, 3, 4, 6, 8, 14, 24, 36, 48 hrs	Day -1:-24, -23, -22, -20, -18, -12 Day 1: 0, 1, 2, 4, 6, 12, 24 Days 3-13: q 24 h Day 14: 0, 4, 8, 12, 24 Post Removal:1, 2, 3, 4, 6, 8, 14, 24, 36, 48 hrs		
Intrinsic Factors							
SP630	Define PK with rotating patch application sites, evaluate ECG effects, safety and tolerability		Daily	Baseline Days 1, 2, 6, 13, 19,. 25,27,29,30, 31, 38		Three 12-lead ECGs (analyzed from 3 to 5 beats each) will be downloaded from the ⟵ flash card within 1 minute (providing 3 ECGs for each time point) at Baseline (Day –1), Day 27, and Day 30 at the following time points: 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 14,	

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
						16, 18, 20, 22, 23:30 hours. On Days 27 and 30 the time points are relative to application of the patch. On Days 25, 26, 28, and 29, three 12-lead ECGs 0, 4, 8, and 12 hours post dose.	
SP596	Evaluate the relative BA and PK in Caucasian vs. Black subjects		Continuously	Pre, 2,4,12,24,36 After 3 min in sitting position		Pre,2,6,25	
SP717	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects		qAM	BP & HR predose, 4, 12, 24, 36 and 48 h after administration		predose, 4, 12, 24, 36 and 48 h after administration	Labs predose day 1, days 3, 6, 9 ,11 and follow-up
SP718	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects			blood pressure and heart rate predose days 1, 3, 4, 6, 7, 9, 11 and follow -up		predose days 1, 3, 4, 6, 7, 9 , 11 and follow-up	
SP671	Evaluate PK, safety and tolerability in subjects with impaired hepatic function		Qday	Days 1-3: Pre, Day :3 4, 8, 12, 24, 48, 72 hr BP & HR After 5min in suprine		Days 1-3: Pre Day :3 4, 8, 12, 24, 48, 72 hr	
SP672	Evaluate PK, safety and		Qday	Pre, 4, 12, 24, 36, 72 hr and at FU		Pre, 2,4,12,24,36, and 72 hrs	

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
	tolerability in subjects with impaired renal function					After 5 min at rest	
Extrinsic Factor							
SP626	Investigate influence of application site on the bioavailability of rotigotine		Continuously	Pre, 2,4,12,24,36 After 3 min at rest sitting		Pre, 2, 6, 25	
SP627	Evaluate influence of cimetidine on PK of rotigotine in healthy volunteers		Each Day	blood pressure and heart rate Days 1-6 & 14-19 Predose, 2 , 4, and 12 hrs Days 7 & 20 2 hours post removal and @ D/C		Days 1-6 & 14-19 Predose, 2 , 4, and 12 hrs Days 7 & 20 2	
SP628	Evaluate PK of rotigotine and levodopa/ carbidopa in subjects with RLS		Each Day	Days 0, 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, FU 0,1, 6, 12, 13 hours		Days 0, 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, FU 0,1, 6, 12, 13 hours	
SP670	Evaluate influence of domperidone on PK, safety and tolerability of rotigotine in healthy volunteers		Qday	Days 0- 6: 0 hrs Day 4: also at 4 & 8 hours		Days 1-3, 5, 6: 0 Day 4: 0, 4 ,8	
Clinical Pharmacology							
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites)		Come back to				
SP673	Sensitization potential in healthy volunteers		Come back to				
Pivotal Bioequivalence Studies							

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
SP581	BE evaluation of rotigotine from two different batches of silicone patches in healthy volunteers			SBP, DBP, Pulse Sitting Pre and Post study		Pre and Post Study	
Patient PD and PK/PD Trial Reports							
Patient PK and Initial Tolerability Trial Reportsb b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.							
SP534 Part 1	Evaluate safety and tolerability of fixed doses		Ea visit	Ea Visit			
SP534 Part 2	Evaluate safety and tolerability of dose escalation					Day 1: Pre, 2, 4, 6 Days 2-4 & 8, 15, 22,: Pre Day 5 & 29: 0, 6	
SP535	Evaluate safety and tolerability		Weekly	Days -1, 1, 8,15,22,29 0, 2, 4,6,8,10.12	Day 1 Continuous	Days -1, 1, 8,15,22,29 0, 2, 4,6,8,10.12, Day 2 24	
SP506	Evaluate efficacy, safety and tolerability		Days 0, 14, 28, 49 77, 98	Days 0, 14, 28, 49 77, 98		Days 0, 14, 28, 49 77, 98	
SP540	Evaluate efficacy and safety		Weekly	Days ½, 8/9, 15/16, 22/23, 27/28: QOhr while awake prior to removal day.		Days ½, 8/9, 15/16, 22/23, 27/28: prior to removal day.	
Population PK Trial Reportsc Population PK analyses were done in SP512 Part 1) and SP513 Part 1] which appear under "Controlled Clinical Trials."							
SP512	Evaluate PK						
SP512 Part I	Evaluate efficacy, safety, and PK compared to placebo		1,8,15,16, 44, 72, 100, 128, 156, 174, 213			1, 15,16, 100, 174, 213	
SP513 Part I	Evaluate efficacy safety, and PK of rotigotine compared to		Day 1, 8, 15, 22, 29, 43, 57, 71, 85, Week 0,1,2,3,4,6,8,10,12,13,17,21,24,29,33,37,41,w/d	Day 1, 8, 15, 22, 29, 43, 57, 71, 85, Week 0,1,2,3,4,6,8,10,12,13,17,21,24,29,33,37,41,w/d		Week 0, 4,6, 13,25,37,41, w/d	Wt: Day 1, 8, 15, 22, 29, 43, 57, 71, 85, Week 0,1,2,3,4,6,8,10,12,13,17,21,24,29,33,37,41,w/d Labs: Week 0,1,2,3,4,6,8,10,12,13,25,37,41, w/d

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
	placebo and ropinirole,						
Uncontrolled Clinical Trials							
SP512 Part IId SP702	Evaluate long-term safety					Baseline, Week 1,3, 4,16,28,32,w/d	
SP513 Part IId SP716	Evaluate long-term safety		Q visit Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd. 4 wk fu	Qvisit Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd. 4 wk fu		Week 5,8,10,q12, EoRx/wd. 4 wk fu	Labs & Wt Week 1,2,3,4,5,6,7,8,9,10,q12, EoRx/wd. 4 wk fu
Other Trial Reports							
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease						
SP511	Assess dose groups of rotigotine in subjects with advanced Parkinson's disease						
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease						
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's						

Study No.	Trial Objective(s) Description	Arm	AEs	VS	ECGs		Comments
					Holter	12 Lead ECG	
	disease						
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease						
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS						
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS						

a Daily dose, unless otherwise specified.
b Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, SP533, and SP591.
c Population PK analyses were done in SP512 (Part 1) and SP513 (Part 1) which appear under "Controlled Clinical Trials."
d Report includes data available as of 31 Dec 2003.
e The protocol and clinical trial report for SP540 refers to the trial as a single-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.
f The protocol and clinical trial report for SP533 refer to the trial as a double-blind trial; however, investigator and subjects were aware that rotigotine was being administered. The trial was blinded with respect to dose.
- 24, -23, -22, -20, -18, -12, 0, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 4, 8, 12, 24, 1, 2, 3, 4, 6, 8, 14, 24, 36, 48

Table 112 Study Designs - Tolerance and Adhesion

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
Initial Exploratory PK/PD Proof of Concept Studies										
SP803										
SP804										
SP805										
Formulation Development										
Mass Balance										
SP610		ibid	ibid			0 full 1 edges slightly peeled off 2 patch shifted or partially peeled off 3 Entirely Off				
SP606	Pre removal Only.	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm)	Also had another full CRF for Morphology, Localizaiton Margin & Rx of skin rxns	—	—				
Healthy Subject PK and Initial Tolerability Trial Reports										
SP503	0.5, 1, 3 h post each TDS removal	None Sl	None Marginal	Photo Documentation	Prior to each TDS removal	Very good Good	Very good Good	Photo Documentation	Easy Difficult	

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
		Evident Mod Severe	Sl (i.e. elevated) Evident (≤ 1 mm) Severe (> 1 mm) & extending beyond TDS area			Average Poor Difficult	Average Bad Fell Off			
Intrinsic Factors										
SP630	Skin assessment at each of the 6 application sites (abdomen, flank, shoulder, upper arm, thigh, and hip) will be performed prior to the first application and at least 120 minutes after removal on Days 1, 3, 6, and 25, 27, 29, and 31.			Skin reactions Dermal response: 0 = no evidence of irritation 1 = minimal erythema, barely perceptible 2 = definite erythema, readily visible; or minimal edema or minimal papular response 3 = erythema and papules 4 = definite edema 5 = erythema, edema, and papules 6 = vesicular eruption 7 = strong reactions spreading beyond test site Other effects: A = slight glazed appearance B = marked glazing C = glazing with peeling and cracking F = glazing with fissures G = film of dried serous exudate covering all or part of the patch site H = small petechial erosions and/or scabs Subjective effects such as itching and/or pain at the skin sites as well as skin effects due to occlusive reactions (e.g. folliculitis, miliaria) will be documented.	Patch adhesiveness is assessed prior to each patch removal on Days 1, 3, 6, 13, 19, 25 through 31.	0 = 90% or greater adhered (essentially no lift off of the skin) 1 = 75 - <90% adhered (some edges only lifting off of the skin) 2 = 50 - <75% adhered (less than half the system lifting off of the skin) 3 = <50% adhered (more than half the system lifting off of the skin without falling off) 4 = patch detached (patch completely off the skin				
SP596	Pre, 3, 24 hr post removal	0 None 1 Sl	0 None 1 Marginal		Prior to removal	0 none 1 edge lift				

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
		2 Evident 3 Papular 4 Vesiculation	2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending beyond TDS area			2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
SP717	predose, 24 h (immediately after patch removal), 27 h (3 h after patch removal), 48 h (24 h after patch removal)	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending		Prior to removal	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
SP718	prior to each patch application, 0, 3h and 24 h after each patch removal	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending		each patch application	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
SP671	predose, 27 h (3 h after patch removal), 48 h (24 h after patch removal)	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending beyond TDS area		Prior to removal	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
SP672	predose, 27 h (3 h after patch removal), 48 h (24 h after patch removal)	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending beyond TDS area		Prior to removal	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%	6	Erythema 1-2 and edema 1-2 not reported as AES		
Extrinsic Factors										
SP626	Pre, 3, 24 hr post removal	0 None 1 Sl 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 Sl (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending		Prior to removal	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
SP627	Pre, 3, 24 hr post removal	0 None 1 Sl 2 Evident	0 None 1 Marginal 2 Sl (i.e. elevated)		Prior to removal	0 none 1 edge lift 2 1%-19%				

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
		3 Papular 4 Vesiculation	3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending			3 20% - 49% 4 50%-79% 5 80%-100%				
SP628	Day 1 Grp A Predose Day 3 Grp B Predose 3, 24 hr post removal	0 None 1 SI 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 SI (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending		Prior to removal qd	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%		According to flow chart, but chart is confusing therefore uncertain if correct		
SP670	Day 1, 4 & 5 of each period	0 None 1 SI 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 SI (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm) & extending		Prior to removal qd	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79% 5 80%-100%				
Clinical Pharmacology										
SP629	QD, prior to first 0.833-1 hr post 24 hr post last	Dermal response: 0 = no evidence of irritation 1 = minimal erythema, barely perceptible 2 = definite erythema, readily visible; or minimal edema or minimal papular response 3 = erythema and papules 4 = definite edema 5 = erythema, edema, and papules 6 = vesicular eruption 7 = strong reactions spreading beyond test site Other effects: A = slight glazed appearance B = marked glazing C = glazing with peeling and cracking F = glazing with fissures G = film of dried serous exudate covering all or part of the patch site H = small petechial erosions and/or scabs		Scored until max score allowed is reached i.e. 3 or higher or ≥F Also subjective effects recorded		Adhesiveness score: 0 = 90% adhered (essentially no lift off of the skin) 1 = 75 - < 90% adhered (some edges only lifting off of the skin) 2 = 50 - < 75% adhered (less than half the system lifting off of the skin) 3 = < 50% adhered (more than half the system lifting off of the skin without falling off) 4 = patch detached (patch completely off the skin)			Photo doc	
SP673	Come back to									
Pivotal BE Study										
SP581	0, 12, 24 hr post removal	0 None 1 SI 2 Evident 3 Papular 4 Vesiculation	0 None 1 Marginal 2 SI (i.e. elevated) 3 Evident (≤ 1 mm) 4 Severe (> 1 mm)		2, 6, 12, 24 h	0 none 1 edge lift 2 1%-19% 3 20% - 49% 4 50%-79%				

