were obtained in only 15 subjects. A trial specific linear correction of QT was derived as was a log-transformed model that produced almost the same exponent as the Fridericia correction.

SP534 Part I
This was a single center, phase 2, double-blind, randomized, placebo-controlled, parallel group, MTD safety and efficacy trial of transdermal rotigotine in subjects with early stage PD. Subjects were randomized to rotigotine or placebo (ratio=5:1). Twelve subjects were enrolled into the first two trial cohorts (6 subjects per cohort), 8 completed. The trial was stopped after the second of five planned cohorts (the second cohort included 5 subjects receiving rotigotine 13.5mg and 1 subject receiving placebo). Analysis of the relationship between rotigotine concentration and QT interval were done using the same averaging of slope method used in SP502.

SP534 Part II
The original SP534 protocol was designed to evaluate a dose range of rotigotine without an individual dose titration. The maximum tolerated dose with this fixed dose regime in subjects with early PD was 13.5 mg (30cm2), the main limiting side-effect being nausea and vomiting and stopped as described above. The SP534 protocol was consequently amended as SP534 part II to include a weekly dose titration (of 4.5 mg/10 cm2 increments) to achieve an upper dose limit of 18.0 mg/40cm2. The trial had open-label screening and placebo run-in periods, followed by a double-blind dose titration period (4.5 mg up to 18.0 mg drug or placebo equivalent) with a safety follow-up period off any study medication. Subjects were randomized to rotigotine or placebo in a ratio of 5:1. A total of 12 subjects were randomized and treated - 10 with rotigotine and 2 with placebo. All subjects completed the trial. Analysis of the relationship between rotigotine concentration and QT interval were done using the same averaging of slope method used in SP502.

SP535
This trial was a single-site, double-blind, placebo-controlled, dose escalation trial of rotigotine transdermal patches in subjects with early stage Parkinson's disease. Ten subjects were randomized to rotigotine or placebo (ratio = 4:1). Trial periods included an open-label screening and placebo run-in period (7 days maximum); a 28-day, double-blind, dose-titration period (dose titration occurred on a weekly basis at each in clinic visit); and a 28-day safety follow-up period after the subject received the final dose of trial medication. ECG results were not compared to plasma rotigotine levels. The Fridericia correction was used as the primary technique.

SP540
This was a multicenter, single-blind, dose-escalating trial designed to establish the maximum tolerated dose (MTD) of rotigotine in subjects with early-stage, idiopathic Parkinson's disease. The trial had a single treatment arm with planned dose escalations of 4.5mg, 9.0mg, 13.5mg and 18.0mg of rotigotine. When it was deemed a subject had reached their MTD the subject entered the maintenance period on that dose; otherwise the

dose was titrated up to the next level. 12-Lead ECGs were taken at screening, pre-trial period (day .1 and day 1 pre-dosing), and on various study days, prior to patch removal and 2 and 5 hours post patch application. Safety ECGs recorded on the follow-up visit. Analyses of the relationship between rotigotine concentration and QT interval were done using the same averaging of slope method used in SP502.

SP591
This was a multicenter, parallel, randomized, open-label, dose-escalation trial which assessed the individual maximal achievable dose (MAD) with two titration schemes. In Group 1 subjects had dose escalation steps of 9.0mg (20cm2) of rotigotine patches, in weekly increments whereas Group 2 had weekly dose escalating steps of 4.5mg (10cm2) patches. Subjects who developed clinically significant intolerance at a particular dose level were back-titrated to the nearest lower tolerated dose of rotigotine (defined then as the MAD) and remained on this dose during the maintenance phase. Multiple ECGs were taken at all trial visits prior to patch removal and after new patch application, where applicable. Plasma rotigotine levels were not compared to ECGs. ECG changes from baseline were analyzed using the Fridericia correction.

SP506
Although a phase 2 study, this trial was considered a pivotal trial by the sponsor and its results were pooled with studies SP512 and SP513 in the Sponsor's Integrated Summary of safety. This was a multicenter, double-blind, placebo controlled, parallel group, dose ranging trial of rotigotine in subjects with early stage PD. Subjects were randomized to four active treatment arms (4.5mg, 9mg, 13.5mg and 18mg of rotigotine) or placebo. Standard 12-lead ECGs were obtained at screening, dose titration, dose maintenance and dose de-escalation periods, prior to patch removal and shortly post patch application (where applicable). Three ECGs were done at the safety follow-up visit. A trial-specific linear correction was derived and as well as an exponential correction that was nearly identical to the Fridericia correction. Scatterplots and correlation coefficients were generated comparing QT intervals and change in QT intervals using both Bazett and Fridericia corrections with plasma rotigotine levels at each visit so that only one observation per subject was compared.

Reviewer Comment: The use of scatterplots and correlation coefficients limited to a single observation per subject does not avoid the problem of ecological fallacy described in my previous comment.

Phase 3
SP512
This trial was a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial of rotigotine in subjects with early-stage, idiopathic Parkinson's disease. Rotigotine doses included 4.5mg/day, 9.0mg/day, and 13.5mg/day. Trial periods consisted of a 4-week pre-treatment (washout) period, a 3-week dose escalation period, a 24-week dose maintenance period, and a 4-week follow-up period for a total duration of 38 weeks. Standard 12-lead ECGs were taken pre-treatment, at the end of titration, at the

commencement of the maintenance phase, after 12 and 24 weeks of the maintenance phase and at the safety follow-up assessment. ECG changes, QT intervals with Bazett and Fridericia corrections were used to compare changes from baseline. Plasma rotigotine levels were not obtained.

SP513
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. Rotigotine doses included 4.5mg/day, 9.0mg/day, 13.5mg/day, and 18.0mg/day. Ropinirole doses included 0.75, 1.5, 2.25, 3.0, 4.5, 6.0, 7.5, 9.0, 12.0, 15.0, 18.0, 21.0 or 24.0mg/day. Trial periods consisted of pre-treatment (washout) period of up to 4 weeks, a dose escalation period of up to 13 weeks, a 24-week dose maintenance period, a mandatory dose de-escalation phase of up to 12 days, and a 4-week safety follow-up period. Total trial duration was up to 48 weeks. Standard 12-lead ECGs were taken pre-treatment, during titration, at the commencement of the maintenance phase, after 12 and 24 weeks of the maintenance phase and at the safety follow-up assessment. ECG changes, QT intervals with Bazett and Fridericia corrections were used to compare changes from baseline. Plasma rotigotine levels were not obtained.

Dedicated QT Study
SP630
At the pre NDA meeting on 17 Dec 2003, the Division requested that the sponsor conduct a trial to evaluate the steady state pharmacokinetic profile of rotigotine at the highest proposed dose in subjects with early stage Parkinson's disease at multiple sites for placement of the patch. In addition, the Division advised the sponsor to collect ECG data in parallel in order to evaluate the potential electrocardiographic effects of rotigotine at maximal therapeutic exposure. The SP630 trial was designed to address these issues.

This trial investigated the pharmacokinetic profile and cardiac safety over 24 hours under maximal therapeutic conditions (18.0mg, steady state), with rotation of the patch to 6 different application sites in early-stage Parkinson's subjects.

This was an open-label, multi-site, randomized trial with daily doses of rotigotine patch applied to rotating sites on the skin of subjects. Forty-eight subjects with early-stage Parkinson's disease (24 female and 24 male subjects with each group consisting of 12 subjects <65 years of age and 12 subjects ≥65 years of age) were planned to be randomized to treatment. Randomized subjects had plasma samples collected while patches were applied to 6 different patch application sites (abdomen, flank, upper arm, shoulder, thigh, hip).

The Treatment Phase consisted of a Titration Phase of 24 days (4.5 to 18.0mg doses; incremental increases of 4.5mg every 6 days), a Maintenance Phase of 6 days (18.0mg dose), and a De-escalation Phase of 6 days (13.5/9.0/4.5mg decreasing doses, every 2 days). Each block of 6 days used the 6 different patch application sites in the randomized

sequence. Subjects fulfilling the Inclusion and Exclusion Criteria started the Treatment Phase 3 to 28 days after the Eligibility Assessment. Safety and tolerability were assessed throughout the trial.

This trial did not incorporate design elements recommended by the FDA in order to be considered a "thorough QTc trial". The sponsor argued that design changes proposed by FDA were not feasible for the following reasons as discussed at the pre-NDA meeting (17 Dec 2003):

> Since healthy subjects could not be selected for this trial, and it was considered not to be justified to withdraw a patient from their anti-Parkinson treatment or other treatments over a period of about 4 weeks for the purpose of a Phase 1 trial, a placebo arm was not incorporated into the trial design. A large majority of patients in elderly populations use concomitant cardiovascular medication during the study, which could similarly not be withdrawn for several weeks.
>
> For the same reason, a positive control (e.g., moxifloxacin) was not used, as this compound would have been given as a separate treatment arm or as a subgroup within the placebo arm. Information about possible drug-drug interactions between rotigotine and moxifloxacin are currently not available; the administration of moxifloxacin in addition to the rotigotine treatment could therefore lead to false results and could not serve as a parameter for the "assay sensitivity." This vulnerable population was not ideal to use a drug that prolongs QT. It would be potentially confounded by other medications and would add little to what is demonstrated by intense monitoring at this high expected dose.

To adjust for changes in heart rate, 4 different heart rate correction formulas were applied: individual, Bazett, Fridericia, and population-derived (QTcI, QTcB, QTcF, QTcP). The centrally read ECG data were analyzed by time-matched, time averaged, and outlier analyses. Baseline values were compared with post-treatment values, and in addition, QTcI values were correlated with rotigotine plasma concentrations.

Reviewer Comment: This study was requested with the intention of testing the effects of the highest clinically conceivable plasma drug levels of rotigotine on the ECGs of subjects who might be susceptible to prolongation of the QT interval. SP630 does not fulfill these intentions.

A positive control is essential to demonstrate the susceptibility of subjects to possible QT effects. The explanation given by the sponsor for omitting a positive control is not persuasive. They contend that "it was considered not to be justified to withdraw a patient from their anti-Parkinson treatment or other treatments over a period of about 4 weeks" *in order to participate in a placebo arm but do find it justifiable to withdraw treatment in order for them to receive rotigotine even though the safety and efficacy (or, at least, the efficacy relative to safety) of rotigotine is not yet established. The sponsors do not explain how this reasoning would allow the use of a placebo group in the many placebo-*

controlled trials submitted with this application, in particular the Phase 3 studies in which much larger numbers of subjects were placed on placebo for much longer periods of time. Also, as this is a study of subjects with early Parkinson's disease, the pre-trial anti-Parkinson treatment that would be withheld during the study should not be substantial or enormously beneficial. Furthermore, it is possible to incorporate a positive control into the trial design without using a placebo arm by exposing all subjects to moxifloxacin immediately after obtaining baseline ECGs, measuring their response and then beginning rotigotine treatment after a suitable washout period (and creating an enrichment design by eliminating subjects who did not show a response to moxifloxacin). Subjects could be analyzed by comparing their QT response to rotigotine to their response to moxifloxacin. The sponsor also implies that the justification for omitting placebo and positive controls from the dedicated QT study was discussed and accepted by the Division at the 17 December 2003 meeting; the Division's minutes do not support that contention. Furthermore, at a meeting on 18 October 2004 with the sponsor to discuss [redacted], the Division expressed these reservations about the SP630 study.

This study design does little to assure that there would be adequate observation of subjects with the highest levels of plasma rotigotine that are clinically plausible. Most of the observations are at concentrations less than 1.0 ng/ml and few are greater than 2.0-2.5 ng/ml even though levels as high as 14.5 ng/ml were observed in this study. Although many of these subjects may not have tolerated higher dosages of rotigotine due to lack of previous exposure to high levels of dopamine agonists, the study population did not have to be limited to subjects with early Parkinson's disease. A more suitable population for QT studies could be subjects with more advanced Parkinson's disease [redacted]. This suggestion was made at the 18 October 2004 meeting.

Finally, the sponsors have utilized the same scatterplots and correlations over populations that they previously criticized.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Studies SP502, SP503, SP534 Parts I and II, and SP540 primarily relied upon the method of averaged individual slopes for determining the relationship between plasma rotigotine levels and rate-adjusted QT intervals that is problematic for reasons already described.

In the SP502 study, no statistical analyses were performed that compared mean rate-adjusted QT intervals before and during rotigotine treatment.

In SP503, no statistical tests were reported but from the data provided it is possible to compare changes from baseline in rate-adjusted QT interval. For 28 time-matched comparisons between baseline and active drug, the change in rate-adjusted QT interval

from baseline was positive in 18 of the comparisons (p=0.18). Comparing all 25 measurements made 24 hours or more after the drug was started to a baseline measurement taken 24 hours before drug initiation, the rate-adjusted QT interval was longer in 19 (p=0.01). When the means of individual differences from baseline are divided by the standard error of the mean for each time point, rate-adjusted QT values are increased over baseline at ten of fourteen observation points on active drug (p=0.18).

In SP534 Part I, no statistical tests were reported other than the slope analysis but from the data provided it is possible to compare changes from baseline in rate-adjusted QT interval in the placebo group with the groups receiving rotigotine. At three time-matched intervals, representing six comparisons between placebo and the two dosages, the change in rate-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in one of the comparisons (p=0.22). By dosage level, the change was longer than placebo in none of three comparisons (p=0.25) for subjects receiving 9 mg/day and one of three for subjects receiving 13.5 mg/day (p=1.00). Among all nine pairwise comparisons the higher drug dosage was associated with a longer change in rate-adjusted QT interval four times (p=1.00).

In SP534 Part II, one comparison was presented that compared change from baseline to the final treatment visit in rate-adjusted QT interval between subjects receiving rotigotine and subjects receiving placebo. The average change from baseline in rate-adjusted QT interval was 5.8 ms longer in the rotigotine-treated subjects than in the subjects given placebo (p=0.28). No other statistical tests were reported other than the slope analysis but from the data provided it is possible to compare changes from baseline in rate-adjusted QT interval in the placebo group with the group receiving rotigotine. At 46 time-matched intervals, representing 46 comparisons between placebo and active drug, the change in rate-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in 20 of the comparisons (p=0.46). By dosage level, the change was longer than placebo in 12 of 16 comparisons (p=0.08) when active drug subjects received 4.5 mg/day, one of ten when active drug subjects received 9 mg/day (p=0.02), two of ten when active drug subjects received 13.5 mg/day (p=0.11), and five of ten when active drug subjects received 18 mg/day (p=0.02). Among all 60 pairwise comparisons of different dosage levels in the active treatment group, the higher drug dosage was associated with a longer change in rate-adjusted QT interval 26 times (p=0.43).

In SP535, no statistical tests were reported but from the data provided it is possible to compare changes from baseline in Fridericia-adjusted QT interval in the placebo group with the group receiving rotigotine. At 14 time-matched intervals, representing 47 comparisons between placebo and the four dosages, the change in Fridericia-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in 28 of the comparisons (p=0.24). By dosage level, the change was longer than placebo in 8 of 11 comparisons (p=0.23) when active drug subjects received 4.5mg/day, 9 of 11 comparisons (p=0.07) when subjects received 9 mg/day, 3 of 11 when subjects received 13.5 mg/day (p=0.23) and 8 of 14 when subjects received 18 mg/day (p=0.21). Among all 66 pairwise comparisons of different dosage levels in the active treatment group, the

higher drug dosage was associated with a longer change in rate-adjusted QT interval 24 times (p=0.04)

In SP540, no statistical tests were reported but from the data provided it is possible to compare changes from baseline in Fridericia-adjusted QT interval. For 22 comparisons between baseline and the four dosages, the change in Fridericia-adjusted QT interval from baseline was positive in 5 of the comparisons (p=0.02). By dosage level, the rate-adjusted QT interval was longer than baseline in 1 of 4 comparisons (p=0.62) when the target dose was 4.5mg/day, 2 of 6 comparisons (p=0.69) when subjects received 9 mg/day, 2 of 6 when subjects received 13.5 mg/day (p=0.69) and 0 of 6 when subjects received 18 mg/day (p=0.03). Among all 52 pairwise comparisons of different dosage levels, the higher drug dosage was associated with a longer change in rate-adjusted QT interval 18 times (p=0.04)

In SP591, plasma rotigotine levels were not compared with ECGs and no statistical analyses were reported on QT interval data. The raw ECG data (60 pages) are included in printed form in the study report but not as a statistical dataset.

