CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21829

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 21-829
Drug: Rotigotine (Neupro)
Route: transdermal patch
Indication: early Parkinson's disease
Sponsor: Schwarz Biosciences
Reviewer: Alice Hughes, M.D.

In this memorandum, I will discuss selected clinical safety issues from Schwarz's response to the approvable letter for the rotigotine NDA, which was issued on February 28, 2006. Drs. Leonard Kapcala, Gerard Boehm, and Marc Stone have reviewed the sponsor's responses to our questions regarding clinical safety issues in detail. In this memorandum, I will restrict my comments to the topics covered in the reviews by Safety Team reviewers Drs. Stone and Boehm: the overall safety profile of rotigotine as reflected by the final safety update, compulsive behavior, cardiac arrhythmia, weight gain, and laboratory abnormalities. I will briefly review and comment on the safety reviewers' assessments and recommendations pertaining to each of these topics and offer my own recommendations.

1 Laboratory abnormalities

In the safety review of the original NDA, Dr. Stone identified an association between rotigotine and declines in serum hemoglobin, hematocrit, mean cellular volume, and albumin. At the time, there was a concern that some of the statistically significant results may have reflected chance rather than a true association, given the multiple comparisons that were being made. In addition, the potential clinical significance of small mean declines in albumin and hemoglobin were not clear. To better characterize the laboratory abnormalities observed, the Division requested complete laboratory datasets for all clinical studies (including ≥14 days of rotigotine exposure).

With this dataset, Dr. Stone conducted analyses assessing the development of laboratory abnormalities according to treatment assignment. He calculated odds ratios (ORs) for abnormal laboratory values associated with treatment (using random effects logistic regression stratified by study). He also performed analyses of central tendency, looking at absolute and percentage changes in laboratory parameters over the course of rotigotine treatment. Finally, he examined hemoglobin changes associated with treatment across studies (vs. placebo for the placebo-controlled trials and vs. baseline for all studies).

Dr. Stone concluded that his analyses confirmed his earlier finding with respect to declines in hemoglobin. 7.6% of rotigotine-treated patients had a low hemoglobin at any point during treatment compared to 4.9% of placebo-treated patients; 8.1% of rotigotine-

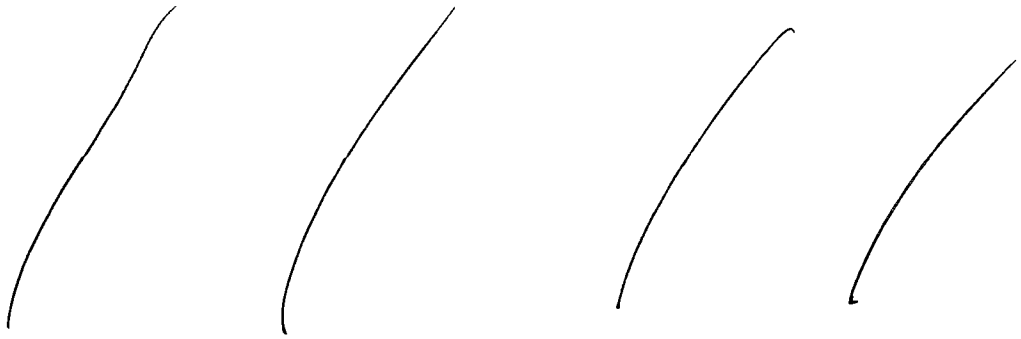
treated patients had a low hematocrit at any point during treatment compared to 5.8% of placebo-treated patients. The odd ratio for low hemoglobin was 2.1 (95% CI 1.7-2.5) and for hematocrit was 1.6 (95% CI 1.4-2.0) for rotigotine-treated patients (vs. placebo-treated patients). The net treatment effect was small: 2.85 g/L (.3 g/dL) for hemoglobin and 0.88% for hematocrit (representing a 2% decline for each parameter). Dr. Stone's analyses looking at treatment effects across studies showed that hemoglobin declines were observed in most studies. Declines relative to baseline were observed all but two studies. Declines in hemoglobin in rotigotine-treated patients relative to placebo-treated patients were observed in six of the nine placebo-controlled studies. A decline was not observed in the one study in which iron studies were measured per protocol, SP709.

Dr. Stone also concluded that rotigotine treatment was associated with declines in serum albumin, increases in blood urea nitrogen (BUN), and decreases in total cholesterol levels, based both on his analyses of the distribution of abnormal laboratory values in rotigotine-treated patients vs. placebo-treated patients and his analyses of absolute change in laboratory values during treatment. His findings with respect to albumin support the findings from his prior analyses. Net treatment effect was 0.21 mmol/L for BUN (a 4% increase), 0.86 g/L for albumin (a 2% decline), and -0.30 mmol/L for total cholesterol, a 6% decrease. In addition, Dr. Stone concluded that rotigotine was associated with a higher incidence of hypoglycemia; 7% of rotigotine-treated patients had a low blood glucose during treatment compared to 4% of placebo-treated patients (OR for low blood glucose 1.73; 95% CI 1.3—2.3). Dr. Stone noted that his prior observations in the initial NDA safety review pertaining to abnormalities in ALT (alanine transaminase), white blood cell count, monocyte count, and platelet count were not replicated in his analysis of the complete laboratory dataset submitted in the sponsor's response to the approvable letter.

Dr. Stone argued that his findings with respect to hemoglobin, BUN, and albumin changes provide evidence for renal effects of rotigotine that could lead to fluid retention and weight gain (discussed further below). He argued that hemodilution could be a partial, although not a complete, explanation for the changes in hemoglobin and albumin observed with rotigotine.

Dr. Stone proposed the following for the *Laboratory changes* section of labeling:

Laboratory changes

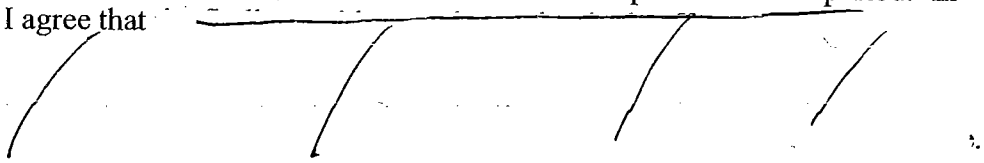


Dr. Stone also recommended a phase 4 commitment for the further study of rotigotine's effect on renal function, hemoglobin, and albumin in controlled clinical studies, including study of laboratory parameters after treatment cessation (to assess recovery from any abnormalities).

1.1 Team Leader comment

Dr. Stone's analyses of the laboratory dataset provided in the sponsor's response to the approvable letter provide persuasive evidence that rotigotine is associated with a decline in hemoglobin levels. The general consistency in this finding across studies argues against the result being due to chance alone. The effect as evident in the NDA database was small, although there is a chance that in a vulnerable population or over a longer period of treatment, the effect could be larger and/or more clinically significant.

The reason for rotigotine's effect on hemoglobin levels remains unclear. Dr. Stone's renal hypothesis is intriguing but is not adequately supported at this time. I agree with his recommendation for a phase 4 commitment to further study rotigotine's effect on hemoglobin and renal function, with close attention to the post-treatment period. In addition, I agree that



In terms of the other laboratory anomalies noted by Dr. Stone, we do not have the same data for these other parameters that we have for hemoglobin showing a consistency (or lack thereof) across individual studies. Therefore, I do not think that Dr. Stone's findings with respect to BUN and albumin are quite as persuasive. In addition, the changes in BUN and albumin that Dr. Stone's analyses demonstrate are small and of uncertain clinical significance.

The association between rotigotine and weight gain and fluid retention in some patients does provide evidence in support of Dr. Stone's hypothesis that rotigotine may affect renal function, and this should be investigated further in a phase 4 study. The study of changes in laboratory parameters in the subset of patients with weight gain and fluid retention would have been elucidating. Currently, we do not have evidence that the same

patients who developed weight gain had increases in BUN; such evidence would have been compelling.

I do not believe that the findings with respect to albumin and BUN are robust enough, or meaningful enough, to warrant labeling language describing these changes at this time.

Although rotigotine-treated patients were more likely to have high blood glucoses than low blood glucoses (14% of both rotigotine- and placebo-treated patients had a high blood glucose value), I am concerned regarding the increased incidence of hypoglycemia in rotigotine-treated patients compared to placebo-treated patients noted by Dr. Stone, particularly in light of two hypoglycemia serious adverse events in the NDA database (pool S3). I recommend that

2 Weight gain

In the review of the original NDA, Dr. Stone noted that the incidence of weight gain of at least 10% was greater in rotigotine-treated patients than in placebo-treated patients. In the approvable letter, the sponsor was asked to conduct an investigation of subjects who experienced increases in weight of more than 10% of baseline, assessing whether "the weight gain was due to benign causes such as improved appetite or to less benign causes such as fluid retention."

In their response, the sponsor provided updated estimates of the percentage of patients who experienced weight gain ≥10%: 3% (41/1390) of rotigotine-treated and <1% (3/566) of placebo-treated patients in all PD and RLS double-blind, placebo-controlled trials. The sponsor conducted analyses of the association between weight gain of at least 10% and adverse events. Edema-related adverse events were the only adverse events found to have an association with post-baseline weight gain>10% at any time point. Dr. Stone reported that 33% of patients with weight gain ≥10% had an adverse event related to edema compared to 10% of those without weight gain of this magnitude (in all PD and RLS trials), and that no such correlation was found for any other adverse event. Dr. Stone's review of patient narratives supported this correlation between weight gain and edema in some patients, and did not provide strong evidence of serious clinical consequences of weight gain and edema in these patients. He notes, however, that patients with pre-existing renal disease or compromised cardiac function may be more vulnerable to deleterious effects.

Dr. Stone concluded that the sponsor's proposal for labeling with respect to weight gain and edema is inadequate and proposed the following *Precautions* subsection:

Weight Gain and Fluid Retention.

Subjects taking Neupro had a higher incidence of substantial weight gain (more than 10% of baseline weight). This weight gain was frequently associated with the development of peripheral edema, suggesting that Neupro may cause substantial fluid retention in some patients. Although the weight gain was usually well-tolerated in subjects observed in clinical trials, it could cause greater difficulty in patients who may be especially

vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

2.1 Team Leader Comment

I agree with Dr. Stone's conclusion that weight gain appears to be associated with peripheral edema in patients treated with rotigotine who experience a weight gain of at least 10% (although edema was not reported for the majority of patients with weight gain of this magnitude). I agree that this finding should be conveyed in labeling, and a *Precautions* subsection seems appropriate. The effect of rotigotine on weight is not, however, straightforward. As Drs. Boehm and Stone noted in their initial NDA safety review, rotigotine-treated patients were also more likely than placebo-treated patients to have a weight decrease of at least 10%, and studies showed a net decline in weight at the beginning of the maintenance period. As discussed above, I do not believe that we have sufficient evidence at this time that this weight gain is due to renal effects of rotigotine, although this is a possibility that should be considered.

3 Compulsive behavior

Because of a relatively recent concern regarding the potential risk for pathological gambling and other forms of compulsive behavior with dopaminergic drugs, the Division asked the sponsor to identify any events in rotigotine-treated subjects that represented compulsive gambling, compulsive eating, hypersexuality or any other compulsive behavior. The NDA had not included an analysis or other discussion of the potential for compulsive behaviors in association with rotigotine. There was no active surveillance for these events during the rotigotine development program

As discussed in detail by Dr. Boehm, the sponsor did identify compulsive behavior events in their NDA database. Overall, 1% (29/2775) of rotigotine-treated patients had compulsive behavior events. All of the events took place in PD trials; there were no such events in RLS studies. In all placebo-controlled PD trials, 5 rotigotine-treated patients (5/1335; 0.4%) and 0/612 placebo-treated patients had compulsive behavior adverse events. Dr. Boehm does not believe that the available data for these adverse events permit either any assessment regarding causality or any quantification of risk (primarily because the events were not well described and the temporal relationship to rotigotine exposure was unclear in many cases, given that history of these events was not ascertained). He makes recommendations for improved data collection and active monitoring in ongoing and future trials. He also recommends that the same class labeling language that was requested in October, 2006 of all dopaminergic drugs be implemented for rotigotine:

Precautions section, *Information for Patients* subsection
There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new

or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

3.1 Team Leader comment

The difference in the incidence of compulsive behaviors in rotigotine-treated patients compared to placebo-treated patients suggests that rotigotine may cause these types of behaviors. I agree with Dr. Boehm regarding the limitations of the available data, but still think that the data are valuable. Placebo-controlled trials data assessing the risk for this event are rare. I agree with Dr. Boehm that adequate risk estimates for the development of compulsive behaviors with rotigotine are not possible based on the data available, both because there was not active surveillance for compulsive behavior events (and underreporting was likely great), and because we do not have adequate information on compulsive behavior history in these patients. I agree with Dr. Boehm that the class labeling language should be implemented. In addition, I think that labeling

4 Cardiac arrhythmia

Because cardiac arrhythmia adverse events and two sudden deaths in rotigotine-treated patients were identified in the original NDA safety review, Schwarz was asked to perform a re-analysis of cardiac arrhythmia adverse events. There was a concern that in the original NDA data presentation, splitting of terms and indications did not permit an adequate assessment of the risk for arrhythmias associated with rotigotine treatment. In the requested re-analysis, relevant events from completed phase II and III PD and RLS trials were recoded by cardiologists blinded to patients' treatment assignments. In this reanalysis, 5% of rotigotine-treated patients had an arrhythmia compared to 6% of placebo-treated patients (and 4% of ropinirole-treated patients and 6% of pramipexole-treated patients). In his review, Dr. Boehm discusses the sponsor's analyses of risks for each indication and for specific arrhythmias. He concludes that the incidence of palpitations was elevated in rotigotine-treated patients compared to placebo-treated patients in PD trials, but that the risk for specific arrhythmias was similar among treatment groups. He stated that it was difficult to determine the clinical significance of the increased incidence of palpitations given that the term is non-specific and does not denote a particular arrhythmia type.

4.1 Team leader comment

I agree with Dr. Boehm's assessment. The sponsor's re-analysis does not indicate an increased risk of a particular type of arrhythmia. The results of the analysis do not support the need for a study using Holter monitoring prior to approval or as a post-approval commitment, nor do they support the need for any particular labeling language. We continue to await the sponsor's report of their Thorough QT Study so we can have a more thorough assessment of whether rotigotine has any effect on the QT interval. No

clinically significant effect on the QT interval is evident based on available data. We expect the final study report in —

5 Overall safety profile

Dr. Boehm concluded that his review of the final safety update did not indicate any safety concerns with rotigotine that had not previously been identified. He concluded that the final safety update was consistent with his prior assessment of rotigotine's overall safety profile.

5.1 Team Leader comment

I agree with Dr. Boehm's assessment. The new deaths, serious adverse events, discontinuations due to adverse events, and common adverse events do not indicate any new safety concerns with rotigotine. Of note, given the hemoglobin and hematocrit effects uncovered by Dr. Stone's analyses, there were four serious adverse events of anemia from advanced PD trials reported in the final safety update. Review of the narratives for these cases indicates a clear gastrointestinal bleeding source in three of the four cases. In the fourth case, the anemia resolved after treatment with iron and omeprazole; thus, a gastrointestinal source of bleeding seems likely in this case as well. The anemia does not appear to be a result of rotigotine treatment in any of these cases.

CLINICAL REVIEW OF SPONSOR'S COMPLETE RESPONSE TO APPROVABLE LETTER

Application Type	NDA
Submission Number	21829
Submission Code	AZ
Letter Date	11/7/06
Stamp Date	11/9/06
PDUFA Goal Date	5/9/07
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	4/4/07
Established Name	Rotigotine patch
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopaminergic agonist
Applicant	Schwarz Pharmaceuticals
Priority Designation	S
Formulation	Transdermal patch
Dosing Regimen	Once daily
Indication	Treatment of Early Parkinson's Disease
Intended Population	Early Parkinson's Disease

Table of Contents

1 EXECUTIVE SUMMARY

Background / Introduction

The sponsor submitted (to the DNP) NDA 21829 for the indication of treatment of early Parkinson's Disease for a non-ergot, dopaminergic agonist patch, rotigotine on 1/19/05. On 2/28/06, an approvable letter was issued with requests for several additional analyses. One set of analyses focused on Study SP506, a randomized, double-blind, placebo-controlled study trial (329 patients) using several fixed doses of rotigotine. **The main purpose of requesting additional analyses of this study was to determine if there were dose-related/dose-dependent effects of rotigotine on treatment-emergent adverse events (TEAEs), clinical laboratory analytes, and orthostatic vital signs (VS).**

1. FDA Request for Study 506, Question No.1 :

*Analyze and present the incidence of treatment-emergent (TE) AEs, SAEs, and study discontinuations according to **randomized** treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and **any** rotigotine dose). For each of the 3 types of analyses (i.e. TEAEs, TE-SAEs, TEAEs causing study discontinuation), please provide separate analyses based upon: 1) the development of an event during the **whole, 4 week titration period;** 2) the development of an event during the **whole, 7 week maintenance period;** 3) the development of an event in the 4 week titration period and persistence into the 7 week maintenance period. You will need to define this last category (e.g. when it is considered "persistent" such as if an event starting in the titration period persists > 7 days into the maintenance period). In these analyses, also show the total number of specific events and the total number of patients experiencing these events.*

Tabular analyses showing this information should be conducted without respect to severity or causality of TEAE and should show results for all 5 randomized treatments (and any rotigotine treatment if possible) on the same page. For example, the reader should be able to see the frequency of nausea for placebo and all 4 randomized rotigotine treatments (and any rotigotine treatment if possible) on the same page.

Sponsor's Summary/Conclusions

The sponsor noted that TEAEs occurred more frequently in the titration period than in the maintenance period for both placebo and rotigotine treatments. Although the sponsor acknowledged that in few TEAE instances (especially application site reations and nausea) there appeared to be a dose-related risk, the sponsor's main overview of the various analyses was that rotigotine for the most part did not exhibit dose-related increased risks for TEAEs. It is relevant to note that the sponsor did not outline its criteria for determining the existence of dose-related relationships.

Reviewer's Summary/Conclusions

Criteria for considering the existence of the "shape" of a dose-response curve were developed by this reviewer and then applied to the various TEAE frequency analyses. The sponsor did not specify any criteria for assessing any dose-response relationships.

A dose-related effect of rotigotine is considered to be suggested when the following criteria are satisfied :

- 18 mg dose group consists of ≥ 2 patients with the event or ≥ 2 events (for TEAE rate analyses)
  AND
- 18 mg dose group more frequent than 4.5 mg dose group
  AND
- If 18 mg dose group (%) is highest and > placebo **and** 4.5 mg **and** 9.0 mg **and** 13.5 mg dose groups, the difference must be ≥ 1.0 % above 4.5 mg **and** placebo groups
  OR
- If 18 mg dose group (%) is not highest as per above criterion, then 9.0 mg, **and** 13 5 mg, **and** 18.0 mg dose groups must be > 4.5 mg **and** placebo groups
  OR
- If 18 mg dose group (%) is not highest as per above criterion, then 13 5 mg **and** 18.0 mg dose groups must be > 4.5 mg **and** 9.0 mg **and** placebo groups

Many different TEAEs appeared to be dose-related according to defined criteria for assessing a dose-response curve relationship. Although in some instances the apparent "shape" of the dose-response curve for a specific TEAE suggested that the "maximal" effect occurred at a range of doses including one or more lower rotigotine doses, the vast majority of these TEAEs suggested that the greatest frequency occurred at the highest daily dose of rotigotine (18 mg). The incidence of dose-related TEAEs in the titration period and in the maintenance periods is shown in Table 1 and Table 2, respectively.