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
			& extending beyond TDS area			5 80%-100%				
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	Ea Visit	0 none 1 minimal 2 definite 3 erythema and papules	4 definite edema 5 erytema edema and papules 6 vesicles 7 strong reaction beyond test site							
SP534 Part 2										
SP535	Day 1,8,15,22,29 pre/post									
SP506										
SP540	Day 1,8,15,22,29 pre/post	Dermal response: 0 = no evidence of irritation 1 = minimal erythema, barely perceptible 2 = definite erythema, readily visible; or minimal edema or minimal papular response 3 = erythema and papules 4 = definite edema 5 = erythema, edema, and papules 6 = vesicular eruption 7 = strong reactions spreading beyond test site								
Population PK/PD Trial Reports										
SP512 Part I	1,8,15,16, 44, 72, 100, 128, 156, 174, 213									
SP513 Part I										

Study No.	Tolerance				Adhesion				Removal	
	Freq	Scoring		Comments	Freq	Scoring		Comments		
		Redness	Edema			Investigator	Subject		Investigator	Subject
Uncontrolled Clinical Trials										
SP512 Part IId SP702										
SP513 Part IId SP716	Week 2,3,4,5,6,7,8,9,10,q12, EoRx/wd.	Not specified in protocol	Not specified in protocol							
Other Trial Reports										
SP533										
SP511										
SP650 Part Id										
SP650 Part IId (SP715)										
SP591										
SP666										
SP709d										

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

Table 113 Study Designs – Assays and Sample Handling

Study No	Trial Objective(s)	Analyte(s)	Matrix	Anticoagulant	Centrifugation	Storage Container	Freezing	Storage Temp	Analysis Site	Assay	Date	Comments
Initial Exploratory PK/PD Proof of Concept Studies												
SP803	Evaluate safety and efficacy	N-0923	Plasma									
SP804	Evaluate safety and efficacy	N-0923	Plasma									
SP805	Evaluate safety and efficacy		Plasma									
Formulation Development												
Mass Balance												
SP610	Absorption, metabolism and excretion of 14C-SPM 962 in healthy volunteers	Total Radioactivity	Whole Blood							LSC		
		Total Radioactivity Rotigotine 2 Major Metabolites	Plasma							HPLC- LSC HPLC-MS		
			Urine									
			Feces									
SP606	Absorption and excretion of 14C-SPM 962 in healthy volunteers	Rotigotine Total Radioactity	Plasma							LC-MS/MS		
		Total Radioactivity	Urine							LSC		

Study No	Trial Objective(s)	Analyte(s)	Matrix	Anticoagulant	Centrifugation	Storage Container	Freezing	Storage Temp	Analysis Site	Assay	Date	Comments
			Feces									
			Skin Wash									
			Skin Strip							LSC		
			Patches									
Healthy Subject PK and Initial Tolerability Trial Reports												
SP503	Evaluate PK, safety and tolerability in healthy volunteers	Parent Catacholamine metabolites	Plasma					20 °C				
Intrinsic Factors												
SP630	Define PK with rotating patch application sites, evaluate ECG effects, safety and tolerability											
		Rotigotine and main metabs	Urine					-20 °C				
SP596	Evaluate the relative BA and PK in Caucasian vs. Black subjects	Rotigotine	Plasma					-20 °C		LC-MS/MS		
SP717	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects	rotigotine (unconjugated and total), despropyl- and desthienylmetabolites (unconjugated and total)	Plasma					-70 °C		LC-MS/MS		
SP718	Evaluate PK, safety and tolerability in healthy Japanese vs. healthy Caucasian subjects	rotigotine (unconjugated and total),	Plasma					-70 °C		LC-MS/MS		
SP671	Evaluate PK, safety and tolerability in subjects with impaired hepatic function	rotigotine (unconjugated and total),	Plasma					-20 °C		LC-MS/MS		
		rotigotine (unconjugated and total), despropyl- and desthienylmetabolites (unconjugated and total)	Urine							LC-MS/MS		
SP672	Evaluate PK, safety and tolerability in subjects with impaired renal function	rotigotine (unconjugated and total),	Plasma					-70 °C		LC-MS/MS		
		rotigotine (unconjugated and total),	Urine							LC-MS/MS		

Study No	Trial Objective(s)	Analyte(s)	Matrix	Anticoagulant	Centrifugation	Storage Container	Freezing	Storage Temp	Analysis Site	Assay	Date	Comments
		despropyl- and desthienylmetabolites (unconjugated and total)										
Extrinsic Factor												
SP626	Investigate influence of application site on the bioavailability of rotigotine	Rotigotine uncong	Plasma							LC-MS/MS		
SP627	Evaluate influence of cimetidine on PK of rotigotine in healthy volunteers	Rotigotine	Plasma							LC-MS/MS		
		rotigotine (unconjugated and total), despropyl- and desthienylmetabolites (unconjugated and total)	Urine									
SP628	Evaluate PK of rotigotine and levodopa/ carbidopa in subjects with RLS	rotigotine (unconjugated and total),	Plasma							LC-MS/MS		
		Carbidopa, Levodopa, 3-O-methyldopa	Plasma							HPLC-ECD		
		rotigotine (unconjugated and total), despropyl- and desthienylmetabolites (unconjugated and total)	Urine							LC-MS/MS		
SP670	Evaluate influence of domperidone on PK, safety and tolerability of rotigotine in healthy volunteers	rotigotine (unconjugated	Plasma									
		Catechol-rotigotine rotigotine (unconjugated and total), despropyl- and desthienylmetabolites (unconjugated and total)	Urine									
Clinical Pharmacology												
SP629	Evaluate cumulative skin irritation after repeat application, (same skin site vs. rotating skin sites)	Come back to										
SP673	Sensitization potential in healthy volunteers	Come back to										
Pivotal BE Study												
SP581	BE evaluation of rotigotine	Rotigotine	Plasma									

Study No	Trial Objective(s)	Analyte(s)	Matrix	Anticoagulant	Centrifugation	Storage Container	Freezing	Storage Temp	Analysis Site	Assay	Date	Comments
.	from two different batches of silicone patches in healthy volunteers				@ 4 °C w/i 15 min of collection							
Patient PD and PK/PD Trial Reports												
Patient PK and Initial Tolerability Trial Reports by Additional patient PK analyses were done in Phase 2 trials SP534 Part I, SP534 Part II, SP535, SP506, SP540, (SP533, and SP591 – Advanced PD).												
Efficacy and Safety Trials												
SP534 Part 1	Evaluate safety and tolerability of fixed doses		Plasma									
SP534 Part 2	Evaluate safety and tolerability of dose escalation											
SP535	Evaluate safety and tolerability		Plasma							LC-MS/MS		
SP506	Evaluate efficacy, safety and tolerability		Plasma									
SP540	SB, Fixed dose escalating PII Efficacy Study		Plasma									
	Population PK/PD Trial Reports											
SP512	Evaluate PK											
SP512 Part I	Evaluate efficacy, safety, and PK compared to placebo	N about 50 Rotigotine contralateral	Plasma									
SP513 Part I	Evaluate efficacy safety, and PK of rotigotine compared to placebo and ropinirole,											
Uncontrolled Clinical Trials												
SP512 Part IId SP702	Evaluate long-term safety											
SP513 Part IId SP716	Evaluate long-term safety											
Other Trial Reports												
SP533	Evaluate safety, efficacy and tolerability in subjects with advanced Parkinson's disease											
SP511	Assess dose groups of rotigotine in subjects with											

Study No	Trial Objective(s)	Analyte(s)	Matrix	Anticoagulant	Centrifugation	Storage Container	Freezing	Storage Temp	Analysis Site	Assay	Date	Comments
	advanced Parkinson's disease											
SP650 Part Id	Evaluate efficacy and safety in subjects not well controlled on levodopa in subjects with advanced Parkinson's disease											
SP650 Part IId (SP715)	Evaluate long-term safety in subjects with advanced Parkinson's disease											
SP591	Evaluate safety and tolerability in subjects with advanced Parkinson's disease											
SP666	Evaluate dose-response relationship, safety and tolerability in subjects with RLS											
SP709d	Evaluate safety and efficacy of rotigotine in subjects with RLS											

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

5.2 Appendix 2 - Subject Demographics

Table 114 Subject Demographics by Study

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
Initial Exploratory PK/PD Proof of Concept Studies															
SP803	DB, PBO Ctrl Dose Escalating PD/PD S/T Study	US	All Subjects Both Arms	Pxts with mild to moderate PD H&Y II - IV	12 rotigotine/	II – 6/1 F III – 3/1F IV – 3/1F	9 / 3	12/0/0/0/0/0	60.7 ± 10.8 (17.9) 39 - 75 [62.5]	—	76.6 ± 12.6 (16.4) 57 - 101.3 [77]	—	NR	NR	
							9 M	9/0/0/0/0/0	59.4 ± 11.7 (19.7) 39 - 75 [61]	—	79.2 ± 12.5 (15.8) 57.4 - 101.3 [77]	—			
							3 F	3/0/0/0/0/0	64.3 ± 8.5 (13.2) 56 - 73 [64]	—	68.8 ± 11.1 (16.1) 57 - 79 [70.4]	—			
			Phase A: 10 min IVI			II – 2 III – 1 IV – 2	4 / 1 M M M/F	5/0/0/0/0/0	55.8 ± 13.2 (23.6) 39 - 70 [61]	—	75.3 ± 11.1 (14.7) 57 - 87.1 [77]	—			
					Only subject with PK Data	IV	F 1	1/0/0/0/0/0	64	—	58.3				Only subject with PK Data
			Phase B: 4 hr CIVI PK		Only subjects with PK Data		2 / 1	3/0/0/0/0/0	59 ± 4.4 (7.4) 56 - 64 [57]	—	62.8 ± 8.6 (13.7) 57.4 - 72.7 [58.3]				Only subjects with PK Data
SP804	Rising Dose Finding PK/PD Study IV LD & CIVI	US			9 rotigotine		6 / 3	9/0/0/0/0/0	63.4 ± 4.6 (7.3) 56 - 72 [63]	171.3 ± 11.1 (6.5) 152 - 187 [175]	76.5 ± 17.6 (23.0) 47.7 - 108.2 [77.0]				
							6 M	6/0/0/0/0/0	62.3 ± 4.2 (6.8) 56 - 67 [63]	178.0 ± 4.8 (2.7) 173 - 187 [177.5]	85.2 ± 13.6 (15.9) 68.2 - 108.2 [83.85]				
							3 F	3/0/0/0/0/0	65.7 ± 5.5 (8.4) 62 - 72 [63]	158.0 ± 5.6 (3.5) 152 - 163 [159]	59.2 ± 10.3 (17.5) 47.7 - 67.7 [62.3]				
SP805	CIVI dose titrated to effect	US		III – 3 IV - 4	8 rotigotine 7 PK		6 / 2 - PD 6 / 1 - PK		62.7 ± 7.2 (11.4) 51 - 70 [62]	—	87.9 ± 13.1 (14.9) 68 - 103 [84]				

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
Formulation Development															
Mass Balance Studies															
SP610		Czech Republic			6 rotigotine/		6 / 0	6/0/0/0/0/0	28.8 ± 4.6 (16.0) 25.0 - 36.0 [27.5]	181.7 ± 9.7 (5.3) 173.0 - 197.0 [178.0]	84.2 ± 8.8 (10.4) 74.0 - 98.0 [83.0]				
SP606		Netherlands			6 rotigotine/		6 / 0	6/0/0/0/0/0	29.8 ± 10.5 (35.3) 17 - 42 [29.5]	182.9 ± 5.2 (2.9) 176.3 - 191.3 [182.25]	75.5 ± 4.8 (6.4) 67.7 - 80.5 [77.0]		3 / 3	4 / 2	
Healthy Subject PK and Initial Tolerability Trial Reports															
SP503		Germany			30 rotigotine		30 / 0	30/0/0/0/0	32.9 ± 5.1 (15.5) 24 - 43 [32.5]	178.8 ± 7.0 (3.9) 164 - 191 [180.0]	83.0 ± 7.6 (9.2) 66.4 - 96.5 [83.5]	26.0 ± 1.8 (6.9) 22.6 - 29.7 [26.4]	9 / 30	15 1 - 5/wk	29 completers range did not change