Reviewer Comment: This is potentially one of the most useful studies in that there is extensive ECG data with dosages up to 54 mg/day and plasma rotigotine levels up to 8.76 ng/ml but the sponsor has not provided adequate analysis. I obtained the statistical dataset and performed my own analysis. The baseline data fit the rate-correction formula: $QTc = QT/RR^{0.39}$. Using this correction there was no statistically significant relationship between rotigotine dose and rate-corrected QT (p=0.72). Similar results were obtained using the Fridericia (p=0.64) and Bazett (p=0.89) corrections. There were only a few subjects for whom rotigotine levels were obtained, so it is not possible to directly compare possible QT effects with rotigotine levels. The rotigotine levels that were obtained showed a good correlation with dose levels and provide some assurance that a significant portion of the subject population was exposed to high rotigotine levels.

In SP506 no statistical tests were reported but from the means and standard deviations provided it is possible to compare changes from baseline in Fridericia-adjusted QT interval in the placebo group with the groups receiving rotigotine and calculate t-statistics. There were 5 time-matched intervals, representing 20 comparisons between placebo and the four dosage groups; none were statistically significant. The change in Fridericia-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in 15 of the comparisons (p=0.04). By dosage level, the change was longer than placebo in 4 of 5 comparisons (p=0.38) when active drug subjects received 4.5mg/day, 4 of 5 comparisons (p=0.378) when subjects received 9 mg/day, 3 of 5 when subjects received 13.5 mg/day (p=1.00) and 4 of 5 when subjects received 18 mg/day (p=0.38). Among all 60 pairwise comparisons of different dosage levels, the higher drug dosage was associated with a longer change in rate-adjusted QT interval 29 times (p=0.90).

In SP512, no statistical tests were reported but from the means and standard deviations provided it is possible to compare changes from baseline in Fridericia-adjusted QT

interval in the placebo group with the group receiving rotigotine and calculate t-statistics. There were 4 time-matched intervals, representing 4 comparisons between placebo and the active drug group; none were statistically significant. The change in Fridericia-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in one of the comparisons (p=0.62). The prevalence of ventricular ectopy during treatment among subjects without ventricular on any baseline ECG 5.1% for placebo and 4.5% for rotigotine (p=1.00).

In SP513, no statistical tests were reported but from the means and standard deviations provided it is possible to compare changes from baseline in Fridericia-adjusted QT interval in the placebo group with the group receiving rotigotine and calculate t-statistics. There were 5 time-matched intervals, representing 5 comparisons between placebo and the active drug group; none were statistically significant. The change in Fridericia-adjusted QT interval from baseline was longer in the rotigotine-treated subjects in two of the comparisons (p=1.00). The prevalence of ventricular ectopy during treatment among subjects without ventricular on any baseline ECG 5.7% for placebo and 3.1% for rotigotine (p=0.22)

In SP630, there were extensive statistical analyses presented. In comparing a subject's rate-adjusted QT interval averaged over all baseline ECGs with those obtained on the two active treatment days (Days 27 and 30) with ECGs collected at the same time points, there was no statistically significant change on either day when the Bazett adjustment was used, a statistically significant reduction is QT interval on both days when the Fridericia adjustment was used, and a significant reduction on Day 27 and no change on Day 30 when the individual and population derived adjustments were used. When all ECGs are compared to baseline on a time-matched basis, there are 48 comparisons. Using the Fridericia adjustment, 41 comparisons showed a shorter QT interval on rotigotine (p<0.000001); with the Bazett adjustment, 25 comparisons showed a shorter QT interval on rotigotine (p=0.77); with individualized adjustments, 36 comparisons showed a shorter QT interval on rotigotine (p=0.0003); and with the population derived adjustment, 35 comparisons showed a shorter QT interval on rotigotine (p=0.001). Five of the 48 comparisons were individually statistically significant (p<0.05) using the Fridericia adjustment; none of the comparisons were individually statistically significant using any of the other adjustments.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

In the SP502 and SP503 studies, there were no reported cases of QT intervals longer than 500ms or increases in QT interval of more than 60 ms.

In the SP511 study, 1.54% of ECGs taken from subjects receiving placebo showed an increase of more than 60 ms in Bazett-adjusted QT interval. This threshold was also exceeded by 0.44% of ECGs in subjects receiving 9 mg/day, 1.09% of ECGs in subjects receiving 13.5 mg/day, 0.79% of ECGs in subjects receiving 18 mg/day, 1.43% of ECGs in subjects receiving 22.5 mg/day and 0.76% of ECGs in subjects receiving 27 mg/day.

Using the Fridericia adjustment, 1.29% of ECGs from subjects on placebo showed increased in QT interval of more than 60 ms; the figures for 9 mg/day, 13.5 mg/day, 18 mg/day, 22.5 mg/day and 27 mg/day were 0.58% 0.36% 0.59% 1.43% and 0.76%, respectively. Using the Bazett adjustment, 0.05% of ECGs from subjects on placebo showed a QT interval of more than 500 ms; the figures for 9 mg/day, 13.5 mg/day, and 18 mg/day were 0.14% 0.00% and 0.00%, respectively. Using the Fridericia adjustment, there were no ECGs showing a QT interval of more than 500 ms. The results for dosages of 22.5 mg/day and 27 ng/day were not reported.

In both parts of the SP534 study there were no QT intervals of more than 500 ms or increases in QT interval of more than 60 ms using either the Fridericia or Bazett adjustments.

In the SP540 study, no ECGs taken from subjects receiving placebo showed an increase of more than 60 ms in Bazett-adjusted QT interval. This threshold was exceeded by 0.53% of ECGs in subjects receiving 4.5 mg/day, 1.06% of ECGs in subjects receiving 9 mg/day, 1.27% of ECGs in subjects receiving 13.5 mg/day and 1.39% of ECGs in subjects receiving 18 mg/day. Using the Fridericia adjustment, 1.82% of ECGs from subjects on placebo showed increased in QT interval of more than 60 ms; the figures for 4.5 mg/day, 9 mg/day, 13.5 mg/day and 18 mg/day were 0.53% 0.53%, 0.63% and 0.69%, respectively. Using the Bazett adjustment, there were no ECGs that showed a QT interval of more than 500 ms. Using the Fridericia adjustment, there was one ECG in a subject receiving 13.5 mg/day that showed a QT interval of more than 500 ms.

In the SP591 study, an increase of more than 60 ms in Bazett-adjusted QT interval was exceeded by 0.81% of ECGs in subjects receiving 9 mg/day, 1.67% of ECGs in subjects receiving 13.5 mg/day, 1.55% of ECGs in subjects receiving 18 mg/day, 0.00% of ECGs in subjects receiving 22.5 mg/day, 0.81% of ECGs in subjects receiving 27 mg/day, 3.70% of ECGs in subjects receiving 31.5 mg/day, 2.21% of ECGs in subjects receiving 36 mg/day, 1.69% of ECGs in subjects receiving 40.5 mg/day, 0.65% of ECGs in subjects receiving 45 mg/day, 0.00% of ECGs in subjects receiving 49.5 mg/day and 2.15% of ECGs in subjects receiving 54 mg/day. An increase of more than 60 ms in Fridericia-adjusted QT interval was exceeded by 0.00% of ECGs in subjects receiving 9 mg/day, 1.67% of ECGs in subjects receiving 13.5 mg/day, 0.78% of ECGs in subjects receiving 18 mg/day, 1.79% of ECGs in subjects receiving 22.5 mg/day, 0.00% of ECGs in subjects receiving 27 mg/day, 0.00% of ECGs in subjects receiving 31.5 mg/day, 0.74% of ECGs in subjects receiving 36 mg/day, 1.69% of ECGs in subjects receiving 40.5 mg/day, 0.00% of ECGs in subjects receiving 45 mg/day, 0.00% of ECGs in subjects receiving 49.5 mg/day and 0.43% of ECGs in subjects receiving 54 mg/day. Using either adjustment, there were no QT intervals of more than 500 ms for 9 mg/day, 13.5 mg/day, and 18 mg/day. The results for dosages of 22.5 mg/day and more were not reported.

In the SP506 study, no ECGs taken from subjects receiving placebo showed an increase of more than 60 ms in Bazett-adjusted QT interval. This threshold was exceeded by

0.83% of ECGs in subjects receiving 4.5 mg/day, 0.98% of ECGs in subjects receiving 9 mg/day, and none of the ECGs in subjects receiving 13.5 mg/day or 18 mg/day. Using the Fridericia, Framingham and two study specific adjustments, no ECGs showed increased in QT interval of more than 60 ms. Using the linear study-specific adjustment, there was one ECG in a placebo recipient (0.24%) that showed a QT interval of more than 500 ms. This threshold was not exceeded in any other subject or by using any other adjustment.

In the SP512 study, nine placebo subjects (9.38%) on nine occasions had an increase from baseline in Bazett-adjusted QT interval of 30 ms or more; there were 26 rotigotine subjects (14.4%) with 30 occasions (p=0.259 for a difference in proportion of subjects). For an increase of 60 ms or more, there was one placebo subject (1.04%) on one occasion and there were four rotigotine subjects (2.22%) on four occasions (p=0.661). Six placebo subjects (6.25%) on six occasions had an increase from baseline in Framingham-adjusted QT interval of 30 ms or more; there were 21 rotigotine subjects (13.3%) with 25 occasions (p=0.202 for a difference in proportion of subjects). For an increase of 60 ms or more, there were no placebo subjects and one rotigotine subject (0.56%) on one occasion (p=1.00). Eight placebo subjects (8.33%) on nine occasions had an increase from baseline in Fridericia-adjusted QT interval of 30 ms or more; there were 24 rotigotine subjects (13.3%) with 28 occasions (p=0.242 for a difference in proportion of subjects). For an increase of 60 ms or more, there were no placebo subjects and two rotigotine subjects (1.11%) on two occasions (p=0.545). There were no cases of QT intervals of more than 500 ms using any adjustment.

In the SP513 study, 34 placebo subjects (28.8%) on 51 occasions had an increase from baseline in Bazett-adjusted QT interval of 30 ms or more; there were 57 rotigotine subjects (26.5%) with 82 occasions and 54 ropinirole subjects (23.7%) with 61 occasions (p=0.584 for a difference in proportion of subjects). For an increase of 60 ms or more, there were six placebo subjects (5.08%) on eight occasions, eight rotigotine subjects (3.72%) on ten occasions and seven ropinirole subjects (3.08%) on eight occasions (p=0.627). Twenty-one placebo subjects (17.8%) on 31 occasions had an increase from baseline in Framingham-adjusted QT interval of 30 ms or more; there were 38 rotigotine subjects (17.7%) with 58 occasions and 31 ropinirole subjects (13.7%) with 34 occasions (p=0.43 for a difference in proportion of subjects). For an increase of 60 ms or more, there were four placebo subjects (3.39%) on six occasions, four rotigotine subjects (1.86%) on four occasions and four ropinirole subjects (1.76%) on four occasions (p=0.566). Twenty-seven placebo subjects (22.9%) on 37 occasions had an increase from baseline in Fridericia-adjusted QT interval of 30 ms or more, 40 rotigotine subjects (18.6%) with 64 occasions and 37 ropinirole subjects with 40 occasions (p=0.327 for a difference in proportion of subjects). For an increase of 60 ms or more, there were six placebo subjects (5.08%) with eight occasions, four rotigotine subjects (1.86%) on five occasions and four ropinirole subjects (1.76%) on four occasions (p=0.182). Using the Bazett adjustment, there were three placebo subjects (2.54%), two rotigotine subjects (0.93%) and two ropinirole subjects (0.88%) all with single occurrences of QT intervals of more than 500 ms (p=0.387). Using either the Fridericia or Framingham adjustments,

one placebo subject (0.85%), one rotigotine subject (0.47%) and no ropinirole subject (0.88%) had single occurrences of QT intervals of more than 500 ms (p=0.353).

In the SP630 study, only one subject had an increase from baseline in adjusted QT interval of more than 60 ms, occurring on five occasions. Two subjects had QT intervals over 500 ms only when individualized QT adjustments were used. In both of these cases the adjustment factors were extreme outliers and the results should be considered artifacts of this particular method. Looking at changes from baseline in excess of 30 ms, the percentage of ECGs crossing this threshold increased throughout the maintenance period when the individualized and population-derived adjustment factors are used but not when the Fridericia adjustment is used.

Among all of the randomized, placebo-controlled studies in early Parkinson's disease there were single incidences of the following serious treatment emergent adverse events among 1017 subjects receiving rotigotine: sudden death, atrial fibrillation, palpitation, tachycardia and ventricular tachycardia. There were two reports of syncope. None of these events were reported in the 144 placebo subjects (p> 0.40).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In the SP502 and SP503 studies, no cases of QT intervals longer than 500ms or increases in QT interval of more than 60 ms were reported.

In SP502, one subject had a rate-adjusted QT interval greater than 440 ms on one occasion. The calculated QT interval using the Bazett adjustment was 445 ms; the unadjusted QT interval was 352 ms and the Fridericia and Framingham adjustments produced QT intervals of 411 ms and 410 ms, respectively. A repeat ECG done three minutes later and the calculated QT interval using the Bazett adjustment was 444 ms; the unadjusted QT interval was 371 ms and the Fridericia and Framingham adjustments produced QT intervals of 418 ms and 417 ms, respectively. The subject's baseline QT interval was not reported. A single slightly elevated reading is likely not significant. We do not know if this is a substantial change from baseline and may simply be an artifact of the Bazett adjustment.

In SP511, there were 14 cases of subjects whose ECGs on rotigotine had adjusted QT intervals longer than 500 ms or more than 60 ms longer than baseline. In nine of these cases, there was considerable variability seen in rate-adjusted QT interval for ECGs administered before drug was given. In most cases the ECG designated as baseline had a rate-adjusted QT interval that was unusually short, shorter than previous ECGs with similar or faster heart rates. In four of the remaining five cases, the subjects had abnormalities at baseline that could cause, contribute to or signify variability in depolarization: bundle-branch block or other intraventricular conduction delay, atrial fibrillation or substantial and consistent bradycardia. In only one case does the subject appear normal at baseline. In all cases the QT abnormality is transient and does not persist.

In the SP540 study, there were six cases of subjects whose ECGs on rotigotine had adjusted QT intervals more than 60 ms longer than baseline. In four of these cases, considerable variability was seen in rate-adjusted QT interval for ECGs administered before drug was given and the abnormality was transient. One other subject with likely ischemic heart disease had an episode of QT prolongation that persisted for more than two hours. In another subject with a history of ischemic heart disease, QT prolongation and ventricular ectopy developed as the subject completed the 9 mg dose phase and began the 13.5 mg dose. He was then withdrawn from the trial.

In the SP591 study, there were six cases of subjects whose ECGs on rotigotine had adjusted QT intervals more than 60 ms longer than baseline. In all of these cases the ECG designated as baseline had a rate-adjusted QT interval that was unusually short, shorter than previous ECGs with similar or faster heart rates.