Table 1 Incidence (%) of Dose-Related TEAEs During the Titration Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

Preferred Term Adverse Event	Placebo N = 64	Daily Rotigotine Dose (patch content) 4.5 mg N = 67	9.0 mg N = 63	13.5 mg N = 65	18.0 mg N = 70	"Any" N = 265
Application site reaction	10.9	14.9	15.9	24.6	**35.7**	23.0
Mouth dry	1.6	1.5	1.6	0	**2.9**	1.5
Fatigue	1.6	7.5	9.5	4.6	**10.0**	7.9
Nausea	9.4	32.8	31.7	**43.1**	**40.0**	37.0
Anorexia	0	0	1.6	7.7	**4.3**	3.4
Constipation	1.6	0	**3.2**	**4.6**	**2.9**	2.6
Hiccup	0	1.5	0	1.5	**2.9**	1.5
SGPT increased	0	1.5	0	0	**2.9**	1.1
Weight decrease	0	0	0	0	**2.9**	0.8
Somnolence	1.6	11.9	11.1	16.9	**18.6**	14.7
Insomnia	4.7	4.5	**7.9**	**6.2**	**7.1**	6.4
Dreaming abnormal	0	0	3.2	1.5	**4.3**	2.3
Hallucination	0	0	1.6	1.5	**2.9**	1.5
Rhinitis	0	1.5	0	0	**2.9**	1.1
Upper respiratory tract infection	0	0	1.6	0	**2.9**	1.1
Vision abnormal	0	1.5	0	**7.7**	**2.9**	3.0

Table 2 Incidence (%) of Dose-Related TEAEs During the Maintenance Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses

Preferred Term Adverse Event	Placebo N = 57	Daily Rotigotine Dose (patch content)				
		4.5 mg N = 62	9.0 mg N = 59	13.5 mg N = 61	18.0 mg N = 66	"Any" N = 248
Application site reaction	8.8	11.3	5.1	14.8	**16.7**	12.1
Dizziness	3.5	3.2	3.4	6.6	**9.1**	5.6
Nausea	1.8	4.8	**6.8**	**13.1**	**6.1**	7.7
Diarrhea	0	0	1.7	0	**3.0**	1.2
Myalgia	0	0	1.7	0	**3.0**	1.2
Insomnia	1.8	3.2	3.4	3.3	**4.5**	3.6
Rash erythematous	0	0	1.7	1.6	**3.0**	1.2
Eosinophilia	0	0	1.7	0	**3.0**	1.2

Specific TEAEs considered to be dose-related in each study phase were generally different with the exception that only 3 (application site reactions, nausea, insomnia) TEAEs were judged to be dose-related in both the maintenance and titration periods. The most frequent dose-related TEAEs that had their onset in the titration period and persisted ($\geq$ 7 days) into the maintenance period were application site reaction, fatigue, nausea, anorexia, somnolence, and insomnia.

The only dose-related TEAE prompting study discontinuation in the maintenance (P = 0 %, 4.5 mg = 1.6 %, 9 mg = 0 %, 13.5 mg = 1.6 %, 18 mg = 6.1 %) or whole study period (P = 0 %, 4.5 mg = 1.5 %, 9 mg = 0 %, 13.5 mg = 3.1 %, 18 mg = 5.7 %) was application site reaction. However, these results in the whole study period were driven by results in the maintenance period. No TEAEs causing study discontinuation in the titration period were considered dose-related.

Additional analyses were requested for assessing the frequency of TEAEs in the titration period because the simple analysis of comparing the incidence of TEAEs occurring in the 4 week titration period was confounded by different exposure times to various doses of rotigotine. One of theses additional analyses assessed the rates of TEAEs in the 4 week titration period. Another analysis considered to provide a useful perspective examined the treatment effect (rotigotine % - placebo %) for different timeframes in the titration period when the same duration of placebo treatment was used to adjust for the total time of exposure to rotigotine as titration to the randomized target dose occurred. The sponsor's original analyses of TEAEs in the titration period in the original NDA submission had utilized this approach but the sponsor had not presented the data in an easily digestible manner in which a dose-relationship might be readily assessed. Both of these different perspective analyses of the frequency of TEAEs in the titration period provided generally similar results (and suggested a similar profile of dose-related TEAEs) to the simple analysis of TEAEs occurring any time during the 4 week titration period according to randomized treatment assignment. For example all dose-related TEAEs in the rate analysis were also identified in the simple analysis of the titration period (Table 1). Approximately 80 % of the TEAEs considered dose-related in the simple analysis were also characterized as dose-related in the analysis of the treatment effect. These other analyses further supported the view that many TEAEs with onset during the titration

period are dose-related, and most typically the highest frequency of TEAEs occurs at the highest rotigotine dose (18 mg).

2. FDA Request for Study 506 Question No.2 :

Analyze and present laboratory data for ALL analytes according to each randomized treatment. Please try to show all results for each visit along with each randomized treatment on a singlpage and present results for all subsequent visits of each single analyte on consecutive pages. In this manner, the reader would see all results over time for one analyte (e.g. Hgb) on consecutive pages and the next section for a different analyte would show all results (according to each randomized treatment) over time for the next analyte (e.g. Hct) on consecutive pages.

• Present tables showing laboratory results for mean results and mean change from baseline for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum.

• Present shift tables (e.g. shift from low, normal or high at baseline to low, normal or high during treatment at a specific time/visit) showing laboratory results for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg).

• Present markedly abnormal laboratory result shift tables (e.g. tables showing shift from markedly low, markedly high, or not markedly low or high at baseline to markedly low, markedly high, or not markedly low or high at a specific posttreatment time/visit). Present markedly abnormal shift table results over time according to treatment (placebo or rotigotine dose at the time). Please apply the markedly abnormal criteria recommended by DNP and applied for the markedly abnormal analyses in the last Safety Update.

• Present analyses showing the incidence of low and high abnormalities for each analyte and the incidence of markedly low and markedly high abnormalities for each analyte according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg). Please try to show results for all 4 abnormal laboratory categories for each analyte for the whole 4 week titration period (week 2/visit 3 AND week 4/visit 4), for the whole 7 week maintenance period (week 7/visit 5 AND week 11/visit 6), for, and for the whole study treatment period (all 11 weeks) according to all randomized treatments on a single page.

Sponsor's Summary/Conclusions

The sponsor did not conclude that any safety concerns were identified with these analyses and did not specify that there were any dose-related effects of rotigotine.

Reviewer's Summary/Conclusions

My review did not suggest that any clinical laboratory abnormalities/changes appeared to be dose-related. These analyses were not evaluated to show whether specific analytes were altered by rotigotine treatment (the original Safety review focused on this) but to indicate whether there appeared to be any dose-related effect of rotigotine on any analyte.

3. FDA Request for study 506 question No.3 :

Analyze and present various orthostatic vital sign analyses according to each randomized treatment based upon the example tables shown in the appendix. Please complete the requested analyses in the tables provided so that results for each table (Tables 2 – 7) can be viewed on a single page with the exception of Table 1 that may need to show all results on 2 pages. Please also provide separate tabular analyses for orthostatic vital sign data collected at 1 minute after standing, at 3 minutes after standing, and after 1 and 3 minutes after standing for each of the tables requested. You had presented similar analyses of the pooled data for the 3 pivotal trials at 1, 3, and 1 and 3 minutes after standing. Data source tables that would be used to compile summary results for each of the appended tables should also be submitted.

Sponsor's Summary/Conclusions

The sponsor's analyses of data indicated that rotigotine treatment did not result in a consistent increase in any measure of othostatic hypotension across visits, nor was there any evidence of a dose-dependent effect of rotigotine on orthostatic hypotension. Likewise, rotigotine did not selectively change SBP, DBP, or pulse. In addition, the incidence of abnormal vital signs with rotigotine treatment was not affected by position (ie, supine, standing, or changing from supine to standing). No safety concerns with respect to vital signs were identified.

Reviewer's Summary/Conclusions

Although some analyses (Table 14) suggested that there is an increased risk for orthostatic hypotension with rotigotine treatment (vs placebo), these analyses did not always suggest that this effect was dose-related. There did appear to be dose-related increased frequency (Table 13) in the incidence of mild systolic orthostatic hypotension (decrease > 20 mm Hg but < 40 mm Hg) at treatment at 4 weeks (end of titration period) and at 7 weeks (middle of maintenance period). Other orthostatic outlier analyses (Table 15) of VS parameters for different severities and different timeframes suggested that that rotigotine exhibited dose-related increased risks for particular changes. Many of these dose-related effects appeared to result in increased risks for certain blood pressure increments (i.e. hypertensive effects).

4. FDA Request for study 506 question No.4 :

Provide analyses of TEAEs, TE-SAEs, and TE study discontinuations for AEs/SAEs that are suggestive of falls or orthostatic hypotension/postural dizziness. Please show these analyses according to ***randomized*** *treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and* ***any*** *rotigotine dose) and show results for all treatment (and any rotigotine dose if possible) on the same page.*

These analyses of special interest represent a conservative approach of assessing the possible frequency of particular events of interest that may not have been captured as a particular event because of AE coding vagaries. These analyses include :

• ***Events possibly suggestive of falls.*** *Search for a variety of AE terms that might be suggestive of a fall despite the fact that the AE had not been coded as a fall. AE terms (****e.g. some examples but not a complete list****) that might be included in this search are fall, abrasion, laceration, fracture, hematoma (any*

type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the vent was not a result of a fall. Present the incidence, total number of events, and total number of patients for events that may have been suggestive of a fall for TEAEs, TESAEs, and study discontinuations for a TEAE (further broken down as to whether the event was an SAE or non-serious AE).

• ***Events possibly suggestive of orthostatic hypotension / postural dizziness.*** *Search for a variety of AE terms that might be suggestive of orthostatic hypotension / postural dizziness despite the fact that the AE had not been coed as such. AE terms* ***(e.g. some examples but not a complete list)*** *that might be included in this search are hypotension, postural hypotension, decreased blood pressure, syncope, dizziness, vertigo, postural dizziness, light-headedness, postural light-headedness, impaired balance, and feeling drunk. Present analyses as described for events possibly suggestive of falls.*

Sponsor's Summary/Conclusions

The incidence of TEAEs or serious TEAEs suggestive of falls, as well as discontinuations because of TEAEs suggestive of falls, was uncommon and was not increased or decreased with randomization to rotigotine treatment. The incidence of TEAEs suggestive of orthostatic hypotension/postural dizziness was increased in subjects randomized to receive rotigotine. This increase was not dose-dependent. Most TEAEs were classified as dizziness, which is a common dopaminergic AE and is usually not related to orthostasis. Serious TEAEs and discontinuations because of TEAEs suggestive of orthostatic hypotension/postural dizziness were uncommon.

Reviewer's Summary/Conclusions

The incidence of TEAEs suggestive of falls did not suggest a dose-related effect of various doses of rotigotine nor of "any" dose of rotigotine vs placebo.

Although the incidence of TEAEs suggestive of orthostatic hypotension/postural dizziness did not suggest a dose-related effect of various doses of rotigotine, the incidence of orthostatic hypotension/postural dizziness associated with "any" dose of rotigotine did suggest a treatment effect of rotigotine (22 %) vs placebo (11 %) indicating a 2 fold increased risk. As described in my review of orthostatic VS analyses in question # 3 , other analyses suggested that some patients experience an increased risk for orthostatic hypotension and in some instances this risk appeared to be dose-related.

5. Reviewer Conclusions

- **Based upon my comments and conclusions outlined in other sections (especially relative to the highest dose, 18 mg), I conclude that there is an increased dose-related risk for rotigotine for many TEAEs (during the titration and maintenance periods and onset during the titration and persistence into the maintenance period) and many outlier "abnormalities" for decreased and increased blood pressure and increased heart rate.**

- [redacted] **should be included in the label.**
- [redacted]

6. Recommendation on Regulatory Action

- I concluded in my previous efficacy review that rotigotine is effective for treating early Parkinson's Disease.

- I have not conducted the safety of rotigotine and therefore cannot directly vouch for the safety of rotigotine for this indication. However, in the absence of information from another safety reviewer (from the review of the Sponsor's Response to the Approvable Letter) to argue against the safety of rotigotine for this indication, and considering my knowledge of the safety reviews from the original NDA submission, I believe that it is reasonable to conclude that rotigotine is safe and effective for this indication.

- I believe that the rotigotine is safe and effective to approve for treating early Parkinson's Disease using total content rotigotine doses of 9 mg (4 mg delivered) and 13.5 mg (6 mg delivered).

7. Recommendation on Postmarketing Actions

- I do not have any recommendations for post-marketing actions (e.g. risk management or phase 4 commitments).

2 INTRODUCTION AND BACKGROUND

The sponsor submitted (to the DNP) NDA 21829 for the indication of treatment of early Parkinson's Disease for a non-ergot, dopaminergic agonist patch, rotigotine on 1/19/05. On 2/28/06, an approvable letter was issued with requests for several additional analyses. One set of analyses focused on Study SP506, a randomized, double-blind, placebo-controlled study trial using several fixed doses of rotigotine. **The main purpose of requesting additional analyses of this study was to determine if there were dose-related/dose-dependent effects of rotigotine on treatment-emergent adverse events (TEAEs), clinical laboratory analytes, and orthostatic vital signs (VS).**

Study SP506 was a phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, **fixed dose (dose-finding)** study to compare the efficacy, safety, and tolerability of of 4 doses of rotigotine transdermal delivery system ("patch") versus placebo in early-stage Parkinson's disease patients during a period of up to about 12-weeks. Patients were randomized to receive 1 of 4 target doses of rotigotine (4.5mg/day, 9.0mg/day, 13.5mg/day, 18.0mg/day or placebo). A total of 329 patients were randomized to rotigotine (67 patients to 4.5mg, 63 patients to 9.0mg, 65 patients to 13.5mg, and 70 patients to 18.0mg) and placebo (64 patients).

The trial consisted of a 28-day (maximum) screening period that included a 4- to 7-day open-label, placebo-run-in period; a 28-day double-blind, dose-titration period (dose titration occurred on a weekly basis); a 49-day dose-maintenance period; and a 7-day dose de-escalation period. The study was conducted in 51 sites (36 sites in the US and Canada and 15 sites in Estonia, India, Latvia, Lithuania, Poland, South Africa, and Ukraine).

The patch was applied to the upper abdomen and the site of application was rotated on a daily basis. Patients underwent a weekly titration (increasing the number of patches consisting of 4.5 mg increments at weekly intervals) of placebo or rotigotine patches over 4 weeks such that the randomized, target dose treatment of rotigotine was initiated after 3 weeks and would be administered over the fourth week of the titration phase (Figure 1, Figure 2). Patients then continued on treatment for a 7 week maintenance phase followed by a down titration over the last week. Back/down titration by a single patch (i.e. 4.5 mg decrement of rotigotine or placebo) at a time was permitted for intolerable adverse events. Depending on randomized dose assignment, patients received rotigotine for a total of approximately 8-11 weeks prior to collection of primary efficacy data. There was a brief grace period associated with the planned visits.

Table 3 shows the time and schedule of events/data collection throughout the study.

Table 4 shows the effects of various rotigotine fixed doses (4.5, 9.0, 13.5, 18.0 mg) to which patients were randomized compared to placebo for the change of UPDRS parts II + III from baseline (the primary analysis of the primary efficacy endpoint) for the modified ITT population (randomized patients who had post-treatment efficacy data collected). Rotigotine produced a dose-dependent benefit in this primary efficacy endpoint. Although 4.5 mg rotigotine showed a numerical clinical benefit/improvement (reduction in UPDRS parts II + III from baseline), this effect was not statistically significant from placebo. All higher doses were statistiscally significant from placebo. There was progressively increasing numerical clinical benefit for the primary efficacy endpoint until a maximal therapeutic effects occurred at

13.5 mg, which was similar to the therapeutic effect produced by 18.0 mg. Figure 3 shows these same results depicted as a figure for the change from baseline for the primary efficacy endpoint. These data are represented according the average amount of rotigotine projected to be delivered with each patch (2 mg delivered = 4.5 mg total content; 4 mg delivered = 9.0 mg total content; 6 mg delivered = 13.5 mg total content; 8 mg delivered = 18.0 mg total content).

Figure 1 Proposed Patch Treatment Application Scheme : Study SP506

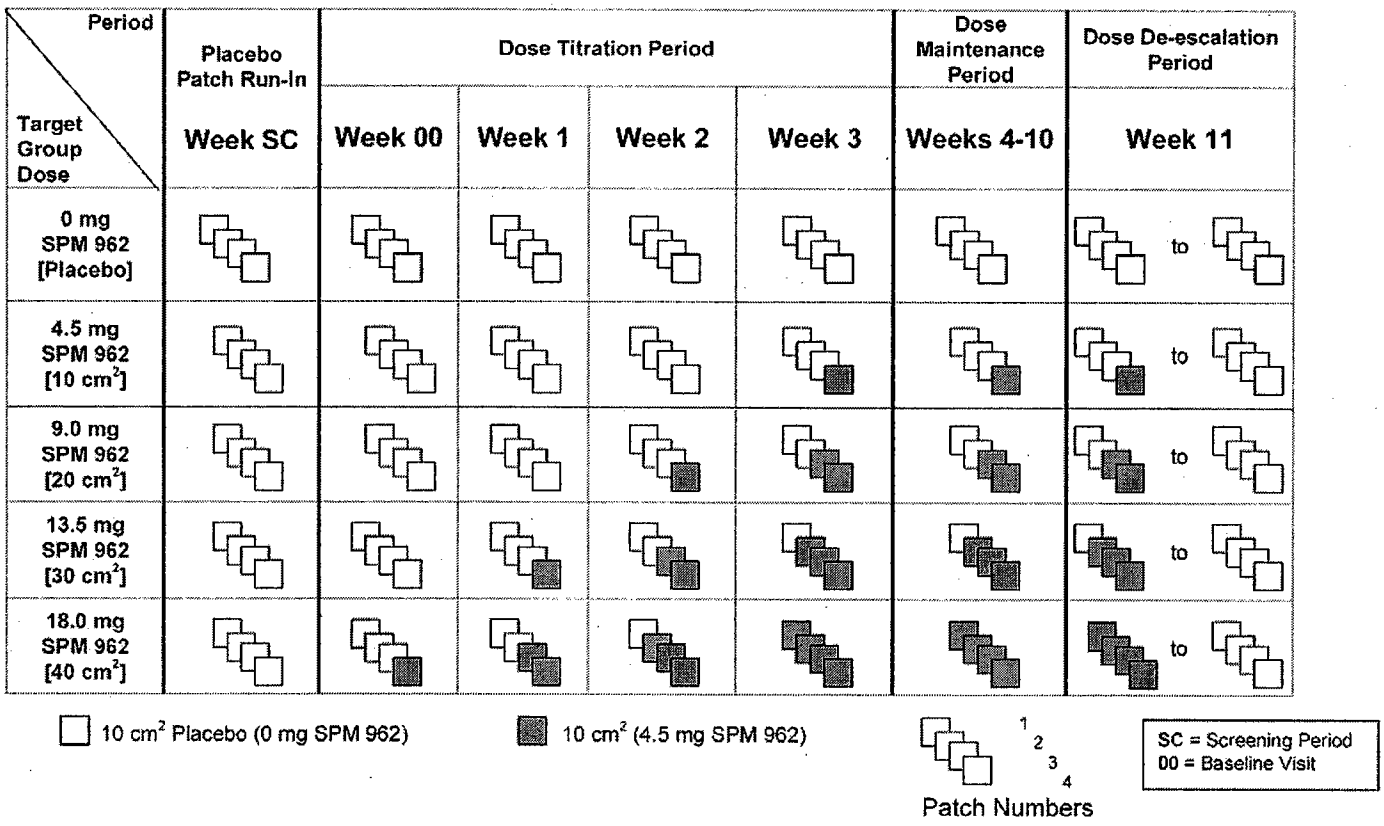


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Figure 2 **Schematic of SP506 Study Visits/Periods**

SCHEMATIC RESPRESENTATION OF STUDY VISITS/PERIODS
SP506

Visit 1	Visit 2	Telephone 1	Visit 3	Telephone 2	Visit 4	Visit 5	Visit 6	Telephone 3	Visit 7
Day 28 to -4	Day 0	Day 8 or 9	Day 14 +/- 3 days	Day 22 or 23	Day 28 +/- 3 days	Day 49 +/- 3 days	Day 77 +/- 3 days	Day 84-86	Day 98 +/- 5 days
Screening Visit	Baseline Visit		Titration Visit		Maintenance Visit I	Maintenance Visit II	De-escalation Visit		Safety Follow-up Evaluation Visit