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
Intrinsic Factors															
SP630	Age Gender and Dose Linearity some time effect	United States, South Africa	< 65 yo M	Healthy Young & elderly Male and Female Volunteers	70 rotigotine/		17	16/1/0/0/0/0	56.1 ± 6.7 (11.9) 38 - 64 [57]	173.7 ± 6.2 (3.5) 160 - 183.5 [172.7]	91.2 ± 15.6 (17.1) 71.2 - 122 [86.3]				
			< 65 yo F				18	15/0/1/0/0/2	56.9 ± 5.6 (9.9) 44 - 63 [58.5]	160.4 ± 4.7 (2.9) 151 - 168 [161.75]	70.2 ± 15.1 (21.5) 48.2 - 108.2 [67.85]				
			≥ 65 yo M				19	18/0/0/1/0/0	70.3 ± 5.3 (7.6) 65 - 81 [68]	173.3 ± 7.1 (4.1) 162.5 - 186.5 [173]	76.3 ± 13.5 (17.7) 57.7 - 102.1 [73.5]				
			≥ 65 yo F				16	16/0/0/0/0/0	71.6 ± 4.8 (6.8) 65 - 80 [72]	160.6 ± 6.6 (4.1) 149.9 - 170 [161]	64.7 ± 11.8 (18.3) 43.1 - 85.4 [64.65]				
			< 65 yo M				16	C	56.3 ± 6.9 (12.2) 38 - 64 [57]	174.5 ± 5.2 (3.0) 166.9 - 183.5 [172.7]	92.4 ± 15.4 (16.7) 71.2 - 122 [87.2]				
							1	B	53	160	73.5				
			< 65 yo F				15	C	56.7 ± 6.1 (10.8) 44 - 63 [58]	160.3 ± 4.1 (2.5) 151 - 165 [161.5]	69.7 ± 14.4 (20.7) 55.4 - 108.2 [67.3]				
							1	A	55	151.6	48.2				
							2	Mixed Race	59 - 59	162.5 - 168	80.8 - 89.2				
			≥ 65 yo M				18	C	70.5 ± 5.4 (7.7) 65 - 81 [68]	172.9 ± 7.1 (4.1) 162.5 - 186.5 [172.85]	76.5 ± 13.9 (18.1) 57.7 - 102.1 [73.7]				
							1	H	67	180.3	73.5				
SP596	Effect of Race	France	Black	Healthy Young Male Volunteers	48 rotigotine		48 / 0	23 Black,	28.4 ± 7.3 (25.5) 19 - 48 [27]	178 ± 7 (4.0) 165 - 191 [178]	73.2 ± 9.6 (13.1) 52.4 - 98.8 [72.8]	23.0 ± 2.3 (9.9) 18.2 - 27.4 [23.2]			
			Caucasian					25 Caucasian	29.6 ± 8.2 (27.6) 20 - 47 [27.5]	1.79 ± 7 (3.7) 1.66 - 1.95 [1.775]	73.9 ± 11.3 (15.3) 57.8 - 107.6 [73.6]	23.1 ± 2.6 (11.1) 18.3 - 28.3 [23.1]			

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
SP717	Effect of Race Japanese vs. Caucasian (SD Study)	Germany			50 rotigotine		12 M	Caucasian	28.9 ± 6 (20.8) 20 - 40 [30]	179 ± 5 (26) 168 - 185 [180.5]	68.36 ± 6.5 (9.5) 57 - 78 [69]	21.26 ± 1.8 (8.5) 19 - 24 [21]	Occ 2 (17%) Reg 1 (8%)	Occ 10 (83%)	
							12 M	Japanese	28.9 ± 7.7 (26.6) 20 - 44 [28]	173 ± 4 (21) 165 - 177 [173]	62.4 ± 4.4 (7.1) 56 - 74 [62.5]	21 ± 1.2 (5.7) 20 - 24 [21]	Occ 1 (8%) Reg 1 (8%)	Occ 7 (58%) Reg 4 (33%)	
							14 F	Caucasian	32.2 ± 6.3 (19.6) 23 - 43 [31.5]	168 ± 7 (42) 160 - 181 [165.5]	58.3 ± 5.4 (9.3) 49 - 68 [56.5]	20.7 ± 1.3 (6.3) 19 - 23 [21]	Reg 4 (29%)	Occ 10 (71%) Reg 1 (4%)	
							12 F	Japanese	32.3 ± 5.9 (18.3) 23 - 41 [31]	158 ± 6 (3.8) 150 - 172 [159]	53.3 ± 8.4 (15.8) 44 - 75 [51.5]	21.2 ± 2 (9.4) 19 - 25 [21.5]	Occ 4 (17%) Reg 4 (17%)	Occ 11 (92%) Reg 1 (8%)	
SP718	Effect of Race Japanese vs. Caucasian (MD Study)	Germany			26 rotigotine		6 M	Caucasian	25.3 ± 2.1 (8.3) 23 - 28 [25.5]	181 ± .45 (2.5) 176 - 187 [179.5]	74 ± 7.1 (9.6) 64 - 83 [74]	22.6 ± 1.6 (7.1) 20 - 25 [22.5]	1 x 0.25 ppd		
							6 F	Caucasian	27 ± 2.8 (10.4) 23 - 30 [27]	165 ± 4 (2.5) 159 - 169 [165]	57.5 ± 6.8 (11.8) 52 - 70 [55.5]	21.2 ± 2.3 (10.8) 19 - 25 [20.1]	1 x 0.25 ppd		
							6 M	Japanese	25.5 ± 1.6 (6.3) 23 - 28 [25.5]	168 ± 3 (1.5) 166 - 173 [167.5]	60.2 ± 4.4 (7.3) 56 - 67 [58.5]	21.3 ± 1.2 (5.6) 20 - 23 [21.2]	3 x 0.25 ppd	1 – 2 u/day	
							8 F	Japanese	27 ± 3.3 (12.2) 21 - 30 [29]	158 ± 3 (1.7) 152 - 160 [158]	51.3 ± 5.7 (11.1) 46 - 58 [50.5]	20.6 ± 1.8 (8.7) 18 - 23 [20.7]	2 x 0.25 ppd	1 – 1 u/day	
SP671	Hepatic Impairment Study	Slovac Republic		Healthy Young Male vols			8 M	Caucasian	45.9 ± 4.7 (10.3) 40.0 - 52.0 [46.0]	179.0 ± 3.5 (2.0) 174.0 - 184.0 [179.0]	83.8 ± 4.5 (5.4) 76.0 - 91.0 [83.5]	26.2 ± 1.7 (6.4) 24.5 - 29.6 [25.9]	4 x 0.75 ppd	8 occ	
				Mild – Mod Hepatic Impairment			9 M	Caucasian	47.3 ± 6.8 (14.4) 39.0 - 60.0 [49.0]	179.8 ± 4.7 (2.6) 174.0 - 186.0 [180.0]	84.0 ± 5.7 (6.8) 76.0 - 95.0 [85.0]	26.0 ± 2.3 (9.0) 22.8 - 30.7 [26.2]	1 x 0.5 ppd 3 x 0.75 ppd	4 occ	

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
SP672	Renal Impairment Study	Poland	Grp 1: Healthy				5 M	5/0/0/0/0/0	34.2 ± 20.8 (61.0) 18 - 67 [22]	1.72 ± 0.08 (4.6) 1.63 - 1.84 [1.71]	70.2 ± 10.5 (15.0) 57 - 84 [72]	23.7 ± 2.5 (10.7) 20.81 - 26.9 [24.6]	occ	Occ	
							3 F	3/0/0/0/0/0	43.3 ± 9.1 (20.9) 33 - 50 [47]	1.59 ± 0.01 (0.4) 1.59 - 1.60 [1.59]	72.3 ± 8.6 (11.9) 63 - 80 [74]	28.5 ± 3.6 (12.5) 24.6 - 31.6 [29.3]		Occ	
			Grp 2: Mild RD				1 M	1/0/0/0/0/0	39	1.78	78	24.6		Occ	
			Grp 3: Moderate RD				5 M	5/0/0/0/0/0	52.8 ± 11.2 (21.2) 42 - 69 [50]	1.77 ± 0.07 (4.2) 1.64 - 1.81 [1.81]	78.0 ± 11.9 (15.2) 63 - 93 [79]	24.9 ± 2.6 (10.6) 21.4 - 28.4 [25.2]		2 u per dau	
							2 F	3/0/0/0/0/0	62.0 ± 11.3 (18.2) 54 - 70 [62]	1.57 ± 0.01 (0.9) 1.56 - 1.58 [1.57]	77.0 ± 0.0 (0.0) 77 - 77 [77]	31.2 ± 0.6 (1.8) 30.8 - 31.6 [31.2]			
			Grp 4: Severe RD				5 M	5/0/0/0/0/0	41.2 ± 14.3 (34.6) 20 - 56 [48]	1.71 ± 0.02 (1.3) 1.68 - 1.74 [1.7]	74.8 ± 8.1 (10.8) 64 - 85 [74]	25.7 ± 3.0 (11.7) 21.1 - 29.1 [25.6]	1 x 0.1 ppd	Occ	
							3 F	3/0/0/0/0/0	42.0 ± 15.1 (36.00 30 - 59 [37]	1.68 ± 0.05 (2.8) 1.63 - 1.72 [1.7]	72.0 ± 20.7 (28.7) 53 - 94 [69]	25.3 ± 6.5 (25.8) 20.0 - 32.5 [23.3]		Occ	
			Grp 5: ESRD				5 M	5/0/0/0/0/0	45.6 ± 8.8 (19.4) 32 - 53 [48]	1.75 ± 0.02 (1.2) 1.73 - 1.78 [1.74]	69.0 ± 10.0 (14.6) 58 - 82 [64]	22.6 ± 2.9 (13.0) 19.4 - 26.8 [21.4]		Occ	
							3 F	3/0/0/0/0/0	54.7 ± 5.7 (10.4) 50 - 61 [53]	1.65 ± 0.05 (3.0) 1.60 - 1.70 [1.65]	74.3 ± 7.2 (9.7) 66 - 79 [78]	27.3 ± 1.6 (6.0) 25.8 - 29.0 [27.0]		Occ	
Extrinsic Factors															
SP626	Effect of Application Site on BA	Germany			24 rotigotine/		24 / 0	Caucasian 24/0/0/0/0/0	37.8 ± 6.4 (16.8) 25 - 48 [37.5]	178.1 ± 6.4 (3.6) 167 - 190 [177.5]	76.2 ± 7.6 (10.0) 60.5 - 89.8 [76.75]	NR	5	NR	4 drop outs
SP627	DDI Cimetidine	Germany			12 rotigotine/		12 M	12/0/0/0/0/0	33.1 ± 6.3 (19.0) 22.0 - 43.0 [33.5]	180.8 ± 5.0 (2.8) 173.0 - 190.0 [180.5]	75.5 ± 10.6 (14.0) 61.0 - 96.0 [74.0]	23.1 ± 2.8 (12.1) 19.7 - 29.0 [22.9]	No	NR	

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
SP628	DDI- Carbidopa-Levodopa (CD-LD)	Germany		Healthy Vols	24 rotigotine/		12 M	12/0/0/0/0/0	54.9 ± 10.5 (19.2) 35 - 65 [57.5]	173.4 ± 5.9 (3.4) 166 - 184 [173]	76.2 ± 7.2 (9.5) 59 - 84 [78.5]	25.4 ± 2.6 (10.1) 21 - 30 [25.5]	4	NR	
							12 F	12/0/0/0/0/0	55.2 ± 8.6 (15.5) 41 - 64 [59]	163.4 ± 6.0 (3.6) 156 - 175 [162]	70.7 ± 15.1 (21.4) 56 - 108 [67.5]	26.3 ± 4.8 (18.1) 22 - 35 [24.5]	4	NR	
SP670	DDI - Domperidone	France		Healthy Vols	16 rotigotine		16 M	16/0/0/0/0/0	30.3 ± 7.8 (48.7) 21 - 44 [28]	73.0 ± 7.0 (44.0) 59.5 - 85.2 [74.6]	176.1 ± 6.0 (37.4) 167 - 186 [176.5]	23.5 ± 1.8 (11.5) 21.2 - 26.9 [23.5]		7 x occ	
Clinical Pharmacology Studies															
SP629		Germany			40 placebo and rotigotine		43% / 58%	40/0/0/0/0/0						2 x 1 unit /day	
							M 17	17/0/0/0/0/0							
							F 23	23/0/0/0/0/0							
SP673		Germany			229 placebo and rotigotine		36% / 64%		34 years (18 - 49)						
Pivotal Bioequivalence Study															
SP581		Germany			30 rotigotine		30/0	30/0/0/0/0/0	37 ± 9.8 (26.5) 18 - 50 [39]	179.1 ± 6.9 (3.8) 167 - 201 [179.5]	76.4 ± 8.6 (11.2) 64.0 - 98.4 [75.4]		11	NR	NR - not reported
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		US			2 placebo 10 rotigotine		10/ 2								
SP534 Part 2		US			2 placebo 10 rotigotine		8 / 4								
SP535					2 placebo 8 rotigotine		7 M/ 3 F								
SP506		Canada, Europe, India, South Africa, Ukraine, US			64 placebo, 265 rotigotine		62% /39%								
SP540		Europe, South Africa			31 placebo and rotigotine		42% /58%								

Study No	Study Description	Country or Region(s)	Study Arm	Vols/Pxts	Treatment	Hoehn & Yahr Stage	M/F	Race / Ethnicity C/B/A/H/NA/Ot	Mean Age (Range)	Ht	Wt	BMI	Smk	EtOH	Comments
Population PK/PD Trial Reports															
SP512		US, Canada			56 rotigotine/				63 years (32 - 86)						
SP512 Part I		Canada, US			96 placebo, 181 rotigotine/		65% / 35%								
SP513 Part I		Europe, Israel, New Zealand, South Africa, Switzerland Australia			118 placebo, 215 rotigotine, 228 ropinirole/		58% / 42%								
Uncontrolled Clinical Trials															
SP512 Part IId SP702		Canada, US			213 rotigotine		68% / 32%								
SP513 Part IId SP716		Europe, Israel, New Zealand, South Africa, Switzerland Australia					61% / 39%								
Other Trial Reports															
SP533					10 rotigotine/		8 /2								
SP511					84 placebo, 240 rotigotine/		61% / 39%								
SP650 Part Id					461 totale		64% / 36%		65.7 years (33 - 87)						
SP650 Part IId (SP715)					197 rotigotine		66% / 56%		66.5 years (34 - 88)						
SP591					34 rotigotine/		63% / 37%		69.1 years (44 - 86)						
SP666					14 placebo, 49 rotigotine		16 / 33		58.3 years (37 - 74)						
SP709d					112 totale		32% / 67%		58 years (22 - 75)						