In the SP506 study, three subjects had ECGs on rotigotine with had adjusted QT intervals more than 60 ms longer than baseline. In two of these cases the ECG designated as baseline had a rate-adjusted QT interval that was unusually short, shorter than previous ECGs with similar or faster heart rates. In the other case, three ECGs taken five minutes apart on the final visit on active treatment showed QT intervals that were 51-74 ms longer than baseline using the Bazett adjustment and 47-69 ms longer using the Fridericia adjustment with the same heart rate as on the baseline ECG. The subject was a 44 year-old male non-smoker with no history of heart disease. His baseline ECG (and subsequent ECGs) showed early repolarization.

In the SP512 study, there were four cases of subjects whose ECGs on rotigotine had adjusted QT intervals more than 60 ms longer than baseline. Two of these subjects had chronic atrial fibrillation. One subject with atrial fibrillation developed the prolonged QT interval coincident with atrial flutter. The other developed QT prolongation on the last study visit. The other two cases were described as single readings that resolved on subsequent ECGs and were not reported with any detail.

In the SP513 study, there were eight cases of subjects whose ECGs on rotigotine had adjusted QT intervals more than 60 ms longer than baseline. These cases are not described in detail. In seven of eight cases the QT prolongation occurred in only a single instance and resolved on subsequent ECGs and subjects were not withdrawn from the study. In one case the increase from baseline was 153 ms and the subject was withdrawn from the study. The subject had no history of cardiac disease and repeated follow-up ECGs also showed QT intervals more than 60 ms over baseline. In this case the persistence of QT interval prolongation after withdrawal of the drug would suggest a cause other than rotigotine.

In the SP630 study, only one subject showed increases in rate-adjusted QT interval of 60 ms or more. This occurred on a number of occasions independent of adjustment method (heart rates were similar to baseline). No clinical detail was provided.

Reviewer Comment: In most cases, the apparent increase in QT interval can be attributed to an unusually short QT interval present at baseline. Many of the other cases involve subjects with underlying heart disease and whether the prolongation is a result of the heart disease alone or in combination with the drug is unclear. In the remaining cases the question is whether the prolongation is due to rotigotine, some unknown cause, natural fluctuation or measurement error. The absence of a greater frequency of QT prolongation in rotigotine-treated subjects in comparison to placebo-treated subjects would tend to support the absence of a drug effect on the QT interval, but a role for the drug cannot be ruled out in individual cases.

Serious Treatment_Emergent Adverse Events Possibly Related to Cardiac Conduction

Atrial Fibrillation. A 68 year-old man with history of an episode of atrial fibrillation three years earlier had a recurrence of atrial fibrillation during the titration period of the open-label extension. His baseline ECG showed frequent atrial ectopy. Rotigotine was withdrawn and the subject subsequently received a pacemaker.

Reviewer Comment: Given the subject's past history, the event is unlikely to be related to rotigotine.

Sudden Death. A 50 year-old man with no past history of heart disease had a normal baseline ECG and blood pressure but cholesterol of 6.9 mmol/L upon entry to the open-label extension of SP513. At the time he was taking atenolol for recently diagnosed mild hypertension. During the titration period of the trial and 11 days after the start of open-label rotigotine, the subject suddenly died. On the preceding day the subject returned from a swimming pool complaining of tiredness. Early the next morning, after returning from the bathroom, the subject said a few words to his wife who then noticed he had unusual breathing and then he stopped breathing. Cardiopulmonary resuscitation was unsuccessful. An independent cardiologist reviewed the case and identified Grade 1 hypertension and elevated cholesterol as cardiovascular risk factors. He also noted negative T waves in leads III and aVF and ST-segment depression in leads aVF, V5 and V6 on a previous ECG, which he considered pathological and probably indicative of asymptomatic posterolateral wall myocardial ischemia.

Reviewer Comment: Silent coronary artery disease leading to sudden cardiac death unrelated to rotigotine is a plausible explanation for this event. QT prolongation was not noted on ECG.

Syncope. A 53 year-old woman with no known cardiac risk factors or ECG abnormalities was taking rotigotine 18 mg/day during the double-blind phase of SP506 when after driving about 3 hours she had a brief blackout, during which she went off the road. When the car hit the gravel, she was aroused and was able to maintain control of the car. She did not have an accident or any injuries. She reported feeling that her head and body were "2 separate things" and that she felt "disconnected." Two days earlier the subject's blood pressure was 120/70 while sitting and 110/70 upon standing. The dizziness was ongoing

nine days later. The subject stated that the motion from driving seemed to make her dizziness worse and that she had to stop after 2 to 3 miles. She also complained of tiredness, that she often felt like she was going to black out and that she occasionally had tunnel vision. Medication was stopped.

Reviewer Comment: This incident appears to be related to a sleep disorder rather than a cardiac event.

Ventricular Tachycardia. An 87 year-old man with no history of cardiac disease fainted 17 days after beginning the open-label phase of the SP512 trial (dosage 13.5 mg/day). Tests performed at the hospital (labs, electrocardiogram) did not show cardiac damage. A subsequent electrophysiology study indicated inducible ventricular tachycardia and sinus node dysfunction leading to fainting. QT prolongation was not reported; rotigotine was not discontinued.

Reviewer Comment: Although it is conceivable that rotigotine could predispose the subject to the abnormal electrophysiology that was discovered, there is no reason to make this attribution.

Syncope. A 72 year-old woman with a history of fluctuating blood pressure but no cardiac disease was taking rotigotine 13.5 mg/day in the open-label phase of SP512. Nineteen days into the phase, she was taken to the emergency room (ER) after an episode of unresponsiveness at home. She had been sleeping in her chair and when she awoke felt diaphoretic and faint. The subject then fainted. This adverse event "syncope" lasted approximately 2 minutes and was possibly accompanied by a syncopal induced generalized tonic-clonic seizure. Afterwards she was definitely postictal and confused. Although she was feeling better and did not have any chest pain upon arrival at the ER, the treating physicians were initially concerned that the unresponsiveness at home may have been cardiac related. The subject had a similar episode without seizure during the double-blind phase. (double-blind treatment was rotigotine) that the investigator considered to be orthostatic hypotension at the time. The subject described both episodes as being similar (sleeping, awoke diaphoretic, was nauseated, and fainted). Therefore, the investigator considered that the previous event during SP512 Part I was possibly syncope. Although the subject's history included occasional dizzy feelings and fluctuating blood pressure, she had never lost consciousness. In addition, the subject's blood pressure records from her trial visits were always within normal limits. A cardiological examination revealed no evidence of coronary heart disease or left ventricular dysfunction. A Holter monitor showed an episode of asymptomatic tachycardia with doubtful clinical relevance. To exclude a neurological cause of the events a computed tomography (CT) scan and 2 electroencephalograms (EEGs) were subsequently performed. The cerebral CT scan revealed a previously unknown small lacunar infarction in the right internal capsule. The EEG's provided no evidence for epileptiform abnormalities.

Reviewer Comment: These circumstances suggest an autonomic cause rather than a primary cardiac arrhythmia.

Palpitations. A 45 year-old man with no history of heart disease but a history of palpitations during exercise or with high caffeine ingestion experienced palpitations while taking rotigotine 13.5 mg/day. The subject did not experience chest pain or any other symptoms during the episodes of increased palpitations. Due to the fact that the subject reported an increase in palpitations after being started on study medication, the investigator ordered a Holter monitor that showed a significant number of ventricular ectopics. The subject was de-escalated from study drug. The investigator reported that the palpitations abated after discontinuation of study drug and had completely resolved one month later. A cardiologist saw the subject when the palpitations increased and the subject subsequently had another Holter monitor study and a stress test. The second Holter monitor, which was done after discontinuing study drug, showed a reduced number of ectopics. The stress test revealed no evidence of ischemia and multifocal ventricular ectopic beats at rest and exercise with no increase in exercise.

Reviewer Comment: Although the onset of palpitations may have been coincidental, the timing, persistence and resolution of these symptoms along with the absence of other causes suggest a role for rotigotine. The mechanism is unclear; there is no mention of QT prolongation.

A narrative for the serious treatment- emergent adverse event of tachycardia listed in the tables could not be identified.

Events from the 120-day safety follow-up

Sudden Death. A 57 year-old man with a history of diabetes but no known heart disease or other risk factors had an unwitnessed sudden death during the maintenance phase of the open-label extension of SP513.(dosage 18 mg/day). All ECGs performed during the subject's trial participation, were assessed by the investigator as normal. In addition, the subject's heart rate and QT values were always within normal ranges (Bazett-adjusted QT between 378 and 393ms).

Reviewer Comment: While this case can be plausibly considered to be a sudden cardiac death there is no indication of rotigotine-induced conduction abnormality.

Events from trials for other indications

A 71 year-old man with right bundle-branch block and left anterior hemiblock was withdrawn from a trial of rotigotine for advanced Parkinson's disease (SP 533) when Bazett-adjusted QT intervals of 489 ms and 476 ms (baseline was 412 ms) were observed by local investigators at a dosage of 27 mg/day. The subject also had readings of 476 ms and 477 ms three days after patch removal. The central readings of ECGs could not

confirm any episodes of Bazett-adjusted QT intervals of more than 470 ms while the subject was on the drug.

Reviewer Comment: Even if the QT prolongation on rotigotine occurred, the variation is consistent with the subject's underlying conduction disorder as seen by similar prolongation observed off drug.

A 63 year-old man with a history of sinus bradycardia and first degree atrioventricular block was receiving rotigotine 4.5 mg/day in a trial of rotigotine for restless legs syndrome (SP709). He was found to have a Bazett-adjusted QT interval of 501 ms, 49 ms over baseline. The Fridericia-adjusted QT interval was 478 ms, 39 ms over baseline. The drug was withdrawn and subsequent ECGs showed QT intervals that were not prolonged relative to baseline.

Reviewer Comment: This is an increase of borderline significance in a subject with known conduction abnormalities.

Reviewer's Conclusions
In most of these studies, rotigotine is associated with an increase in heart rate (see the analysis of vital sign data). This greatly complicates the analysis of any possible effect the drug may have on QT interval because the results are greatly influenced by the methods used to adjust QT interval for heart rate. Choosing a method based upon whatever method performs best (i.e., reduces any correlation between heart rate and the adjusted QT interval) on subjects when they are not receiving rotigotine (baseline or placebo) is only valid for the distribution of heart rates used in that sample. The adjustment may not be accurate when applied to a different distribution of heart rates particularly if the average heart rate is significantly higher or lower. For example, the Fridericia adjustment will make proportionately smaller upward adjustments in QT interval relative to the Bazett adjustment as the heart rate increases beyond 60 beats per minute. So even though it may provide the best adjustment for subjects when they are not receiving rotigotine it will make greater reductions when subjects' heart rates increase on rotigotine treatment. This could explain the observed tendency for Fridericia-adjusted QT intervals to decrease when subjects are placed on rotigotine rather than remaining unchanged.

Furthermore, as already noted, the data provided by the sponsor fails to demonstrate assay sensitivity. Most of the ECG measurements have been made in the presence of relatively low plasma rotigotine levels (<1.0 ng/ml) and almost all have been less than 3.0 ng/ml even though observed levels can exceed 5.0 ng/ml. So while little effect is observed at lower rotigotine levels, insufficient data exist regarding effects at higher but clinically plausible plasma rotigotine levels. Equally important is the need for a positive control to document the safety of rotigotine in subjects known to be susceptible to QT prolongation.

The clinical data provided in this application show little adverse effect of rotigotine on electrocardiographic parameters. There were no dramatic changes in heart rate, rhythm or electrical conductivity attributable to rotigotine. The data, however, are insufficient to conclude that the potential for adverse effects on cardiac electrophysiology suggested by preclinical data does not exist in the clinical setting.

7.1.10 Immunogenicity

In immunotoxicity studies in rats (3 months) and monkeys (2 months) Schwarz observed thymic involution. These findings were reportedly not seen in longer studies (rat 6 month, monkey 12 month). Schwarz also reported that a Plaque Forming Cell assay in rats did not show immunosuppressive properties (Nonclinical Overview, p.34).

In their Nonclinical Overview, Schwarz reported that administration of clinically relevant patches to rodents did not reveal substance specific influence on local tolerance and that administration of rotigotine via subcutaneous and transdermal routes to rabbits, guinea pigs, and monkeys did not reveal irritating or sensitizing potential compared to placebo controls (Nonclinical Overview, p.33). Schwarz observed local effects (wheals, residues at application site) in subcutaneous toxicity studies and noted inflammation at injection sites with corresponding histopathological findings. Schwarz did not consider these effects substance related but instead attributed them to the route and form of administration (Nonclinical Overview, p.33).

As noted earlier in this review, Schwarz performed two phase I studies to examine skin irritation and sensitization potential in humans. In study SP673, Schwarz reported that none of the 221 subjects showed sensitization reactions. Study SP629 found higher measures of irritation for the rotigotine patch compared to placebo or the low irritancy control and slightly lower measures of irritation for rotigotine compared to the high irritancy control. The investigators reported that four subjects had reactions that could be indicative of sensitization and that upon further testing 2 of these subjects developed type-IV contact dermatitis (clinical diagnosis supported by skin biopsies) at the rotigotine but not the placebo patch sites.

7.1.11 Human Carcinogenicity

At the Division's request, Schwarz submitted information about malignancies diagnosed during the rotigotine development program. Schwarz identified 18 cancer diagnoses in 16 rotigotine subjects through the Safety Update cutoff. Skin cancers were most commonly reported malignancies among rotigotine subjects and the database included 8 basal cell carcinomas, 3 squamous cell carcinomas, 2 skin cancers NOS, and one melanoma. The remaining cancer diagnoses were renal cell cancer (2), uterine adenocarcinoma, and prostate cancer.

In the phase II/III early-stage PD trials (pool S1), the overall malignancy risk was 0.62% (4/649) for rotigotine compared to 2.42% (7/289) for placebo and 0.88% (2/228) for ropinirole.

Melanoma
In the reviews of recent applications for Parkinson's disease treatments, the Division has assessed the risk for melanoma. The Division requested that Schwarz submit datasets that identify subjects diagnosed with melanoma, by type of study (controlled vs. open label). Schwarz was also asked to provide patient time exposure datasets for the development program studies included in the data sets.

Schwarz identified no rotigotine subjects from controlled trials and one rotigotine subject from an open label trial diagnosed with melanoma. The controlled trials datasets included information from 8 rotigotine studies during which 1155 subjects received at least one dose of rotigotine. The open label trial database included information from 3 trials during which 852 subjects received at least one dose of rotigotine.

The subject identified as being diagnosed with melanoma was from study SP512OL and was an 81 year old white male who received placebo in RCT SP512 and then was treated with rotigotine in an open label extension for 62 days prior to being diagnosed with melanoma. This subject was not taking levodopa during the study. Although the Division requested narratives for subjects diagnosed with melanoma, Schwarz did not include a narrative for this subject in this submission.

7.1.12 Special Safety Studies

Skin Sensitivity and Sensitization
Special studies SP629 and SP673 were discussed above. Study SP629 was conducted to evaluate the cumulative skin irritation after repeat patch application and study SP673 examined skin sensitization in healthy volunteers.

Effect on QT
At the pre NDA meeting on 17 Dec 2003, the Division requested that the sponsor conduct a trial to evaluate the steady state pharmacokinetic profile of rotigotine at the — — dose in subjects with early stage Parkinson's disease at multiple sites for placement of the patch. In addition, the Division advised the sponsor to collect ECG data in parallel in order to evaluate the potential electrocardiographic effects of rotigotine at maximal therapeutic exposure. This trial investigated the pharmacokinetic profile and cardiac safety over 24 hours — (18.0mg, steady state), with rotation of the patch to 6 different application sites in early-stage Parkinson's subjects.