Weeks SV	Week 00	Week 1	Week 2	Week 3	Weeks 4, 5 and 6	Weeks 7, 8, 9 and 10	Week 11	Weeks 12 and 13
Screening Period (Maximum 4 Weeks) Placebo Patch Run-in Period* (1 Week)	Dose Titration Period (4 Weeks)				Dose Maintenance Period (7 Weeks)		Dose De-escalation (1 Week)	Safety Follow-up Period (2 Weeks)

* The Placebo Patch Run-in Period is the final seven (7) days (maximum) of the Screening Period.
Weeks SV = Screening Period Weeks
Week 00 = Baseline Visit Week

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Table 3 Study SP506 Time and Schedule of Events

Assessment	Visit Name	Screening and Placebo Patch Run-In Period (Open-Label)	Dose Titration Period (Double-Blind)				Dose Maintenance Period (Double-Blind)		Dose De-escalation (Double-Blind)	Safety Follow-up Period		Premature Withdrawal Evaluation Visit	Optional Unscheduled Visit (Dose Titration Period Only)
			Baseline Visit										
	Week	SC	00	1	2	3	4	7	11	12	14		
	Visit	1	2		3		4	5	6		7		
	Day	-28 to -4	0	8 or 9	14	22 or 23	28	49	77	84-86	98		
					+/- 3d		+/- 3d	+/- 3d	+/- 3 d		+/- 3d		
Informed Consent		X											
Demographics		X											
Medical History		X											
Eligibility Criteria		X	X										
Risk Factor Assessment		X											
MMSE		X											
Neurological Exam		X							X			X	
Physical Examination		X							X		X	X	
Hoehn and Yahr		X	X				X		X			X	
UPDRS (Part I, II, and III)			X		X		X	X	X		X	X	X
Vital Signs[1]		X	X		X		X	X	X		X	X	X
Height		X											
Weight		X	X		X		X	X	X		X	X	X
Hematology, Blood Chem, Urinalysis		X	X		X		X	X	X		X[8]	X	
Pharmacokinetics		X[5]					X[6]	X[6]	X[6]			X	
Pregnancy Test (if applicable)		X									X	X	
12-Lead ECG		X[2]	X[3]		X[3]		X[2]	X[2]	X[2]		X[2]	X[2]	X[2]
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessment (Adverse Event(s))		X	X	X	X	X	X	X	X	X	X	X	X
Patch Practice Session		X											
Randomization			X										
Medication Dispensing		X	X				X	X	X				X
Medication Return and Compliance			X		X		X	X	X		X	X	X
Telephone Call		X[7]		X		X				X			

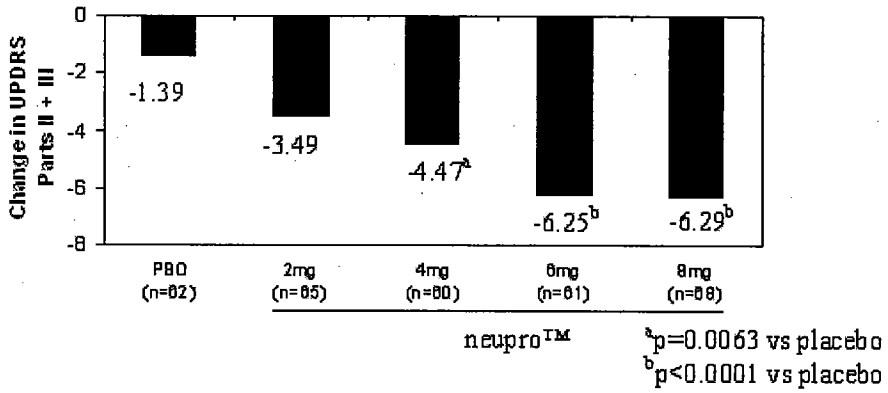
1 Including assessment of orthostatic hypotension
2 Three 12-lead ECGs (done serially, no longer than 15 minutes apart)
3 Four 12-lead ECGs (2 ECGs prior to patch removal and 2 ECGs post patch application) done serially, no longer than 15 minutes apart
4 Two 12-lead ECGs recorded prior to placebo patch removal and two 12-lead ECGs recorded post placebo patch removal
5 All subjects prior to patch application and removal practice session
6 All subjects immediately prior to patch removal
7 To remind subjects to apply their placebo run-in patches
8 Repeated only for lab values that are abnormal at Visit 6

Table 4 Change from Baseline to End of Maintenance Treatment (EOT) in UPDRS II + III Total Scores by Treatment Group- ITT Population

UPDRS II + III	Placebo (N=62)	Rotigotine 4.5mg (N=65)	Rotigotine 9.0mg (N=60)	Rotigotine 13.5mg (N=61)	Rotigotine 18.0mg (N=68)
Baseline (Visit 2) mean (SD)	28.02 (11.114)	28.48 (12.050)	28.52 (11.205)	27.57 (13.462)	27.13 (13.405)
EOT (Visit 6) mean (SD)	26.63 (13.491)	24.98 (11.789)	24.05 (11.528)	21.33 (13.328)	20.84 (11.511)
Mean change from baseline (SD)	-1.39 (7.904)	-3.49 (7.233)	-4.47 (6.808)	-6.25 (6.777)	-6.29 (7.825)
ANCOVA comparison I[a]					
Effect estimate		-2.148	-3.123	-4.909	-5.035
p-value		0.0393	0.0063	<0.0001	<0.0001
[95% CI]		[-4.544, 0.248]	[-5.571, -0.675]	[-7.341, -2.477]	[-7.406, -2.665]

a Model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate; a 1-sided p-value was obtained. Each significance test was performed at the 2.5% level.

Figure 3 **Study 506: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population**



Rotigotine dose shown as delivered dose (2 mg delivered = 4.5 mg total patch content)

3 SUBMISSION CONTAINING SPONSOR RESPONSES TO FDA REQUESTS

DOSE RESPONSE ANALYSIS OF ADVERSE EVENTS IN STUDY 506

The following requests pertain to analyses of adverse events, laboratory results, and vital sign results for Study 506.

3.1 FDA Request for Study 506, Question No.1 :

*Analyze and present the incidence of treatment-emergent (TE) AEs, SAEs, and study discontinuations according to **randomized** treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and **any** rotigotine dose). For each of the 3 types of analyses (i.e. TEAEs, TE-SAEs, TEAEs causing study discontinuation), please provide separate analyses based upon: 1) the development of an event during the **whole, 4 week titration period;** 2) the development of an event during the **whole, 7 week maintenance period;** 3) the development of an event in the 4 week titration period and persistence into the 7 week maintenance period. You will need to define this last category (e.g. when it is considered "persistent" such as if an event starting in the titration period persists > 7 days into the maintenance period). In these analyses, also show the total number of specific events and the total number of patients experiencing these events.*
Tabular analyses showing this information should be conducted without respect to severity or causality of TEAE and should show results for all 5 randomized treatments (and any rotigotine treatment if possible) on the same page. For example, the reader should be able to see the frequency of nausea for placebo and all 4 randomized rotigotine treatments (and any rotigotine treatment if possible) on the same page.

3.1.1 SPONSOR'S SUMMARY ANSWER :

Treatment-emergent adverse event (TEAE) data have been analyzed and summarized primarily by randomized treatment group (with a few analyses by actual treatment). Depending on the variable assessed, randomized treatment groups include placebo, rotigotine 4.5mg/day, 9.0mg/day, 13.5mg/day, 18.0mg/day, or any rotigotine dose. In addition, separate analyses were performed based on the development of events during the 4-week Titration Period and 7-week Maintenance Period as well as the persistence of events starting in the Titration Period into the Maintenance Period.

The overall incidence of TEAEs throughout the entire trial was comparable between subjects randomized to receive placebo and all rotigotine doses (placebo: 83%, rotigotine 4.5mg/day: 84%, rotigotine 9.0mg/day: 78%, rotigotine 13.5mg/day: 83%, rotigotine 18.0mg/day: 84%). Over all placebo-treated subjects and rotigotine-treated subjects, TEAEs occurred less frequently in the Maintenance Period than in the Titration Period. Subjects randomized to receive any dose of rotigotine were more likely than placebo subjects to experience a TEAE beginning during the Titration Period and persisting into the Maintenance Period. The most common persistent TEAEs were consistent with the overall most common AEs (ie, nausea, application site reaction, and somnolence).

For the complete presentation of adverse event data, please see Section 4.1, Treatment-emergent Adverse Events of the SP506 Revised Safety Section FDA Response.

In these various analyses, the sponsor noted that most TEAEs (including non-serious, serious, and TEAEs prompting study discontinuation) from various perspectives were not dose-related.

3.1.2 Reviewer Comments :

- The DNP had requested that the sponsor conduct several analyses of safety data (TEAEs, SAEs, non-serious TEAEs, TEAEs causing study discontinuation, clinical laboratory data, orthostatic vital signs-VS) primarily to assess whether rotigotine exhibited dose-dependent/dose-related effects in which higher doses produced more frequent and/or greater adverse changes or abnormalities in these safety parameters. The 506 study was a good one to investigate dose-related effects on safety parameters because this was the only study of a significant number of early Parkinson's Disease patients (N = 329) who were administered treatment for a significant duration (nearly 3 months). This study compared effects of one of 4 fixed doses of rotigotine (4.5 or 9.0 or 13.5 or 18.0 mg) with placebo . Evaluation of efficacy data from this study had shown a clear dose-response relationship. Although the lowest rotigotine daily dose (4.5 mg) showed a greater clinical benefit than that of placebo, this effect was not statistically significant. However, the next higher dose (9.0 mg) showed a greater clinical benefit than that of the 4 .5 mg dose group and this effect was statistically superior to placebo. The next higher dose (13.5 mg) also showed a greater clinical benefit than that of the immediately lower dose and this effect was statistically greater than placebo. Although the highest dose (18.0 mg) was statistically superior to placebo for clinical benefit for the primary efficacy endpoint, the numerical clinical benefit was similar to that of the 13.5 mg dose suggesting that 13.5 mg was the maximal therapeutic dose. Thus, the 506 was thought to be a good study to investigate dose-related effects of rotigotine on safety parameters to

help characterize the dose-response curve for safety/toxicity particularly with the dose-response for efficacy to asses the risk/clinical benefit ratio.

- **The sponsor did not specify how it assessed whether rotigotine resulted in dose-related effect on the various analyses of these safety parameters.** My impression is that the sponsor considered that a dose-related effect occurred **only** when there was as monotonic effect in which increasing doses progressively exerted increased severity of frequency of adverse effects on the safety parameters and the rotigotine effect was greater than that of placebo.

- I differ with the sponsor's approach for assessing a dose-related/dose-dependent effect because I think that expecting or requiring a "perfect" monotonic increment in the severity of frequency of adverse effects in which the frequency associated with each dose is progressively higher is overly simplistic. In envisioning how there could be a real dose-related effect, I do not think that it is realistic to expect a progressive monotonic increment at each higher dose particularly when one considers that these safety analyses were not powered for statistical significance and that the frequency of "adjacent" doses may be statistically indistinguishable and on the same part of the shape of the dose response curve .Furthermore, this study was not powered to show statistically significant effects for any dose with regard to safety parameters. It is conceivable that there could be different shape of the dose-response curve for different adverse reactions and that some events might increase only at the highest dose (18 mg) or at the highest doses (13.5 and 18 mg). Furthermore one could expect some normal variability in the frequency of events at different doses. Consequently, I believe that a more sensitive and more realistic approach would be to define a set of criteria that would suggest a possible dose-related effect and to assess these safety parameters with the consideration that the shape of the dose response curve could be different for different events. With this method of analysis, it is possible that a higher dose (e.g. 9.0 mg) could show a lower numerical incidence (e.g. 6 %) of a certain adverse event than the incidence (8.0 %) of the lower dose and perhaps even be numerically lower than the placebo (7.%). If the two highest doses (13.5 mg and 18.0 mg) showed higher incidences (e.g.12 % and 14 % respectively), I would conclude that there was a dose-related effect but that the effect did not start until 13.5 mg was administered and 18.0 mg may be even worse. However, even if the incidence (e.g. 10 or 11 % at the highest dose (18.0 mg) was lower than the incidence at 13.5 mg but higher than the incidence for placebo and all doses $\leq$ 9.0 mg, then I would conclude that there seemed to be a dose-related effect but that the effect was likely to be "statistically" similar to for the 13.5 and 18.0 mg dose groups. Correspondingly, the shape of the dose-response curve would be somewhat different based upon both of these examples. From another perspective, one could envision that a range of the doses studied exerted the same effect (or lack of effect on the shape of the dose-response curve).

  The following criteria are the ones that I applied to most of the sponsor's analyses in determining whether there was a suggestion of a dose-related effect on the various safety parameters. These criteria were generated and then applied to the various analyses. Various sets of criteria were not generated and tested to indicate a set of criteria that most frequently identified TEAEs as being considered to be dose-related.

A dose-related effect of rotigotine is considered to be suggested when the following criteria are satisfied :

- 18 mg dose group consists of ≥ 2 patients with the event or ≥ 2 events (for TEAE rate analyses)
  AND
- 18 mg dose group more frequent than 4.5 mg dose group
  AND
- If 18 mg dose group (%) is highest and > placebo **and** 4.5 mg **and** 9.0 mg **and** 13.5 mg dose groups, the difference must be ≥ 1.0 % above 4.5 mg **and** placebo groups
  OR
- If 18 mg dose group (%) is not highest as per above criterion, then 9.0 mg, **and** 13 5 mg, **and** 18.0 mg dose groups must be > 4.5 mg **and** placebo groups
  OR
- If 18 mg dose group (%) is not highest as per above criterion, then 13 5 mg **and** 18.0 mg dose groups must be > 4.5 mg **and** 9.0 mg **and** placebo groups

Table 5 Incidence (%) of Dose-Related TEAEs During the Whole Study Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

Preferred Term Adverse Event		Daily Rotigotine Dose (patch content)				
	Placebo N = 64	4.5 mg N = 67	9.0 mg N = 63	13.5 mg N = 65	18.0 mg N = 70	"Any" N = 265
Application site reaction	18.9	23.9 %	20.6	33.8	**45.7**	31.1
Mouth dry	1.6	3.0	3.2	0	**4.3**	2.6
Hyperkinesia	0	0	0	0	**2.9**	0.8
Nausea	10.9	34.3	38.1	**47.7**	**41.4**	40.4
Vomiting	3.1	10.4	**15.9**	**20.0**	**11.4**	14.3
Hiccup	0	1.5	1.6	1.5	**2.9**	1.9
Bundle branch block	1.6	1.5	1.6	1.6	**2.9**	1.9
QT increased	0	1.5	0	0	**4.3**	1.5
Weight decrease	0	0	0	1.5	**2.9**	1.1
Myalgia	0	0	1.6	1.5	**2.9**	1.5
Somnolence	3.1	13.4	15.9	18.5	**21.4**	17.4
Insomnia	7.8	6.0	12.7	13.8	**14.3**	11.7
Dreaming abnormal	0	1.5	4.8	3.1	**7.1**	4.2
Hallucination	1.6	0	1.6	**3.1**	**2.9**	1.9
Rhinitis	1.6	1.5	0	0	**4.3**	1.5
Respiratory disorder	0	0	0	0	**2.9**	0.8
Rash erythematous	1.6	1.5	**6.3**	**3.1**	**2.9**	3.4
Eosinophilia	0	1.5	1.6	0	**4.3**	1.9

- When my criteria for determining a dose-relationship were applied, many TEAEs were considered dose-related in the whole study (Table 5). Whereas some TEAEs appeared to suggest that the maximal dose-related effect occurred at a range of doses (either 13.5-18 mg or 9-18 mg), most TEAEs showed the maximal effect at the highest randomized dose (18.0 mg).

Table 6 Incidence (%) of Dose-Related TEAEs During the Titration Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

Preferred Term Adverse Event	Placebo N = 64	Daily Rotigotine Dose (patch content)				
		4.5 mg N = 67	9.0 mg N = 63	13.5 mg N = 65	18.0 mg N = 70	"Any" N = 265
Application site reaction	10.9	14.9	15.9	24.6	**35.7**	23.0
Mouth dry	1.6	1.5	1.6	0	**2.9**	1.5
Fatigue	1.6	7.5	9.5	4.6	**10.0**	7.9
Nausea	9.4	32.8	31.7	**43.1**	**40.0**	37.0
Anorexia	0	0	1.6	7.7	**4.3**	3.4
Constipation	1.6	0	**3.2**	**4.6**	**2.9**	2.6
Hiccup	0	1.5	0	1.5	**2.9**	1.5
SGPT increased	0	1.5	0	0	**2.9**	1.1
Weight decrease	0	0	0	0	**2.9**	0.8
Somnolence	1.6	11.9	11.1	16.9	**18.6**	14.7
Insomnia	4.7	4.5	**7.9**	**6.2**	**7.1**	6.4
Dreaming abnormal	0	0	3.2	1.5	**4.3**	2.3
Hallucination	0	0	1.6	1.5	**2.9**	1.5
Rhinitis	0	1.5	0	0	**2.9**	1.1
Upper respiratory tract infection	0	0	1.6	0	**2.9**	1.1
Vision abnormal	0	1.5	0	**7.7**	**2.9**	3.0

- When my criteria for determining a dose-relationship were applied to the titration period, many TEAEs appeared to be dose-related (Table 6). The maximal dose-related effect occurred at a range of doses (either 13.5 - 18 mg or 9-18 mg) for a few TEAEs (as in the analysis of the whole study). The majority of these TEAEs (~ 60 %) showe that the maximal effect occurred at the highest randomized dose (18.0 mg). Results from this analysis in the titration period showed overlap of several TEAEs in both analyses but there were also differences in which TEAEs appearing dose-related in one period did not appear so in the other period (and vice-versa).

- When my criteria for determining a dose-relationship were applied to the maintenance period, several TEAEs also appeared to be dose-related (Table 7). With the exception of nausea (in which the maximal dose-related effect occurred at a range of doses between 9-18 mg), most of these TEAEs showed that the maximal effect occurred at the highest randomized dose (18.0 mg). Many

(6/8 = 75 %) of these TEAEs also occurred in the analysis of the whole study period. However, only 3 (application site reactions, nausea, insomnia) judged to be dose-related in the maintenance period were also considered dose-related in the titration period.

Table 7 Incidence (%) of Dose-Related TEAEs During the Maintenance Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

Preferred Term Adverse Event	Placebo N = 57	Daily Rotigotine Dose (patch content) 4.5 mg N = 62	9.0 mg N = 59	13.5 mg N = 61	18.0 mg N = 66	"Any" N = 248
Application site reaction	8.8	11.3	5.1	14.8	**16.7**	12.1
Dizziness	3.5	3.2	3.4	6.6	**9.1**	5.6
Nausea	1.8	4.8	**6.8**	**13.1**	**6.1**	7.7
Diarrhea	0	0	1.7	0	**3.0**	1.2
Myalgia	0	0	1.7	0	**3.0**	1.2
Insomnia	1.8	3.2	3.4	3.3	**4.5**	3.6
Rash erythematous	0	0	1.7	1.6	**3.0**	1.2
Eosinophilia	0	0	1.7	0	**3.0**	1.2

- When my criteria for determining a dose-relationship were applied to the maintenance period, several TEAEs also appeared to be dose-related (Table 7). The maximal dose-related effect occurred at a range of doses (either 13.5 and 18 mg or 9-18 mg) for a few TEAEs (as in the analysis of the whole study). The majority of these TEAEs (~ 60 %) showed the maximal effect occurred at the highest randomized dose (18.0 mg).