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

5.3 Appendix 3 - Rotigotine Pharmacokinetic Metrics

Table 115 Rotigotine PK Summary Metrics by Study – Part 1

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Dur n	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
Initial Exploratory PK/PD – Proof of Concept Studies																					
SP803	DB, PBO Ctrl Dose Escalating PD/PD S/T Study	10 min IV Bolus			F	1													based on ave t1/2		
		4 hr CIVI	Pxts with mild to moderate PD H&Y II - IV	Caucasian	M & F	2 / 1						4.8 ± 3.1 (64.7) 1.25 - 7 [6]		2.3 ± 0.6 (24.7) 2 - 3 [2]	0.91 ± 0.55 (60.4) 0.3 - 1.36 [1.06]			2.66 ± 1.31 (49.1) 1.16 - 3.51 [3.33]	2.91 ± 1.39 (47.8) 1.30 - 3.74 [3.69]	9.1 ± 3.5 (38.7) 5.0 - 11.3 [10.9]	
SP804	Rising Dose Finding PK/PD Study	30 min IV LD			M & F	9						9.1 ± 5.6 (61.2) 2.0 - 16.0 [8.0]		0.43 ± 0.11 (25.6) 0.25 - 0.5 [0.5]	1.57 ± 1.14 72.7 0.44 - 4.27 [1.25]			1.34 ± 0.79 (58.9) 0.46 - 2.82 [1.30]	1.44 ± 0.79 (55.1) 0.52 - 2.89 [1.49]	10.0 ± 10.0 (100.2) 2.3 - 33.3 [6.2]	
					M	6						9.0 ± 5.9 (65.5) 2 - 16 [8]		0.42 ± 0.13 (31.0) 0.25 - 0.50 [0.50]	1.34 ± 0.61 (45.5) 0.44 - 1.89 [1.53]			1.23 ± 0.63 (50.9) 0.46 - 2.02 [1.21]	1.37 ± 0.64 (47.0) 0.54 - 2.11 [1.44]	12.8 ± 11.4 (89.0) 4.5 - 33.3 [6.9]	
					F	3						9.3 ± 6.1 (65.5) 4 - 16 [8]		0.46 ± 0.07 (15.7) 0.38 - 0.50 [0.50]	2.03 ± 1.95 (96.4) 0.71 - 4.27 [1.10]			1.54 ± 1.18 (76.7) 0.50 - 2.82 [1.30]	1.60 ± 1.20 (75.2) 0.52 - 2.89 [1.38]	4.3 ± 1.9 (44.6) 2.3 - 6.2 [4.5]	
		IV LD & MD			M & F	7						3.9 ± 2.1 (52.3) 1.7 - 6.8 [3.4]		1.0 ± 1.3 (139.2) 0.3 - 4.0 [0.5]	2.0 ± 1.3 (64.8) 0.8 - 4.3 [1.4]			4.1 ± 2.7 (67.4) 2.4 - 10.0 [2.9]	4.2 ± 2.8 (66.9) 2.4 - 10.2 [3.1]	3.4 ± 1.1 (33.2) 1.9 - 5.2 [3.6]	
					M	4						3.9 ± 2.1 (54.6) 1.7 - 6.8 [3.5]		0.4 ± 0.1 (28.6) 0.3 - 0.5 [0.5]	1.5 ± 0.6 (43.9) 0.9 - 2.4 [1.3]			3.2 ± 1.2 (37.2) 2.4 - 4.9 [2.9]	3.4 ± 1.3 (37.1) 2.4 - 5.1 [3.0]	3.8 ± 1.1 (29.0) 2.5 - 5.2 [3.7]	
					F	3						4.0 ± 2.5 (60.8) 2.0 - 6.8 [3.4]		1.7 ± 2 (121.2) 0.5 - 4.0 [0.5]	2.2 ± 1.9 (86.0) 0.8 - 4.3 [1.4]			5.2 ± 4.2 (80.3) 2.6 - 10.0 [2.9]	5.3 ± 4.3 (80.0) 2.7 - 10.2 [3.1]	3.0 ± 1.3 (42.8) 1.9 - 4.4 [2.7]	
SP805		CIVI dose titrated to effect			M & F	7						Ave 3.9 ± 2.0 (49.8) 1.9 - 7.3 [4.2]	Max ko 9.0 ± 2.0 (22.3) 6.2 - 11.9 [8.0]		12.1 ± 14.9 (123.1) 1.5 - 42.0 [5.5]			143.1 ± 160.9 (112.4) 11.8 - 392.4 [74.2]	145.6 ± 162.7 (111.7) 129 - 398 [74.4]	3.2 ± 2.8 (90.3) 0.2 - 8.6 [2.3]	
Formulation Development																					

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Dur	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
Mass Balance																					
SP610		IV					IV	1.2 mg	IV			Sponsor only reported total radioactivity not rotigotine alone									
		TDS					Form 3	4.5 mg /10 cm^2				2.90 ± 0.3 (10.8) 2.5 - 3.4 [2.9]	2.83 ± 1.3 (46.9) 1.0 - 4.0 [3.0]	15.5 ± 5.0 (32.6) 12.0 - 25.0 [14.0]	4.71 ± 1.14 (24.1) 3.78 - 6.47 [4.16]			8.3 ± 2.0 (24.4) 5.7 - 11.4 [8.4]	8.5 ± 2.0 (23.9) 5.9 - 11.7 [8.6]	1.98 ± 1.0 (48.5) 1.1 - 3.6 [1.7]	
SP606		TDS					Form 3	4.5 mg /10 cm^2				1.3 ± 0.3 (25.2) 0.9 - 1.8 [1.2]	3.3 ± 1 (31) 2 - 4 [4]	23.7 ± 7 29.5 12 - 34 [24]	0.288 ± 0.162 (56.1) 0.107 - 0.565 [0.260]			10.0 ± 6.6 (66.5) 5.3 - 23.1 [7.8]	11.2 ± 7.1 (63.2) 5.5 - 23.5 [8.85]	5.2 ± 4.1 (80.1) 1.2 - 11.1 [4.5]	
Healthy Subject PK and Initial Tolerability Trial Reports																					
SP503		Day 1										2.30 ± 0.72 (31.2) 0.62 - 3.75 [2.36]	4.2 ± 1.8 (42.1) 2 - 12 [4]	20.3 ± 5.6 (27.9) 12.0 - 24.0 [24.0]	0.225 ± 0.229 (101.7) 0.044 - 1.280 [0.160]	0.177 ± 0.098 (55.6) 0.044 - 0.566 [0.160]		3.4 ± 2.5 (73.7) 0.6 - 13.1 [2.8]	4.5 ± 2.9 (64.1) 0.94 - 14.3 [3.7]	27.1 ± 6.6 (24.2) 8.4 - 36.2 [27.2]	
		Day 14				29						2.56 ± 0.84 (32.8) 0.82 - 3.96 [2.46]		13.5 ± 7.0 (52.1) 4 - 24 [12]	307 ± 165 (53.7) 76 - 933 [277]	Cmin 179 ± 72 (40.1) 66 - 360 [167]	Tmin 10.5 ± 10.4 (99.6) 0 - 24 [8.0]		R	1.5 ± 0.5 (33.2) 0.7 - 2.9 [1.6]	6.07 ± 2.80 (46.1) 1.74 - 14.87 [5.61]
		Days 1 - 14	4.5 mg /10 cm^2	Form 3								2.57 ± 0.76 (29.7) 0.43 - 4.55 [2.54]		133 ± 51 (38.3) 42 - 254 [128]	383 ± 231 (60.5) 99.6 - 1280		Tmin 119 ± 121 (101.6) 24 - 336 [72]	72.4 ± 22.3 (30.8) 26.2 - 117.8 [75.4]			
		Ratios Data from all days													Cmin:Cmax %	39.5 ± 12.5 (31.8) 4.51 - 62.6 [37.9]	R Cmax: Cmin	3.4 ± 3.8 (111.7) 1.60 - 22.2 [2.64]		R accum AUC Day 14 to Day 1	1.54 ± 0.51 (33.2) 0.7 - 2.9 [1.59]

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
Intrinsic Factors																					
			Site	Age	Sex	N						dose		tmax	Cmax,ss	PTF	Cavg,ss		AUC0-t,ss		PTF
SP 630		<65 Female	Abd	<65	Female	7						7.74 ± 1.62 (20.86) 4.92 - 9.38 [7.99]		16.2 ± 5.5 (33.8) 8.0 - 23.5 [18.0]	1.37 ± 0.62 (45.27) 0.83 - 2.50 [1.21]	124 ± 86 (69) 67 - 314 [88]	0.778 ± 0.203 (26.091) 0.605 - 1.196 [0.707]		18.28 ± 4.77 (26.08) 14.22 - 28.10 [16.61]		124 ± 86 (69) 67 - 314 [88]
			Flank			6						6.84 ± 1.94 (28.38) 4.83 - 9.79 [6.33]		21.1 ± 3.3 (15.5) 16.0 - 23.5 [22.8]	1.96 ± 0.90 (46.15) 0.62 - 2.83 [2.29]	140 ± 51 (37) 72 - 195 [139]	1.015 ± 0.391 (38.526) 0.389 - 1.416 [1.047]		23.85 ± 9.19 (38.52) 9.14 - 33.27 [24.61]		140 ± 51 (37) 72 - 195 [139]
			Hip			3						6.36 ± 1.48 (23.20) 4.87 - 7.82 [6.39]		20.0 ± 2.0 (10.0) 18.0 - 22.0 [20.0]	2.03 ± 0.86 (42.26) 1.09 - 2.77 [2.22]	146 ± 40 (27) 105 - 185 [148]	1.073 ± 0.417 (38.830) 0.600 - 1.386 [1.232]		25.21 ± 9.79 (38.81) 14.11 - 32.58 [28.95]		146 ± 40 (27) 105 - 185 [148]
			Shoulder			5						8.07 ± 3.05 (37.81) 3.53 - 11.20 [8.08]		11.8 ± 8.6 (73.0) 0.0 - 20.0 [12.0]	1.96 ± 1.62 (82.51) 0.93 - 4.81 [1.19]	127 ± 31 (24) 102 - 171 [109]	1.099 ± 0.776 (70.568) 0.524 - 2.458 [0.802]		25.83 ± 18.23 (70.58) 12.32 - 57.77 [18.84]		127 ± 31 (24) 102 - 171 [109]
			Thigh			3						6.04 ± 1.65 (27.28) 4.35 - 7.64 [6.12]		10.0 ± 11.1 (111.4) 0.0 - 22.0 [8.0]	1.37 ± 0.71 (51.56) 0.56 - 1.78 [1.78]	131 ± 87 (66) 80 - 232 [82]	0.731 ± 0.432 (59.063) 0.356 - 1.203 [0.634]		17.18 ± 10.14 (59.01) 8.38 - 28.27 [14.90]		131 ± 87 (66) 80 - 232 [82]
			Upper Arm			6						5.67 ± 1.67 (29.49) 3.90 - 8.38 [5.59]		12.7 ± 10.5 (82.8) 0.0 - 22.0 [16.0]	1.52 ± 0.50 (33.09) 0.92 - 2.16 [1.44]	90 ± 17 (19) 73 - 112 [83]	1.022 ± 0.373 (36.502) 0.637 - 1.626 [1.004]		24.01 ± 8.76 (36.49) 14.97 - 38.20 [23.58]		90 ± 17 (19) 73 - 112 [83]
		<65 Male	Abd	<65	Male	4						4.81 ± 1.54 (32.02) 3.88 - 7.09 [4.13]		14.0 ± 9.7 (69.0) 0.0 - 22.0 [17.0]	1.04 ± 0.67 (64.47) 0.50 - 1.96 [0.84]	95 ± 34 (36) 74 - 145 [80]	0.700 ± 0.440 (62.835) 0.377 - 1.338 [0.543]		16.45 ± 10.34 (62.86) 8.85 - 31.44 [12.75]		95 ± 34 (36) 74 - 145 [80]
			Flank			6						7.01 ± 2.21 (31.55) 4.63 - 10.11 [6.95]		14.2 ± 4.9 (34.7) 7.0 - 20.0 [15.0]	1.84 ± 0.53 (28.65) 1.29 - 2.47 [1.70]	135 ± 37 (28) 88 - 200 [130]	1.051 ± 0.430 (40.912) 0.546 - 1.701 [1.021]		24.70 ± 10.11 (40.92) 12.83 - 39.98 [23.98]		135 ± 37 (28) 88 - 200 [130]
			Hip			7						7.93 ± 2.13 (26.87) 4.94 - 10.33 [8.76]		11.6 ± 7.8 (67.3) 0.0 - 20.0 [16.0]	1.95 ± 1.44 (73.74) 0.60 - 4.44 [1.35]	113 ± 51 (45) 61 - 198 [94]	1.111 ± 0.627 (56.422) 0.361 - 1.931 [0.928]		26.12 ± 14.73 (56.40) 8.49 - 45.38 [21.82]		113 ± 51 (45) 61 -