This was an open-label, multi-site, randomized trial with daily doses of rotigotine patch applied to rotating sites on the skin of subjects. Forty-eight subjects with early-stage Parkinson's disease (24 female and 24 male subjects with each group consisting of 12 subjects <65 years of age and 12 subjects ≥65 years of age) were planned to be randomized to treatment. Randomized subjects had plasma samples collected while patches were applied to 6 different patch application sites (abdomen, flank, upper arm, shoulder, thigh, hip).

The Treatment Phase consisted of a Titration Phase of 24 days (4.5 to 18.0mg doses; incremental increases of 4.5mg every 6 days), a Maintenance Phase of 6 days (18.0mg dose), and a De-escalation Phase of 6 days (13.5/9.0/4.5mg decreasing doses, every 2 days). Each block of 6 days used the 6 different patch application sites in the randomized sequence. Subjects fulfilling the Inclusion and Exclusion Criteria started the Treatment Phase 3 to 28 days after the Eligibility Assessment. Safety and tolerability were assessed throughout the trial.

This trial did not incorporate design elements recommended by the FDA in order to be considered a "thorough QTc trial". The sponsor argued that design changes proposed by FDA were not feasible for the following reasons as discussed at the pre-NDA meeting (17 Dec 2003):

> Since healthy subjects could not be selected for this trial, and it was considered not to be justified to withdraw a patient from their anti-Parkinson treatment or other treatments over a period of about 4 weeks for the purpose of a Phase 1 trial, a placebo arm was not incorporated into the trial design. A large majority of patients in elderly populations use concomitant cardiovascular medication during the study, which could similarly not be withdrawn for several weeks.
>
> For the same reason, a positive control (e.g., moxifloxacin) was not used, as this compound would have been given as a separate treatment arm or as a subgroup within the placebo arm. Information about possible drug-drug interactions between rotigotine and moxifloxacin are currently not available; the administration of moxifloxacin in addition to the rotigotine treatment could therefore lead to false results and could not serve as a parameter for the "assay sensitivity." This vulnerable population was not ideal to use a drug that prolongs QT. It would be potentially confounded by other medications and would add little to what is demonstrated by intense monitoring at this high expected dose.

To adjust for changes in heart rate, 4 different heart rate correction formulas were applied: individual, Bazett, Fridericia, and population-derived (QTcI, QTcB, QTcF, QTcP). The centrally read ECG data were analyzed by time-matched, time averaged, and outlier analyses. Baseline values were compared with post-treatment values, and in addition, QTcI values were correlated with rotigotine plasma concentrations.

There were extensive statistical analyses presented. In comparing a subject's rate-adjusted QT interval averaged over all baseline ECGs with those obtained on the two active treatment days (Days 27 and 30) with ECGs collected at the same time points, there was no statistically significant change on either day when the Bazett adjustment was used, a statistically significant reduction is QT interval on both days when the Fridericia adjustment was used, and a significant reduction on Day 27 and no change on Day 30 when the individual and population derived adjustments were used. When all ECGs are compared to baseline on a time-matched basis, there are 48 comparisons. Using

the Fridericia adjustment, 41 comparisons showed a shorter QT interval on rotigotine ($p<0.000001$); with the Bazett adjustment, 25 comparisons showed a shorter QT interval on rotigotine ($p=0.77$); with individualized adjustments, 36 comparisons showed a shorter QT interval on rotigotine ($p=0.0003$); and with the population derived adjustment, 35 comparisons showed a shorter QT interval on rotigotine ($p=0.001$). Five of the 48 comparisons were individually statistically significant ($p<0.05$) using the Fridericia adjustment; none of the comparisons were individually statistically significant using any of the other adjustments.

Only one subject had an increase from baseline in adjusted QT interval of more than 60 ms, occurring on five occasions. This occurred on a number of occasions independent of adjustment method (heart rates were similar to baseline). No clinical detail was provided. Two subjects had QT intervals over 500 ms only when individualized QT adjustments were used. In both of these cases the adjustment factors were extreme outliers and the results should be considered artifacts of this particular method. Looking at changes from baseline in excess of 30 ms, the percentage of ECGs crossing this threshold increased throughout the maintenance period when the individualized and population-derived adjustment factors are used but not when the Fridericia adjustment is used.

This study was requested with the intention of testing the effects of the highest clinically conceivable plasma drug levels of rotigotine on the ECGs of subjects who might be susceptible to prolongation of the QT interval. SP630 does not fulfill these intentions.

A positive control is essential to demonstrate the susceptibility of subjects to possible QT effects. The explanation given by the sponsor for omitting a positive control is not persuasive. They contended that "it was considered not to be justified to withdraw a patient from their anti-Parkinson treatment or other treatments over a period of about 4 weeks" in order to participate in a placebo arm but did find it justifiable to withdraw treatment in order for them to receive rotigotine even though the safety and efficacy (or, at least, the efficacy relative to safety) of rotigotine was not yet established. The sponsors did not explain how this reasoning would allow the use of a placebo group in the many placebo-controlled trials submitted with this application, in particular the Phase 3 studies in which much larger numbers of subjects were placed on placebo for much longer periods of time. Also, as this is a study of subjects with early Parkinson's disease, the pre-trial anti-Parkinson treatment that would be withheld during the study should not be substantial or enormously beneficial. Furthermore, it would have been possible to incorporate a positive control into the trial design without using a placebo arm by exposing all subjects to moxifloxacin immediately after obtaining baseline ECGs, measuring their response and then beginning rotigotine treatment after a suitable washout period (and creating an enrichment design by eliminating subjects who did not show a response to moxifloxacin). Subjects could be analyzed by comparing their QT response to rotigotine to their response to moxifloxacin. The sponsor also implied that the justification for omitting placebo and positive controls from the dedicated QT study was discussed and accepted by the Division at the 17 December 2003 meeting; the Division's minutes do not support that contention. Furthermore, at a meeting on 18 October 2004

with the sponsor to discuss [redacted] the Division expressed these reservations about the SP630 study.

This study design did little to assure that there would be adequate observation of subjects with the highest levels of plasma rotigotine that are clinically plausible. Most of the observations are at concentrations less than 1.0 ng/ml and few are greater than 2.0-2.5 ng/ml even though levels as high as 14.5 ng/ml were observed in this study. Although many of these subjects may not have tolerated higher dosages of rotigotine due to lack of previous exposure to high levels of dopamine agonists, the study population did not have to be limited to subjects with early Parkinson's disease. A more suitable population for QT studies could be subjects with more advanced Parkinson's disease [redacted] This suggestion was made at the 18 October 2004 meeting.

Within the considerable limitations of the study, there was little indication of QT prolongation by rotigotine.

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For the same reason, a positive control (e.g., moxifloxacin) was not used, as this compound would have been given as a separate treatment arm or as a subgroup within the placebo arm. Information about possible drug-drug interactions between rotigotine and moxifloxacin are currently not available; the administration of moxifloxacin in addition to the rotigotine treatment could therefore lead to false results and could not serve as a parameter for the "assay sensitivity." This vulnerable population was not ideal to use a drug that prolongs QT. It would be potentially confounded by other medications and would add little to what is demonstrated by intense monitoring at this high expected dose.

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Within the considerable limitations of the study, there was little indication of QT prolongation by rotigotine.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Schwarz considers the drug abuse potential of rotigotine low based on the following two factors: data from the broad receptor screen and the fact that patch administration results in stable plasma levels, without spikes. Schwarz reported that three studies (cocaine discrimination in rats, cocaine discrimination in squirrel monkeys, and effects of rotigotine pretreatment on intravenous cocaine self administration in Rhesus monkeys) did not show any drug seeking behavior (Summary of Clinical Safety, p.276).

Schwarz acknowledged that neuroleptic malignant syndrome (NMS) has been reported in association with rapid dose reduction changes or discontinuation of antiparkinsonian treatment. No cases of NMS were observed in the rotigotine safety database.

Rotigotine early-stage PD controlled trials included dose de-escalation phases because of the potential for AEs related to rapid withdrawal of treatment. To assess patients for evidence of AEs related to withdrawal of rotigotine, subjects who prematurely discontinued or who declined participation in open label trials had follow up visits 28 days after beginning de-escalation. In early-stage PD controlled trials, during the follow up period, 14% (19/132) of placebo subjects and 14% (53/368) of rotigotine subjects who prematurely discontinued or who did not participate in extensions experienced AEs. Schwarz summarized these AEs in table ISS 39.1. No AE observed during the follow up period occurred in >=1% of rotigotine subjects. The AEs occurring in more than one rotigotine subjects were asthenia, ECG abnormal, arthralgia, somnolence (3 each), accident NOS, heart murmur, dizziness, headache, parasthesias, hyperglycemia, insomnia, and bronchitis (2 each).

Subjects who participated in early-stage PD controlled trials SP512 and SP 513, and who agreed to participate in an open label extension, had their dose de-escalated to 4.5mg/day while subjects who participated in SP506 had their dose de-escalated to zero prior to beginning an extension study. The overall AE risks observed during the de-escalation phases for subjects who participated in these early-stage PD extension studies are provided below.

Overall AE Risks Occurring during Dose De-escalation in Early-Stage PD Subjects Who Completed Controlled Trials and Continued into Open Label Extension Studies

AE Risk	SP512		SP513		SP506	
	Rotigotine	Placebo	Rotigotine	Placebo	Rotigotine	Placebo
	N=166	N=91	N=186	N=102	N=(197)	N=(80)
Overall	16% (15)	12% (20)	9% (17)	12% (12)	17% (34)	13% (10)

The AEs occurring in at least 2 rotigotine subjects during de-escalation during study SP512 were somnolence (n=6) and skeletal pain (n=2), (SP512DB CTR Table 24.5). The AEs occurring in at least 2 rotigotine subjects during de-escalation during study SP513 were somnolence (n=5), and upper respiratory tract infection (n=2) (SP513DB CTR Table 24.5). The AEs occurring in at least 2 rotigotine subjects during de-escalation during study SP506 were insomnia (n=7), anxiety (n=3), fatigue (n=3), depression (n=2),

somnolence (n=2), dystonia (n=2), hyperkinesias (n=2), and yawning (n=2) (SP506 CTR Table 11.2.7.1).

7.1.14 Human Reproduction and Pregnancy Data

There are no data from trials using rotigotine in pregnant women. Through the Safety Update, Schwarz identified two pregnancies in women taking rotigotine. Both of these events were from phase I trials. I provide information from these events below.

Study SP673 Subject 80125, female, 29 years of age, discontinued the trial on Day 16 (17 Dec 2003) for personal reasons. At the follow-up visit 13 days later (30 Dec 2003), the result of the pregnancy test performed at that day showed a value of 102.0IU/L for β-human chorionic gonadotropin (HCG). Due to suspected pregnancy, the subject visited her gynecologist where another pregnancy test was performed with a positive result, however the pregnancy could not be confirmed by ultrasonography. On [redacted] the subject was admitted to the hospital due to lower abdominal pain and vaginal bleeding. A pregnancy test resulted in a similar value (β-HCG: 128IU/L) and a sonography again did not confirm a pregnancy but led to a laparascopic cyst removal and adhesiolysis of the left ovary. During the overnight stay in the hospital, the subject had a spontaneous abortion. The further course was without any findings. A pregnancy test which was performed before the subject was discharged from the hospital resulted in a β-HCG level of 17.2IU/L. The subject was finally contacted by the investigator on 09 Feb 2004. The subject explained she felt well, that a final gynecological examination was without pathological findings, and that her menstrual cycle was normal under her usual oral contraceptive again. The subject had taken oral contraception throughout the trial and stated that she temporarily used a barrier method in addition. The last menstruation was reported for Day -1 to Day 5. There were no indications as to why the contraception failed, eg, diarrhea or an interruption of oral contraception. The only AE reported during the treatment phase was tiredness on Day 3. The pregnancy was not reported as an AE according to the sponsor's standards, the spontaneous abortion and the surgery of the ovarian cyst were documented as SAEs.

Study SP 673 Subject 80254, female, 18 years of age, informed the investigator on trial Day 36 (04 Jan 2004) about missing her menses for 2 weeks, prior to the patch application of the challenge phase. The subject was consequently not treated further and was withdrawn from the trial. A pregnancy test showed an elevated β-HCG value of 75.3IU/L. For this reason the subject was requested to visit her gynecologist, who diagnosed "no pregnancy" on 09 Jan 2004 (report was not provided by the gynecologist). As part of the safety follow-up examination on 09 Jan 2004, a β-HCG test gave a value of 1454IU/L. The subject therefore visited another gynecologist, who confirmed the pregnancy by sonographic examination on 15 Jan 2004. The subject did not wish to continue the pregnancy and after abortion counseling, the pregnancy termination was performed on [redacted]. The subject had her first treatment on 30 Nov 2003. She had taken oral contraceptives throughout her participation in the trial but did not inform the investigator about the stop of the second method of contraception (condom) after start of the trial. She stated that her menstrual period was on 25 Nov 2003 and that the she missed her next menstrual period after 21 days of oral contraception intake (up to 21 Dec 2003, the last day of the induction phase). A safety follow-up examination was performed on 05 Feb 2004 without any clinically relevant findings.

Schwarz reported that rotigotine and its metabolites are excreted in rat breast milk but it is not known if rotigotine is excreted in human breast milk.

7.1.15 Assessment of Effect on Growth

Rotigotine is intended for the treatment of Parkinson's disease and therefore would not be administered to children. There were no children exposed to rotigotine in the development program and therefore no human growth data.

7.1.16 Overdose Experience

There were no reports of rotigotine overdose in the NDA or Safety Update. Schwarz expects that effects of overdose would include nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, tingling in the extremities, convulsions, and other signs of dopaminergic stimulation (Summary of Clinical Safety, p.276). Treatment for overdose is supportive measures and dialysis is not expected to be helpful based on information from a study in subjects with renal impairment.

7.1.17 Postmarketing Experience

To date, rotigotine has not been marketed and there are no available postmarketing data.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Schwarz's NDA safety database includes subjects exposed to rotigotine in trials for early- and advanced-stage Parkinson's disease, restless leg syndrome, and phase I trials. The original NDA included data accrued through December 30, 2003. The 120-day safety update included data accrued through July 1, 2004.

Three unique transdermal delivery systems for rotigotine were used during its development program. The first patch used was a — prototype patch containing — This patch was used in two trials—one phase 1 trial with 4 healthy subjects (TD-0923-001) and one phase 2a trial with 9 patients with early-stage Parkinson's disease (TD-0923-002). Two subsequent trials used an — prototype patch — /3 subjects/patients were exposed to this patch in one phase 1 trial (TD-0923-003; 8 subjects received rotigotine) and one phase 2a trial (TD-0923-004; 65 patients with early-stage Parkinson's disease received rotigotine).

Most exposure to rotigotine occurred via the third patch formulation used in clinical development. This patch was a silicon-based formulation containing 9.0 mg rotigotine — per 20 cm^2. The relative bioavailability and safety of rotigotine were compared for this patch and the — patch in the phase 1 trial SP 502, in which 14 subjects received rotigotine. All subsequent clinical trials used this silicone patch containing rotigotine —

7.2.1.1 Study type and design/patient enumeration

The table below summarizes overall exposure to the rotigotine silicone patch, which is the formulation proposed for marketing, through July 1, 2004.