Table 8 Incidence (%) of Dose-Related TEAEs With Onset in Titration Period and Persistence into Maintenance Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses

Preferred Term Adverse Event	Placebo N =	Daily Rotigotine Dose (patch content) 4.5 mg N =	9.0 mg N =	13.5 mg N =	18.0 mg N =	"Any" N =
Application site reaction	7.8	9.0	12.7	16.9	**25.7**	16.2
Fatigue	0	1.5	**4.8**	**3.1**	**4.3**	3.8
Nausea	1.6	3.0	3.2	7.7	**11.4**	6.4
Anorexia	0	0	1.6	**7.7**	**4.3**	3.4
SGPT	0	1.5	0	0	**2.9**	1.1
Weight decrease	0	0	0	0	**2.9**	0.8
Somnolence	1.8	0	4.8	**9.2**	**5.7**	4.9
Insomnia	3.1	3.0	4.8	3.1	**5.7**	4.2
Dreaming abnormal	0	0	1.6	0	**2.9**	1.1

- There were also several TEAEs which had their onset in the titration period and which persisted (≥ 7 days) into the maintenance period that were dose-related by applying my criteria (Table 8). All of these TEAEs were also dose-related when they had their onset in the titration period.(Table 6).

- I did not find that there were any SAEs with their onset in the titration or maintenance periods or during the whole study that were dose-related. There were no dose-related TEAEs prompting study discontinuation in the titration period. The only dose-related TEAE prompting study discontinuation in the maintenance (P = 0 %, 4.5 mg = 1.6 %, 9 mg = 0 %, 13.5 mg = 1.6 %, 18 mg = 6.1 %) or whole study period (P = 0 %, 4.5 mg = 1.5 %, 9 mg = 0 %, 13.5 mg = 3.1 %, 18 mg = 5.7 %) was application site reaction. However, these results in the whole study period were driven by results in the maintenance period. There were no dose-related SAEs that were "persistent" (onset in titration and persistence into maintenance period) SAEs in the whole study nor were there any dose-related TEAEs prompting study discontinuation that were "persistent."

- I wanted to explore how the sponsor's new analyses of the whole study period, and the titration and maintenance periods separately for Study SP506 compared to results of the pooled analyses of the 3 pivotal studies (study 506, and flexible dose studies 512 and 513 in including doses up to 13.5 and 18.0 mg respectively) for the whole study period [redacted] Table 9 shows the incidence of TEAEs for any rotigotine dose (4. 5, 9.0, 13.5, or 18.0 mg) vs placebo in the pooled analyses of the 3 pivotal studies [redacted] For comparison, Table 10 shows the incidence of TEAEs (according to the same criteria) not only for the whole study period of study 506, but also separately for the titration period, for the maintenance period, and for TEAEs with onset in the titration period and persistence into the maintenance period. The analyses of "any" dose in the whole study period showed that results were generally similar for the pooled analyses (of 3 pivotal studies including study 506) vs results in study 506 alone. The magnitude of the treatment effect (Rotigotine % - Placebo %) was also generally similar in both sets of analyses. A few TEAEs (i.e. depression, upper respiratory tract infection, purpura) that did not appear in the TEAE analysis [redacted] were recognized in the analysis of study 506 alone as rotigotine related but none of these appeared to be dose-related during the whole study period. The only TEAE (of these 3) that appeared to dose-related was upper respiratory tract infection, which was dose-related in the titration phase analysis of study 506. Considering that the frequency is relatively low for each of these TEAEs, I am not necessarily convinced that this finding is real [redacted] I think that this exploratory analysis helps confirm the perspective that the TEAEs described in the table [redacted] are really related to rotigotine treatment.

Table 9 Treatment-Emergent Adverse Event (Regardless of Causal Relationship) Incidence in Double-Blind, Placebo-Controlled Early-Stage Parkinson's Disease Trials (
(Events ≥ 2% of Subjects Treated with Rotigotine and Numerically More Frequent Than in the Placebo Group)

Body system/preferred term	Placebo N=289 (%)	Rotigotine N=649 (%)
Application site disorders		
Application site reactions	14	37
Autonomic nervous system disorders		
Sweating increased	2	4
Mouth dry	1	3
Body as a Whole – general disorders		
Fatigue	7	8
Accident NOS	4	5
Cardiovascular disorders general		
Extremity edema[a]	6	7
Hypertension	2	3
Central and peripheral nervous system disorder		
Dizziness	11	18
Headache	10	14
Vertigo	2	3
Gastrointestinal system disorders		
Nausea	15	38
Vomiting	2	13
Constipation	4	5
Dyspepsia	1	4
Anorexia	1	3
Musculoskeletal system disorders		
Back pain	5	6
Arthralgia	3	4
Psychiatric disorders		
Somnolence	16	25
Insomnia	5	10
Dreaming abnormal	<1	3
Hallucination	1	2
Respiratory system disorders		
Sinusitis	2	3
Skin and appendage disorders		
Rash erythematous	1	2
Urinary system disorders		
Urinary tract infection	1	3
Vision disorders		
Vision abnormal	1	3

Table 10 Incidence (%) of TEAEs at Different Time Periods (Whole Study, Titration Phase, Maintenance Phase, Onset in Titration Period and Persistence into Maintenance Period) of Any Rotigotine Dose in 506 Fixed Dose Study (REVIEWER ANALYSES)

Preferred Term Adverse Event	**Placebo**	**Rotigotine - Any Dose (4.5. 9.0, 13.5, or 18.0 mg)**
Whole Study Period	**N = 64**	**N = 265**
Application site reaction	18.8	31.3
Sweating increased	3.1	4.9
Mouth dry	1.6	2.6
Fatigue	3.1	10.9
Dizziness	10.9	20.4
Nausea	10.9	40.4
Vomiting	3.1	14.3
Constipation	3.1	3.8
Anorexia	0	4.2
Back pain	3.1	4.2
Somnolence	3.1	17.4
Insomnia	7.8	11.7
Anxiety	3.1	3.8
Dreaming abnormal	0	4.2
Depression	0	**2.3**
Upper respiratory tract infection	1.6	**3.8**
Sinusitis	1.6	2.6
Erythematous rash	1.6	3.4
Urinary tract infection	1.6	2.6
Purpura	0	**2.3**
Titration Period	**N = 64**	**N = 265**
Application site reaction	10.9	23.0
Sweating increased	1.6	4.2
Fatigue	1.6	7.9
Dizziness	7.8	16.2
Nausea	9.4	37.0
Vomiting	1.6	2.8
Constipation	1.6	2.6
Anorexia	0	3.4
Somnolence	1.6	14.7
Insomnia	4.7	6.4
Dreaming abnormal	0	2.3
Erythematous rash	1.6	2.6
Vision abnormal	0	3.0
Maintenance Period	**N = 57**	**N = 248**
Application site reaction	8.8	12.1
Dizziness	3.5	5.6
Nausea	1.8	7.7
Insomnia	1.8	3.6
Somnolence	1.8	3.2
Upper respiratory tract infection	0	**2.4**
Onset in Titration and Persists into Maintenance	**N = 64**	**N = 265**
Application site reaction	7.8	16.2
Fatigue	0	3.8
Nausea	1.6	6.4
Anorexia	0	3.4
Somnolence	1.6	4.9
Insomnia	3.1	4.2

Bolded and underlined TEAE and bolded incidence for rotigotine indicates that this TEAE was not included in — table showing TEAEs with an incidence of ≥ 2.0 and numerically greater than Placebo

3.1.3 Additional Analyses of TEAEs With Onset During the Titration Period

This reviewer also requested that the sponsor conduct and submit the following additional analyses (shown below in italics) of TEAEs occurring in the titration period.

1. Conduct additional separate analyses for study 506 of `TEAE onset in the titration period according to different perspectives of study treatment (placebo or rotigotine dose) during titration period including : 1) TEAE onset within 7 days for each actual rotigotine dose used during titration and within 7 days of initiation of placebo treatment; and 2) TEAE onset within 7 days of achievement/treatment with the randomized, targeted rotigotine dose (i.e. the 4th week of treatment during the titration phase) vs TEAE onset during the 4 th week of treatment in the titration phase for the placebo patients. In the first analysis, there would be a larger number of patients exposed to lower rotigotine doses during titration to higher doses and progressively lower number of patients receiving higher doses. In the second analysis, the incidence of TEAEs would be assessed only within 7 days of achievement of the targeted, assigned rotigotine dose after randomization.

2. Conduct a separate analysis for study 506 of TEAE onset in the titration period according to different perspectives of study treatment (placebo or rotigotine dose) during titration period to show : 1) the rate (# specific TEAEs/4 week treatment) of specific TEAEs according to preferred terms and according to the actual dose at which the TEAE occurred; and 2) the rate (# specific TEAEs/4 week treatment) of specific TEAEs according to preferred terms and the randomized treatment assignment.

3. Conduct a separate analysis of the data already analyzed for the incidence of TEAEs with onset in the titration phase in the original analysis for study 506 report in the original NDA submission. Calculate the incidence of the treatment effect (rotigotine incidence - placebo incidence) of TEAEs for each randomized rotigotine dose according to the preferred term for a TEAE of any severity. Present this treatment effect incidence in a table such that the results for each of the 4 randomized rotigotine doses are shown for each preferred term TEAE of any severity on the same page (the complete analysis would likely be spread over several pages). Thus, the treatment effect incidence of each randomized rotigotine dose for each preferred term TEAE of any severity can be compared across all 4 rotigotine treatment doses because these results are presented on the same page.

3.1.4 Reviewer Comments :

- The analyses as conducted during the titration period (in which all TEAEs occurring during the 4 week titration period were considered) were confounded by rotigotine dose and time because patients were exposed to the target dose for different durations in the titration phase. Thus, the main goal of my requests for additional analyses was to assess how some different analytical perspectives might influence results and the suggestion of whether there was or was not dose-related effects. It should be noted by assessing results (requests 1.1 and 2.1) according to actual dose received during the titration period and during which each patient receiving different doses during up-titration each patient could provide TEAE results in different dose-groups despite possibly having demonstrated a TEAE at a lower dose.

- The sponsor submitted analyses in response to my request to assess the frequency of TEAEs in the titration period considering some different analytical perspectives, especially when the frequency

can potentially be confounded by exposure time to different treatments/doses. For requests 1.1) and 2.1) there were no TEAEs that were dose-related by the previously outlined criteria. For request 1.2), the only dose-related TEAE was application site reactions. For request, 2.2), there were many TEAEs that were dose-related (Table 11). This host of dose-related TEAEs (N=15) identified by an analyses of rates was almost identical (with the exception of hiccups) to the set (N=16) of dose-related TEAEs identified by an incidence analysis (Table 6). This observation not only further supports the clear dose-relationship of these events but also suggests that these specific events develop in different individual patients rather recur in one or a few individuals.

Table 11 Frequency (Rate = # TEAEs/4 weeks) of Dose-Related TEAEs in the Titration Period
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

Preferred Term Adverse Event	Placebo N =	Daily Rotigotine Dose (patch content) 4.5 mg N =	9.0 mg N =	13.5 mg N =	18.0 mg N =
Application site reaction	0.160	0.172	0.211	0.285	**0.482**
Mouth dry	0.016	0.016	0.018	0	**0.031**
Fatigue	0.016	0.125	0.123	0.134	**0.140**
Nausea	0.096	0.484	0.492	0.636	**0.637**
Anorexia	0	0	0.018	**0.084**	**0.047**
Constipation	0.016	0	**0.035**	**0.050**	**0.031**
SGPT increased	0	0.016	0	0	**0.031**
Weight decrease	0	0	0	0	**0.031**
Somnolence	0.016	0.141	0.176	0.218	**0.280**
Insomnia	0.048	0.062	**0.088**	**0.067**	**0.078**
Dreaming abnormal	0	0	0.035	0.017	**0.047**
Hallucination	0	0	0.018	0.017	**0.031**
Rhinitis	0	0.016	0	0	**0.031**
Upper respiratory tract infection	0	0	0.018	0	**0.031**
Vision abnormal	0	0.016	0	**0.117**	**0.062**

- Results from analyzing request # 3 were quite interesting when a different (1, 2, 3, or 4 weeks) placebo duration (in the titration period) was considered and applied/matched for the same duration as that during which rotigotine was administered while titrating up to each randomized, targeted dose. This analysis was essentially the analysis conducted by the sponsor in the original NDA submission. However, the sponsor had presented these results for each dose with the respective placebo data along with the targeted rotigotine dose on different pages and did not calculate a treatment effect by subtracting the placebo incidence from that of the incidence for each dose. This analytical presentation did not facilitate digesting the results for assessing possible dose-related effects as did the requested analysis submitted now. Of significant interest, results from this analysis suggested a very similar impression of what TEAEs were dose-related/dose-dependent as had the main titration analysis (Table 6) in which the incidence of TEAEs occurring

during the 4 week titration period for each treatment was assessed according to randomized treatment assignment. Almost all (~ 90 %) TEAEs considered dose-related in Table 6 were also considered dose-related (applying similar criteria) in this analysis (Table 12) and the "shape" (e.g. reflected by bolded numbers in each table) of the dose-response curve also appeared to be identical in both sets of analyses. The only dose-related TEAEs suggested in Table 6 that did not appear as dose-related Table 12 were constipation and rhinitis, TEAEs occurring at a relatively low frequency. When on considers the several "dose-related" TEAEs occurring in this additional analysis reflected in Table 12 that were not included in Table 6, all reflected a very low treatment effect (1.4 %) in the highest dose group (18.0 mg) and presumably were related to results of a single patient. This observation suggests that the difference was not likely to be real but rather was more likely related to background "noise."

I thought that the results of this analysis (request # 3) were very important in helping validate the suggestion of TEAEs that are dose-related and that were reflected in the analysis shown in Table 6.

Table 12 Treatment Effect (Rotigotine % - Placebo %) for Incidence of TEAEs in Titration Period
(Placebo Experience Adjustment Matched to # of Weeks on Any Rotigotine Dose for Each Targeted Rotigotine Dose)

TEAE	Rotigotine (mg)			
	4.5	9.0	13.5	18.0
Application site reaction	4.0	4.9	13.7	**24.8**
Mouth dry	-0.1	0	**1.5**	**1.4**
Impotence	0	0	**1.5**	**1.4**
Fatigue	5.9	8.0	3.1	**8.4**
Edema Peripheral	0	0	0	**1.4**
Dysphonia	0	0	0	**1.4**
Neuralgia	0	0	0	**1.4**
Nausea	23.5	22.4	**33.7**	**30.6**
Anorexia	0	1.6	**7.7**	**4.3**
Hiccup	1.5	0	1.5	**2.9**
SGPT increased	1.5	0	0	**2.9**
GGT increased	0	0	0	**1.4**
Dehydration	0	0	**1.5**	**1.4**
Weight decrease	0	0	0	**2.9**
Glycosuria	0	0	0	**1.4**
Myalgia	0	0	**1.5**	**1.4**
Myocardial ischemia	0	0	0	**1.4**
Somnolence	10.0	9.5	15.4	**17.0**
Insomnia	-0.2	**3.2**	**1.5**	**2.5**
Dreaming abnormal	0	3.2	1.5	**4.3**
Hallucination	0	1.6	1.5	**4.3**
Sleep disorder	0	0	0	**1.4**
Somnambulism	0	0	0	**1.4**
Erythrocytes abnormal	0	0	**1.5**	**1.4**
Penis disorder	0	0	0	**1.4**
Upper respiratory tract infection	0	1.6	0	**2.9**
Hyperkeratosis	0	0	0	**1.4**
Seborrhea	0	0	0	**1.4**
Purpura	0	0	0	**1.4**
Vision abnormal	1.5	0	**7.7**	**2.9**

3.1.5 Reviewer Conclusions :

- [redacted] **should be included in the label.**
- [redacted]

3.2 FDA Request for Study 506 Question No.2 :

Analyze and present laboratory data for ALL analytes according to each randomized treatment. Please try to show all results for each visit along with each randomized treatment on a single page and present results for all subsequent visits of each single analyte on consecutive pages. In this manner, the reader would see all results over time for one analyte (e.g. Hgb) on consecutive pages and the next section for a different analyte would show all results (according to each randomized treatment) over time for the next analyte (e.g. Hct) on consecutive pages.

• Present tables showing laboratory results for mean results and mean change from baseline for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg). Tables should show multiple parameters including N, mean, SD, minimum, median, and maximum.
• Present shift tables (e.g. shift from low, normal or high at baseline to low, normal or high during treatment at a specific time/visit) showing laboratory results for each laboratory analyte over time according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg).
• Present markedly abnormal laboratory result shift tables (e.g. tables showing shift from markedly low, markedly high, or not markedly low or high at baseline to markedly low, markedly high, or not markedly low or high at a specific posttreatment time/visit). Present markedly abnormal shift table results over time according to treatment (placebo or rotigotine dose at the time). Please apply the markedly abnormal criteria recommended by DNP and applied for the markedly abnormal analyses in the last Safety Update.

• Present analyses showing the incidence of low and high abnormalities for each analyte and the incidence of markedly low and markedly high abnormalities for each analyte according to randomized, treatment (placebo, 4.5, 9, 13.5, 18 mg). Please try to show results for all 4 abnormal laboratory categories for each analyte for the whole 4 week titration period (week 2/visit 3 AND week 4/visit 4), for the whole 7 week maintenance period (week 7/visit 5 AND week 11/visit 6), for, and for the whole study treatment period (all 11 weeks) according to all randomized treatments on a single page.

3.2.1 SPONSOR'S SUMMARY ANSWER :

Summaries of hematology and chemistry laboratory parameters over time were evaluated by visit and randomized treatment group and include changes from Baseline. In addition, shift tables comparing Baseline values with values at each visit (by dose) were produced for hematology and blood chemistry laboratory results using normal ranges as well as using ranges to classify results as markedly low, markedly high, or not markedly low or high. These analyses were completed for values at each visit according to randomized treatment group. The incidences of abnormal and markedly abnormal laboratory values were also analyzed by parameter according to randomized treatment during the Titration Period, Maintenance Period, and Entire Treatment Period (inclusive of the Titration Period, Maintenance Period).

No safety concerns with respect to laboratory findings were identified. For the complete presentation on laboratory data, please see Section 4.2, Clinical Laboratory Evaluation of the SP506 Revised Safety Section FDA Response.

3.2.2 Reviewer Comments :

- There were no noteworthy dose-related clinical laboratory changes/abnormalities for the various, requested clinical laboratory analyses based upon my criteria for dose-related event and clinical judgement of the overall significance of the magnitude and/or type of event.

3.2.3 Reviewer Conclusion :

- I am unable to conclude that there were any clinical laboratory abnormalities that appeared to be dose-related.

3.3 FDA Request for study 506 question No.3 :

Analyze and present various orthostatic vital sign analyses according to each randomized treatment based upon the example tables shown in the appendix. Please complete the requested analyses in the tables provided so that results for each table (Tables 2 – 7) can be viewed on a single page with the exception of Table 1 that may need to show all results on 2 pages. Please also provide separate tabular analyses for orthostatic vital sign data collected at 1 minute after standing, at 3 minutes after standing, and after 1 and 3 minutes after standing for each of the tables requested. You had presented similar analyses of the pooled data for the 3 pivotal trials at 1, 3, and 1 and 3 minutes after standing. Data source tables that would be used to compile summary results for each of the appended tables should also be submitted.

3.3.1 SPONSOR'S SUMMARY ANSWER :

Per the Division's request, various orthostatic hypotension and vital signs data (ie, systolic blood pressure [SBP], diastolic blood pressure [DBP], or pulse rate) over time were summarized by visit according to randomized treatment group. SCHWARZ BIOSCIENCES analysis of these data indicates that rotigotine treatment did not result in a consistent increase in any measure of orthostatic hypotension across visits, nor was there any evidence of a dose-dependent effect of

rotigotine on orthostatic hypotension. Likewise, rotigotine did not selectively change SBP, DBP, or pulse. In addition, the incidence of abnormal vital signs with rotigotine treatment was not affected by position (ie, supine, standing, or changing from supine to standing). No safety concerns with respect to vital signs were identified.

For the complete presentation on orthostatic hypotension and vital signs data, please see Section 4.3, Vital Signs of the SP506 Revised Safety Section FDA Response.

3.3.2 Reviewer Comments :

- The sponsor applied VS outlier criteria for changes (SBP increase of decrease $\geq$ 20 or $\geq$ 40 mm Hg; DBP increase or decrease $\geq$ 10 or $\geq$ 20 mm Hg; pulse increase or decrease $\geq$ 15 or $\geq$ 30) as per DNP recommendations.