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
																					198 [94]
			Shoulder			4						7.48 ± 2.70 (36.02) 5.02 - 11.10 [6.91]		15.8 ± 5.9 (37.5) 7.0 - 20.0 [18.0]	1.05 ± 0.50 (47.47) 0.43 - 1.52 [1.13]	91 ± 14 (15) 76 - 109 [89]	0.725 ± 0.360 (49.697) 0.319 - 1.056 [0.762]		17.03 ± 8.46 (49.67) 7.51 - 24.82 [17.89]		91 ± 14 (15) 76 - 109 [89]
			Thigh			6						7.94 ± 2.39 (30.11) 5.13 - 11.57 [7.58]		15.7 ± 5.3 (33.7) 6.0 - 20.0 [17.0]	1.44 ± 0.54 (37.47) 0.69 - 2.12 [1.32]	83 ± 20 (25) 60 - 106 [82]	1.011 ± 0.390 (38.570) 0.437 - 1.449 [0.981]		23.77 ± 9.17 (38.58) 10.27 - 34.06 [23.06]		83 ± 20 (25) 60 - 106 [82]
			Upper Arm			5						5.64 ± 3.64 (64.65) 1.06 - 10.10 [6.36]		10.6 ± 9.0 (85.3) 0.0 - 20.0 [8.0]	1.32 ± 0.93 (70.94) 0.40 - 2.87 [1.15]	117 ± 32 (27) 80 - 168 [116]	0.868 ± 0.674 (77.655) 0.218 - 1.979 [0.761]		20.39 ± 15.83 (77.63) 5.13 - 46.50 [17.88]		117 ± 32 (27) 80 - 168 [116]
			Site	Age	Sex	N						dose		tmax	Cmax,ss	PTF	Cavg,ss		AUC0-t,ss		PTF
		≥65 Female	Abd	≥65	Female	5						4.41 ± 2.04 (46.22) 1.61 - 7.15 [4.84]		10.6 ± 6.5 (61.7) 2.0 - 18.0 [10.0]	1.48 ± 1.07 (72.42) 0.78 - 3.35 [1.09]	95 ± 42 (44) 59 - 154 [79]	0.961 ± 0.592 (61.630) 0.443 - 1.950 [0.841]		22.59 ± 13.92 (61.63) 10.41 - 45.82 [19.76]		95 ± 42 (44) 59 - 154 [79]
			Flank			4						8.49 ± 2.59 (30.50) 5.59 - 11.19 [8.60]		15.9 ± 6.5 (41.2) 8.0 - 23.5 [16.0]	2.14 ± 1.65 (77.25) 1.19 - 4.61 [1.38]	89 ± 45 (51) 43 - 137 [87]	1.442 ± 1.011 (70.123) 0.634 - 2.921 [1.106]		33.89 ± 23.75 (70.10) 14.91 - 68.64 [26.00]		89 ± 45 (51) 43 - 137 [87]
			Hip			6						5.43 ± 1.87 (34.49) 3.36 - 8.57 [5.21]		12.0 ± 9.7 (81.0) 0.0 - 22.0 [15.0]	1.32 ± 0.33 (24.80) 0.97 - 1.92 [1.29]	111 ± 37 (33) 71 - 176 [104]	0.815 ± 0.201 (24.646) 0.587 - 1.181 [0.776]		19.14 ± 4.72 (24.67) 13.78 - 27.76 [18.23]		111 ± 37 (33) 71 - 176 [104]
			Shoulder			3						7.70 ± 1.15 (14.95) 6.68 - 8.95 [7.48]		9.0 ± 3.6 (40.1) 5.0 - 12.0 [10.0]	2.23 ± 0.95 (42.60) 1.63 - 3.33 [1.74]	98 ± 31 (32) 78 - 134 [83]	1.471 ± 0.409 (27.801) 1.163 - 1.935 [1.315]		34.57 ± 9.60 (27.77) 27.34 - 45.46 [30.90]		98 ± 31 (32) 78 - 134 [83]
			Thigh			8						4.88 ± 2.04 (41.83) 2.55 - 9.26 [4.79]		10.8 ± 9.2 (85.5) 0.0 - 20.0 [14.0]	1.41 ± 0.95 (67.08) 0.47 - 3.45 [1.16]	133 ± 78 (59) 57 - 312 [115]	0.819 ± 0.579 (70.738) 0.314 - 1.964 [0.627]		19.25 ± 13.62 (70.73) 7.37 - 46.16 [14.73]		133 ± 78 (59) 57 - 312 [115]
			Upper Arm			4						6.18 ± 1.40 (22.58) 4.82 - 7.77 [6.07]		12.5 ± 9.0 (72.0) 0.0 - 20.0 [15.0]	1.82 ± 0.76 (41.95) 1.09 - 2.83 [1.68]	109 ± 38 (35) 56 - 144 [118]	1.118 ± 0.433 (38.767) 0.754 - 1.688 [1.015]		26.28 ± 10.18 (38.75) 17.73 - 39.68 [23.85]		109 ± 38 (35) 56 - 144 [118]

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Dur n	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
		≥65 Male	Abd	≥65	Male	4						4.45 ± 1.19 (26.63) 3.22 - 5.80 [4.39]		10.3 ± 10.4 (101.5) 1.0 - 22.0 [9.0]	1.19 ± 0.36 (29.80) 0.77 - 1.61 [1.20]	117 ± 26 (22) 88 - 150 [115]	0.712 ± 0.271 (38.074) 0.411 - 1.061 [0.687]		16.72 ± 6.37 (38.09) 9.66 - 24.94 [16.14]		117 ± 26 (22) 88 - 150 [115]
			Flank			7						7.59 ± 2.91 (38.36) 5.17 - 13.52 [6.47]		10.0 ± 8.3 (83.3) 0.0 - 20.0 [14.0]	1.26 ± 0.72 (57.43) 0.58 - 2.69 [1.00]	131 ± 45 (34) 75 - 196 [123]	0.771 ± 0.534 (69.336) 0.286 - 1.818 [0.505]		18.11 ± 12.56 (69.34) 6.73 - 42.73 [11.86]		131 ± 45 (34) 75 - 196 [123]
			Hip			4						5.95 ± 1.65 (27.80) 3.49 - 7.06 [6.62]		17.4 ± 7.9 (45.6) 6.0 - 23.5 [20.0]	2.08 ± 2.17 (104.61) 0.62 - 5.31 [1.20]	113 ± 48 (42) 83 - 184 [93]	1.096 ± 0.838 (76.464) 0.429 - 2.321 [0.816]		25.74 ± 19.68 (76.46) 10.09 - 54.54 [19.17]		113 ± 48 (42) 83 - 184 [93]
			Shoulder			10						6.76 ± 1.78 (26.36) 3.56 - 9.68 [6.68]		13.5 ± 7.3 (54.0) 0.0 - 22.0 [16.0]	1.41 ± 0.53 (37.50) 0.96 - 2.58 [1.18]	102 ± 23 (22) 72 - 136 [99]	0.947 ± 0.392 (41.346) 0.573 - 1.852 [0.806]		22.25 ± 9.20 (41.35) 13.46 - 43.51 [18.93]		102 ± 23 (22) 72 - 136 [99]
			Thigh			3						4.63 ± 1.01 (21.74) 3.48 - 5.35 [5.06]		16.7 ± 1.2 (6.9) 16.0 - 18.0 [16.0]	0.97 ± 0.43 (44.34) 0.52 - 1.38 [1.01]	101 ± 20 (20) 87 - 124 [91]	0.650 ± 0.331 (50.908) 0.300 - 0.958 [0.693]		15.29 ± 7.78 (50.87) 7.06 - 22.52 [16.29]		101 ± 20 (20) 87 - 124 [91]
			Upper Arm			6						7.77 ± 1.61 (20.76) 5.49 - 10.21 [7.85]		14.7 ± 3.5 (23.9) 10.0 - 20.0 [15.0]	1.35 ± 0.54 (39.97) 0.75 - 2.23 [1.28]	84 ± 24 (28) 51 - 120 [85]	0.943 ± 0.414 (43.876) 0.504 - 1.462 [0.896]		22.17 ± 9.72 (43.86) 11.85 - 34.35 [21.06]		84 ± 24 (28) 51 - 120 [85]
SP630				Form 4	F yng	15		4.5mg / 10 cm^2								0.154 ± 0.076 (49.4) 0.059 - 0.289 [0.141]					
					M yng	16										0.177 ± 0.107 (60.7) 0.027 - 0.381 [0.151]					
					F Eld	15										0.205 ± 0.131 (63.8) 0.076 - 0.585 [0.176]					
					Male Eld	17										0.139 ± 0.074 (53.5) 0.049 - 0.344					

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Dur n	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
																[0.122]					
					F yng	15										0.452 ± 0.301 (66.6) 0.181 - 1.160 [0.373]					
					M yng	16										0.446 ± 0.466 (104.4) 0.109 - 2.090 [0.316]					
					F Eld	15		9.0mg / 20 cm^2								0.422 ± 0.228 (53.9) 0.191 - 0.917 [0.403]					
					Male Eld	17										0.341 ± 0.207 (60.8) 0.149 - 0.902 [0.269]					
					F yng	15										0.604 ± 0.380 (62.9) 0.273 - 1.570 [0.487]					
					M yng	16										0.579 ± 0.335 (57.8) 0.134 - 1.440 [0.522]					
					F Eld	15		13.5mg / 30 cm^2								0.655 ± 0.359 (54.8) 0.232 - 1.390 [0.581]					
					Male Eld	17										1.417 ± 3.385 (238.9) 0.094 - 14.500 [0.626]					
					F yng	90										0.904 ± 0.543 (60.1) 0.166 - 2.980 [0.820]					
					M yng	96		2 x 9 mg / 20 cm^2								0.878 ± 0.618 (70.4) 0.076 - 4.150 [0.767]					
					F Eld	90										0.963 ± 0.618 (64.2) 0.170 - 4.610 [0.839]					
					Male Eld	102										0.747 ± 0.436 (58.4) 0.170 - 1.980					

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Dur n	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
																[0.631]					
SP596	Effect of Race			C		24		4.5mg/10 cm^2					1.7 ± 0.5 (29) 1 - 2 [2]	17 ± 7 (39) 8 - 26 [15]	338 ± 126 (37) 181 - 615 [303])			6.2 ± 2.5 (40) 3.0 – 11.0 [5.5]]	6.4 ± 2.7 (41) 3.2 – 12.4 [5.7]	3.2 ± 2.4 (73.0) 1.1 - 12.4 [2.7]	
				Blk		23							2.9 ± 1.7 (59.7) 1 - 8 [2]	17.6 ± 6.4 (36.7) 8.0 - 27.0 [15]	335 ± 235 (70.2) 88 - 1210 [310]			5.3 ± 2.4 (46.0) 0.84 – 10.4 [5.7]	5.6 ± 2.5 (44.7) 0.94 – 10.8 [5.8]	5.3 ± 4.3 (81) 1 - 20.3 [4.0]	
SP717	Effect of Race Japanese vs. Caucasian (SD Study)		4	C	F	12		4.5mg/10 cm^2				2.28 ± 0.5 (24.1) 1.73 - 3.46 [2]	4.3+2.4 55.1 2-8 4	16.2 ± 4.8 (29.9) 8 - 25 [16]	294.4 ± 319.2 (108.4) 98.9 - 1270 [222]			6.0 ± 6.5 (107.4) 1.5 – 25.7 [4.6]	5.9 ± 6.7 (113.5) 0.2 – 26.0 [4.8]		
				C	M	12						1.88 ± 0.6 (29.8) 1.14 - 3.32 [1.82]	5.5+2.3 41.4 2-8 4	18.4 ± 6.5 (35.4) 8 - 26 [16]	197.7 ± 155.3 (78.5) 83.8 - 675 [158]			4.2 ± 3.4 (81.3) 1.7 – 14.6 [3.7]	4.3 ± 3.4 (78.4) 1.8 – 14.7 [3.8]		
				J	F	12						2.03 ± 0.5 (26.1) 1.35 - 3.05 [1.88]	4.7+2.7 58.7 2-12 4	18.1 ± 4.8 (26.5) 12 - 25 [16]	307 ± 96.7 (31.5) 133 - 507 [319.5]			6.0 ± 2.0 (33.7) 2.6 – 9.2 [6.1]	6.2 ± 2.1 (33.4) 2.8 – 9.3 [6.3]		
				J	M	12						1.97 ± 0.5 (25.4) 0.94 - 2.75 [2.0]	4.2+1.3 32.1 2-8 4	17.7 ± 4.0 (22.6) 12 - 24 [16]	198.9 ± 109.6 (55.1) 74.5 - 390 [158]			3.8 ± 1.9 (50.4) 1.5 – 7.2 [3.6]	3.9 ± 1.9 (48.6) 1.6 – 7.4 [3.7]		
SP718	Effect of Race Japanese vs. Caucasian (MD Study)				CF			4.5mg/10 cm^2				2.7 ± 0.2 (8.9) 2.5 - 3.1 [2.7]		8.7 ± 5.9 (67.9) 0.0 - 16.0 [10.0]	120.5 ± 62.7 (52.0) 76.1 - 282.0 [87.4]	104.5 ± 57.2 (54.8) 11.0 - 255.0 [150.5]					5958.2 ± 1480.1 (25.1) 3937.0 - 7476.0 [4849.5]
					CM							2.7 ± 0.5 (18.3) 2.2 - 3.5 [2.7]		10.6 ± 7.9 (79.6) 0.0 - 16.0 [14.0]	143.9 ± 48.2 (33.5) 98.1 - 217.0 [125.5]	152.5 ± 64.6 (42.3) 69.0 - 239.0 [162.0]					4148.7 ± 1884.5 (45.4) 1778.0 -

