London, 6 April 2006
Product name: **Sifrol**
Procedure number: **EMEA/H/C/133/II/30**

SCIENTIFIC DISCUSSION

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1. Introduction

Pramipexole is a non-ergot dopamine agonist with high in vitro specificity at the D2 subfamily of dopamine receptors. Pramipexole is a full agonist and exhibits higher affinity for the D3 receptor subtype than for D2 or D4 receptor subtypes. It is structurally different from the ergot-derived drugs.

Pramipexole tablets were approved in the US in 1997 for the treatment of signs and symptoms of Parkinson's disease, followed by marketing authorisations in the European Union (EU), Norway, Switzerland, Australia, Canada, Japan, Eastern European countries, countries in the Near and Far East, and South America.

In addition to the approved indication in advanced and early stage Parkinson's disease the MAH has submitted an application for the extension of the indication to

"Sifrol tablets are indicated for symptomatic treatment of idiopathic Restless Legs Syndrome (RLS) ".

Consequential changes were introduced in section 4.2 (dose adjustment), 4.4 (augmentation phenomenon), 4.8 (hallucination) and 5.1 (addition of subheadings "Clinical trials in Parkinson's disease" and "Clinical trials in Restless Legs Syndrome").

RLS is a neurological sensory-motor disorder characterised by four essential diagnostic criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and updated in 2003, with an estimated prevalence in the general population of 2.5% to 15%. The majority of patients who consult a primary care physician receive inappropriate treatment. The current treatment options for RLS are levodopa/benserazide. Although treatment with levodopa is effective in the short term, the long-term use of levodopa is complicated by the frequent occurrence of augmentation. Dopamine agonists, including pramipexole, were regarded as first line treatment in 'Principles and Practice of Sleep Medicine' (3rd Ed., Saunders, 2000).

Prior to initiation of pivotal clinical trials, the MAH sought scientific advice from CHMP on the clinical trial programme (EMEA/CHM P/5122/02, 17 October 2002).

The CHMP asked for a 3-month double-blind placebo controlled study to assess short-term efficacy. However for the assessment of maintenance efficacy randomised double-blind trials of 6-12 months duration were deemed necessary. In these trials also rebound and augmentation were to be evaluated. The RLS rating scale was considered an adequate endpoint for the pivotal trials. The primary analysis based on mean difference from baseline may be strengthened by a secondary responder analysis. The MAH did not consider it feasible to run a 6-month parallel group, placebo controlled study as the drop out rate in the placebo group was expected to be very high, which could have led to an imbalanced treatment group size at the end of the study jeopardizing the acceptance of the statistical analysis. In such a situation the ICH guideline topic E 10 recommends a long-term, placebo-controlled withdrawal design. The MAH expected that a long-term trial (6-12 months duration) would be jeopardized by a high drop out rate in the placebo group and therefore chose a withdrawal design. However, the ICH guideline E10 does not specify that an expected high dropout rate necessarily should lead to the preference of the withdrawal design. It is the opinion of the CHMP that a positive 6-12 months placebo controlled trial would lead to significant more information with regard to efficacy and safety.

The CHMP proposed a long-term active comparator trial with levodopa as the best choice. An active comparator study with L-dopa/benserazide was not performed as this combination was registered for idiopathic RLS only in Germany and Switzerland. Thus it could not be regarded as an accepted 'gold standard' throughout Europe. Although levodopa/benserazide was not approved in all involved countries, a comparative trial would have provided very valuable insight into the efficacy and safety of pramipexole (e.g. augmentation). This is further exemplified by the fact that 42% of patients in study 248.546 had previously taken dopa and dopa derivatives.

The CHMP accepted the concept of the inclusion of a mixed population in the development programme, including pre-treated and *de novo* patients. The MAH included a mixed population in the development programme, including pre-treated and *de novo* patients. The inclusion of a mixed population was endorsed by both parties. This gives an opportunity for post-hoc/secondary analysis of efficacy in relation to baseline disease state (IRLSRS/CGI).