- The sponsor analyzed and presented the frequency of orthostatic orthostatic hypotension at different times throughout the study. Table 13 shows the incidence of dose-related events over time, The only events that met the dose-related criteria were mild-moderate systolic decrements and these effects occurred at the end of the titration period (at 13.5 and 18 mg) and midway through the maintenance period (at 9, 13.5, and 18 mg).

Table 13 Dose-Related Incidence (%) of VS Outlier Criteria for Orthostatic Hypotension (OH) at Various Times Throughout the Study
(Bolded Incidence Numbers Indicates Apparent Highest Dose Effect or Maximal, Plateau Dose Effect in Range of Doses)

VS Outlier Criterion		Daily Rotigotine Dose (patch content)			
	Placebo N = 64	4.5 mg N = 67	9.0 mg N = 63	13.5 mg N = 65	18.0 mg N = 70
SBP OH $\geq$ 20 mm Hg (at start of wk 4, end of titration)	3.1	0	0	**6.2**	**4.3**
SBP OH $\geq$ 20 mm Hg (at start of wk 7)	1.6	1.5	**3.2**	**3.1**	**2.9**

- These analyses over time also assessed whether rotigotine increased the frequency of orthostatic hypotension in patients who did not exhibit orthostatic hypotension at baseline by determining the frequency of all patients this event relative to the frequency with this event at baseline. Although these analyses did not show any dose-related effect, there were several instances in which there was a noteworthy increase in the percentage of patients with orthostatic hypotension (relative the baseline frequency of 100 %) for each treatment. Table 14 shows the incidence of orthostatic hypotension over time for % of patients with specific outlier criterion at a specific visit compared to the % (100 %) with orthostatic hypotension as baseline/prior to treatment. There were several instances in different rotigotine treatment groups in which there was an increase in the number/percentage of patients with "new onset" of orthostatic hypotension.

Table 14 Incidence of Orthostatic Hypotension (OH) Over Time for Percentage of Patients with Specific Outlier Criterion at a Specific Visit Compared to the Percentage (100 %) with Orthostatic Hypotension as Baseline

VS Outlier Criterion and Study Time of Event	Placebo N = 64	Daily Rotigotine Dose (patch content) 4.5 mg N = 67	9.0 mg N = 63	13.5 mg N = 65	18.0 mg N = 70
SBP OH ≥ 20 mm Hg (at start of wk 2, middle of titration)	100 %	0 %	**300 %**	0 %	100 %
DBP OH ≥ 10 mm Hg (at start of wk 2, middle of titration)	0 %	66.7%	**300 %**	50 %	0 %
SBP OH ≥ 20 mm Hg (at start of wk 4, end of titration)	66.7 %	0 %	0 %	**400 %**	**150 %**
DBP OH ≥ 10 mm Hg (at start of wk 4, end of titration)	0 %	0 %	**300 %**	50 %	0 %
SBP OH ≥ 20 mm Hg (at start of wk 7, middle of maintenance)	33.3 %	100 %	**200 %**	**200 %**	100 %
DBP OH ≥ 10 mm Hg (at start of wk 7, middle of maintenance)	0 %	100 %	**300 %**	16.7 %	0 %
SBP OH ≥ 20 mm Hg (at start of wk 11, end of maintenance)	66.7 %	0 %	**200 %**	100 %	100 %
DBP OH ≥ 10 mm Hg (at start of wk 11, end of maintenance)	0 %	66.7 %	**600 %**	50 %	0

Bolded percentage above 100 % (baseline %) indicates increase in frequency of new patients with orthostatic hypotension.
0 % means that none of patients experiencing orthostatic hypotension at this specific time had experienced orthostatic hypotension at baseline prior to treatment.

- The sponsor also analyzed the data to indicate the incidence of the "new onset" (not present at baseline but occurring during treatment in the study) orthostatic hypotension (for various outlier criteria) when **changing from supine to standing position on treatment compared to baseline over the whole study period.** Analyses were performed according to the randomized treatment/targeted rotigotine dose and according to the actual rotigotine treatment received (including doses administered during titration to higher targeted dose) at the time of the event. There was slight increase (Placebo-7.8 %, 4.5 mg-3.0 %, 9.0 mg-9.5 %, 13.5 mg-10.8 %, 18 mg-10.0 %) in the incidence of mild-moderate systolic decrements (≥ 20 but < 40 mm Hg) . This dose-related effect appeared to have plateaued at doses of 9-18 mg (relative to the % with placebo and 4.5 mg). There were no other events that appeared to be dose-related by my criteria. Although

my analyses have focused on assessing for dose-related effects, I note that these analyses also revealed that one patient randomized to the 4.5 mg dose achieved a very severe outlier criterion for "new onset" diastolic blood pressure orthostatic hypotension. This patient experienced a diastolic decrement $\geq$ 20 mm Hg to an absolute value of $\leq$ 50 mm Hg. In addition, the incidence of a rotigotine treatment effect for "new onset" diastolic orthostatic hypotension (compared to baseline) was 1.9 % for all rotigotine doses (i.e. without dose-related effect) vs 0 % for placebo.

- The sponsor had also conducted many outlier analyses of orthostatic VS for different time frames. Results that were considered to show a dose-response relationship are presented in Table 15. Although most of the outlier abnormalities suggest a mild to moderate dose-related increased risk according to the shape of the dose-response curves (using my dose-response criteria) for these various vital sign abnormalities during orthostatic maneuvers, a few outlier abnormalities suggested a more significant increased risk related to rotigotine dose.

Table 15 Incidence of Dose-Related Rotigotine VS Outliers for Different Positions, Study Time Frames, and Doses

VS	Position	Outlier Criterion	Time Frame	% Placebo N = 64	% 4.5 mg N = 66	% 9.0 mg N = 63	% 13.5mg N = 65	% 18.0 mg N = 70
SBP	Standing	≥ 20 Increment	Any Visit	20.3	12.1	15.9	**23.1**	**22.9**
	Supine to Standing	≥ 20 Increment	Any Visit	12.5	0	4.8	12.3	**21.4**
	Standing	≥ 20 Increment	Final Visit	9.4	4.5	7.9	**12.3**	**10.0**
	Supine to Standing	≥ 20 Increment	Final Visit	3.1	0	3.2	7.7	**8.6**
	Standing	≥ 20 Increment	Titration Period	14.5	4.6	6.7	13.1	**20.6**
	Standing	≥ 20 Decrement	Titration Period	16.1	15.4	10.0	8.2	**17.6**
	Supine to Standing	≥ 20 Increment	Titration Period	9.7	0	1.7	8.2	**13.2**
	Supine to Standing	≥ 20 Increment	Maintenance Period	4.7	0	3.2	9.2	**14.3**
	Supine to Standing	≥ 20 Increment	Titration Persist To Maintenance	1.6	0	0	4.9	**5.9**
DBP	Supine	≥ 10 Increment	Any Visit	35.9	36.4	31.7	27.7	**41.4**
	Supine to Standing	≥ 10 Decrement	Final Visit	9.4	13.6	15.9	10.8	**17.1**
	Supine	≥ 10 Increment	Titration Period	21.0	26.2	21.7	21.3	**33.8**
	Standing	≥ 10 Increment	Titration Period	22.6	27.7	21.7	19.7	**29.4**
	Standing	≥ 10 Decrement	Titration Period	25.8	21.5	21.7	18.0	**27.9**
	Supine	≥ 10 Increment	Titration Persist To Maintenance	16.1	10.8	18.3	11.5	**20.6**
	Standing	≥ 10 Increment	Titration Persist To Maintenance	14.5	10.8	13.3	14.8	**19.1**
	Standing	≥ 20 Increment	Titration Persist To Maintenance	1.6	1.5	0	0	**2.9**
Pulse	Standing	≥ 15 Increment	Final Visit	4.7	7.6	3.2	4.6	**10.0**
	Supine	≥ 15 Increment	Titration Persist To Maintenance	6.5	7.7	0	1.6	**8.8**
	Standing	≥ 15 Increment	Titration Persist To Maintenance	4.8	6.2	0	1.6	**10.3**

- It is relevant to note the Precautions section of the draft label for the approvable letter

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✓ Draft Labeling

_____ Deliberative Process

3.3.3 Reviewer Conclusions :

- My review suggest that there were several dose-related abnormalities related to changes in orthostatic VS.
- [redacted] should be included the label.
- It would also seem desirable that results of one analysis contained in question # 4 also be inserted into the label in the section about symptomatic hypotension/orthostatic hypotension.This analysis found that the incidence of a possibly syndrome of orthostatic hypotension/postural dizziness (as a "worst case" scenario syndrome) associated with "any" dose of rotigotine (22 %) was twice that of the incidence with placebo (11 %).

3.4 FDA Request for study 506 question No.4 :

Provide analyses of TEAEs, TE-SAEs, and TE study discontinuations for AEs/SAEs that are suggestive of falls or orthostatic hypotension/postural dizziness. Please show these analyses according to ***randomized*** *treatment (placebo, 4.5, 9, 13.5, or 18 mg rotigotine and* ***any*** *rotigotine dose) and show results for all treatment (and any rotigotine dose if possible) on the same page.*

These analyses of special interest represent a conservative approach of assessing the possible frequency of particular events of interest that may not have been captured as a particular event because of AE coding vagaries. These analyses include :

• ***Events possibly suggestive of falls.*** *Search for a variety of AE terms that might be suggestive of a fall despite the fact that the AE had not been coded as a fall. AE terms (****e.g. some examples but not a complete list****) that might be included in this search are fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb. You should consider such events possibly suggestive of a fall unless there is information to suggest that the vent was not a result of a fall. Present the incidence, total number of events, and total number of patients for events that may have been suggestive of a fall for TEAEs, TESAEs, and study discontinuations for a TEAE (further broken down as to whether the event was an SAE or non-serious AE).*

• ***Events possibly suggestive of orthostatic hypotension / postural dizziness.*** *Search for a variety of AE terms that might be suggestive of orthostatic hypotension / postural dizziness despite the fact that the AE had not been coed as such. AE terms (****e.g. some examples but not a complete list****) that might be included in this search are hypotension, postural hypotension, decreased blood pressure, syncope, dizziness, vertigo, postural dizziness, light-headedness, postural light-headedness, impaired balance, and feeling drunk. Present analyses as described for events possibly suggestive of falls.*

3.3.4 SPONSOR'S SUMMARY ANSWER :

A review of TEAEs was conducted to determine the occurrence of TEAEs suggestive of falls or orthostatic hypotension. The incidence of TEAEs or serious TEAEs suggestive of falls, as well as discontinuations because of TEAEs suggestive of falls, was uncommon and was not increased or decreased with randomization to rotigotine treatment. The incidence of TEAEs suggestive of

orthostatic hypotension/postural dizziness was increased in subjects randomized to receive rotigotine. This increase was not dose-dependent. Most TEAEs were classified as dizziness, which is a common dopaminergic AE and is usually not related to orthostasis. Serious TEAEs and discontinuations because of TEAEs suggestive of orthostatic hypotension/postural dizziness were uncommon. For a complete analyses of TEAEs suggestive of falls or orthostatic hypotension, please see Section 4.1.4, Other Significant Treatment-emergent Adverse Events of the SP506 Revised Safety Section FDA Response.

The following represents the sponsor's more detailed response to this request.

TEAEs suggestive of falls were categorized as WHO-ART preferred terms accident NOS, myalgia, fall, leg pain, back pain, and purpura. The incidence of TEAEs suggestive of falls was similar in subjects randomized to receive placebo (6%) and any dose of rotigotine (4%). Results did not suggest an effect of rotigotine dose on the incidence of TEAEs suggestive of falls (rotigotine 4.5mg/day: 5%, rotigotine 9.0mg/day: 2%, rotigotine 13.5mg/day: 3%, rotigotine 18.0mg/day: 7%). At the highest rotigotine dose, 18.0mg/day, 5 subjects experienced 5 TEAEs suggestive of falls.

There were no serious TEAEs suggestive of falls in any of the rotigotine groups.

There were no TEAEs suggestive of falls leading to early discontinuation in subjects randomized to receive rotigotine; the rate of occurrence was also low in subjects randomized to receive placebo (preferred term of fall: 2%; preferred term of accident NOS: 2%).

TEAEs suggestive of orthostatic hypotension/postural dizziness were categorized as WHO-ART preferred terms of dizziness, gait abnormal, ataxia, vertigo, and syncope. Seven (11%) subjects randomized to placebo and 58 (22%) subjects randomized to rotigotine experienced TEAEs suggestive of orthostatic hypotension/postural dizziness during treatment. Rotigotine administration did not result in a dose-dependent effect on TEAEs suggestive of orthostatic hypotension/postural dizziness. With the exception of 1 TEAE in the rotigotine 18.0mg/day group (syncope), all TEAEs suggestive of orthostatic hypotension/postural dizziness were classified as WHO-ART body system central and peripheral nervous system disorders, with dizziness occurring most frequently (placebo: 11%, rotigotine 4.5mg/day: 21%, rotigotine 9.0mg/day: 16%, rotigotine 13.5mg/day: 23%, and rotigotine 18.0mg/day: 21%). As displayed in Table 4.5, dizziness encompasses several reported terms which may or may not be indicative of orthostatic hypotension/postural dizziness, including dizziness, dizzy, faintness, and feeling faint. Also, dizziness is a common dopaminergic AE and usually not related to orthostasis. Thus, the increased incidence of dizziness in subjects randomized to receive rotigotine may not be indicative of an increased incidence of orthostatic hypotension/postural dizziness.

One serious TEAE suggestive of orthostatic hypotension/postural dizziness, with a WHO-ART preferred term of syncope, occurred in a subject randomized to the rotigotine 18.0mg/day group. There were no serious TEAEs suggestive of orthostatic hypotension/postural dizziness in any other group.

A summary of TEAEs suggestive of orthostatic hypotension/postural dizziness leading to discontinuation is presented in Table 4.3. Two subjects (1%) randomized to any dose of rotigotine discontinued because of a total of 3 TEAEs (rotigotine 13.5mg/day: 1 subject (1%) with 1 event, rotigotine 18.0mg/day: 1 subject (1%) with 2 events). The 2 events reported by the subject randomized to the rotigotine 18.0mg/day

group were classified as serious TEAEs. No subjects randomized to the placebo group discontinued because of a TEAE suggestive of orthostatic hypotension/postural dizziness.

3.3.5 Reviewer Comments :

- The sponsor compiled a more comprehensive list of preferred terms (PTs) to search for these 2 "syndromes' of possible "worst case scenario" events. For possible "falls," the sponsor searched the following PTs : skin laceration, fall, traumatic hematoma, excoriation, contusion, skin injury, muscle Injury, muscle strain, back injury, abrasion, fracture, ecchymosis, joint sprain, joint dislocation, head injury, limb injury, and crush injury. For possible "orthostatic hypotension/postural dizziness," the sponsor search for the following PTs : dizziness, dizziness postural, balance disorder, vertigo, loss of consciousness, feeling abnormal, gait disturbance, hypotension, postural hypotension, decreased blood pressure , syncope, light headedness, postural light headedness, Impaired balance, and drunk feeling. I think that the sponsor compiled a reasonably good list of PTs to search for the possible incidence of both of these syndromes.

- The incidence of TEAEs suggestive of falls did not suggest a dose-related effect of various doses of rotigotine nor of "any" dose of rotigotine vs placebo.

- Although the incidence of TEAEs suggestive of orthostatic hypotension/postural dizziness did not suggest a dose-related effect of various doses of rotigotine, the incidence of orthostatic hypotension/postural dizziness associated with "any" dose of rotigotine did suggest a treatment effect of rotigotine (22 %) vs placebo (11 %). This drug effect doubled the risk of experiencing this syndrome. Not surprisingly, other analyses suggested that some patients experience an increased risk for orthostatic hypotension (Table 13, Table 14, Table 15) and in some instances this risk appeared to be dose-related (Table 13, Table 15).

3.3.6 Reviewer Conclusions :

- The result of this analysis indicated an increased risk (2 fold) for a syndrome of orthostatic hypotension/postural dizziness (as a "worst case" scenario syndrome) for "any" dose of rotigotine treatment (22 %) compared to placebo treatment (11 %). This analysis did not suggest a dose-relationship to rotigotine.

- Information about this increased risk should be included in the Precautions label section describing symptomatic/orthostatic hypotension.

4

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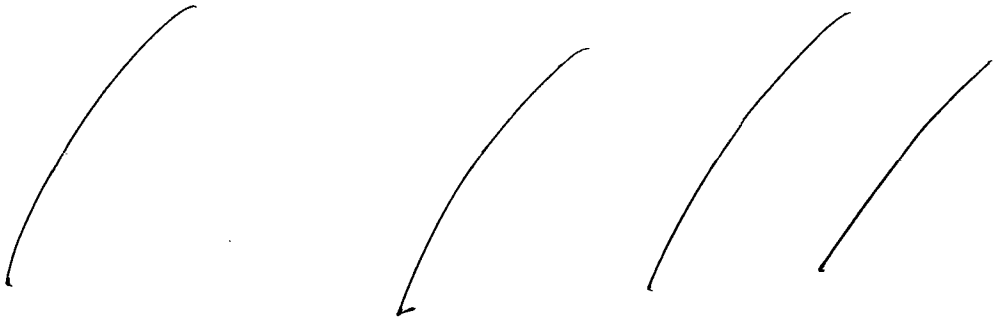
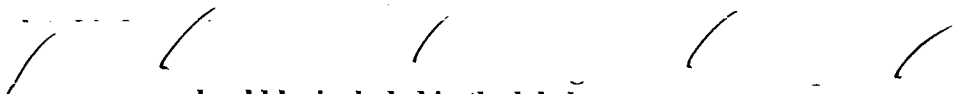


4.3 Reviewer Conclusions :

•



should be included in the label.

5 SPONSOR'S SAFETY SUMMARY AND CONCLUSIONS

As detailed in the original SP506 clinical trial report, rotigotine transdermal patch was safe and well tolerated at doses from 4.5 to 18.0mg/day for 7 weeks of Maintenance. No deaths occurred during the trial.

Analysis of subjects in the present trial according to randomized treatment group has shown :

• The overall incidence of TEAEs throughout the entire trial was comparable between subjects randomized to receive placebo and all rotigotine doses (placebo: 83%, rotigotine 4.5mg/day: 84%, rotigotine 9.0mg/day: 78%, rotigotine 13.5mg/day: 83%, rotigotine 18.0mg/day: 84%).

• The most common TEAEs reported by subjects randomized to receive rotigotine were nausea (40%), application site reactions (31%), dizziness (20%), somnolence (17%), headache (14%), vomiting (14%), insomnia (12%), fatigue (11%), and sweating increased (5%). The incidence of all of these TEAEs was higher in rotigotine than placebo randomized subjects.

• Of the most common TEAEs, the incidence of nausea, application site reactions, somnolence, and insomnia increased with increasing rotigotine dose.

• The overall incidence of AEs was higher in the Titration Period (66% placebo vs 74%

rotigotine) than the Maintenance Period (54% placebo vs 48% rotigotine).

• For subjects randomized to any dose of rotigotine, the incidence of the most common TEAEs occurred at a lower rate in the Maintenance Period than the Titration Period.

• For subjects randomized to receive placebo and any dose of rotigotine, overall TEAEs occurred less frequently in the Maintenance Period than in the Titration Period.

• Subjects randomized to receive any dose of rotigotine were more likely than placebo subjects to experience a TEAE beginning during the Titration Period and persisting into the Maintenance Period. The most common persistent TEAEs were consistent with the overall most common AEs (ie, nausea, application site reaction, and somnolence).

• Serious TEAEs were uncommon overall and occurred at a similar rate between subjects randomized to receive placebo and rotigotine. The incidence of serious TEAEs was also similar across groups during the Titration and Maintenance Periods, as well as when developing during the Titration Period and persisting into the Maintenance Period.

• The overall incidence of discontinuations because of TEAEs was similar between subjects randomized to receive placebo and rotigotine. The incidence was also comparable across groups during the Titration and Maintenance Periods, but was slightly less across groups when developing during the Titration Period and persisting into the Maintenance Period.

• The incidence of TEAEs or serious TEAEs suggestive of falls, as well as discontinuations because of TEAEs suggestive of falls, was uncommon and was not increased or decreased with randomization to rotigotine treatment.