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
																					6039.0 [4514.5]
					JF							2.1 ± 0.4 (19.9) 1.7 - 2.6 [2.1]		17.1 ± 5.0 (29.2) 12.0 - 24.0 [16.0]	285.3 ± 90.2 (31.6) 174.0 - 420.0 [252.0]	208.2 ± 143.0 (68.7) 65.4 - 503.0 [137.0]					4392.3 ± 1880.3 (42.8) 2782.0 - 8159.0 [4015.0]
					JM							2.3 ± 0.6 (25.1) 1.6 - 3.3 [2.2]		8.8 ± 8.0 (90.1) 0.0 - 16.0 [10.0]	229.8 ± 94.4 (41.1) 90.9 - 344.0 [251.0]	167.3 ± 53.7 (32.1) 114.0 - 237.0 [157.5]	-				4152.2 ± 1415.7 (22.1) 3240.0 - 5597.0 [3858.5]
SP671	Hepatic Impairment Study		4.5mg/ 10 cm^2		Healthy Young Male vols																
					Mild – Mod Hepatic Impairment																
SP672	Renal Impairment Study				Grp 1: Healthy																
					Grp 2: Mild RD																
					Grp 3: Moderate RD																
					Grp 4: Severe RD																
					Grp 5: ESRD																
Extrinsic Factor																					
SP626	Effect of Application Site on BA	Vental Abdomen	4.5mg/ 10 cm^2			20							3.5 ± 1.4 (39.7) 2 - 6 [4]	18.5 ± 7.15 (38.6) 6.0 - 24.1 [23.0]	396.6 ± 216.0 (54.5) 136 - 930 [328.0]			7.0 ± 4.5 (64.1) 2.4 – 21.3 [5.9]	7.8 ± 4.8 (61.5) 2.6 – 21.8 [6.4]		
		Arm				18							2.9 ± 1.2 (40.3) 1 - 4 [2]	14.2 ± 7.6 (53.6) 4.0 - 25.0 [12.0]	504.9 ± 373.1 (73.9) 167 - 1830 [423.5]			9.4 ± 6.5 (68.6) 3.2 – 31.3 [6.8]	9.8 ± 6.62 (67.3) 3.3 – 31.5 [7.2][1]		
		leg				21							2.5 ± 1.0	16.8 ± 7.72	567.6 ± 369.1			10.2 ± 7.0	10.6 ± 7.3		

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
													(41.2) 1 - 4 [2]	(45.9) 6.0 - 24.0 [23.0]	(65.0) 218 - 1660 [428.0]			(68.7) 3.5 – 34.2 [8.4]	(68.6) 3.6- 34.4 [8.5]		
SP627	DDI Cimetidine		9mg/10 cm^2																		
SP628	DDI-Carbidopa-Levodopa (CD-LD)																				
SP670	DDI - Domperidone																				
Clinical Pharmacology																					
SP629						—						—	—	—	—	—	—	—	—	—	—
SP673																					
Pivotal BE																					
SP581		Sponsor's Calc Excluding subjs with adhesion <80%			Test			4.5/10						17.1 ± 6.8 (39.5) 4 - 27	323.2 ± 180.8 (56) 109 - 766			5.6 ± 3.0 (53.7) 2.1 – 13.4	5.7 ± 3.0 (51.9) 2.25 – 13.6		
					Ref			4.5/10						17.5 ± 6.5 (37.3) 4 - 26	307.6 ± 152.3 (49.5) 98.1 - 737			5.3 ± 2.6 (48.5) 2.1 - 12.6	5.7 ± 2.6 (44.5) 2.4 - 13.1		
		My Calcs All subjects			Test								4.1 ± 1.6 (38.0) 2 - 8 [4]	16.8 ± 6.9 (41.0) 4 - 27 [15]	309.9 ± 177.4 (57.4) 92.7 - 766 [248.5]			5413+2990 55.2 1532-13379 4644	5717+2966 51.9 2297-13589 5063	3.5+2.4 67.6 1.2-10.1 2.5	
					Ref								4.3 ± 1.6 (38.4) 2 - 8 [4]	18.0 ± 6.5 (36.0) 4 - 26 [23]	307.6 ± 152.3 (49.5) 98.1 - 737 [268.5]			5343+2594 48.5 2134-12910 4885	5624+2678 47.6 2356-13398 5374	4.4+2.8 61.9 1.4-10.4 3.8	

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
SP534 Part 1					9 mg (1 x 20 cm^2) or PBO																
					18 mg (2 x 20 cm^2) or PBO																
					27 mg (3 x 20 cm^2) or PBO																
					36 mg (4 x 20 cm^2) or PBO																
SP534 Part 2																					
SP535					4.5mg/10 cm^2																
					9 mg (1 x 20 cm^2)																
SP540		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
		18.0 mg/ 40 cm^2																			

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
SP506		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
		18.0 mg/ 40 cm^2																			
SP512 Part I		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
SP513 Part I		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
		18.0 mg/ 40 cm^2																			

Study Number	Study Description	Arm	Subject Group			Number of Subjects	Formulation	Dose	Site	Freq	Du rn	Dose	Tlag	Tmax	Cmax	C24	Css	AUClast or AUCt	AUCinf or AUCtau	% extrap	
			Pop	Race / Ethnicity	Gender							mcg/kg/hr	(hrs)	(hrs)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml/hr)	(ng/ml/hr) (aka mcg/L/hr) (ng/ml/min)		
SP512 Part IId SP702		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
		18.0 mg/ 40 cm^2																			
SP513 Part IId SP716		4.5 mg/ 10 cm^2																			
		9.0 mg/ 20 cm^2																			
		13.5 mg/ 30 cm^2																			
		18.0 mg/ 40 cm^2																			
Other																					
SP533																					
SP511																					
SP650 Part Id																					
SP650 Part IId (SP715)																					
SP591																					
SP666																					
SP709d																					

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

ng/ml/hr (aka mcg/L/hr)

(ng/ml/hr)

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ON ORIGINAL

Table 116 Rotigotine PK Summary Metrics by Study – Part 2

Study Number	Study Description	Arm	Dose	Subject Group			N	$t1/2\alpha$	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
Initial Exploratory PK/PD – Proof of Concept Studies																
SP803	DB, PBO Ctrl Dose Escalating PD/PD S/T Study	10 min IV Bolus				F	1									Data is so poorly organized in NDA that it would take an inordinate effort to clarify it.
		4 hr CIVI		Pxts with mild to moderate PD H&Y II - IV	Caucasian	M & F	2 / 1		1.9 ± 0.1 (3.7) 1.9 - 2.0 [1.9]	37.5 ± 13.3 (35.5) 22.4 - 47.2 [43.0]	0.59 ± 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]			Biphasic 1 subj excluded due to high conc post inf if high conc excluded PK near mean
SP804	Rising Dose Finding PK/PD Study	30 min IV LD				M & F	9	3.4 ± 2.3 (69.0) 0.8 - 7.6 [2.9]	1.24 ± 0.91 (73.4) 0.51 - 3.52 [0.91]	233 ± 69 29.5 139 - 341 239	3.1 ± 0.7 22.7 1.8 - 4 2.9		3.63 ± 2.0 (55.2) 1.19 - 8.02 [3.12]	0.73 ± 0.45 (61.9) 0.15 - 1.34 [0.86]	71.5 ± 45.1 (63.1) 24.5 - 179 [59.3]	?prev colc
						M	6	3.8 ± 2.7 (70.0) 0.8 - 7.6 [2.9]	1.49 ± 1.05 (70.4) 0.69 - 3.52 [1.18]	255 ± 69 (27.0) 151 - 341 [258]	3.0 ± 0.8 (26.3) 1.8 - 4.0 [2.8]		4.32 ± 2.08 (48.1) 2.43 - 8.02 [3.45]	0.81 ± 0.44 (54.2) 0.183 - 1.34 [0.914]	86.2 ± 48.6 (56.4) 47.73 - 179 [74.0]	Need to Chck Vd Calcs
						F	3	2.5 ± 1.5 (60.1) 1.0 - 4.1 [2.4]	0.75 ± 0.21 (28.2) 0.51 - 0.91 [0.84]	188 ± 50 (26.7) 139 - 239 [187]	3.2 ± 0.6 (18.4) 2.8 - 3.8 [2.9]		2.25 ± 0.98 (43.4) 1.19 - 3.12 [2.44]	0.57 ± 0.53 (92.5) 0.15 - 1.17 [0.40]	42.1 ± 17.4 (41.3) 24.5 - 59.3 [42.5]	
		IV LD & MD				M & F	7	6.0 ± 3.3 (55.2) 2.4 - 10.6 [4.6]	1.8 ± 0.5 (27.6) 1.3 - 2.7 [1.7]	325 ± 119 36.7 201 - 525 338	4.5 ± 1.3 29.9 3 - 6.1 4.7					
						M	4	6.1 ± 3.7 (60.7) 2.4 - 10.6 [5.7]	1.7 ± 0.4 (25.6) 1.3 - 2.2 [1.7]	408 ± 83 20.3 338 - 525 385	5.0 ± 1.4 27.8 3.1 - 6.1 5.3					
						F	3	5.9 ± 3.5 (60.0) 3.2 - 9.9 [4.6]	2.0 ± 0.6 (32.6) 1.5 - 2.7 [1.7]	215 ± 20 9.1 201 - 237 207	3.8 ± 1.1 28.5 3.0 - 5.0 3.3					
SP805		CIVI dose titrated to effect				M & F	7			248.6 ± 54.3 21.8 188 - 350 233	2.9 ± 0.7 23.5 1.9 - 3.7 2.8					
Formulation Development																

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
Healthy Subject PK and Initial Tolerability Trial Reports																
SP503		Day 1	4.5 mg /10 cm^2		Form 3					622.9 ± 421.4 (67.7) 163.4 - 2265.4 [503.5]	7.6 ± 4.8 (63.1) 2.1 - 23.5 [6.0]					
		Day 14					29		4.4 ± 0.8 (16.9) 2.5 - 5.8 [4.3]	482.6 ± 258.9 53.6 180.5 - 1626.2 418.3	5.8 ± 2.8 48.3 1.9 - 16.9 5.1				53.8 ± 24.9 (46.3) 17.9 - 142.7 [52.8]	
		Days 1 - 14								(L/hr) 39.0 ± 17.2 44.2 17.0 - 94.5 4.1	L/hr/kg 0.471 ± 0.198 42.1 0.225 - 1.096 0.404		94.0 ± 6.6 (7.0) 86.5 - 104.2 [94.7]			
		Ratios Data from all days														
Intrinsic Factors																

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
				Site	Age	Sex	N								HVD	
SP 630		<65 Female		ABDOMEN	<65	Female	7								17.1 ± 7.4 (43.5) 1.2 - 23.4 [20.2]	
				FLANK			6								12.7 ± 6.4 (50.8) 5.7 - 22.9 [12.0]	
				Hip			3								11.7 ± 3.6 (30.8) 7.8 - 14.9 [12.5]	
				Shoulder			5								15.5 ± 4.5 (28.7) 11.7 - 21.1 [13.3]	
				Thigh			3								13.9 ± 10.3 (74.5) 2.0 - 20.8 [18.9]	
				UPPER ARM			6								19.7 ± 2.9 (14.9) 15.2 - 23.2 [20.6]	
		<65 Male		ABDOMEN	<65	Male	4								20.2 ± 4.1 (20.4) 14.2 - 23.5 [21.6]	
				FLANK			6								12.7 ± 4.8 (37.6) 6.9 - 18.8 [11.0]	
				HIP			7								16.8 ± 7.7 (45.7) 4.9 - 23.5 [19.7]	
				Shoulder			4								20.6 ± 2.1 (10.3) 17.9 - 23.0 [20.7]	
				Thigh			6								21.1 ± 3.0 (14.4) 15.9 - 23.5 [22.0]	
				UPPER ARM			5								17.3 ± 3.3 (18.9) 13.1 - 22.0 [16.8]	
		≥65 Female		ABDOMEN	≥65	Female	5								20.1 ± 3.6 (18.1)	

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
															15.3 - 23.5 [20.8]	
				FLANK			4								18.5 ± 6.0 (32.7) 11.3 - 23.5 [19.6]	
				HIP			6								16.9 ± 4.1 (24.2) 10.8 - 22.5 [17.4]	
				Shoulder			3								21.4 ± 0.9 (4.0) 20.4 - 21.9 [21.9]	
				Thigh			8								14.9 ± 6.3 (42.4) 2.6 - 23.5 [15.3]	
				UPPER ARM			4								17.4 ± 5.3 (30.2) 10.8 - 23.5 [17.7]	
		≥65 Male		ABDOMEN	≥65	Male	4								15.6 ± 4.5 (29.2) 10.7 - 21.2 [15.2]	
				FLANK			7								13.5 ± 6.4 (47.6) 4.5 - 22.3 [12.5]	
				HIP			4								15.2 ± 7.9 (52.3) 3.8 - 20.8 [18.1]	
				Shoulder			10								18.0 ± 4.8 (26.5) 9.6 - 22.8 [19.4]	
				Thigh			3								18.4 ± 3.2 (17.5) 14.7 - 20.3 [20.3]	
				UPPER ARM			6								19.8 ± 3.9 (19.7) 13.5 - 23.5 [20.6]	
SP630				4.5mg / 10 cm^2	Form 4	F yng	15									
						M yng	16									