Overall rotigotine exposure with final silicone formulation

Population	Subjects n (%)	Subject-years of exposure
Phase 1		
Healthy volunteers	547	—
Subjects with hepatic or renal impairment	33	—
Phase 2/3		
Subjects with early-stage Parkinson's disease (Pool S3)[a]		
>0 months	1093 (100)	979
>6 months	575 (53)	885
>12 months	485 (44)	815
>24 months	128 (12)	277
Subjects with advanced-stage Parkinson's disease		
>0 months	589 (100)	397
>6 months	235 (40)	319
>12 months	170 (29)	269
>24 months	23 (4)	51
Subjects with Restless Legs syndrome[b]		
>0 months	389 (100)	156
>6 months	190 (49)	133
>12 months	10 (3)	10
>24 months	0	—

a This population included 70 subjects who participated in a Phase 1 trial (SP630).

b This population included 24 subjects who participated in a Phase 1 trial (SP628).

Data source: ISS Table 257.1, ISS Table 257.2, SUI Table 1.1, SUI Table 246.1, SUI Table 252.1

From 120-Day Safety Update, p. 19.

A listing of all clinical trials in the rotigotine development program from the original NDA (including trials using the — formulation) is provided in Appendix Table 3.

Schwarz used six trial groupings, which they termed pools (Pools S1—S6), for the analysis and presentation of integrated safety data from trials in patients with early-stage Parkinson's disease. In addition, they presented pooled data from other trial groupings to

summarize demographic and exposure data. They did not, however, pool data from other indications or from phase I trials in subjects without early-stage Parkinson's disease for analyses of other types of safety data.

The following table describes the trial groupings Schwarz used in their presentations of safety data:

FDA Table 7.2.1.1.

Pool	Description of pool	Trials included in pool	Number of rotigotine-treated subjects
Pool S1	Primary pool; consists of double-blind data from all controlled phase 2/3 trials with treatment durations ≥3 months in patients with early-stage Parkinson's disease	SP506;[7] SP 512 (DB portion); SP513 (DB portion)	649
Pool S2	double-blind data from all controlled phase 2/3 trials in patients with early-stage Parkinson's disease	SP506; SP512 (DB); SP513 (DB); SP534 (Parts 1 and 2); SP540; SP535	708
Pool S3	data from all phase 2/3 trials (double-blind and open-label) in patients with early-stage Parkinson's disease	SP506; SP512 (DB and OL); SP513 (DB and OL); SP534 (Parts 1 and 2); SP540; SP535; SP630	1093
Pool S4	double-blind data from all phase 3 trials in patients with early-stage Parkinson's disease	SP512 (DB) and SP513 (DB)	396
Pool S5	data from phase 3 trials in patients with early-stage Parkinson's disease treated at least once in open-label	SP512 (DB and OL) and SP 513 (DB and OL)	276
Pool S6	open-label data from phase 3 trials in patients with early-stage Parkinson's disease treated at least once in open-label	SP512 (OL) and SP513 (OL)	596
Pool P11	Data from healthy subjects in phase 1 trials	SP502; SP503; SP581; SP596; SP606; SP610; SP626; SP627; SP629; SP670; SP673; SP717; SP718; SP671 (data from healthy subjects only); SP672 (data from healthy subjects only)	547
Pool P12	Data from patients with hepatic or renal impairment in phase 1 trials	SP671 (data from patients with hepatic impairment only); SP672 (data from patients with renal impairment only)	33
Pool AS1	Data from trials in patients with advanced-stage Parkinson's disease	SP533; SP591; SP511; SP 650 (DB and OL)	589
Pool	Data from trials in patients with	SP666; SP628I; SP 709; SP710	389

[7] The sponsor noted differences in the design of trial SP506 compared to SP512 and SP513. They stated that differences in dosing and patch placement protocols may have affected the appropriateness of pooling data from SP506 with data from SP512 and SP513. In SP506, the subjects in the two lowest dose groups (4.5 mg/day and 9 mg/day) did not receive higher doses at any point during the trial. In contrast, rotigotine doses were titrated higher in SP512 and SP513. In SP506, rotigotine patches were applied to the upper abdomen only. In SP512 and SP513, rotigotine patches were rotated between abdomen, thigh, hip, flank, shoulder, and upper arm.

RLS	restless leg syndrome		

To be included in one of the safety pools listed above, a patient had to receive at least one dose of trial medication. To be included in the efficacy pools, however, patients also had to have baseline and at least one post-baseline Unified Parkinson's disease rating scale (UPDRS) score. The safety pools thus correspond to the efficacy pools but include more patients. The efficacy pools E1, E2, and E3 are subsets of the safety pools S4, S5, and S6.

Schwarz submitted updated safety information with the 120-Day Safety Update for Pools S3, S6, AS1, and RLS. They submitted updated laboratory data analyses for Pool S1. These updated analyses included data accrued through July 1, 2004. They did not update other analyses using Pool S1 or any analyses using data from Pools P11, P12, S2, S4, or S5. Data cutoff dates thus vary across the pools.

All data presentations in this review include data through the Safety Update for those pools for which updated data were provided.

7.2.1.2 Demographics

The following table summarizes demographic data for pool S3, which includes all data from double-blind and open-label studies in patients with early-stage Parkinson's disease:

FDA Table 7.2.1.2.
Demographic and baseline characteristics for Pool S3*

Demographic variable		Placebo (n=140)	Rotigotine (n=1093)	Ropinirole (n=68)	Overall (n=1301)
Mean age; SD (min-max)		59.9; 11.08 (32.0-80.0)	61.7; 10.19 (30.0—86.0)	63.2; 11.27 (34.0-86.0)	61.5;10.42 (30.0-86.0)
Age category N (%)					
	<65	87 (62.1%)	631 (57.7%)	38 (55.9%)	756 (58.1%)
	≥65	53 (37.9%)	462 (42.3%)	30 (44.1%)	545 (41.9%)
	≥75	17 (12.1%)	17 (12.1%)	8 (11.8%)	123 (9.5%)
Gender					
	Male	75 (53.6%)	665 (60.8%)	40 (58.8%)	780 (60.0%)
	Female	65 (46.4%)	428 (39.2%)	28 (41.2%)	521 (40.0%)
Race	White	123 (87.9%)	1015 (92.9%)	64 (94.1%)	1202 (92.4%)
	Black	2 (1.4%)	10 (0.9%)	0	12 (0.9%)
	Asian	1 (0.7%)	13 (1.2%)	1 (1.5%)	15 (1.2%)
	Other	14 (10.0%)	55 (5.0%)	3 (4.4%)	72 (5.5%)
BMI	Mean; SD (min-max) [kg/m^2]	26.2; 4.73 (17.8-45.2)	27.0 ; 4.62 (14.4-53.8)	25.8; 3.57 (17.7-33.5)	26.9; 4.59 (14.4-

					53.8)
BMI category (for patients with available data)	<18.5	4 (2.9%)	12 (1.1%)	1 (1.5%)	17 (1.3%)
	18.5-24	56 (40.0%)	369 (33.8%)	32 (47.1%)	457 (35.1%)
	25-29	56 (40.0%)	475 (43.5%)	27 (39.7%)	558 (42.9%)
	≥30	24 (17.1%)	229 (21.0%)	8 (11.8%)	261 (20.1%)
Alcohol use		88 (62.9%)	663 (60.7%)	44 (64.7%)	795 (61.1%)
Tobacco use		11 (7.9%)	84 (7.7%)	8 (11.8%)	103 (7.9%)
Geographical Region	North America	78 (55.7%)	498 (45.6%)	0	576 (44.3%)
	Non-North America	62 (44.3%)	595 (54.4%)	68 (100%)	725 (55.7%)
Subjects who took Parkinson's disease medication within 1 month prior to enrollment[8]		77 (55.0%)	611 (55.9%)	30 (44.1%)	718 (55.2%)

*Data from subjects initially treated with ropinirole or placebo who switched to rotigotine are presented in the rotigotine data column

†In some trials, anti-Parkinsonian medications were recorded only for the month prior to enrollment; lack of medication in this period does not necessarily mean that the patients had no prior history of anti-Parkinson's disease treatment.

From Schwarz Table 15.3; 120-Day Safety Update page 312.

Demographic data for other pools are summarized in the following tables:

- Pool S1: Table 15.1 (page 444; NDA Integrated Summary of Safety [ISS])
- Pool S2: Table 15.2 (page 447; NDA ISS)
- Pool S4: Table 15.4 (page 453; NDA ISS)
- Pool S5: Table 15.5 (page 456; NDA ISS)
- Pool S6: Table 15.6 (page 315; 120-Day Safety Update)
- Pool P11: Table 261.1 (page 4817; NDA ISS)
- Pool P12: Table 261.2 (page 4819; NDA ISS)
- Pool AS1: Table 250.1 (page 2664; 120-Day Safety Update)
- Pool RLS: Table 256.1 (page 2670; 120-Day Safety Update)

[8] Exclusion criteria pertaining to concomitant medication in the early-stage Parkinson's disease trials were as follows: dopamine agonist therapy concurrently or within 28 days of screening; ≥6 months of carbidopa-levodopa therapy since diagnosis; methylphenidate, amphetamine, catechol-o-methyl transferase (COMT) inhibitors, MAO-A inhibitors, reserpine, alpha-methyldopa, cinnarizine, neuroleptics within 28 days to 6 months (depending on the trial and specific medication) of the baseline visit. The following medications were allowed if the patient had been on a stable dose for at least 28 days prior to baseline and remained on that dose for the duration of the trial: sedatives, hypnotics, antidepressants, anxiolytics, anticholinergic agents, MAO-B inhibitors, NMDA-antagonists.

7.2.1.3 Extent of exposure (dose/duration)
In randomized trials, exposure to rotigotine was defined as beginning with the application of the first patch after randomization and ending with removal of the last patch. Subjects with placebo phases prior to or after rotigotine treatment (e.g., back-titrations) were considered to have been exposed to rotigotine for the entire patch administration period. In the open-label trials, exposure to rotigotine was defined as beginning with the first day of titration in the open-label period and ending either on the safety data cutoff date (July 1, 2004) or the date of last patch removal, whichever came first. Medication gaps occurring between the double-blind and open-label periods were taken into account for exposure calculations.

Overall, 1093 patients with early-stage Parkinson's disease were exposed to rotigotine during the development program, through the 120-day Safety Update. 575 patients were exposed to rotigotine for at least 6 months and 485 were exposed to rotigotine for at least one year.

An additional 978 patients were exposed to rotigotine in trials for advanced-stage Parkinson's disease (589) and restless leg syndrome (389). 452 of these patients were exposed to rotigotine for at least 6 months (319 patients with advanced-stage Parkinson's disease and 133 patients with restless leg syndrome) and 279 for at least one year (269 patients with advanced-stage Parkinson's disease and 10 with restless leg syndrome).

547 healthy subjects were exposed to rotigotine; 279 (51%) of these subjects were exposed for fewer than 14 days. 33 subjects with hepatic or renal impairment were exposed to rotigotine; the majority of these subjects (72.7%; 24/33) were treated for one day and none were exposed for more than one week.

Total exposure duration, mean daily dose, maximum dose, and dose of longest duration were determined for all rotigotine-treated patients. These data were pooled and presented according to the trial groupings described above in FDA Table 7.2.1.1 and are summarized below.

FDA Table 7.2.1.3.

Parameter	Pool									
	S1 n=649	S2 n=708	S3 n=1093	S4 n=396	S5 n=585	S6 n=596	P11 n=547	P12 n=33	AS1 n=589	RLS n=389
Treatment duration; days (mean +/- SD)	149.3 ± 81. 6	139.1 ± 85.1	327 ± 280.1	194.3± 74.3	386.6± 170.2	431.6± 159.4	13.3 ±10.3	1.8 ± 1.4	246.0 4.5 ± 234.4	146.0 ± 116.8
Mean daily dose; mg/d (mean +/- SD)	11.6 ± 5.0	11.6 ± 4.8	12.6 ± 4.5	14.1± 3.0	14.6 ± 2. 7	14.8 ± 3.1	3.2 ± 2.4	4.5 ± 0	18.5 ± 8.0	4.7 ± 2.3
Maximum daily dose; mg/d (mean	13.6 ± 4.6	13.8 ± 4. 6	15.0 ± 4.5	15.5± 2.9	16.2 ± 3.0	16.1 ± 3.4	3.5 ± 3.1	4.5 ± 0	22.9 ± 9.9	5.8 ± 2.8

+/- SD)										
Dose of longest duration; mg/d (mean +/- SD)	13.1 ± 5.3	13.3 ± 5.2	14.1 ± 4.8	15.2 ± 3.4	15.3 ± 3.1	15.2 ± 3.5	3.3 ± 2.8	4.5 ± 0	21.3 ± 10.3	5.2 ± 2.8

In the sections that follow, I summarize exposure duration by mean daily dose for each pool. In the NDA, Schwarz also presented rotigotine exposure duration categories by maximum dose and dose of longest duration.

7.2.1.3.1 Exposure in patients with early-stage Parkinson's disease

Rotigotine 9.0 mg/day is considered to be the minimally therapeutic dose. Rotigotine 4.5 mg/day is the recommended starting dose. Schwarz describes this dose as "marginally therapeutic." Schwarz recommends target rotigotine doses of 13.5– [redacted] mg/day for maintenance.

Pool S1
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	6 (0.9%)	0	0	0	6 (0.9%)
8-29	4 (0.6%)	12 (1.8%)	3 (0.5%)	0	0	19 (2.9%)
30-60	6 (0.9%)	7 (1.1%)	17 (2.6%)	10 (1.5%)	0	40 (6.2%)
61-91	76 (11.7%)	47 (7.2%)	56 (8.6%)	64 (9.9%)	0	243 (37.4%)
92-182	0	4 (0.6%)	19 (2.9%)	23 (3.5%)	0	46 (7.1%)
183-364	1 (0.2%)	10 (1.5%)	135 (20.8%)	149 (23.0%)	0	295 (45.5%)
365-729	0	0	0	0	0	0
≥730	0	0	0	0	0	0
Any duration	87 (13.4%)	86 (13.3%)	230 (35.4%)	246 (37.9%)	0	649 (100%)

Pool S2
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	6 (0.8%)	0	1 (0.1%)	0	7 (1.0%)
8-29	4 (0.6%)	19 (2.7%)	43 (6.1%)	4 (0.6%)	0	70 (9.9%)
30-60	6 (0.8%)	7 (1.0%)	24 (3.4%)	10 (1.4%)	0	47 (6.6%)
61-91	76 (10.7%)	47 (6.6%)	56 (7.9%)	64 (9.0%)	0	243 (34.3%)
92-182	0	4 (0.6%)	19 (2.7%)	23 (3.2%)	0	46 (6.5%)
183-364	1 (0.1%)	10 (1.4%)	135 (19.1%)	149 (21.0%)	0	295 (41.7%)
365-729	0	0	0	0	0	0
≥730	0	0	0	0	0	0
Any duration	87 (12.3%)	93 (13.1%)	277 (39.1%)	251 (35.5%)	0	708 (100.0%)

Pool S3
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	14 (1.3%)	0	1 (<.1%)	0	15 (1.4%)
8-29	4 (0.4%)	21 (1.9%)	44 (4.0%)	4 (0.4%)	0	73 (6.7%)
30-60	6 (0.5%)	10 (0.9%)	92 (8.4%)	13 (1.2%)	0	121 (11.1%)
61-91	76 (7.0%)	48 (4.4%)	63 (5.8%)	73 (6.7%)	0	260 (23.8%)
92-182	0	1 (<.1%)	18 (1.6%)	30 (2.7%)	0	49 (4.5%)
183-364	0	4 (0.4%)	29 (2.7%)	55 (5.0%)	1 (<.1%)	89 (8.1%)
365-729	0	11 (1.0%)	127 (11.6%)	208 (19.0%)	10 (0.9%)	356 (32.6%)
≥730	0	2 (0.2%)	66 (6.0%)	55 (5.0%)	7 (0.6%)	130 (11.9%)
Any duration	86 (7.9%)	111 (10.2%)	439 (40.2%)	439 (40.2%)	18 (1.6%)	1093 (100.0%)