• The incidence of TEAEs suggestive of orthostatic hypotension/postural dizziness was increased in subjects randomized to receive rotigotine; this increase was not dose-dependent. Most TEAEs were classified as dizziness, which is a common dopaminergic AE and is usually not related to orthostasis. Serious TEAEs and discontinuations because of TEAEs suggestive of orthostatic hypotension/postural dizziness were uncommon.

• No safety concerns with respect to laboratory findings or vital signs were identified.

5.1 Reviewer Comment :

- My comments in other sections deal with the sponsor's summary statements and conclusions.

5.2 Reviewer Conclusions :

- **Based upon my comments and conclusions outlined in other sections (especially relative to the highest dose, 18 mg), I conclude that there is an increased dose-related risk for rotigotine for many TEAEs (during the titration and maintenance periods and onset during the**

titration and persistence into the maintenance period) and many outlier "abnormalities" for decreased and increased blood pressure and increased heart rate.

- **should be included in the label.**
-

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ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leonard Kapcala
4/25/2007 08:31:22 PM
MEDICAL OFFICER

John, Here is my review which you have seen.
Please sign and ask if questions if needed.
Thanx. Len

John Feeney
5/11/2007 03:20:20 PM
MEDICAL OFFICER
This information is reflected in labeling.

—Review of Clinical Data

NDA:	21-829
Drug Name:	Generic Name: Rotigotine Proposed Trade Name: Neupro®
Sponsor:	Schwarz
Material Reviewed:	Response to requests for additional information in Approvable letter
Reviewer:	Marc Stone, MD
Date Completed:	26 April 2007

Rotigotine and Weight Gain

In the initial review of the rotigotine NDA, it was noted that subjects who received rotigotine had an incidence rate of weight gain of more than 10% over baseline that was 1.65 times that observed with placebo subjects. In the Approvable letter of 28 February 2006, the Sponsor was requested to investigate rotigotine subjects with weight gain of over 10% to ascertain the reason for weight gain.

In its response the Sponsor identified all cases of weight gain over 10% occurring in clinical trials of rotigotine for all indications: early and advanced Parkinson's Disease and Restless Legs Syndrome. There were no reported cases of 10% weight gain in the restless legs studies but the incidence was clearly greater with rotigotine than placebo in the Parkinson's studies:

Table 1: Subjects with any postbaseline weight gain >10% in the double-blind, placebo-controlled populations

	Placebo n/N (%)	Rotigotine n/N (%)	Odds Ratio (95% CI)
All PD + RLS	3/566 (<1)	41/1390 (3)	5.70 (1.81-28.89)
All PD	3/511 (<1)	41/1110 (4)	6.49 (2.06-32.91)
Early PD	1/293 (<1)	17/677 (3)	7.52 (1.17-315.3)
Advanced PD	2/218 (<1)	24/433 (6)	6.34 (1.55-55.72)

PD=Parkinson's disease; All PD=early- and advanced-stage Parkinson's
Early PD trials include SP506, SP512, SP513, SP534, SP535
Advanced PD trials include SP515, SP650
RLS trials include SP709

The only treatment-emergent adverse events that showed a strong correlation with weight gain were those related to edema. About one-third of subjects receiving rotigotine who experienced 10% or greater weight gain reported edema compared to about 10% of those without such a gain:

Table 2: Rotigotine-treated subjects who experienced any edema-related AE

	With >10% weight gain n/N (%)	Without >10% weight gain n/N (%)	Odds Ratio (95% CI)
All PD + RLS	80/243 (33)	202/2076 (10)	4.55 (3.31-6.23)
All PD	80/230 (35)	191/1763 (11)	4.39 (3.17-6.04)
Early PD	51/130 (39)	114/978 (12)	4.89 (3.19-7.44)
Advanced PD	29/100 (29)	77/785 (10)	3.75 (2.20-6.27)

Includes subjects from all double-blind, placebo-controlled trials; open-label trials; and open-label extension trials that collected postbaseline weight data
n=number of subjects with edema-related AE, N=total number of subjects.
PD=Parkinson's disease; All PD=early- and advanced-stage, Parkinson's disease; RLS=Restless Legs Syndrome
Edema-related AEs include WHO-ART preferred terms of oedema peripheral, oedema, oedema legs, oedema generalised, and oedema dependent
Source data: Sponsor's Table 3.6.1, Table 3.6.2, Table 3.6.3, and Table 3.6.4

Individual Case Narratives

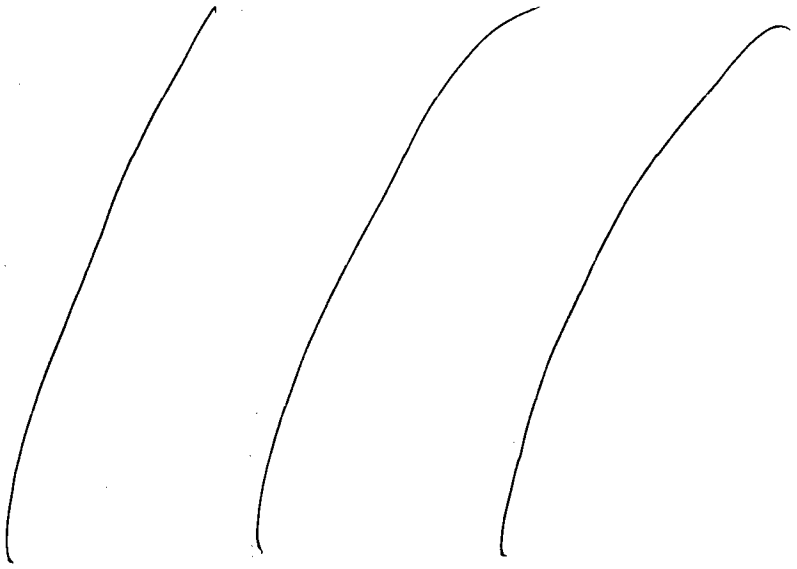
The Sponsor supplied 230 individual case narratives of subjects who experienced a 10% or greater weight gain while taking rotigotine. Very few had pre-existing medical conditions that would have predisposed them to weight gain or peripheral edema. One subject had a history of congestive heart failure but was not noted to have developed edema in conjunction with the observed weight gain. There were four subjects with a history of valvular heart disease; one developed congestive heart failure in association with weight gain while the other three had no other symptoms. There were four subjects with a history of diminished renal function; one developed peripheral edema. Two of seven subjects with a history of peripheral edema developed edema in conjunction with their weight gain. One subject without a history of heart disease developed congestive heart failure. In four subjects, weight gain was associated with increased appetite or compulsive eating but no evidence of edema.

Reviewer's Conclusions and Recommendations

The greater propensity for weight gain observed with rotigotine is, in many if not most cases, the result of fluid retention. This is evidenced by the strong association with the development of edema when the degree of fluid retention was sufficient to cause observable peripheral edema. In a few cases the weight gain may have been due to compulsive eating or an abnormal increase in appetite.

Regardless of cause, the weight gain observed in these clinical studies did not appear to contribute much to the development of serious clinical consequences. The two observed cases of congestive heart failure may be simply coincidental. This does not mean that this fluid retention is inherently benign. The study population contained relatively few subjects who were especially vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

The Sponsor's proposed labeling for Neupro [redacted]



Rotigotine and Abnormal Laboratory Findings

The initial review of the rotigotine NDA showed 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, appeared to be part of a single process, occurring concurrently within the same individuals. Subjects with larger declines in hemoglobin and albumin also showed increases in blood urea nitrogen (BUN) and serum chloride levels.

In response to a request in the Approvable letter, the Sponsor supplied a dataset containing all laboratory data obtained from all clinical studies, regardless of indication. These studies are described in Table 3.

Table 3: Studies Providing Laboratory Data

Clinical Study	Placebo Subjects	Rotigotine Subjects	Indication
511	84	238	Advanced Parkinsonism
515	101	204	Advanced Parkinsonism
533	0	10	Advanced Parkinsonism
591	0	34	Advanced Parkinsonism
650	120	229	Advanced Parkinsonism
826	0	54	Advanced Parkinsonism
Total	*305*	*769*	*Advanced Parkinsonism*
824	0	116	Any Parkinsonism
Total	*0*	*116*	*Any Parkinsonism*
506	64	265	Early Parkinsonism

512	96	180	Early Parkinsonism
513	118	215	Early Parkinsonism
534	4	20	Early Parkinsonism
535	2	8	Early Parkinsonism
540	0	31	Early Parkinsonism
630	0	70	Early Parkinsonism
651	0	36	Early Parkinsonism
825	0	25	Early Parkinsonism
Total	*284*	*850*	*Early Parkinsonism*
503	0	30	Healthy Volunteers
629	0	40	Healthy Volunteers
673	0	229	Healthy Volunteers
Total	*0*	*299*	*Healthy Volunteers*
709	55	285	Restless Legs
Total	*55*	*285*	*Restless Legs*
Total	**644**	**2319**	**All Indications**

Analyses of Abnormal Values

Table 4 shows the distribution of all laboratory results by treatment assignment. The definitions of high or low values are specific to each trial. They show the greatest differences between drug and placebo to be the higher prevalence of abnormally low values for hemoglobin, hematocrit and red blood cell count. Rotigotine-treated subjects were also more likely to have elevated BUN, serum chloride and serum potassium levels but less likely to have elevated levels of total cholesterol. Table 5 looks at the proportions of subjects who experienced any abnormal laboratory values during treatment (excluding open-label extensions). The patterns of abnormality for hemoglobin, hematocrit, red blood cell count and total cholesterol are similar to those in Table 4 but show a less striking pattern of elevation of BUN and serum chloride. Table 5 also shows stronger relationships of treatment with hypoglycemia and lymphopenia.

Table 4: Distribution of Laboratory Results by Treatment Assignment

Laboratory Test	Assignment	Low	Normal	High	p value (Chi-squared)
Hematocrit	Placebo	5.3%	93.2%	1.6%	**<0.001**
	Rotigotine	8.7%	90.0%	1.4%	
	Total	8.2%	90.4%	1.4%	
Hemoglobin	Placebo	4.7%	94.6%	0.7%	**<0.001**
	Rotigotine	8.2%	91.1%	0.6%	
	Total	7.7%	91.7%	0.6%	
% Lymphocytes	Placebo	6.1%	92.1%	1.8%	**0.25**
	Rotigotine	6.4%	92.3%	1.3%	
	Total	6.4%	92.2%	1.4%	
% Monocytes	Placebo	0.3%	97.9%	1.8%	**0.31**

	Rotigotine	0.5%	98.2%	1.3%	
	Total	0.5%	98.2%	1.4%	
Urine Specific Gravity	Placebo	0.0%	100.0%	0.0%	**0.03**
	Rotigotine	0.0%	98.5%	1.6%	
	Total	0.0%	98.7%	1.3%	
Blood Urea Nitrogen	Placebo	0.3%	96.2%	3.6%	**0.002**
	Rotigotine	0.2%	94.5%	5.4%	
	Total	0.2%	94.8%	5.1%	
Uric Acid	Placebo	8.7%	89.2%	2.1%	**0.26**
	Rotigotine	10.0%	88.3%	1.7%	
	Total	9.8%	88.5%	1.8%	
Glucose	Placebo	2.1%	87.1%	10.8%	**0.27**
	Rotigotine	2.8%	86.7%	10.6%	
	Total	2.7%	86.7%	10.6%	
Albumin	Placebo	0.0%	99.7%	0.3%	**0.001**
	Rotigotine	0.4%	98.8%	0.9%	
	Total	0.3%	98.9%	0.8%	
AST	Placebo	0.7%	98.0%	1.3%	**0.006**
	Rotigotine	0.3%	98.1%	1.7%	
	Total	0.3%	98.1%	1.6%	
Total Cholesterol	Placebo	0.0%	50.0%	50.0%	**<0.001**
	Rotigotine	0.0%	59.2%	40.8%	
	Total	0.0%	57.5%	42.5%	
Serum Potassium	Placebo	0.6%	98.9%	0.6%	**<0.001**
	Rotigotine	0.5%	97.1%	2.4%	
	Total	0.5%	97.4%	2.1%	
Serum Chloride	Placebo	0.4%	97.7%	1.9%	**<0.001**
	Rotigotine	0.4%	95.8%	3.8%	
	Total	0.4%	96.1%	3.5%	
RBC Count	Placebo	4.5%	94.9%	0.7%	**<0.001**
	Rotigotine	8.0%	91.4%	0.6%	
	Total	7.5%	91.9%	0.6%	
Absolute Lymphocytes	Placebo	4.4%	95.0%	0.6%	**0.27**
	Rotigotine	5.1%	94.5%	0.4%	
	Total	5.0%	94.6%	0.4%	

Absolute Monocytes	Placebo	4.0%	95.8%	0.3%	**0.21**
	Rotigotine	4.6%	94.9%	0.5%	
	Total	4.5%	95.1%	0.4%	

Table 5: Subjects Developing Laboratory Abnormalities during Treatment

Laboratory Test	Assignment	Low	p value (Chi-squared)l	High	p value (Chi-squared)
Hematocrit	Placebo	5.8%	**0.07**	2.0%	**0.28**
	Rotigotine	8.1%		1.4%	
	Total	7.6%		1.5%	
Hemoglobin	Placebo	4.9%	**0.03**	0.8%	**1.00**
	Rotigotine	7.6%		0.8%	
	Total	7.0%		0.8%	
% Lymphocytes	Placebo	6.5%	**0.20**	3.6%	**0.01**
	Rotigotine	8.4%		1.6%	
	Total	7.9%		2.1%	
% Monocytes	Placebo	0.2%	**0.04**	3.8%	**0.04**
	Rotigotine	1.3%		2.1%	
	Total	1.0%		2.5%	
Urine Specific Gravity	Placebo	0.0%	**NA**	0.0%	**0.19**
	Rotigotine	0.0%		2.5%	
	Total	0.0%		2.1%	
Blood Urea Nitrogen	Placebo	0.2%	**0.41**	4.9%	**0.34**
	Rotigotine	0.1%		6.0%	
	Total	0.1%		5.7%	
Uric Acid	Placebo	7.3%	**0.68**	1.9%	**0.12**
	Rotigotine	6.7%		0.9%	
	Total	6.8%		1.2%	
Glucose	Placebo	4.1%	**0.02**	13.6%	**0.93**
	Rotigotine	6.8%		13.7%	
	Total	6.1%		13.7%	
Albumin	Placebo	0.0%	**0.23**	0.5%	**0.01**
	Rotigotine	0.3%		1.3%	
	Total	0.2%		1.1%	
AST	Placebo	1.0%	**0.30**	1.6%	**0.27**
	Rotigotine	0.6%		2.4%	
	Total	0.7%		2.2%	

Total Cholesterol	Placebo	0.0%	**NA**	30.3%	**<0.001**
	Rotigotine	0.0%		18.2%	
	Total	0.0%		21.7%	
Serum Potassium	Placebo	0.5%	**0.39**	1.0%	**0.01**
	Rotigotine	0.9%		2.9%	
	Total	0.8%		2.5%	
Serum Chloride	Placebo	0.7%	**0.90**	3.4%	**0.47**
	Rotigotine	0.6%		4.1%	
	Total	0.6%		4.0%	
RBC Count	Placebo	4.3%	**0.01**	0.5%	**0.58**
	Rotigotine	7.2%		0.7%	
	Total	6.6%		0.6%	
Absolute Lymphocytes	Placebo	4.4%	**0.04**	0.8%	**0.24**
	Rotigotine	6.8%		0.4%	
	Total	6.2%		0.4%	
Absolute Monocytes	Placebo	6.3%	**0.18**	0.3%	**0.13**
	Rotigotine	8.0%		0.9%	
	Total	7.6%		0.8%	

The results for Tables 4 and 5 were not adjusted for differences among studies or the number of measurements per subject. Because the proportion of subjects on placebo to those on active drug differ among studies, factors other than treatment that affect the probability of observing an abnormal value will confound the results if these factors also differ among studies. The likelihood of observing an abnormal value will differ among studies because of differences in subject populations, laboratory procedures and standards for abnormality and, most importantly, the number of measurements per subject – the more observations, the greater likelihood there is of finding an abnormal value. Random effects logistic regression was used to look at effect of treatment assignment on the proportion of tests results that were abnormal in each subject stratified by study. The results of these analyses using are shown in Table 6.

Table 6: Odds Ratios for Abnormal Laboratory Values Associated with Treatment

Laboratory Test	Result	OR	95%CI		p value
Hematocrit	Low	1.63	1.35	1.97	0.000
	High	0.77	0.55	1.07	0.119
Hemoglobin	Low	2.06	1.69	2.51	0.000
	High	0.71	0.46	1.09	0.120
%Lymphocytes	Low	1.30	1.03	1.63	0.025
	High	0.74	0.50	1.11	0.150

%Monocytes	Low	0.64	0.37	1.12	0.112
	High	0.91	0.60	1.38	0.670
Blood Urea Nitrogen	Low	0.48	0.17	1.37	0.170
	High	1.79	1.41	2.26	0.000
Uric Acid	Low	1.10	0.87	1.38	0.431
	High	1.05	0.68	1.62	0.824
Glucose	Low	1.73	1.31	2.28	0.000
	High	1.24	1.04	1.48	0.018
Albumin	Low	1.52	0.74	3.13	0.260
	Low(<35gm/L)	2.35	1.18	4.67	0.015
	Low(<40gm/L)	2.31	1.94	2.75	0.000
	High	0.75	0.50	1.12	0.164
AST	Low	0.49	0.27	0.88	0.017
	High	1.30	0.96	1.76	0.094
Total Cholesterol	Low(<4mmol/L)	3.05	2.37	3.94	0.000
	High	0.37	0.32	0.44	0.000
Serum Potassium	Low	1.04	0.63	1.72	0.888
	High	1.23	0.94	1.61	0.137
Serum Chloride	Low	1.20	0.65	2.21	0.567
	High	1.03	0.84	1.26	0.761
RBC Count	Low	1.48	1.23	1.79	0.000
	High	0.84	0.52	1.34	0.455
Absolute Lymphocytes	Low	1.38	1.10	1.73	0.005
	High	0.62	0.36	1.08	0.090
Absolute Monocytes	Low	1.13	0.93	1.36	0.220
	High	1.26	0.73	2.19	0.411

Random effects (subject) logistic regression stratified by trial.
Exclusions: OLE for placebo, post-treatment for both.

The patterns observed in Table 6 are similar to those in Tables 4 and 5. Rotigotine was associated with a greater likelihood of abnormally low values for blood hemoglobin, hematocrit, red blood cell count, glucose, and lymphocyte counts. There were very few serum albumin levels classified as abnormally low, but a higher likelihood of albumin levels lower than 35 or 40 grams per liter was seen in subjects assigned to rotigotine. Similarly, rotigotine subjects showed a much higher likelihood of a level of total cholesterol below 4.0 mmol per liter. Rotigotine was also associated with a higher incidence of abnormally elevated levels of BUN.

In the previous review; consisting of only the three pivotal trials, SP506, SP512 and SP513; higher incidences for abnormalities in blood hemoglobin, hematocrit, red blood cell count and monocyte count were also noted. The review also noted a higher incidence of marked abnormalities in BUN, replicated here, and in ALT, WBC count, monocyte count and platelet count that were not replicated in this analysis.

Analyses of Central Tendency

In order to take maximum advantage of the extensive laboratory dataset provided, laboratory values were analyzed using a repeated measures mixed effects model. This model distinguishes treatment effect from variability attributable to differences among studies and among individual subjects within studies. The model treated both trial and individual subject identity as random effects and treatment itself as a random effect among trials, to account for differences in dosages and other differences in treatment protocols. Laboratory values were excluded if they were obtained after treatment was ended (except for trial SP503 where laboratory tests were not performed during treatment but were obtained immediately after treatment was ended) or were obtained during open-label treatment of subjects originally assigned to placebo.

Estimates of treatment effect upon selected laboratory tests are given as absolute changes in Table 7 and as percentage change in Table 8. The largest proportional change was an average 5.7% decline in serum total cholesterol. There were average increases of 3.7% in AST and BUN and an average decline of 3.5% in absolute lymphocyte count. Declines in blood hemoglobin, hematocrit, red blood cell count and serum albumin were all about 2 percent. There were no significant changes in mean corpuscular volume (MCV). There were no significant net effects on serum potassium or chloride levels.