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	t1/2$_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
						F Eld	15									
						Male Eld	17									
						F yng	15									
				9.0mg / 20 cm^2		M yng	16									
						F Eld	15									
						Male Eld	17									
						F yng	15									
				13.5mg / 30 cm^2		M yng	16									
						F Eld	15									
						Male Eld	17									
						F yng	90									
				2 x 9 mg / 20 cm^2		M yng	96									
						F Eld	90									
						Male Eld	102									
SP596	Effect of Race			4.5mg/10 cm^2	C		24		6.49 ± 3.65 (56) 1.71 - 19.7 [6.09]							
					Blk		23		7.6 ± 3.1 (41.0) 2.5 - 16.0 [7.0]							
SP717	Effect of Race Japanese vs. Caucasian (SD Study)			4.5mg/10 cm^2	C	F	12		5.8 ± 2.6 (44.6) 3.44 - 10.76 [4.54]	294.1 ± 144.8 (49.2) 104.9 - 488.5 [335.8]	4.9 ± 2.2 (45.0) 1.9 - 7.9 [5.5]	3852 ± 1892 (49.1) 1908 - 7693 [3246]	64.2 ± 27.7 (43.1) 34.1 - 113.1 [50.6]			
					C	M	12		5.6 ± 1.8 (32.6) 3.53 - 9.03 [4.96]	213.9 ± 85.3 (39.9) 72.8 - 389.0 [215.6]	3.1 ± 1.1 (36.2) 1.3 - 5.3 [3.1]	4157 ± 1829 (44.0) 1604 - 7066 [3781]	60.3 ± 23.9 (39.6) 22.0 - 97.0 [55.8]			
					J	F	12		5.5 ± 2.5 (44.7) 3.3 - 12.4 [4.7]	155.6 ± 56.2 (36.1) 81.3 - 277.0 [140.1]	2.9 ± 0.9 (30.9) 1.6 - 5.2 [2.8]	2624 ± 940 (35.8) 1814 - 4847 [2223]	51.4 ± 22.6 (43.9) 24.2 - 96.9 [44.3]			
					J	M	12		5.2 ± 2.5 (49.0) 2.4 - 10.6 [4.1]	242.9 ± 96.9 (39.9) 121.2 - 478.1 [249.6]	3.9 ± 1.5 (38.9) 2.0 - 7.5 [4.2]	3942 ± 1533 (38.9) 1486 - 6683 [4017]	62.7 ± 22.5 (35.9) 25.6 - 92.0 [63.8]			
SP718	Effect of Race Japanese vs. Caucasian					CF			6.5 ± 1.6 (24.9) 4.2 - 9.3			4879.8 (30.2) 3222.1				

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
	(MD Study)								[n.s]			2876.9 - 5973.9 [5250.2]				
				4.5mg/10 cm²		CM			5.6 ± 1.2 (20.7) 3.8 - 7.6 [5.9]			6014.1 ± 1401.9 (23.3) 4346.0 - 8062.6 [5819.6]				
						JF			7.0 ± 1.6 (22.8) 4.7 - 9.9 [6.2]			5157.9 ± 1660.0 (32.2) 3151.0 - 7252.8 [5069.1]				
						JM			5.8 ± 0.3 (4.9) 5.6 - 6.3 [5.7]			3698.3 ± 773.9 (20.9) 2885.4 - 5114.9 [3484.8]				
SP671	Hepatic Impairment Study	Healthy Young Male vols		4.5mg/10 cm²												
		Mild – Mod Hepatic Impairment														
SP672	Renal Impairment Study	Grp 1: Healthy														
		Grp 2: Mild RD														
		Grp 3: Moderate RD														
		Grp 4: Severe RD														
		Grp 5: ESRD														
Extrinsic Factor																
SP626	Effect of Application Site on BA	Vental Abdomen		4.5mg/10 cm²			20		5.6 ± 2.2 (39.7) 3.0 - 11.2 [5.5]							
		Arm					18		7.1 ± 3.6 (51.0) 1.4 - 16.1 [6.6]							
		leg					21		5.8 ± 1.7 (29.0) 3.2 - 9.3 [5.3]							
SP627	DDI Cimetidine			9mg/10 cm²												

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
SP628	DDI- Carbidopa-Levodopa (CD-LD)															
SP670	DDI - Domperidone															
Clinical Pharmacology																
SP629							—	—	—	—	—	—	—	—	—	—
SP673																
Pivotal BE																
SP581		Sponsor's Calc Excluding subjs with adhesion <80%				Test			6.3 ± 2.1 (33.2) 3.3 - 12.1							
						Ref			7.1 ± 2.3 (32.3) 2.7 - 10.7							
		My Calcs All subjects				Test			6.1 ± 2.2 (36.0) 3.1 - 12.1 [5.6]	383+118 30.8 175-622 362						
						Ref			6.4 ± 2.6 (40.4) 1.6 - 10.7 [6.3]	399+155 38.9 166-971 383						
SP534 Part I		9 mg (1 x 20 cm^2) or PBO														

Study Number	Study Description	Arm	Dose	Subject Group			N	t1/2α	t1/2$_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
		18 mg (2 x 20 cm^2) or PBO														
		27 mg (3 x 20 cm^2) or PBO														
		36 mg (4 x 20 cm^2) or PBO														
SP534 Part 2																
SP535		4.5mg/10 cm^2														
SP540		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
		18.0 mg/ 40 cm^2														
		9 mg (1 x 20 cm^2)														
SP506		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
		18.0 mg/ 40 cm^2														
SP512 Part I		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
SP513 Part I		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
		18.0 mg/ 40 cm^2														
SP512 Part IId SP702		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
		18.0 mg/ 40 cm^2														
SP513 Part IId SP716		4.5 mg/ 10 cm^2														
		9.0 mg/ 20 cm^2														
		13.5 mg/ 30 cm^2														
		18.0 mg/ 40 cm^2														
Other Studies																
SP533																
SP511																

Study Number	Study Description	Arm	Dose	Subject Group			N	$t1/2\alpha$	$t1/2_{term}$	Cl	Cl	Vdss	Vdss	Vc	MRT	Comment
				Population	Race / Ethnicity	Gender		(min)	(hrs)	(L/hr)	L/hr/kg	L	L/kg	L/kg	(min)	
SP650 Part Id																
SP650 Part IId (SP715)																
SP591																
SP666																
SP709d																

Table 117 PK Outliers by Study

Study Number	Formulation	Typical Values			Outliers				Comments
		Cmaxs (ng/ml)	Ct (ng/ml)	Reported AUCinf (ng/ml x hr^{-1})	Tmax (hrs)	Cmax (ng/ml)	Tmax (hrs)	AUCinf (ng/ml x hr^{-1})	
805									
799									42.0
800									

5.4 Appendix 4 - Bioanalytic Assay Validation

Insufficient time to review.

5.5 Appendix 5 - Consults

None.

5.6 Appendix 6 - Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-829	**Brand Name**	Neupro
OCPB Division (I, II, III)	I	**Generic Name**	Rotigotine
Medical Division	DNPD	**Drug Class**	Dopamine Agonist
OCPB Reviewer	Ron Kavanagh	**Indication(s)**	Parkinson's Disease
OCPB Team Leader – Acting	Sally Yasuda	**Dosage Form**	Transdermal System
INDs	47,852: Parkinson's disease	**Dosing Regimen**	Once Daily
Date of Resubmission	January 19, 2005	**Date of Original Submission**	September 24, 2004
Date of Filing Meeting for Resubmission	February, 25, 2005	Approximate Date of Filing Meeting for Original Submission	~ November 22, 2004
Estimated Due Date of OCPB Review	September 19, 2005	**Route of Administration**	Dermally
PDUFA Due Date	November 28, 2005	**Sponsor**	Schwarz Biosciences
Division Due Date	October 6, 2005	**Priority Classification**	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X	4		
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	20		
I. Clinical Pharmacology				
Mass balance:	?	1		MD PK including metabolites
Isozyme characterization:	X	3		
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Transporters	X	1		
Healthy Volunteers-		15		
single dose:	X	1		
multiple dose:	X	1		
Patients-		2		
single dose:				
multiple dose:	X	3		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	X	2		
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	3		
gender:				
pediatrics:		0		
geriatrics:	X	4		Geriatric Disease
renal impairment:	X	1		
hepatic impairment:	X	1		

PD:				
Phase 2:	X			several
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			Several
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):	X	2		
Bio-wavier request based on BCS				TDS - Not Applicable
BCS class				TDS - Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT Studies	X			
Hepatocyte Induction	X	1		
pGP Transport	X	1		
Dermal Tolerability	X	5		
Adhesion	X	1		
Total Number of Studies		51 studies 20 Assay Validation Reports		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	X (Yes)	~~Unable to open electronic files containing phase II and III efficacy studies and pop PK analyses.~~
Comments sent to firm?	~~No~~	~~See attachment.~~
QBR questions (key issues to be considered)	• What is the tolerability of the largest size patch size? • What are the adhesion characteristics of the largest patch size? • Is there sufficient information on all proposed sites of application. • A common problem with treatment of Parkinsonism is on/off phenomenon due to short duration of action. Since rotigotine has a 2 hour half-life and the patch has a Tlag of 8 hours, the question of time course of effect and whether this is the appropriate formulation for this drug is of critical importance. • Can't tell if adequate studies of transdermal formulation in elderly or in different ethnic groups.	

Other comments or information not included above	• This is a resubmission. The original submission was not filed due to problems with the eCTD. The primary problem was that the phase II and III efficacy studies could not be opened, for a list of OCPB filing issues sent to the sponsor see Appendix 1. • Except for protocols SP 515 and [redacted] mentioned in comment # 1 in Appendix 1. all other OCPB filing issues appear to be resolved. For question # 1 the sponsor was called on February 22, 2005 and a voice mail message was left for Betsy Waldheim, Head US Regulatory Affairs (919-767-2560). A reply voicemail on February 23, 2005 indicated that SP515 is a protocol for advanced parkinsonism that is ongoing, (the current submission is for early parkinsonism, and protocol [redacted] • Based upon the above information OCPB finds the resubmission filable. • Differences between the OCPB filing memo for the resubmission and the OCPB filing memo for the original submission are indicated by red text. • **In the clinical trials of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm).** • **Several studies are listed under 'patch formulation used in studies', but no study reports are included.**
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: **NDA 21-829**
HFD-850 (P. Lee)
HFD-860 (M. Mehta, RahmanA, YasudaS, BawejaR, KavanghR)
HFD-120 (Wheelous)
HFD-120 (KapcalaL, FeeneyJ, KatzR)
CDR

Appendix 1 Comments Sent to Sponsor

1) Three studies were found listed under section 2.3.P.2.2 Drug product, subsection 2.3.P.2.2.1 Formulation development that are not found elsewhere in the submission, including the following: [redacted]

2) None of the studies listed in, Table 1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, were able to be opened nor did links to these documents work.

Table1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Section	Protocol Number	Study Title
5.3.5.1.1	SP 800 (TD-0923-002)	A pilot evaluation of a transdermal patch containing the dopamine D2 agonist N-0923 in patients with Parkinson's disease
5.3.5.1.2	SP 534 Part I	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease
5.3.5.1.3	SP 534 Part II	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease
5.3.5.1.4	SP 535	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease
5.3.5.1.5	SP 506	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of escalating transdermal doses of rotigotine (SPM 962) in subjects with early-stage Parkinson's disease
5.3.5.1.6	SP 512	A multi-center, multinational, phase III, randomized, double-blind, placebo controlled trial, of the efficacy and safety of the rotigotine patch in subjects with early-stage, idiopathic Parkinson's disease (Part 1).
5.3.5.1.7	SP 512	Pharmacokinetics of total rotigotine in patients with early-stage idiopathic Parkinson's disease
5.3.5.1.8	SP 513	A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and ropinirole-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic PD.

3) A number of studies in the human clinical studies section are placed in the wrong subfolders. Selected examples are shown in below, (see Table 2). N.B. This is list is not exhaustive and a number of other incorrect file placements were also noted.

Tabel 2 Incorrect Study Report Locations in eCTD

Study Report		Current Incorrect Locations		Correct Locations	
Study Number	**Title / Description**	**Section**	**Subfolder**	**Section**	**Subfolder**
SP 512	Pharmacokinetics of total rotigotine in patients with early-stage idiopathic Parkinson's disease	5.3.5.1.7	Study Reports Of Controlled Clinical Studies	5.3.3.5	Population Pk Study Reports
SP 671	Liver Impairment	5.3.3.5	Population Pk Study Reports	5.3.3.3	Intrinsic Factor Pk Study Reports
SP672	Renal Failure	5.3.3.5	Population Pk Study Reports	5.3.3.3	Intrinsic Factor Pk Study Reports

4) File names of links in subfolders are much too long making navigation extremely difficult. Currently filenames or links as named as in the following example:

Section number	Study number	Study Title	Subsection Link
5.3.5.1.2	SP 534 Part I	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease	1 Synopsis

We suggest that the except for the first link/listing that the study title be excluded as the section number ans study number should be adequate identification. Such an approach is recommended according to guidance documents.