As noted above, subjects in pool S3 studies were also classified by rotigotine dose of longest duration received during their study. Schwarz reported that through the safety update, 509 pool S3 subjects were exposed to 18mg for the longest duration, 355 subjects were exposed to 13.5mg for the longest duration, 109 subjects were exposed to 9mg for the longest duration and 89 subjects were exposed to 4.5mg for the longest duration (SU Table 4.3, p.299)

Pool S4
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	4 (1.0%)	0	0	0	4 (1.0%)
8-29	0	9 (2.3%)	2 (0.5%)	0	0	11 (2.8%)
30-60	0	3 (0.8%)	11 (2.8%)	8 (2.0%)	0	22 (5.6%)
61-91	0	1 (0.3%)	9 (2.3%)	9 (2.3%)	0	19 (4.8%)
92-182	0	4 (1.0%)	18 (4.5%)	23 (5.8%)	0	45 (11.4%)
183-364	1 (0.3%)	10 (2.5%)	135 (34.1%)	149 (37.6%)	0	295 (74.5%)
365-729	0	0	0	0	0	0
≥730	0	0	0	0	0	0
Any duration	1 (0.3%)	31 (7.8%)	175 (44.2%)	189 (47.7%)	0	396 (100%)

Pool S5
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	1 (0.2%)	0	0	0	1 (0.2%)
8-29	0	2 (0.3%)	1 (0.2%)	0	0	3 (0.5%)
30-60	0	3 (0.5%)	5 (0.9%)	1 (0.2%)	0	9 (1.5%)
61-91	0	1 (0.2%)	0	0	0	1 (0.2%)
92-182	0	0	7 (1.2%)	37 (6.3%)	1 (0.2%)	45 (7.7%)
183-364	0	13 (2.2%)	75 (12.8%)	115 (19.7%)	4 (0.7%)	207 (35.4%)
365-729	0	4 (0.7%)	146 (25.0%)	145 (24.8%)	4 (0.7%)	299 (51.1%)
≥730	0	0	1 (0.2%)	2 (0.3%)	0	3 (0.5%)
Any duration	0	24 (4.1%)	242 (41.4%)	310 (53.0%)	9 (1.5%)	585 (100%)

Pool S6
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1-7	0	3 (0.5%)	0	0	0	3 (0.5%)
8-29	0	5 (0.8%)	4 (0.7%)	0	0	9 (1.5%)
30-60	0	4 (0.7%)	6 (1.0%)	3 (0.5%)	0	13 (2.2%)
61-91	0	2 (0.3%)	8 (1.3%)	9 (1.5%)	0	19 (3.2%)
92-182	0	1 (0.2%)	9 (1.5%)	12 (2.0%)	1 (0.2%)	23 (3.9%)
183-364	0	2 (0.3%)	18 (3.0%)	57 (9.6%)	1 (0.2%)	78 (13.1%)
365-729	0	23 (3.9%)	184 (30.9%)	224 (37.6%)	18 (3.0%)	449 (75.3%)
≥730	0	0	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
Any duration	0	40 (6.7%)	230 (38.6%)	306 (51.3%)	20 (3.4%)	596 (100.0%)

7.2.1.3.2 Exposure in phase 1 studies

Pool P11
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/day)							
Duration (days)	<1.125	1.125 to <2.25	2.25 to <4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1	0	0	0	121 (22.1%)	2 (0.4%)	0	0	123 (22.5%)
2-7	0	3 (0.5%)	4 (0.7%)	78 (14.3%)	0	12 (2.2%)	0	97 (17.7%)
8-29	0	257 (47.0%)	7 (1.3%)	63 (11.5%)	0	0	0	327 (59.8%)
≥30	0	0	0	0	0	0	0	0
Any duration	0	260 (47.5%)	11 (2.0%)	262 (47.9%)	2 (0.4%)	12 (2.2%)	0	547 (100%)

Pool P12
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/day)							
Duration (days)	<1.125	1.125 to <2.25	2.25 to <4.5	4.5 to <9.0	9.0 to <13.5	13.5 to <18.0	≥18.0	Any dose
1	0	0	0	24 (72.7%)	0	0	0	24 (72.7%)
2-7	0	0	0	9 (27.3%)	0	0	0	9 (27.3%)
8-29	0	0	0	0	0	0	0	0
≥30	0	0	0	0	0	0	0	0
Any duration	0	0	0	33 (100%)	0	0	0	33 (100%)

7.2.1.3.2 Exposure in patients with advanced Parkinson's disease and restless leg syndrome

Pool RLS
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)					
Duration (days)	<1.125	1.125 to <2.25	2.25 to <4.5	4.5 to <6.75	≥6.75	Any dose
1-7	0	0	1 (0.3%)	5 (1.3%)	0	6 (1.5%)
8-29	0	20 (5.1%)	17 (4.4%)	24 (6.2%)	24 (6.2%)	85 (21.9%)
30-60	0	15 (3.9%)	20 (5.1%)	35 (9.0%)	19 (4.9%)	89 (22.9%)
61-91	0	0	1 (0.3%)	1 (0.3%)	0	2 (0.5%)
92-182	0	6 (1.5%)	4 (1.0%)	1 (0.3%)	6 (1.5%)	17 (4.4%)
183-364	0	27 (6.9%)	45 (11.6%)	68 (17.5%)	40 (10.3%)	180 (46.3%)
≥365	0	0	2 (0.5%)	4 (1.0%)	4 (1.0%)	10 (2.6%)
Any duration	0	68 (17.5%)	90 (23.1%)	138 (35.5%)	93 (23.9%)	389 (100.0%)

Pool AS1
Number (%) of patients exposed to rotigotine by duration and mean daily dose

	Mean daily dose of rotigotine (mg/d)						
Duration (days)	<9.0	9.0 to <13.5	13.5 to <18.0	18.0 to <22.5	22.5 to <27.0	≥27.0	Any dose
1-7	0	11 (1.9%)	0	0	0	0	11 (1.9%)
8-29	4 (0.7%)	13 (2.2%)	4 (0.7%)	0	2 (0.3%)	7 (1.2%)	30 (5.1%)
30-60	3 (0.5%)	11 (1.9%)	6 (1.0%)	6 (1.0%)	1 (0.2%)	2 (0.3%)	29 (4.9%)
61-91	70 (11.9%)	6 (1.0%)	59 (10.0%)	4 (0.7%)	64 (10.9%)	25 (4.2%)	228 (38.7%)
92-182	3 (0.5%)	7 (1.2%)	21 (3.6%)	3 (0.5%)	19 (3.2%)	3 (0.5%)	56 (9.5%)
183-364	0	5 (0.8%)	19 (3.2%)	14 (2.4%)	27 (4.6%)	0	65 (11.0%)
365-729	0	7 (1.2%)	20 (3.4%)	41 (7.0%)	76 (12.9%)	3 (0.5%)	147 (27.0%)
≥730	0	0	4 (0.7%)	3 (0.5%)	13 (2.2%)	3 (0.5%)	23 (3.9%)
Any duration	80 (13.6%)	60 (10.2%)	133 (22.6%)	71 (12.1%)	202 (34.3%)	43 (7.3%)	589 (100.0%)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The NDA did not include or refer to any studies for the evaluation of safety other than those described above and those listed in Appendix 3.

7.2.2.2 Postmarketing experience

To date, rotigotine has not been marketed and there are no available postmarketing data.

7.2.2.3 Literature

In subsection 2.7.5 of the Clinical Summary section of the CTD submission, Schwarz provided 4 pages of literature references. The literature references addressed the following topics:

- Parkinson's disease including prevalence, associated autonomic dysfunction, wearing off fluctuations, orthostatic blood pressure changes
- Treatment of Parkinson's disease with ropinirole, amantadine, levodopa
- Valvular hear disease and pergolide

- Adverse events associated with transdermal drug delivery of fentanyl, nicotine, clonidine, and nitroglycerine

The references did not include articles addressing the relationship between dopamine agonist treatment and excessive somnolence and sleep attacks, pathological gambling, or compulsive eating and weight gain.

7.2.3 Adequacy of Overall Clinical Experience

Total exposure to rotigotine at doses greater than or equal to those proposed for clinical use during the development program is slightly less than recommended in the International Conference on Harmonisation (ICH) guidelines for exposure. The number of patients exposed to rotigotine for at least six months and for at least 12 months does, however, meet ICH exposure guidelines.

The table below summarizes exposure by durations relevant to the ICH guidelines (any duration, at least 6 months, and at least 1 year) at doses proposed for clinical use. The table describes the number of patients exposed by two relevant dosing categories—≥9 mg/day and ≥13.5 mg/day. Schwarz considers 9.0 mg/day to be the minimal effective dose for early stage Parkinson's disease and proposes titrating to maintenance doses of 13.5— — mg/day. All indications/safety pools for which this information was available are included. Duration of use by dose was not described for doses ≥6.75 mg/day for Restless Leg Syndrome; the doses used in these trials were generally lower than the doses used in the Parkinson's disease trials.

FDA Table 7.2.3

		Numbers of patients exposed by dose	
Exposure duration	Pool	≥ 9 mg/d	≥ 13.5 mg/d
Any	S3 (Early PD)	896	457
	P11	14	12
	P12	0	0
	AS1 (Advanced PD)	509	449
	All pools listed	1419	918
≥ 6 months	S3 (Early PD)	558	336
	P11	0	0
	P12	0	0
	AS1 (Advanced PD)	235	223
	All pools listed	793	559
≥ 12 months	S3 (Early PD)	473	280
	P11	0	0
	P12	0	0
	AS1 (Advanced PD)	170	163
	All pools listed	643	443

Limitations of the early-stage Parkinson's disease clinical trials with respect to exposure include the following:

- Overall exposure to rotigotine in early-stage Parkinson's disease trials and trials for other indications is relatively limited. Even when trials for all indications are considered together, total exposure at doses greater than or equal to the minimally effective dose of 9.0 mg/day is slightly less than 1500, which is the recommended threshold by ICH guidelines. Total exposure at doses greater than or equal to the recommended therapeutic doses of 13.5— [redacted] mg/day is also limited. Our ability to assess infrequent and rare adverse events will thus be limited by the size of the database. It will be difficult to detect adverse events that occur in fewer than approximately 3/1000 rotigotine-treated patients.
- The majority of rotigotine exposure occurred in patients <64 and only limited exposure occurred in patients ≥75; the population of patients who would be exposed to rotigotine in clinical use is likely to be older.
- Over 88% of patients exposed to rotigotine in all pools were white.
- Patients with renal and hepatic dysfunction were excluded from early-stage Parkinson's disease trials and only 33 patients with hepatic or renal impairment were exposed to rotigotine in phase I trials. The adverse effects of rotigotine in clinical use in hepatically or renally impaired patients will not be well characterized by the data in the rotigotine NDA.
- Allowed concomitant medication use was limited in the early PD studies; the safety of rotigotine when taken in conjunction with other centrally acting medications will not be well characterized by the data in the NDA. Safety data for rotigotine use in subjects taking other PD medications is generally limited to AE data from advanced PD studies. The safety of rotigotine used with carbidopa/L-dopa or other dopamine agonists will not be well characterized.
- The safety of rotigotine in patients with a history of carbidopa/L-dopa use for more than six months will not be characterized; it is possible that rotigotine's dopaminergic effects may manifest themselves differently in these patients.

Tabular Listing of All Clinical Trials; pages 1—17

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical *in vitro* studies of rotigotine in papillary muscles isolated from guinea pig hearts and Purkinje fibers isolated from canine hearts showed increases in action potential duration at 90% repolarization at concentrations of 100 nM. Neither arrhythmia nor early after-depolarizations were observed in any of these preparations. In vitro human ether-a-go-go related gene (hERG) channel testing revealed that rotigotine affected the hERG-mediated potassium current with an IC_{50} of 150 nM. Preclinical cardiovascular effects were studied in anesthetized monkeys, and no statistically significant effects on blood pressure, heart rate, or electrocardiogram intervals were detected up to 4.0mg/kg of rotigotine administered subcutaneously. Although these results are not dramatic, they are sufficient to indicate a potential for rotigotine to cause QT prolongation in the clinical setting.

7.2.5 Adequacy of Routine Clinical Testing

The collection of vital sign data was generally done appropriately for heart rate, blood pressure and weight. Respiratory rate and temperature were not reported in the Phase 3 (Pool S5) studies but it is likely that abnormalities in these vital signs relevant to the drug would have appeared acutely in earlier studies. The sponsor's analyses of vital signs were usually based on "end of treatment" values, but it is not clear whether subjects who withdrew from the study had their "end of treatment" measurements performed while they were still on treatment.

The range of laboratory tests and frequency of testing were generally adequate. One exception was the absence of serum bicarbonate measurements in Phase 3 studies, a useful means of watching out for respiratory or metabolic acid-base disorders. Blood reticulocyte counts and urine hemoglobin were also not reported; they would have been useful. The SP506 study included tests for total thyroxine rather than free thyroxine or thyroid-stimulating hormone, both of which are more sensitive and accurate measurements of thyroid function. Finally, because of the inclusion of open-label extensions with the Phase 3 studies, there was no washout period where the reversibility of any effects of rotigotine could be observed.

The dedicated ECG study did not include a positive control, making it difficult to assess the degree of susceptibility of subjects to any electrophysiological effects of rotigotine and the capacity of the measurements used to detect effects.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Schwarz reported the 2 major biotransformation routes of rotigotine are conjugation of the parent compound and dealkylation with subsequent conjugation (Clinical Overview p.16). CYP2C19 is the major CYP450 isoform involved in the metabolism of rotigotine. Schwarz concluded that no significant inhibition or induction was observed for rotigotine. Rotigotine was not a substrate for P-glycoprotein. Rotigotine does not modulate digoxin transport in vitro and rotigotine was not displaced by warfarin and did not displace warfarin with human serum albumin (Nonclinical overview, p.39).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Schwarz's evaluation of adverse events appeared adequate. Schwarz provided analyses of all AEs in the development program, and provided more in-depth analyses of AEs of special interest, those AEs expected based on rotigotine's pharmacology as well as additional AEs of particular interest.

Schwarz designated sleep attacks, severe application site reactions and cardiac arrhythmias as AEs of special interest and required that these 3 AEs be reported by investigators immediately and be accompanied by written narratives (Study report,

SP512, p.9336-7). Furthermore, the protocols specified that application sites be evaluated and all reactions other than reddening be reported as AEs.

In addition to the three pre-specified AEs of special interest, Schwarz provided post-hoc analyses of AEs that were expected based on rotigotine's pharmacological class (dopamine agonist) and other AEs of interest. The expected AEs were somnolence, postural hypotension, psychotiform reactions, neuroleptic malignant syndrome, fibrosis, nausea, vomiting, insomnia, convulsion, abnormal vision, dyskinesia, and extremity edema (Clinical Overview, p.33). Other AEs of interest were syncope, fall, musculoskeletal pain, headache, abdominal pain, and hypertension (Clinical Overview, p.33). Schwarz explained that for these analyses they re-screened the reported and preferred AE terms for these AEs from studies SP506, SP512, and SP513 (pool S1).

Schwarz noted that orthostatic hypotension is associated with dopaminergic drugs and so protocols required monitoring for this potential AE by recording supine and standing BPs and heart rate at each visit. Identified cases of orthostatic hypotension were to be reported by investigators as AEs.

Schwarz required ECG recordings on study subjects to evaluate the potential effect of rotigotine on cardiac repolarization. The details of ECG monitoring and analysis are presented in the review section covering ECG data.