2. Quality aspects

For the new indication doses of up to 0.75 mg salt will be recommended. Considering that tablets containing 0.75 mg salt are not readily available, this dose can be administered in the form of 3 tablets containing 0.25 mg salt corresponding to 0.54 mg base or 1 tablet each containing 0.5 mg and 0.25 mg salt corresponding to 0.53 mg base. The CHMP considered it acceptable to express the dose as 0.54 mg base in the product information.

3. Non clinical aspects

The definitive pathophysiology of RLS has not been determined, but neuropharmacological evidence might suggest a mild striatal presynaptic dopaminergic dysfunction. A disinhibition of normal CNS pacemakers has also been suggested. There is not any special animal model for this disorder. To support treatment of Parkinson's disease, pramipexole underwent a comprehensive pharmacodynamic, pharmacokinetic and toxicological evaluation, which data has been provided in the initial marketing authorisation application (MAA). The MAH's conclusion of the nonclinical safety assessment provided for pramipexole in Parkinson's disease is therefore endorsed. No safety concerns are predicted from the preclinical point of view associated with the use of pramipexole to RLS patients, in whom the exposure will be substantially lower than that for patients with Parkinson's disease.

4. Clinical aspects

Clinical trials conducted outside the community

According to Art. 8.3(ib) of Directive 2001/83/EC, as amended, and Art. 6 of Regulation (EC) No. 726/2004, the MAH was asked to provide a statement on that the clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The MAH responded that study 248.543 was performed in the US and in the study report it is stated: "The trial was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the ICH tripartite Guideline for Good Clinical Practice (GCP) and in accordance with the applicable regulatory requirements, which was considered acceptable by the CHMP.

Pramipexole tablets containing 0.125mg, 0.25mg, and 0.5mg pramipexole dihydrochloride monohydrate (corresponding to 0.088 mg and 0.35 mg pramipexole base) were used in the RLS clinical trial programme. These 3 dose strengths are already approved / marketed in the EU. For study 248.543 carried out in the US, the same formulation was used.

4.1 Clinical pharmacology

To support the RLS indication, the steady state pharmacokinetics of pramipexole tablets administered once daily to RLS patients was investigated as a sub-study of study 248.546. No other clinical pharmacology studies profiling the pharmacokinetics of pramipexole were conducted as part of the RLS development programme.

The study was performed during the 6-month open-label, uncontrolled phase of the study 248.546, during which all patients were titrated to an individually optimised dose within the first four weeks (starting dose = 0.125 mg; maximum dose = 0.75 mg).

The CHMP considered that the pharmacokinetic parameters in 25 patients suffering from idiopathic RLS provided evidence that the pharmacokinetics of pramipexole is generally comparable between this study and previous studies with pramipexole in healthy volunteers and patients suffering from Parkinson's disease. However, the pharmacokinetic information gained from the present study is limited, but since the dose used in RLS is lower than in Parkinson's disease patients and no other PK factors are believed to differ significantly between healthy subjects and RLS patients, the present study is considered sufficient with regard to PK in patients with RLS. Effects of gender, age and renal function on the pharmacokinetics of pramipexole are essentially the same as previously reported and therefore no new statement is proposed for the SPC.

4.2 Clinical efficacy

4.2.1 Introduction

To confirm efficacy and safety in this therapeutic indication the MAH set up a clinical trial programme consisting of four randomised, double-blind, placebo-controlled trials. This programme included approximately 1000 patients treated for up to 12 weeks. Open continuation trials lasted for up to 1 year. The clinical study programme consisted of the following studies:

1. Pivotal trial: Study 248.543. Multicentre fixed-dose trial conducted in the US
2. Pivotal trial: Study 248.546. Multicentre European (German) sustained efficacy trial
3. Supportive trial: Study 248.515. Single-centre polysomnography study
4. Supportive trial: Study 248.520. Multicentre European flexible-dose trial