Table 7: Net Treatment Effect on Laboratory Values (Absolute Change)

Laboratory Test	Units	Treatment effect	95% CI		p value
% Lymphocytes	%	-0.52	-1.01	-0.02	0.041
% Monocytes	%	0.09	-0.07	0.26	0.273
Absolute Lymphocytes	10^9/L	-0.06	-0.10	-0.03	<0.001
Absolute Monocytes	10^9/L	-0.01	-0.02	0.01	0.369
Albumin	g/L	-0.86	-1.40	-0.33	0.002
AST	u/L	0.77	0.35	1.18	<0.001
Blood Urea Nitrogen	mmol/L	0.21	0.10	0.32	<0.001
Glucose	mg/dl	1.89	-0.42	4.20	0.109
Hematocrit	%	-0.88	-1.30	-0.45	<0.001
Hemoglobin	g/L	-2.85	-4.29	-1.42	<0.001
MCV	fl	-0.09	-0.32	0.15	0.466
RBC Count	10^9/L	-0.10	-0.15	-0.05	<0.001
Serum Chloride	mmol/L	-0.13	-0.46	0.19	0.424
Serum Potassium	mmol/L	0.01	-0.02	0.04	0.448
Total Cholesterol	mmol/L	-0.30	-0.35	-0.25	<0.001
Uric Acid	µmol/l	-1.73	-6.88	3.42	0.511

Table 7: Net Treatment Effect on Laboratory Values (Percent Change)

Laboratory Test	Treatment effect	95% CI		p value
% Lymphocytes	-1.8%	-3.6%	-0.1%	0.040
% Monocytes	1.4%	-1.1%	3.9%	0.274
Absolute Lymphocytes	-3.5%	-5.3%	-1.6%	<0.001
Absolute Monocytes	-1.4%	-4.6%	1.7%	0.368
Albumin	-2.0%	-3.2%	-0.7%	0.002
AST	3.7%	1.7%	5.8%	<0.001
Blood Urea Nitrogen	3.7%	1.8%	5.7%	<0.001
Glucose	1.9%	-0.4%	4.2%	0.110
Hematocrit	-2.1%	-3.1%	-1.1%	<0.001
Hemoglobin	-2.0%	-3.0%	-1.0%	<0.001
MCV	-0.1%	-0.3%	0.2%	0.466
RBC Count	-2.1%	-3.2	-1.0%	<0.001
Serum Chloride	-0.1%	-0.4%	0.2%	0.424
Serum Potassium	0.2%	-0.4%	0.9%	0.449
Total Cholesterol	-5.7%	-6.7%	-4.8%	<0.001
Uric Acid	-0.6%	-2.3%	1.1%	0.511

Changes in hemoglobin levels were examined in more detail by applying the model to individual studies and, for placebo-controlled trials, direct comparison with placebo. Figures 1 and 2 show the results of these analyses.

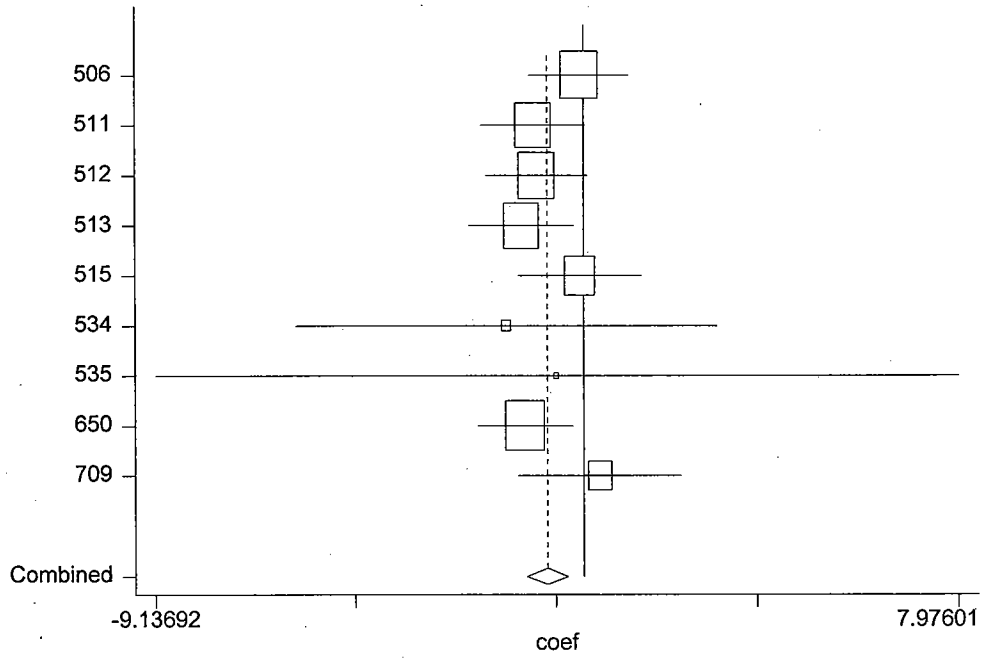


Figure 1: Estimate by Study of Changes in Hemoglobin Level (gm/L) Relative to Placebo (Controlled Studies)

Note: The solid vertical line represents no change relative to placebo. The dotted vertical line indicates the average difference across all trials.

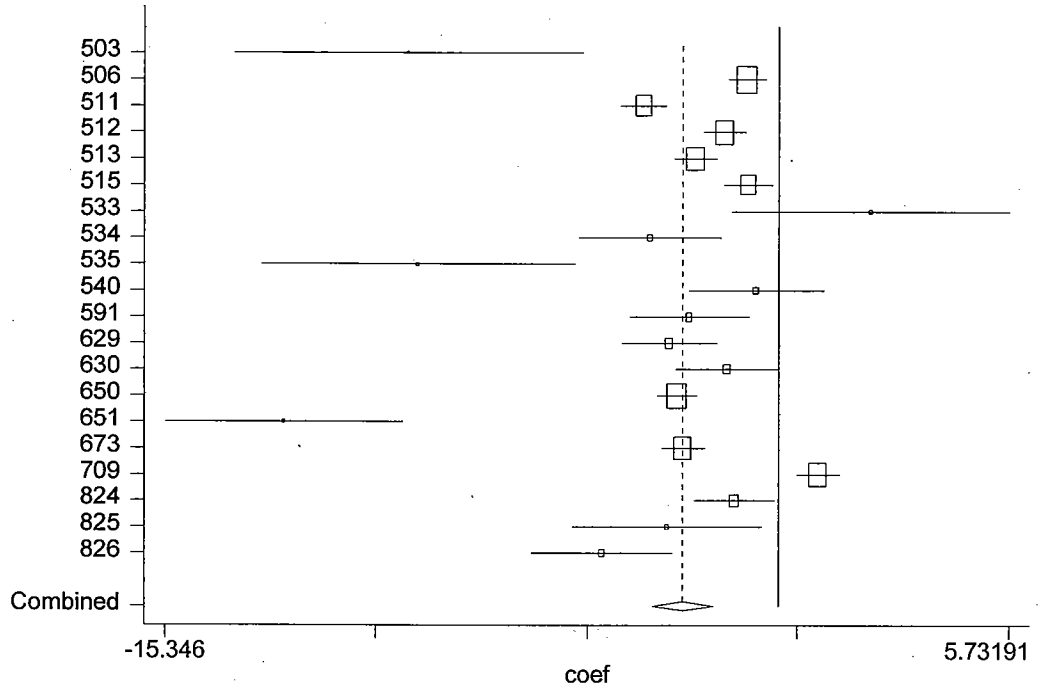


Figure 2: Estimate by Study of Changes in Hemoglobin Associated with Treatment (All Studies)

Note: The solid vertical line represents no change relative to baseline. The dotted vertical line indicates the average difference across all trials

These figures show a pattern of reduction of hemoglobin levels associated with rotigotine treatment in most studies. The only study where ferritin, transferrin, and other tests useful in the diagnosis of anemia were performed was SP709, the only sizable study that did not show a reduction in hemoglobin levels with rotigotine treatment.

Changes in hemoglobin levels and albumin levels showed a moderately strong correlation that was slightly higher in the rotigotine group (0.48 vs. 0.44 with placebo). More modest correlations were seen with hemoglobin and MCV (0.14 vs. 0.09 with placebo), BUN (-0.08 vs. 0.03 with placebo) and serum chloride (0.16 vs. 0.17 with placebo).

Narratives for Subjects with Markedly Abnormal Laboratory Values

The sponsor provided narratives for 422 subjects in studies SP506, SP512 and SP513 who reported markedly abnormal values on a total 527 laboratory tests. In approximately one third of cases, the abnormality was either present to a lesser degree at baseline or the subject had a known medical condition (usually diabetes) that could cause the abnormality. The most common baseline abnormalities were elevated total cholesterol, eosinophilia and hyperglycemia. In the remaining cases, the narratives could not provide any explanation for the abnormality. The narratives did not supply any information related to the subject's clinical condition at the time of the abnormality.

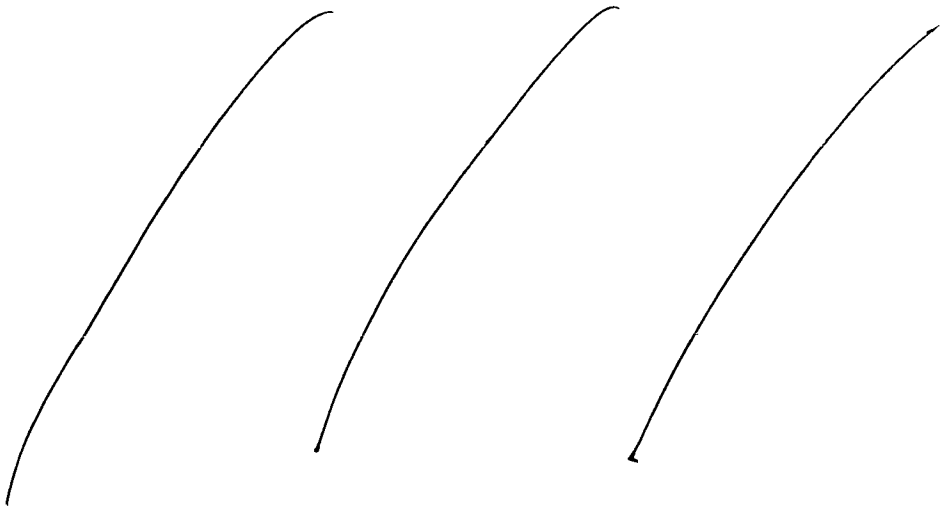
Conclusions Regarding the Effects of Rotigotine on Laboratory Test Results

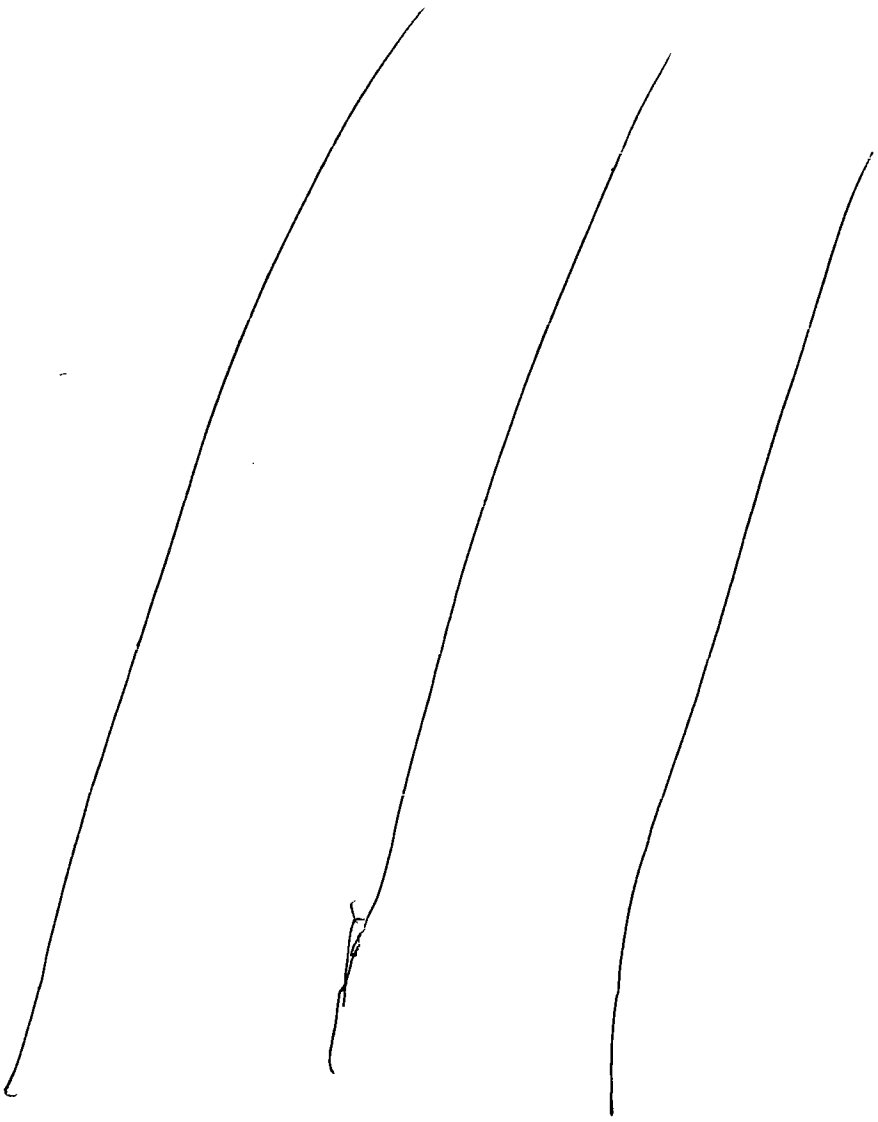
Analyses of the expanded laboratory dataset confirm the previous finding of a decline in hemoglobin and albumin levels with rotigotine treatment. Increases in levels of BUN and the observed higher frequency of abnormally elevated levels can be seen as evidence of renal effects from the drug that may be manifested in the development of weight gain and fluid retention, raising the possibility that the declines in hemoglobin and albumin may be simply the result of dilution. Dilution, however, cannot explain the correlation between changes in hemoglobin and changes in MCV observed with rotigotine. Although this relationship is weaker than what was observed in the pivotal studies alone, the correlation is still higher than that observed with placebo; if dilution were the entire explanation for the fall in hemoglobin values with rotigotine the correlation between hemoglobin and MCV with rotigotine treatment should be much weaker than with placebo because dilution related changes in hemoglobin levels should not be accompanied by any consistent change in MCV.

Two other laboratory tests are worthy of mention. Rotigotine appears to lower cholesterol levels, a finding that has no safety implications but is nonetheless intriguing. The finding of a higher incidence of hypoglycemia whether viewed as proportion of tests or proportion of subjects is of potential clinical importance and merits discussion in the label. Thirty-one subjects had blood glucose levels below 50 mg/dl during treatment, fifteen subjects experienced levels below 40 mg/dl and four subjects had recorded levels below 20 mg/dl. Review of narratives for subjects in studies SP506, SP512 and SP513 showed that only two of thirteen subjects with hypoglycemic episodes had a history of diabetes or were taking hypoglycemic agents. The narratives do not disclose whether any of these episodes of hypoglycemia were symptomatic.

Recommendations

Labeling





Post-Approval Commitments

There is a need to assess the impact of rotigotine on renal function, blood hemoglobin and serum albumin in controlled clinical studies with more extensive monitoring of clinical parameters including iron, transferrin, ferritin, reticulocyte count, red cell morphology, erythropoietin, erythrocyte sedimentation rate, C-reactive protein, haptoglobin and urine hemoglobin as well as hemoglobin; hematocrit; red cell indices; absolute and differential white cell counts; BUN, creatinine, serum electrolytes (including bicarbonate), albumin and globulin. These studies need to include continued detailed monitoring during post-treatment washout in order to assess rate of recovery from reduction of renal function, hemoglobin and albumin. Measurement of red cell volume

and creatinine clearance should be performed before initiating treatment, at the end of treatment and the end of post-treatment washout.

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/s/

Marc Stone
5/8/2007 10:51:54 AM
MEDICAL OFFICER

Alice T. Hughes
5/8/2007 11:21:19 AM
MEDICAL OFFICER

CLINICAL REVIEW OF SELECTED SECTIONS OF COMPLETE RESPONSE TO APPROVABLE LETTER

Application Type	NDA
Submission Number	21829
Submission Code	AZ
Letter Date	11/7/06
Stamp Date	11/9/06
PDUFA Goal Date	5/9/07
Reviewer Name	Gerard Boehm, M.D., M.P.H.
Review Completion Date	4/16/07
Established Name	Rotigotine patch
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopaminergic agonist
Applicant	Schwarz Pharmaceuticals
Priority Designation	S
Formulation	Transdermal patch
Dosing Regimen	Once daily
Indication	Treatment of Early Parkinson's Disease
Intended Population	Early Parkinson's Disease

EXECUTIVE SUMMARY

In their Response to the Approvable letter for the rotigotine NDA, Schwarz provided a final safety update along with replies to specific requests for additional analyses. This memo reviews the final safety update, the cardiac arrhythmia adverse event analysis, and the compulsive behavior adverse event analysis.

The Final Safety Update includes safety data for 706 newly exposed subjects in phase II/III rotigotine trials, with 127 new subjects from early PD trials, 562 new subjects from advanced PD trials and 17 new subjects from RLS trials. The Final Safety Update also includes safety data for subjects exposed to rotigotine in phase I trials and for subjects identified in previous submissions but that are receiving ongoing rotigotine treatment in open label trials.

The Final Safety Update includes 24 new rotigotine deaths, resulting in a cumulative total of 29 rotigotine deaths for the development program. Thirteen deaths are from early PD trials, 16 from advanced PD trials, and no deaths were observed in RLS trials. The reported causes of death appeared to be the types of causes expected in the treated populations.

In the Final Safety Update Schwarz reported SAEs, discontinuation for AEs and all AEs for the treated populations through the 10/31/05 cutoff date. The addition of the new safety data resulted in minimal changes in adverse event risks when compared to previous submissions.

The rotigotine NDA included reports of cardiac arrhythmia adverse events but the relationship between these events and rotigotine was not clear. The Division requested a reanalysis of arrhythmia adverse event data, to look for evidence of increased risk in rotigotine treated subjects compared to placebo and active comparator treated subjects.

The sponsor's reanalysis of arrhythmia related AEs did not find strong evidence of an increased arrhythmia risk with rotigotine. The sponsor's analyses do not support the need for additional studies using Holter monitoring.

The Division requested an analysis identifying AEs of compulsive gambling, compulsive sexual behavior, compulsive shopping and compulsive eating in rotigotine treated subjects. Schwarz identified 29 rotigotine subjects (1%, 29/2775) from the development program with one or more AEs coded to the MedDRA terms suggestive for compulsive behavior. Fifteen of the rotigotine subjects were from early PD trials (1.2%, 15/1220), and 14 subjects were from advanced PD trials (1.2%, 14/1151). No subjects from RLS studies (rotigotine n=404) experienced compulsive behaviors. In the pooled PD (early and advanced) placebo controlled trials, the risk for compulsive behavior AEs was <1% (5/1335) for rotigotine exposed subjects and was 0 (0/612) for placebo controlled subjects. The analysis was limited by incomplete descriptions of these compulsive behavior events. Schwarz should adopt the compulsive behavior class labeling that has been recently proposed for all of the Parkinson's disease medications.

1.0 BACKGROUND

After completing the NDA review for rotigotine, the Division sent Schwarz BioSciences Inc. an approvable letter that listed several requests for additional analyses and information. Schwarz submitted their response to the approvable letter which included a final safety update and the requested analyses. This memo reviews the rotigotine final safety update, the analysis of cardiac arrhythmia AEs, and the analysis of compulsive behavior AEs.

2.0 FINAL SAFETY UPDATE

Schwarz submitted a Final Safety Update as part of their response to the rotigotine Approvable letter. The Final Safety Update has a data cutoff date of 10/31/05.