Dopamine agonists can cause decreases in serum prolactin. For pool S1 studies, Schwarz collected serum prolactin levels only in study SP512DB.

Schwarz provided no analyses of pathological gambling or compulsive eating and weight gain in their submissions.

7.2.8 Assessment of Quality and Completeness of Data

Assessment of the quality and completeness of the safety data relied predominantly on examination of the agreement of the submitted safety data across the various sources submitted by the sponsor and review of the analyses results by the reviewers. To examine the agreement of the data across sources, the sponsor's listings, case report forms (CRFs), case report tabulations (CRTs), narrative summaries, and in some cases, electronic data sets for deaths, selected serious adverse events and selected AEs leading to discontinuation were compared. In addition, we reviewed the results of the sponsor's treatment emergent AE risk calculations and the sponsor's lab and vital sign data analyses.

We encountered content deficiencies but no significant quality deficiencies with the NDA and Safety Update safety data. One notable content deficiency was the lack of narratives for AEs leading to discontinuation for the NDA and Safety Update. These narratives were requested and Schwarz provided the narratives in a 9/15/05 submission. In addition, the sponsors did not provide necessary clinical context for subjects who reported markedly

abnormal laboratory values while receiving rotigotine. Without this information, the likelihood of a causative role for rotigotine cannot be determined.

7.2.9 Additional Submissions, Including Safety Update

Subsequent to the NDA filing, Schwarz submitted additional safety data and analyses. Included among these submissions were a Safety Update and responses to reviewer questions. The safety data and analyses included in these supplemental submissions are reviewed in the appropriate sections of this document. Below is a listing of submissions that included safety data.

- Safety Update 5/27/05
- Response to Request for Fibrosis analysis 6/23/05
- Response to specific reviewer questions 9/2/05, 9/9/05, 9/23/05
- Narratives for AEs leading to discontinuation 9/15/05
- Response to Request for ECG data 9/15/05
- Response to Request for Melanoma data 10/31/05
- Response to Request for all development program malignancies 12/14/05
- Response to Request for person time dose response analysis 12/23/05

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following sections identify AEs that are treatment related and important to consider when using rotigotine.

7.3.1 Application Site Reactions

Application site reactions were some of the most commonly reported AEs in rotigotine subjects with nearly 40% of rotigotine subjects in pool S1 studies experiencing these events. While the majority of these reactions were classified as mild, 23 events were reported as severe and three rotigotine subjects experienced application site reaction SAEs. Approximately 5% of rotigotine subjects discontinued from trials for application site reactions. The reactions were frequently described as erythema and itching although some patients experienced more severe reactions such as blistering. Many of these reactions resolved following only patch removal. A special study found evidence of a type IV contact dermatitis in two subjects who developed application site reactions. Additional information on application site reactions is included in section 7.1.5.6 of this review.

7.3.2 Nausea and Vomiting

Nausea (38%) and vomiting (13%) were commonly reported by rotigotine subjects and more frequently compared to placebo subjects and occurred at similar frequency compared to ropinirole subjects in pool S1 studies. Nausea led to the discontinuation of 2% and vomiting of 1% of rotigotine subjects. Nausea led to the study drug dose reduction for 6% and vomiting for 3% of rotigotine subjects. Nausea and vomiting appeared early in treatment (median time to event 18 and 19 days, respectively) and the

highest frequency was observed during the titration period and at the lowest rotigotine dose. Nausea and vomiting have been associated with use of other dopamine agonists. Additional information on nausea and vomiting is included in section 7.1.5.6 of this review.

7.3.3 Sleep Attacks and Sleep Disturbances

In the pool S1 studies, 1.4% of rotigotine and 1.9% of ropinirole subjects experienced sleep attacks compared to no placebo subjects. For all phase II/III early-stage PD trials, the risk of sleep attacks for rotigotine subjects was 1.3%. Four sleep attacks were SAEs, most occurring while driving, indicating the potential danger associated with this AE.

In pool S1 studies rotigotine and ropinirole subjects had higher risks of somnolence (25% and 29%, respectively) compared to placebo subjects (16%). In addition, 10% of rotigotine subjects experienced insomnia AEs compared to 6% of ropinirole and 5% of placebo subjects. Rotigotine subjects also reported abnormal dreams (3.4%) more frequently than did ropinirole or placebo subjects (0.4% and 0.3%, respectively). Additional information on these sleep related AEs is included in section 7.1.5.6 of this review.

7.3.4 Hallucinations

In pool S1 studies, rotigotine subjects experienced hallucinations (2%) more frequently than did placebo subjects (0.7%) but less frequently than did ropinirole subjects (5.7%). The finding of hallucinations associated with rotigotine is not unexpected since hallucinations have been associated with the use of other dopamine agonists. Additional information on hallucination and other psychiatric AEs is included in section 7.1.5.6 of this review.

7.3.5 Effect on Vital Sign Parameters

Rotigotine on average increases heart rate and increases the incidence of tachycardia although the frequency of large increases in heart rate does not appear increased. The overall effect on blood pressure is less clear but it appears likely that rotigotine can increase the likelihood of substantial increases or decreases in blood pressure. No significant impact by rotigotine on postural changes in heart rate or blood pressure was observed. There is a higher and dose-related incidence of weight loss as well as a higher incidence of weight gain. Tachycardia and hypertension can be explained by the known beta-adrenergic agonist properties of rotigotine and weight loss by the propensity of the drug to cause nausea and anorexia. The sponsor has not considered possible reasons for hypotension and weight gain.

7.3.6 Effect on QT

The clinical data provided in this application show little adverse effect of rotigotine on electrocardiographic parameters. There were no dramatic changes in heart rate, rhythm or electrical conductivity attributable to rotigotine. The data, however, are insufficient to conclude that the potential for adverse effects on cardiac electrophysiology suggested by

preclinical data does not exist in the clinical setting. In most ECG studies, rotigotine is associated with an increase in heart rate. This greatly complicates the analysis of any possible effect the drug may have on QT interval because the results are greatly influenced by the methods used to adjust QT interval for heart rate. In addition, the data provided by the sponsor fails to demonstrate assay sensitivity. Most of the ECG measurements have been made in the presence of relatively low plasma rotigotine levels (<1.0 ng/ml) and almost all have been less than 3.0 ng/ml even though observed levels can exceed 5.0 ng/ml. So while little effect is observed at lower rotigotine levels, insufficient data exist regarding effects at higher but clinically plausible plasma rotigotine levels. Equally important is the need for a positive control to document the safety of rotigotine in subjects known to be susceptible to QT prolongation and the adequacy of the sponsor's methods to detect such changes

7.3.7 Effect on Lab Parameters

There is a strong association between exposure to rotigotine and declines in blood hemoglobin and serum albumin. These changes, along with a decline in mean cellular volume, appear to be part of a single process, occurring concurrently within the same individuals. Although there was no indication of effects on platelets and leukocytes as widespread as was seen with hemoglobin and albumin, the higher incidence of abnormally or markedly low platelet and leukocyte, particularly monocyte, counts suggest an effect on hematopoiesis that goes beyond erythrocytes. Additional studies that could shed light on this process; such as reticulocyte counts, iron studies and inflammatory markers; were not provided. Rotigotine was also associated with a higher rate of marked abnormalities in ALT, BUN and serum potassium levels.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

For their presentations in the NDA Summary of Clinical Safety, Schwarz pooled data from trials. Schwarz also included study reports for individual trials and these reports included analyses that used the data from that individual trial. Therefore, the reviewer had available both pooled analyses as well as analyses of data from individual trials.

Safety Pool S1 was the primary pool that included comparative data from placebo controlled early-stage PD trials (SP512, SP513, and SP506). Trial SP506 was a double blind placebo controlled trial lasting 12 weeks and was conducted in Canada, Europe, India, South Africa, Ukraine, and United States. In this study, subjects were titrated to a randomized target dose but back titrations (up to two) were allowed during the titration phase if a subject experienced intolerable side effects. In trial SP506, patches were applied only to the upper abdomen. Trials SP512 and SP513 were of similar design (double blind randomized placebo controlled, optimal dosing) and duration (27 and up to 37 weeks). Optimal dosing meant that subjects were titrated until either an optimal dose

was identified (based on response and AE profile) or the titration phase was complete. Subjects were allowed back titration (once, during the titration phase) in these trials. SP 512 was conducted in the United States and Canada while study SP513 was conducted in Europe, Israel, New Zealand, Australia, and South Africa. Another difference between these two trials was that SP513 included and active comparator arm (ropinirole) while SP512 had no active comparator arm. In trials SP512 and SP513, patches were rotated among the abdomen, thigh, hip flank shoulder and upper arm. All three trials allowed concomitant treatment with select anti-Parkinson's drugs (anticholinergics, selegiline, amantadine) provided the subject was on a stable dose, and all three trials prohibited the use of carbidopa/levodopa and other dopamine agonists.

Safety Pool S3 was the primary pool used to examine safety in the overall early-stage PD population exposed in controlled and open label studies. This safety pool included data from studies SP506, SP512DB, SP513DB, SP512OL, SP513OL, SP534 (parts I and II), SP535, SP540, and SP630.

Additional Safety pools were used to summarize data from other studies. For a summary of all safety data pools, the reader is referred to FDA table 7.2.1.1 in section 7.2.1.1 of this review.

7.4.1.2 Combining data
For the pooled analyses, Schwarz combined the data from individual studies and no weighting methods were used.

7.4.2 Explorations for Predictive Factors

In their Summary of Clinical Safety, Schwarz provided additional analyses of AEs that stratified on potential predictive factors. Schwarz included these analyses under the heading of Safety in Special Groups and Situations.

7.4.2.1 Explorations for dose dependency for adverse findings
In their ISS, Schwarz noted that rotigotine plasma concentration was not measured at the time of AE occurrence in clinical trials but that plasma level data was sampled at various time points during trials. Schwarz found high inter-individual variability of plasma concentration levels. Schwarz explained that predictable correlation between plasma level and the occurrence of AEs was not established (ISS, p.45).

Schwarz provided dose response analyses for AEs that used administered dose data but interpretation of the results of these analyses is complicated by several factors. The controlled trial pool S1 provided the comparative data for analyses. The designs of the pool S1 studies included titration phases, allowed back titration, and in two studies used titration to optimal dose. These design issues introduce difficulties in classification of subjects by dose and are complicated by time. Schwarz approach to analyzing the dose response data was to classify subjects by their modal dose (the denominator for risk calculation). AEs were classified by the dose at which the event occurred. To calculate risk by dose, the number of subjects with an AE at a given dose was divided by the

number of subjects with that modal dose. Therefore, in the risk calculation, the subject experiencing an AE at a given dose may not be in the denominator of that calculation if the event occurred at a dose other than the subject's modal dose. To address this point, the Division asked Schwarz to provide an alternative dose response analysis that used person time at each dose in the risk calculations. This analysis addressed the issue related to the denominator of the risk calculation but issues related to study design remain. Another factor complicating dose response interpretation was that the duration of exposure for the different doses was different. For example, the lower doses were mainly used during the shorter titration phases while the higher doses were used during the longer maintenance phases. Therefore, there was a greater opportunity to observe events at higher doses and this may impact interpretation of the dose response results. The results of the dose response analyses of AEs are provided in section 7.1.5.6 of this review.

7.4.2.2 Explorations for time dependency for adverse findings
Schwarz's time dependency AE analyses consisted of calculation of the median duration of exposure prior to experiencing one of the three AEs of special interest (sleep attacks, severe cardiac arrhythmia, and application site reactions). Those results are included in section 7.1.5.6 of this review.

7.4.2.3 Explorations for drug-demographic interactions
Schwarz provided analyses of AE risk by age, sex, race, and BMI in pool S1 studies. These analyses were limited to events occurring in at least 5% of subjects. These results are provided in section 7.1.5.6 of this review.

7.4.2.4 Explorations for drug-disease interactions
Schwarz provided ISS table 58.1.2 that displayed AE risk by treatment stratified by presence/absence of concomitant disease/diagnoses (occurring in >10%) for pool S1 studies. This analysis included the following concomitant diseases/diagnoses: cardiac dysrhythmias, essential hypertension, functional digestive disorders, osteoarthrosis, unspecified disorders of the back, allergic rhinitis, disorders of lipid metabolism, disorders not elsewhere classified, depressive disorder, neurotic disorder, general symptoms, and symptoms involving the urinary system. There did not appear to be remarkable variation in AE relative risk for subjects with/without these diseases/diagnoses. The analysis was limited by the non-specific nature of some of the concomitant diseases/diagnoses as well as the small number of subjects in many of these categories.

7.4.2.5 Explorations for drug-drug interactions
Schwarz's drug-drug interaction data come from PK interaction studies and from post-hoc analyses of AE risks using concomitant drug use information from clinical trials.

Schwarz conducted PK trials to look for interactions with cimetidine (SP627), domperidone (SP670), and levodopa/carbidopa (SP628). Schwarz reported that neither cimetidine nor domperidone altered the steady state PK of rotigotine in healthy subjects.

In addition Schwarz stated that carbidopa/levodopa had no effect on the PK of rotigotine, and that rotigotine had no effect on the PK of carbidopa/levodopa in subjects with RLS.

Schwarz provided ISS table 58.1.1 that displayed AE risk by treatment stratified by use/nonuse of concomitant medication (occurring in >10%) for pool S1 studies. This analysis included the following medications: antacid/anti-ulcer/anti-flatulent, mineral supplements, vitamins, antithrombotic agents, agents working on the renin-angiotensin system, beta blockers, calcium channel blockers, diuretics, lipid reducing agents, systemic antibacterials, sex hormones/modulators of the genital system, urologicals, antiinflammatory/antirheumatic, analgesics, anti-Parkinson, psychoanaleptics, psycholeptics, and systemic antihistamines. There did not appear to be remarkable variation in AE relative risks for subjects using/not using medications from these classes. The analysis was limited by the grouping of the concomitant drugs as well as the small number of subjects taking a drug from a given class of medications.

7.4.2.6 Explorations for drug-alcohol and drug-tobacco interactions
Using pool S1 data, Schwarz provided analyses of AE risk by treatment that stratified by concomitant use of alcohol (ISS table 58.1.7) or tobacco (ISS table 58.1.8). For subjects using alcohol, the AE relative risks were similar to relative risks observed among subjects not using alcohol. There was a difference in RR for somnolence where among those using alcohol the RR for rotigotine compared to placebo was 4, (12%/3%); and for those not using alcohol the RR was 14, (13%/0.9%). The difference was driven by a lower risk among the placebo subjects not using alcohol. For subjects using tobacco, the AE relative risks were similar to relative risks observed among subjects not using tobacco.

7.4.3 Causality Determination

The reader is referred to section 7.3 for the major rotigotine related adverse event findings. The strongest evidence of causal relationship, consisting of increases in risk among rotigotine subjects compared to placebo subjects, exists for application site reactions, nausea, vomiting, hallucinations, and sleep attacks and sleep disturbances. There were documented rotigotine related effects on mean change for hemoglobin that are of uncertain clinical significance, without associated increases in hematological adverse events. The class of dopamine agonists is causally linked to increased risk for orthostatic hypotension and syncope but the rotigotine data did not find strong evidence of these increased risks. It is not clear if this is due to a true absence of such risk with rotigotine or is due to characteristics of the rotigotine studies that precluded detection of such increased risks.