Appenidix 2 Rotigotine Studies of Interest to OCPB

Section	Study No.	Study Title	Objective	SD / MD	Subjs/Pxt	N	Age	M/F	Race C/B/H/A/NA/O	Application Site	Dose	Formulation(s)	Comments
5.3.5.3.3		Summary report of data on apparent dose											
5.3.5.3.4		Summary report of in vivo absorption data of rotigotine for trials SP502 and SP581											
5.3.5.3.5		Summary report of the influence of intrinsic and extrinsic factors on the apparent dose											
5.3.5.3.6		Summary QT report for Rotigotine phase I and II trials											
5.3.2.2.4	635-03	Determination of the cytochrome P450 induction potential of rotigotine in human hepatocytes											
5.3.2.2.2	BA 475-02	Interaction of the Compounds SPM 962, SPM, 5907, SPM 9257, SPM 9206, and SPM 9141 with the Cytochrome P 450 Isoenzymes 3A4 and 2D6											
5.3.2.1.1	BA 507-02	Protein binding displacement interaction of rotigotine and warfarin. In-vitro study in human plasma and human serum albumin											
5.3.2.2.3	BA 559-02	Characterization of the Mechanism of the Cytochrome P450 2C19 and 2D6 Inhibition by SPM 962											
5.3.2.2.1	DHGY-1012-00 (incl. Amendment 1)	Interaction of the compounds SPM 962, SPM 5907, SPM 9257, SPM 9206 and SPM 9141 with the cytochrome P450 isoenzymes 3A4 and 2D6											
5.3.2.3.1	DHGY-1031 Amendment 1	Transport of SPM 962 across caco-2 monolayers: Investigation of p-glycoprotein involvement											
5.3.1.2.1	SP 502	Pilot study for the comparative bioavailability and dose proportionality after a single administration of one and two silicone based and one [redacted] transdermal preparations of SPM 962 in a three-way cross-over design in 12 healthy male subjects	Rel BA PK	SD	Healthy	12		M 12			1 x 33.5 mg /20 cm 1 x 9 mg / 20 cm 2 x 9 mg / 20 cm	Dev-2 Dev-3	ECG
5.3.3.1.1	SP 503	Multiple dose pharmacokinetics and pharmacodynamics of SPM 962 and its metabolites during 14 days of q. d. administration to 30 healthy male volunteers	PK/PD	MD x 14		30	18-50	M 30	30/-		4.5 mg / 10 cm	Dev-3	ECG Hormones
5.3.5.1.5	SP 506	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of escalating transdermal doses of rotigotine (SPM 962) in subjects with early-stage Parkinson's disease			Unable to Open							Dev-3	
	SP-511											Dev-3	Listed but Can't find
5.3.5.1.6	***SP 512***	***A multi-center, multinational, phase III, randomized, double-blind, placebo controlled trial, of the efficacy and safety of the rotigotine patch in subjects with early-stage, idiopathic Parkinson's disease (Part 1).***			Unable to Open							TBM	
5.3.5.1.7	***SP 512***	***Pharmacokinetics of total rotigotine in patients with early-stage idiopathic Parkinson's disease***			Unable to Open	Pop PK?						TBM	
5.3.5.2.2	***SP 512***	***Open Label A multi-center, multinational, Phase 3, randomized, double blind, placebo-controlled trial of the efficacy and safety of the rotigotine patch in subjects with early stage, idiopathic Parkinson's disease (Part I), and an open-label extension to assess the***			Unable to Open							TBM	

Section	Study No.	Study Title	Objective	SD / MD	Subjs/Pxt	N	Age	M/F	Race C/B/H/A/NA/O	Application Site	Dose	Formulation(s)	Comments
5.3.5.1.8	SP 513	A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and ropinirole-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic PD.			Unable to Open							TBM	
	SP 515											TBM	Listed but Can't Find
5.3.5.4.2	SP 533	A Single Center, Double-Blind, Placebo-Controlled Parallel Group, Does-Ranging Study to Assess The Safety and Tolerability of Transdermal Doses of SPM962 (Rotigotine) in Subjects with Early-Stage Parkinson's Disease											
5.3.5.1.2	SP 534 Part I	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease			Unable to Open								
5.3.5.1.3	SP 534 Part II	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease			Unable to Open								
5.3.5.1.4	SP 535	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease			Unable to Open								
5.3.5.2.1	SP 540	A Multi-site, Single-blind, Dose-escalation trial to Assess Potential Benefits and Safety Limitations of Transdermal Doses of SPM 962 in Subjects with Early Stage Idiopathic Parkinson's Disease			Pxt MRD PK							Dev-3	
5.3.1.2.2	SP 581	Bioequivalence evaluation of SPM 962 from two different silicone patches in 30 healthy male volunteers	Rel BA	SD	Healthy	30	18-50	M 30	30/-/-/-/-/-		4.5/10	Dev-3 TBM	
5.3.5.4.6	SP 591	A single center, double-blind, placebo-controlled, parallel group, dose-ranging study to assess the safety and tolerability to transdermal doses of SPM 962 (Rotigotine) in subjects with early-stage Parkinson's Disease										Dev-3	
5.3.3.3.2	SP 596	Relative bioavailability and Pharmacokinetics of SPM 962 after Transdermal Administration in Caucasian and Black Volunteers	Ethnicity Tolerability Adhesiveness	SD	Healthy	51	18-50	M	26/25/-		4.5/10	Dev-3	
5.3.1.1.3	SP 606	Absorption and excretion of radioactivity after single dermal application of [14C]-SPM 962 in healthy human subjects	PK Mass Balanace	SD	Healthy			M 6			4.5 mg		Drug Delivery
												TBM	Listed but Can't Find
5.3.1.1.4	SP 610	Absorption and excretion of radioactivity after single dermal application of 14C-SPM 962 in healthy human volunteers	Abs BA Mass Bal	SD	Healthy	6	young	M 6				Dev-3 IV	
5.3.3.3.1	SP 626	Influence of the application site on the absorption of SPM962 in healthy subjects	Application Site	SD	Healthy	24	18-50	M	C	Vent ABD Vent Upper Arm Vent Lat Upper Leg	4.5/10	Dev-3	
5.3.3.4.1	SP 627	Influence of cimetidine comedication on the	DDI - Cimetidine	MD	Healthy	12	18-45	M	C	Vent Abd	1 4.5/10	Dev-3	

Section	Study No.	Study Title	Objective	SD / MD	Subjs/Pxt	N	Age	M/F	Race C/B/H/A/NA/O	Application Site	Dose	Formulation(s)	Comments
		pharmacokinetics of SPM 962 in 12 healthy subjects	Tol	1 x 4 2 x 4									
5.3.3.4.2	SP 628	Open, parallel-group, drug-drug interaction trial to evaluate pharmacokinetics of rotigotine CDS and levodopa/carbidopa in patients with idiopathic Restless Legs Syndrome	DDI - Sinemet	MD 4.5/10 x 3 9/20 x 5	Pxt RLS	24		12/12 M/F			4.5/10 9/20	TBM	
5.3.3.1.2	***SP 629***	***Single-site, placebo-controlled investigation of cumulative skin irritation after repetitive administration of rotigotine transdermal patch (2.5cm2/1.125mg) to the same skin site in comparison to multiple administration of rotigotine transdermal patch (2.5cm2/1.125mg) to daily rotating skin sites in healthy subjects***		***SD MD x 21***	***Healthy***	***38***	***18-60***	***M/F***	***38/-***		***1.125/2.2 PBO***		***Tolerability Adhesiveness***
5.3.3.2.1	SP 630	An open-label, multi-site, randomized trial of the pharmacokinetics and cardiac safety of rotigotine transdermal patch (18.0mg) in subjects with early-stage, idiopathic Parkinson's disease	QT Tolerability PK/PD in pxts	MD 4.5x6 9x6 13.5x6 18x6	Early PD	63	>18 yo (some >65)	M/F		Rotating (abdomen, flank, upper arm, shoulder, thigh, hip).	1x4.5/10 1x 9/20 1 x 13.5/30 2 x 9/20		ECG
5.3.5.4.4	SP 650 Part I	A multi-center, multinational, phase III, randomized, double-blind, parallel group, placebo controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part I) and open label extension to assess the safety of long-term treatment of rotigotine CDS (Part II)										TBM	
5.3.5.4.5	SP 650 Part II	A multi-center, multinational, phase III, randomized, double-blind, parallel group, placebo controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part I) and open label extension to assess the safety of long-term treatment of rotigotine CDS (Part II)										TBM	
5.3.5.4.7	SP 666	Multicenter, double-blind, randomized, placebo-controlled, four-arm, parallel-group trial of rotigotine CDS in patients with idiopathic Restless legs Syndrome (Phase IIa)			Pxt								
5.3.3.4.3	SP 670	Open, randomized, two-fold crossover trial to evaluate the influence of domperidone on the pharmacokinetics and safety/tolerability of multiple dose treatment of rotigotine in young healthy male subjects	DDI Domperidone	MD 4.5/10 x 4 day	Healthy	16	21-44	M	C		4.5/10	TBM	
5.3.3.5.1	SP 671	Open, group-comparison trial to evaluate the influence of liver impairment on the pharmacokinetics and safety/tolerability of multiple dose treatment with rotigotine in hepatic impaired patients	PK MD Hepatic	MD 3x4.5/10	Healthy Mod HI	8/8	18-65	M	C			TBM	
5.3.3.5.2	SP 672	Open-label, group comparison investigation of pharmacokinetics, safety and tolerability of single dose transdermal treatment with rotigotine (10cm2 patch/4.5mg) in patients with impaired renal function including patients requiring dialysis compared to healthy subjects	PK SD ESRD	SD	Healthy Mild – Severe RI ESRD on Dialysis	8 1 7 8 8 32)	18-75	M/F	C		4.5/10		
5.3.3.1.3	SP 673	Two-Site, placebo-controlled investigation of skin	Tolerability	MD x 14	Healthy	221	18-49	M/F			1.125/2.5	TBM	

Section	Study No.	Study Title	Objective	SD / MD	Subjs/Pxt	N	Age	M/F	Race C/B/H/A/NA/O	Application Site	Dose	Formulation(s)	Comments
		sensitization after repeated administration of rotigotine transdermal patch (2.5cm2/1.125mg) in healthy subjects	Adhesion	3x/wk							PBO		
5.3.5.4.8	SP 709	Multi-center, double-blind, randomized, placebo-controlled, six-arm, parallel-group, dose-finding trial to determine efficacy, safety, and tolerability of five different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome			Pxt								
5.3.3.3.3	SP 717	Parallel group trial to evaluate the pharmacokinetics and safety/tolerability of single-dose treatment with rotigotine CDS (10cm2/4.5mg) in Japanese and Caucasian healthy subjects	Ethnicity PK	SD	Healthy	48	20-45	24/24	24/-/-24/-	Vent lat abd	4.5/10	TBM	
5.3.3.3.4	SP 718	Parallel-group trial to evaluate the pharmacokinetics and safety/tolerability of repeated dose treatment with rotigotine CDS in 3 different dosages (5cm2/2.25mg, 10cm2/4.5mg, 20cm2/9mg) in Japanese and Caucasian healthy subjects	PK RMD Ethnicity Tol Adhesion	MD x 3	Healthy		18-45	12/12	12/-/-/12/-	Vent lat abd	2.25/5 4.5/10 9/20	TBM	
5.3.4.2.1	SP 803 (N-0923-001-2601)	A pilot evaluation of the Anti-Parkinson efficacy and safety of a new dopaminergic agonist in Parkinson patients	MD PK/PD IV Modified Columbia Rating Scale	MD	Pxt stg II-IV	12	39-75	9/3			3 – 24 mcg/kg/hr in 50 ml over 10 min or 0.5-7 mcg/kg/hr in 100 ml over 4 hr	IV Soln x 10 min	ECG PAT PVC 6/12
5.3.4.2.2	SP 804 (N-0923-002-01)	A pilot evaluation of the pharmacokinetics, pharmacodynamics and safety of a new dopaminergic D2 agonist, N-0923 in Parkinson patients	MR PK/PD IV Modified Columbia Rating Scale	MD PK/PD IV Pxt M/F eld	Pxt stg II-IV	12	39-75	9/3	C		3 – 24 mcg/kg/hr in 50 ml over 10 min or 0.5-7 mcg/kg/hr in 100 ml over 4 hr	IV Soln	
5.3.4.2.3	SP 805 (N-0923-006-01)	The activity of 7-day N-0923 continuous intravenous infusions in patients with stage III through stage IV Parkinson's disease	PK/PD CIVI Freq of on off phenomenon	MD PK/PD IV Pxt M/F elderly	Pxt stg III-IV	8	52 - 75	6/2	C		1 – 30 mcg/kg/hr x 7 days	IV Soln	AEs Tolerance

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Ron Kavanagh
2/23/2006 01:23:10 PM
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