2.1 Source of New Safety Data

Early Stage PD Trials

The Final Safety Update includes new safety data from the following early PD trials: SP630, SP788, SP651, SP824, SP 825, SP826, and SP833. SP 825 was an active comparator controlled trial and the remaining trials were uncontrolled (Safety Update pp. 19-20).

Advanced Stage PD Trials

The Final Safety Update includes new safety data from the following advanced PD trials: SP515, SP516, SP824, SP826, and SP833. SP515 was an active comparator controlled trial and the remaining trials were uncontrolled (Safety Update p.24).

Restless Leg Syndrome Trials

The Final Safety Update includes new safety data from the following Restless Leg Syndrome trials: SP709 and SP 710. SP709 was a placebo controlled trial and SP710 was the open label extension for SP709 (Safety Update, p.27).

Phase I Trials in Healthy Subjects

The Final Safety Update includes data from 2 phase 1 trials (SP786, SP787) of rotigotine nasal spray formulation in healthy adults (Safety Update, p.28).

2.2 Final Safety Update Data Pools

In the Final Safety Update, Schwarz used a number of safety data pools to present rotigotine safety data. The data pools in the Final Safety Update were generally similar to the pools used in the NDA presentations. I summarize data for the safety pools in the table below. The new safety data for the subjects from Phase I studies was not pooled and is presented separately in the Final Safety Update.

Pool	Description	Included studies
	Early Parkinson's Disease	
S2	Phase 1,2,3 early PD studies, OL extension data excluded. Rotigotine n=884, placebo n=295, ropinirole n=254	SP534 part I and II, SP535, SP540, SP506, SP512 part 1, SP513 part 1, SP630, SP651, SP824, SP825, SP826

S2 new	Phase 1,2,3 early PD studies, OL extension data excluded. Data from early PD studies not included in prior submissions. Rotigotine n=176, ropinirole n=26	SP630, SP651, SP824, SP825, SP826,
S3	Phase 1,2,3 early PD studies, OL extension data included. Rotigotine n=1220, placebo n=140, ropinirole n=73	SP534 part I and II, SP535, SP540, SP506, SP512 part 1 and 2, SP513 part 1 and 2, SP630, SP788, SP651, SP824, SP825, SP826, SP833
S3 new	Phase 1,2,3 early PD studies, OL extension data included. Data from early PD studies not included in prior submissions. Rotigotine n=705, ropinirole n=5	SP512 part 2, SP513 part 2, SP630, SP788, SP651, SP824, SP825, SP826, SP833
S6	Phase 3 early PD studies, from OL extension studies. Total n=596 with n=281 with previous rotigotine tx, n=155 with previous placebo tx, and n=160 with previous ropinirole tx.	SP512 part 2, SP513 part 2
S6 new	Phase 3 early PD studies, from OL extension studies. Data from early PD studies not included in prior submissions. Total n=508 with n=247 with previous rotigotine tx, n=128 with previous placebo tx, and n=133 with previous ropinirole tx.	SP512 part 2, SP513 part 2
Advanced Parkinson's Disease		
AS2	Phase 2, 3 subjects from adv PD studies, OL extension data not included. Rotigotine n=827, placebo n=317, pramipexole n=202.	SP533, SP591, SP824, SP826, SP511, SP650 (DB), and SP515
AS3	Phase 2, 3 subjects from adv PD studies, OL extension data included. Rotigotine n=1151.	SP533, SP591, SP824, SP826, SP833, SP511, SP560 (DB and OL), SP515, and SP516
Restless Leg Syndrome		
RS2	Phase 1 and 2 subjects from restless leg syndrome studies, OL extension data not included. Rotigotine n=358, placebo n=69.	SP628, SP666, and SP709
RS3	Phase 1 and 2 subjects from restless leg syndrome studies, OL extension data included. Rotigotine n=404.	SP628, SP666, and SP709, and SP710

Source Safety Update pp. 22-3, 25-8.

2.3 Exposure

Schwarz provided a table that updated the number of subjects exposed and person time exposure to rotigotine after inclusion of the new safety data. I include that table below.

Rotigotine exposure with final formulation

Population	Subjects, n (%)	Subject-years of exposure
Phase 1[a]		
Healthy volunteers	552	NA
Subjects with hepatic or renal impairment	33	NA
Phase 2/3		
Subjects with early-stage Parkinson's disease (Pool S3 cumulative in Final Safety Update)[b]		
>0 months	1220 (100)	1661
>6 months	654 (54)	1550
>12 months	550 (45)	1481
>24 months	452 (37)	1332
Subjects with advanced-stage Parkinson's disease (Pool AS3 cumulative in Final Safety Update)		
>0 months	1151 (100)	1094
>6 months	682 (59)	984
>12 months	360 (31)	751
>24 months	189 (16)	521
Subjects with Restless Legs Syndrome (RS3 cumulative in Final Safety Update)[c]		
>0 months	404 (100)	466
>6 months	255 (63)	449
>12 months	225 (56)	429
>24 months	69 (17)	148

NA=Not applicable
a. This population now includes 5 additional subjects from SP786.
b. This population includes 106 subjects who participated in the Phase 1 trials SP630 and SP651.
c. This population includes 24 subjects who participated in the Phase 1 trial SP628.
Data source: Table 1.1, Table 501.1, Table 701, Table 801, CTR Listing 5.1 and Listing 5.2.

Compared to the previous safety update, the Final Safety Update includes modest increases in the number of rotigotine exposed subjects from the early PD (n=127) and RLS (n=17) indication studies and a more marked increase in the number of subjects from the advanced PD indication studies (n=562).

2.4 Deaths

New deaths from Early PD Trials

Schwarz reported that since their last Safety Update there have been 11 new deaths in rotigotine treated subjects from early PD trials. All 11 deaths occurred during open label trials. The reported causes of death among the rotigotine treated subjects were myocardial infarction (n=3), carcinoma (n=2), cardiac failure/pulmonary edema, sepsis, cerebrovascular disorder, respiratory insufficiency, cardiopulmonary arrest[1], and

[1] This death was reported by Schwarz as due to respiratory disorder (preferred term acute airway obstruction) but the narrative states that the patient died of a cardiopulmonary arrest and there is no documentation supporting acute airway obstruction.

vasculitis (rheumatoid vasculitis). I summarize information from these deaths in an appendix to this review.

These 11 new deaths occurred among 10 males and 1 female and the mean duration of rotigotine exposure prior to death was 856 days (median 992, range 99 to 1264 days). At the time of death, 1 subject was treated with 4.5mg, 1 subject was treated with 13.5mg, 6 subjects were treated with 18mg, 1 subject was treated with [redacted], and 2 subjects were treated with [redacted] of rotigotine (Final Safety Update, p.90).

Cumulative Deaths Early PD Trials New and Previously Reported Data, Pooled
Through the Final Safety Update cutoff date there have been a total of 13 deaths among rotigotine treated subjects from early PD trials. Eleven deaths were newly reported in the final safety update, one death was reported in the previous safety update and one death was reported in the NDA submission.

Based on the cumulative death total and exposure data, the mortality risk for early PD trials is 1.1% (13/1220) and the mortality rate is 0.8/100 PY (13/1661 PY). The cumulative mortality risk in the Final Safety Update is increased 5.5 fold compared to the mortality risk through the previous safety update (0.2%, 2/1093). The cumulative mortality rate in the final safety update is 4 times higher than the mortality rate through the previous safety update (0.2/100PY, 2/979 PY).

New Deaths from Advanced PD trials
Schwarz reported that since their last Safety Update there have been 13 new deaths among rotigotine treated subjects in advanced PD trials. One death occurred during a double blind RCT and the remaining 12 deaths occurred during open label trials. The reported causes of death were cerebrovascular disorder (2), pneumonia (2), myocardial infarction (2), coronary artery disease, bronchial carcinoma, intestinal obstruction, pulmonary embolism, renal carcinoma, accident, and suicide. I summarize information from these deaths in an appendix to this review. The "accident" death was a motor vehicle accident in which the subject crossed lanes into oncoming traffic and was killed. The autopsy did not find evidence of heart or brain disease that would result in the accident and therefore sleep attack is not excluded as a possible cause of this event.

Twelve of the new advanced PD deaths occurred in males and one occurred in a female. The subject from the RCT that died had been taking rotigotine for 27 days. For the 12 deaths from open label trials, the mean duration of rotigotine exposure prior to death was 488.3 days (median 727.5 days, range 133-1096 days). At the time of death, 1 subject was treated with 4.5mg, 1 subject was treated with 13.5mg, 1 subject was treated with 18mg, 2 subjects were treated with 22.5mg, 6 subjects were treated with 27mg, and 2 subjects were treated with [redacted] of rotigotine (Final Safety Update, p.131).

Cumulative Deaths Advanced PD trials New and Previously Reported Data, Pooled
Schwarz reported that through the Final Safety Update cutoff date there have been a total of 16 deaths among rotigotine treated subjects from advanced PD trials. Thirteen deaths were newly reported in the final safety update, one death was reported in the previous

safety update and two deaths were reported in the NDA submission. Two additional deaths were reported in previous safety update (Subjects SP650/11102, and SP650 11107) but were excluded from the Final Safety Update submission, presumably because these deaths occurred more than 30 days after the last dose of rotigotine.

Based on the cumulative death total and exposure data, the mortality risk for advanced PD trials is 1.4% (16/1151) and the mortality rate is 1.5/100 PY (16/1094 PY). The cumulative mortality risk in the Final Safety Update is increased 2.8 fold compared to the mortality risk through the previous safety update (0.5%, 3/589). The cumulative mortality rate in the final safety update is 1.9 times higher than the mortality rate through the previous safety update (0.8/100PY, 3/397).

Deaths from Restless Leg Syndrome Trials
No deaths have been reported for subjects enrolled in Restless Leg Syndrome studies through the Final Safety Update cutoff.

Deaths from Phase I studies
No deaths have been reported for subjects enrolled in Phase I studies through the Final Safety Update cutoff.

2.5 Serious Adverse Events

As with the death presentation, the SAEs were presented as pooled analyses for the different study indications.

New SAEs from Early PD trials
Schwarz reported that for the new data in the Final Safety Update 128 (18%, 128/705) subjects experienced 211 new SAEs. Schwarz did not detect any clusters of events among the new SAEs (Final Safety Update, p.92). The SAEs reported by at least 1% of the subjects with new safety data in the Final Safety Update were accident (2%, 15/705), myocardial infarction (1.4%, 10/705), arthrosis (1%, 8/705), and fall (1%, 7/705).

In order to identify less frequently reported SAEs of potential concern, I read through table 545.2 that listed all new SAEs reported for subjects in early PD trials in the Final Safety Update. Five subjects had SAEs of hallucinations and 2 subjects had SAEs of sleep attacks. One subject reported each of the following SAEs: application site reaction, arrhythmia, arrhythmia ventricular, and rhabdomyolysis. I summarize these SAEs in an appendix to this review. There were no reported SAEs of hepatic failure, hepatic necrosis, pancreatitis, renal failure, aplastic anemia, neutropenia, or toxic epidermal necrolysis.

Cumulative SAEs Early PD Trials New and Previously Reported Data, Pooled
Through the Final Safety Update cutoff date, 210 rotigotine subjects (17%, 210/1220) have experienced 353 SAEs. The SAEs reported by at least 5 subjects from early PD trials were accident (2%, 21/1220), myocardial infarction (1%, 13/1220), surgical intervention (1%, 12/1220), fall (0.9%, 11/1220), arthrosis (0.8%,10/1220), intervertebral disc disorder (0.7%, 8/1220), application site reaction (0.6%, 7/1220), chest pain (0.6%,

7/1220), hallucination (0.5%, 6/1220), sleep attacks (0.5%, 6/1220), syncope (0.4%, 5/1220), parkinsonism aggravated (0.4%, 5/1220), coronary artery disorder (0.4%, 5/1220), and hernia inguinal (0.4%, 5/1220) (Final Safety Update, p.91).

In the early PD trials, through the previous safety update, 12.1% (132/1093) subjects reported 186 SAEs (NDA Safety Review, p.12). After addition of the new data in the Final Safety update, there has been a 1.4 fold increase in SAE risk among rotigotine treated subjects.

For specific SAEs, there were instances where the risk increased when comparing the combined pooled data including new SAEs in the Final Safety Update to the risks present through the previous safety update. These risk increases were due to relatively small increases in the numbers of SAEs. In the table below, I list the SAEs which had at least a 1.5 fold increase in risk in the Final Safety Update pooled data compared to the previous safety update.

Comparison of Select SAE Risks from Previous Safety Update and the Final Safety Update (pooled data), Early PD Trials.

SAE	Previous Safety Update Risk	Final Safety Update pooled Risk	RR
Hallucination	0.2% (2/1093)	0.5% (6/1220)	2.5
Intervertebral disc disorder	0.3% (3/1093)	0.7% (8/1220)	2.3
Myocardial infarction	0.5% (5/1093)	1% (13/1220)	2.0
Arthrosis	0.4% (4/1093)	0.8% (10/1220)	2.0
Accident	1.2% (13/1093)	2% (21/1220)	1.7
Chest pain	0.4% (4/1093)	0.6% (7/1220)	1.5
Fall	0.6% (7/1093)	0.9% (11/1220)	1.5

Source NDA Safety Review p.12, Final Safety Update, p.91.

Cumulative SAEs from Advanced PD trials through the Final Safety Update Cutoff
Through the Final Safety Update cutoff date, 17% (198/1151) of rotigotine subjects from advanced PD studies experienced 342 SAEs. The SAEs reported by at least 5 subjects from advanced PD trials were accident (2%, 25/1151), parkinsonism aggravated (2%, 19/1151), cerebrovascular disorder (1%, 11/1151), hallucination (0.7%, 8/1151), fall (0.7%, 8/1151), bacterial infection (0.7%, 8/1151), chest pain (0.6%, 7/1151), syncope (0.6%, 7/1151), myocardial infarction (0.6%, 7/1151), atrial fibrillation (0.5%, 6/1151), intervertebral disc disorder (0.5%, 6/1151), cardiac failure (0.5%, 6/1151), dyskinesia (0.4%, 5/1151), pneumonia (0.4%, 5/1151), surgical intervention (0.4%, 5/1151), intracranial hemorrhage (0.4%, 5/1151) (Final Safety Update, p.133).

In order to identify less frequently reported SAEs of potential concern, I read through table 716.2 that listed all the SAEs reported for subjects in advanced PD trials through the Final Safety Update cutoff (cumulative). Four subjects had each of the following SAEs: application site reaction, sleep attack, and anemia. Two subjects experienced acute renal failure and 2 subjects experienced rhabdomyolysis. One subject reported each of the following SAEs: arrhythmia, AV block, jaundice, and bullous eruption. There were no

reported SAEs of hepatic failure, hepatic necrosis, pancreatitis, aplastic anemia, neutropenia, or toxic epidermal necrolysis. In an appendix to this review I summarize clinical details from the SAEs listed above that were not summarized in the NDA review.

Cumulative SAEs from RLS trials through the Final Safety Update Cutoff
Through the Final Safety Update cutoff date, 10% (40/404) of rotigotine subjects from RLS studies experienced 50 SAEs. The SAEs reported by at least 3 rotigotine subjects in RLS studies were accident (<1%, 3/404), syncope (<1%, 3/404), arthrosis (<1%, 3/404), and medical procedure (<1%, 3/404) (Final Safety Update, p.148).

In order to identify less frequently reported SAEs of potential concern, I read through table 816.2 that listed all the SAEs reported for subjects in advanced PD trials through the Final Safety Update cutoff (cumulative). There were no reported SAEs of application site reactions, sleep attacks, anemia, arrhythmia, hallucinations, rhabdomyolysis, hepatic failure, hepatic necrosis, pancreatitis, aplastic anemia, neutropenia, or toxic epidermal necrolysis.

SAEs from Phase I Trials SP786 and SP787
No SAEs were reported for either of these newly completed Phase I trials included in the Final Safety Update (Final Safety Update, p.156).

2.6 Disposition

Early Parkinson's disease Trials New Data
For the new safety data group (pool S3 new), Schwarz reported that 24% (166/705) of rotigotine subjects discontinued from early PD trials. The reasons for discontinuation were adverse event (11%, 74/705), subject withdrew consent (7%, 46/705), lack of efficacy (3%, 21/705), other (1%, 9/705), lost to follow up (1%, 8/705), unsatisfactory compliance of subject (<1%, 5/705) and protocol violation (<1%, 1/705) (Safety Update p.37).

Early PD New and Previously Reported Data, Pooled
When the new safety data were combined with the data from previous submissions (pool S3), Schwarz reported that 32% (394/1220) of subjects discontinued from early PD trials. The reasons for discontinuation for the S3 pool were adverse event (18%, 219/1220), subject withdrew consent (7%, 85/1220), lack of efficacy (6%, 68/1220), other (1%, 14/1220), lost to follow up (<1%, 11/1220), unsatisfactory compliance of subject (<1%, 8/1220) and protocol violation (<1%, 4/1220) (Safety Update, p.36).

2.7 Discontinuations for AEs

Early PD Trials, New Data
For the new safety data group (pool S3 new), Schwarz reported that 9.4% (66/705)[2] of rotigotine subjects discontinued from early PD trials for AEs. Application site reaction (2.8%, 20/705) was the only AE leading to discontinuation of at least 1% of rotigotine subjects included in the new S3 data pool (Final Safety Update, p.99).

In order to identify less frequently reported AEs leading to discontinuation of potential concern, I read through table 553.1 that listed all the new AEs leading to discontinuation reported for subjects in early PD trials in the Final Safety Update. Six rotigotine subjects (<1%, 6/705) discontinued for hallucinations. One subject (512OL 010803) discontinued for SGPT increase, SGOT increased, and GGT increased (listed in table 554.1.3). No new early PD rotigotine subjects discontinued for AEs of sleep attacks, arrhythmia, rhabdomyolysis, hepatic failure, hepatic necrosis, pancreatitis, anemia, aplastic anemia, neutropenia, or toxic epidermal necrolysis. I summarize details for the subject who discontinued for elevated transaminases (512OL/010803) in an appendix to this review.

Early PD New and Previously Reported Data, Pooled
Through the Final Safety Update cutoff date, 227 rotigotine subjects (19%, 227/1220) discontinued for AEs. The AEs leading to discontinuation of at least 5 rotigotine subjects from early PD trials were application site reaction (6%, 73/1220), nausea (2%, 25/1220), somnolence (1.6%, 19/1220), vomiting (1.1%, 14/1220), contact dermatitis (1%, 12/1220), hallucination (<1%, 9/1220), hypotension postural (<1%, 9/1220), headache (<1%, 8/1220), sleep attacks (<1%, 5/1220), depression (<1%, 5/1220), and hypotension (<1%, 5/1220) (Final Safety Update, table 653.2).

In the early PD trials, through the previous safety update, 15.8% (173/1093) subjects discontinued for AEs (NDA Safety Review, p.22). After addition of the new data in the Final Safety update, there has been a slight increase in the percentage of rotigotine subject that have discontinued for AEs.

For specific AEs leading to discontinuation, there were instances where the risk increased when comparing the updated risks in the Final Safety Update to the risks present through the previous safety update. These risk increases were due to relatively small increases in the numbers of discontinuations due to AEs. In the table below, I list the AEs leading to discontinuation which had at least a 1.5 fold increase in risk in the Final Safety Update pooled data compared to the previous safety update.

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[2] As in the NDA, the Safety Update included a discrepancy when reporting discontinuations for AEs. In the Disposition section for pool S3 trials (new), Schwarz reported that 11% of subjects discontinued for AEs, yet in the discontinuation for adverse events section, Schwartz reported that 9.4% of subjects discontinued for AEs. When asked about this apparent discrepancy at the time of the NDA review, Schwartz explained that the difference was primarily due to discrepancies between Trial Termination sheets (reason for termination field, used for the Disposition section) of the CRFs and AE CRF pages (outcome of AE field, used for the Discontinuation for AE section). Schwartz either did not resolve the discrepancies or did not receive responses to queries of investigators about discrepancies.