Appendicies

Reviewer's Appendix 1: Criteria for Marked Abnormalities in Laboratory Values Listed in Sponsor's Laboratory Data Set	
ALBUMIN	< 26 g/L
ALKALINE PHOSPHATASE	>= 3*ULN
BASOPHILS	> 5%
BASOPHILS ABSOLUTE	>=0.4 g/L
BICARBONATE	< 18 or > 38 mmol/L
BUN	>= 14.28 mmol/L
CALCIUM	<= 1.9 or >= 2.75 mmol/L
CHLORIDE	<= 90 or >= 112 mmol/L
CREATININE	>= 2 mg/dL
EOSINOPHILS	>= 10%
EOSINOPHILS ABSOLUTE	>= 1 g/L
GGT	>= 3*ULN
GLUCOSE	< 50 or >= 200mg/dL
HEMATOCRIT	<= 85% LLN or >= 115% ULN%
HEMOGLOBIN	<= 85% LLN or >= 115% ULN%
INORGANIC PHOSPHATE	<= 2 or >= 6 mg/dL
LYMPHOCYTES ABSOLUTE	< 0.6 or > 5 g/L
MONOCYTES	>= 20%
MONOCYTES ABSOLUTE	> 2 g/L
NEUTROPHILS ABSOLUTE	< 1.5 g/L
PLATELET COUNT	<= 100 or >= 600 g/L
POTASSIUM	<= 3 or >= 6 mmol/L
SGOT (AST)	>= 3*ULN
SGPT (ALT)	>= 3*ULN
SODIUM	< 127 or > 151 mmol/L
THYROXINE (T4)	<= 3.8 or >= 13.5 µg/dl
TOTAL BILIRUBIN	>= 2 mg/dL
TOTAL CHOLESTEROL	> 6.475 mmol/L
URIC ACID	> 565.06 µmol/L
WBC COUNT	<= 3 or >= 16 g/L

Reviewer's Appendix 2: Listing of Subjects Assigned to Rotigotine in Pools S1 and S6 with Marked Abnormalities in Laboratory Tests Identified in Reviewer's Table 7.1.7.3.3.1

Subject id	Test	Visit number	Result		Criteria for marked abnormality
506000282	PLATELET	6	53	g/L	<=100
506000282	PLATELET	8	40	g/L	<=100
506000308	BUN	7	14.64	mmol/L	>=14.28
506000326	WBC	6	2.7	g/L	<=3
506000326	WBC	7	3	g/L	<=3
506000326	WBC	8	2.6	g/L	<=3
506000326	WBC	10	2.6	g/L	<=3
506000704	HEMOGLOBIN	4	96	g/L	<=85% LLN
506000704	HEMOGLOBIN	6	93	g/L	<=85% LLN
506000704	HEMOGLOBIN	7	92	g/L	<=85% LLN
506000704	HEMATOCRIT	8	29.2	%	<=85% LLN
506000704	HEMOGLOBIN	8	89	g/L	<=85% LLN
506000704	HEMOGLOBIN	10	91	g/L	<=85% LLN
506001003	WBC	8	2.8	g/L	<=3
506001027	PLATELET	6	614	g/L	>=600
506001031	HEMATOCRIT	4	33.5	%	<=85% LLN
506001031	HEMOGLOBIN	4	103	g/L	<=85% LLN
506001207	PLATELET	8	93	g/L	<=100
506001276	SGPT	6	145	U/L	>= 3*ULN
506001654	BUN	6	14.64	mmol/L	>=14.28
506001656	BUN	6	14.64	mmol/L	>=14.28
512010201	SGPT	9	319	U/L	>= 3*ULN
512011102	MONOCYTES	9	30	%	>=20
512011102	HEMATOCRIT	23	26.9	%	<=85% LLN
512011102	HEMOGLOBIN	23	87.8	g/L	<=85% LLN
512011102	HEMATOCRIT	24	29.3	%	<=85% LLN
512011102	HEMOGLOBIN	24	92.633	g/L	<=85% LLN
512011502	POTASSIUM	4	9	mmol/L	>=6
512011506	POTASSIUM	11	9	mmol/L	>=6
512011901	WBC	13	2.8	g/L	<=3
512012803	WBC	5	2.9	g/L	<=3
512013603	BUN	24	15.5	mmol/L	>=14.28
512013608	HEMATOCRIT	5	34.7	%	<=85% LLN
512015307	SGPT	7.001	160	U/L	>= 3*ULN
512015307	MONOCYTES	8	22.2	%	>=20
513100203	MONOCYTES	23	23	%	>=20
513100808	BUN	5	23.7	mmol/L	>=14.28
513100808	HEMATOCRIT	5	28.9	%	<=85% LLN

Reviewer's Appendix 2: Listing of Subjects Assigned to Rotigotine in Pools S1 and S6 with Marked Abnormalities in Laboratory Tests Identified in Reviewer's Table 7.1.7.3.3.1

Subject id	Test	Visit number	Result		Criteria for marked abnormality
513100808	HEMOGLOBIN	5	95.049	g/L	<=85% LLN
513100808	BUN	10	21.1	mmol/L	>=14.28
513100808	HEMATOCRIT	10	27.9	%	<=85% LLN
513100808	HEMOGLOBIN	10	92.633	g/L	<=85% LLN
513100808	BUN	21	24	mmol/L	>=14.28
513100808	HEMATOCRIT	21	29.3	%	<=85% LLN
513100808	HEMOGLOBIN	21	96.66	g/L	<=85% LLN
513100808	BUN	23	17.9	mmol/L	>=14.28
513100808	HEMATOCRIT	23	28.8	%	<=85% LLN
513100808	HEMOGLOBIN	23	95.049	g/L	<=85% LLN
513100811	HEMOGLOBIN	8	98.271	g/L	<=85% LLN
513100811	HEMOGLOBIN	10	96.66	g/L	<=85% LLN
513100811	HEMOGLOBIN	18	100.688	g/L	<=85% LLN
513100811	HEMOGLOBIN	21	96.66	g/L	<=85% LLN
513101106	POTASSIUM	15	3	mmol/L	<=3
513101703	HEMATOCRIT	8	21.8	%	<=85% LLN
513101703	HEMOGLOBIN	8	62.829	g/L	<=85% LLN
513101703	PLATELET	8	611	g/L	>=600
513101903	WBC	21	3	g/L	<=3
513102003	WBC	15	2.9	g/L	<=3
513102003	WBC	18	2.5	g/L	<=3
513102601	MONOCYTES	21	21.7	%	>=20
513102601	WBC	21	2.4	g/L	<=3
513104504	WBC	18	2.7	g/L	<=3
513105604	SGPT	5.2	159	U/L	>= 3*ULN
513105911	HEMOGLOBIN	8	113.576	g/L	<=85% LLN
513106005	PLATELET	15	93	g/L	<=100
513106101	HEMATOCRIT	5	29.2	%	<=85% LLN
513106101	HEMOGLOBIN	5	95.049	g/L	<=85% LLN
513106101	HEMOGLOBIN	10	96.66	g/L	<=85% LLN
513106301	POTASSIUM	8	3	mmol/L	<=3
513106301	POTASSIUM	10	2.9	mmol/L	<=3
513106905	POTASSIUM	15	3	mmol/L	<=3
513108006	POTASSIUM	21	8.2	mmol/L	>=6
513108205	WBC	18	3	g/L	<=3

Reviewer's Appendix 3: Table of Rotigotine Clinical Trials

Protocol #/ Country	Trial Objective/ Design	Test Product/ Dose Regimen	Duration of Treatment	# Randomized Subjects
TD-0923-001 (SP799) USA	Safety and PK in healthy subjects/ Open label, single dose	Rotigotine HCl/ 10mg, 30mg/ silicone patch	90 hrs (30 per treatment)	4 rotigotine
TD-0923-003 (SP801) USA	Define PK and safety in healthy volunteers/ Open label, single dose	Rotigotine HCL/ 8.4mg, or 33.5mg/ ___ patch	24 hours	8 rotigotine
SP606 Netherlands	Absorption and excretion of ^{14}C-SPM 962 in healthy volunteers/ Open label, single dose	Rotigotine 4.5mg/ silicone patch	24 hours	6 rotigotine
SP610 Czech Republic	Absorption, metabolism, and excretion of ^{14}C-SPM 962 in healthy volunteers	Rotigotine 1.2mg and 4.5mg/ infusion solution and silicone patch	12 hours and 24 hours	6 rotigotine
SP502 Germany	Comparative BA of acrylic vs. silicone patches in healthy volunteers/ Open label crossover, single dose	Rotigotine 9mg silicone or rotigotine HCL 33.5mg ___ patch	24 hours per treatment	14 rotigotine
SP581 Germany	BE evaluation of rotigotine from 2 different batches of silicone batches in healthy volunteers/ Crossover, single dose	Rotigotine 4.5mg, silicone patch	24 hours per treatment	30 rotigotine
SP503 Germany	PK, safety and tolerability in healthy volunteers, open label, repeated dose	Rotigotine 4.5mg silicone patch	14 days	30 rotigotine
SP 629 Germany	Skin irritation, repeat application (same site vs. rotating site), DB, PC, repetitive dose	Rotigotine 1.125mg, up to 2.25mg silicone patch	21 days	40 placebo and rotigotine
SP 673 Germany	Sensitization potential in healthy volunteers, DB, PC	Rotigotine 1.125mg silicone patch	3 weeks and 48 hours	229 placebo and rotigotine
TD-0923-002 (SP 800) USA	Define PK and evaluate safety, Open label multi dose	Rotigotine HCL, 10mg, 20mg, 30mg silicone patch	30 hours	9 rotigotine
SP512 USA, Canada	Evaluate PK, DB multi dose	Rotigotine 4.5mg, 9mg, 13.5mg silicone patch	27 weeks	56 rotigotine
SP630 USA, South Africa	Define PK with rotating patch sites, evaluate EG effects, open label randomized	Rotigotine 4.5mg, 9mg, 13.5mg, 18mg silicone patch	36 days	70 rotigotine
SP596	BA and PK in	Rotigotine 4.5mg	24 hours	48 rotigotine (23

France	Caucasian vs. Black subjects, open label single dose	silicone patch		Black, 25 Caucasian)
SP626 Germany	Influence of patch site on bioavailability, open label single dose randomized crossover	Rotigotine 4.5mg silicone patch	24 hours	24 rotigotine
SP 671 Slovac Republic	PK, safety and tolerability in subjects with impaired hepatic function, open label parallel group	Rotigotine 4.5mg silicone patch	3 days	17 rotigotine
SP672 Poland	PK, safety, and tolerability in subjects with impaired renal function Open label single dose	Rotigotine 4.5mg, silicone patch	24 hours	32 rotigotine
SP717 Germany	PK, safety and tolerability in Japanese vs. Caucasian subjects, open label multi dose	Rotigotine 4.5mg, silicone patch	24 hours	50 rotigotine
SP718 Germany	PK, safety and tolerability in Japanese vs. Caucasian subjects, open label multi dose	Rotigotine 2.25mg, 4.5mg, 9mg	9 days	26 rotigotine
SP627 Germany	Influence of cimetidine on PK of rotigotine, open label crossover, repeated dose	Rotigotine 4.5mg, 9mg silicone patch; Cimetidine 800mg	12 days 7 days	12 rotigotine
SP670 France	Influence of dimperidone on PK, safety and tolerability of rotigotine, open label crossover	Rotigotine 4.5mg silicone patch Domperidone 30mg	8 days 5 days	16 rotigotine
SP628 Germany	PK of rotigotine and levodopa/carbidopa in subjects with RLS, randomized open label parallel group	Rotigotine 4.5mg, 9mg silicone patch Levodopa 200mg Carbidopa 50mg	9 days 6 or 8 days	24 rotigotine
N-0923-001-2601 (SP803) USA	Safety, efficacy, Open label dose escalating	Rotigotine max tolerated iv dose	Up to 14 days	12 rotigotine
N-0923-002-001 (SP804) USA	Safety, efficacy, Open label dose escalating	Rotigotine max tolerated iv dose	9.5 hours	9 rotigotine
N-0923-006-01 (SP805) USA	Safety, efficacy, Open label dose escalating	Rotigotine optimal iv dose	7 days	8 rotigotine
SP 534 part I USA	Safety, tolerability, DB, PC, parallel fixed dose	Rotigotine 9mg, 13.5mg silicone patch	4 weeks	2 placebo, 10 rotigotine
SP 534 part II USA	Safety, tolerability, DB, PC, parallel dose escalation	Rotigotine 4.5mg, 9mg, 13.5mg, 18mg, silicone patch	4 weeks	2 placebo, 10 rotigotine

SP535 USA	Safety, tolerability, DB, PC, dose escalation	Rotigotine 4.5mg, 9mg, 13.5mg, 18mg silicone patch	4 weeks	2 placebo, 8 rotigotine
SP506 Canada, Europe, India, South Aftrica, Ukraine, USA	Efficacy, safety, tolerability, DB, randomized, PC, dose response	Rotigotine 4.5mg, 9mg, 13.5mg, 18mg	12 weeks	64 placebo 265 rotigotine
SP512 part I Canada, USA	Efficacy, safety, PK, DB, randomized, PC, optimal dosing	Rotigotine 4.5mg, 9mg, 13.5mg silicone patch	27 weeks	96 placebo 181 rotigotine
SP513 part I Europe, Israel, New Zealand, S. Africa, Switzerland, Australia	Efficacy, safety, PK, DB, randomized PC and active controlled, optimal dosing	Rotigotine 4.5mg, 9mg, 13.5mg, 18mg silicone patch Ropinirole 0.75-24mg	Up to 37 weeks	118 placebo 215 rotigotine 228 ropinirole
SP512, part II (SP 702) Canada, USA	Long term safety, open label	Year 1: up to 13.5mg Years 2-4 up to 36mg silicone patch	Up to 4 years	213 rotigotine
SP513 part II Europe, Israel, New Zealand, S. Africa, Switzerland, Australia	Long term safety, open label	Year 1: Rotigotine up to 18mg Years 2-4: Rotigotine up to 36mg silicone patch	Up to 4 years	372 rotigotine
SP540 Europe, South Africa	Efficacy, safety, single blind	Rotigotine max tolerated dose up to 18mg silicone patch	28 days	31 placebo and rotigotine
TD-0923-004 (SP802) USA	PK, dose response, efficacy and safety in Advanced PD, Randomized, PC, DB, parallel	Rotigotine HCl, 8.4mg, 16.8mg, 33.5mg, 67mg — patch	21 days	68 rotigotine, 17 placebo
SP533 USA	Safety, efficacy, and tolerability in advanced PD, open label	Rotigotine 9mg to 36 mg, silicone patch	28 days	10 rotigotine
SP511 Europe, S. Africa, United Kingdom	Assess dose groups in advanced PD, DB, randomized, PC, parallel	Rotigotine 9mg, 18mg, 27mg, silicone patch	3 months	84 placebo, 240 rotigotine
SP650 part I Canada, USA	Efficacy, safety in advanced PD subjects not well controlled on levodopa, DB, randomized, PC, parallel	Rotigotine 18mg, 27mg silicone patch	Up to 38 weeks	461 total
SP650 part II Canada, USA	Long term safety in advanced PD subjects	Rotigotine up to 27mg, silicone patch	Up to 4 years	197 rotigotine
SP 591	Safety and tolerability	Rotigotine up to 54mg,	12 weeks	34 rotigotine

Europe, Croatia	in advanced PD subjects, open label, randomized, parallel group	silicone patch		
SP666 Germany	Dose response, safety, tolerability in RLS subjects, DB, randomized, PC, parallel group	Rotigotine 1.125mg, 2.25mg, 4.5mg, silicone patch	1 week	14 placebo, 49 rotigotine
SP709	Safety and efficacy in RLS subjects, DB, randomized	Rotigotine 1.125mg, 2.25mg, 4.5mg, 6.75mg, 9mg, silicone patch	7 weeks	112 total

Safety Labeling

15 Page(s) Withheld

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