4.2.2 Clinical trials

Study 248.543

Methods

With this study, short-term (12 weeks) efficacy and safety of pramipexole was evaluated in a randomised, double-blind, placebo-controlled, fixed-dose design. Patients were randomised to placebo or 0.25 mg, 0.5 mg, or 0.75 mg of pramipexole. The focus was on clinical parameters of RLS. The primary endpoint was the change in the Restless Legs Syndrome Rating Scale (RLSRS) score from baseline and Clinical Global Impression - Improvement (CGI-I) after 12 weeks of treatment. The fixed-dose design permitted a direct comparison of the different pramipexole doses with placebo. In addition, augmentation was evaluated using the Augmentation Severity Rating Scale (ASRS). In total, 344 patients were treated and constituted the safety population. The study was conducted in 45 centres (43 centres treated patients) in the US.

The ***primary endpoint*** was the change in RLSRS total score from baseline to Week 12 (ANCOVA) and the proportion of CGI-I responders at Week 12 (CMH). For the last observation carried forward (LOCF) method, the latest value available was used for endpoint calculation. ***Secondary endpoints*** were the Clinical Global Impression (CGI) subscales (severity of illness, therapeutic effect, side effects), RLSRS-responders, level of daytime sleepiness (ESS), change in visual analogue scales (VAS) of RLS severity, Patient Global Impression (PGI), Augmentation Severity Rating Scale (ASRS), and RLS-related quality of life (Johns Hopkins RLS-QoL).

In the placebo group 75 patients (87.2%), and in the overall pramipexole group 206 patients (79.8%) completed the study. Among the pramipexole dose groups 88.6% (0.25 mg), 76.3% (0.5 mg), and 74.4% (0.75 mg) completed the study. In the placebo group 12.8% of patients discontinued the study prematurely compared with 11.4% (0.25 mg), 23.8% (0.5 mg), and 25.6% (0.75 mg) for each of the pramipexole dose groups. The most frequent reason for premature discontinuation was the occurrence of adverse events in 7.0% (placebo), 5.7% (0.25 mg), 13.8% (0.5 mg), and 17.8% (0.75 mg) of patients. The majority of patients were of Caucasian origin (97.3%), only 2.7% of patients were of African-American or Asian origin. Overall, 62.2% of patients were female and 37.8% were male, the mean age was 51.4 years, and the mean RLSRS total score at baseline was 23.5.

The CHMP considered that a post-hoc analysis in patients with International restless Legs Syndrome study group Scale (IRLSRS) >24 (as defined recently by the CHMP as moderate to severe RLS) should be performed by the MAH. The MAH responded that the results reveal that pramipexole is significantly more effective than placebo in patients with a RLSRS score at baseline ≤24 as well as in patients with a RLSRS score at baseline > 24. This effect is demonstrated across three trials (study grouping: double-blind periods of 248.515, 248.520, 248.543 in the Full Analysis Set (FAS) population). Following assessment of the MAH's responses the CHMP considered that the effect (difference in RLSRS between placebo and pramipexole) was highest in patients with IRLSRS >24 (as defined by the CHMP as moderate to severe RLS). The CHMP concluded that the MAH should adapt the CHMP definition of moderate to severe RLS (IRLSRS > 24) and define this as the RLS population for which pramipexole is indicated.

The CHMP considered that the MAH should discuss the impact of patient withdrawals in the study. The FAS (using LOCF) and the per-protocol set are not sufficient to estimate the extent of bias that has potentially been introduced. Following the MAH's responses the CHMP considered that the discontinuation was dose related (in contrast to the efficacy). Most of discontinued cases had "Other adverse event" stated as the reason for discontinuation. No clear differences could be observed between placebo and pramipexole, besides the number of discontinued patients, with regard to reason for discontinuation. The analysis of RLSRS in patients who discontinued do not raise concern, that the dropout rate influence the efficacy conclusions.

Results

Primary endpoints

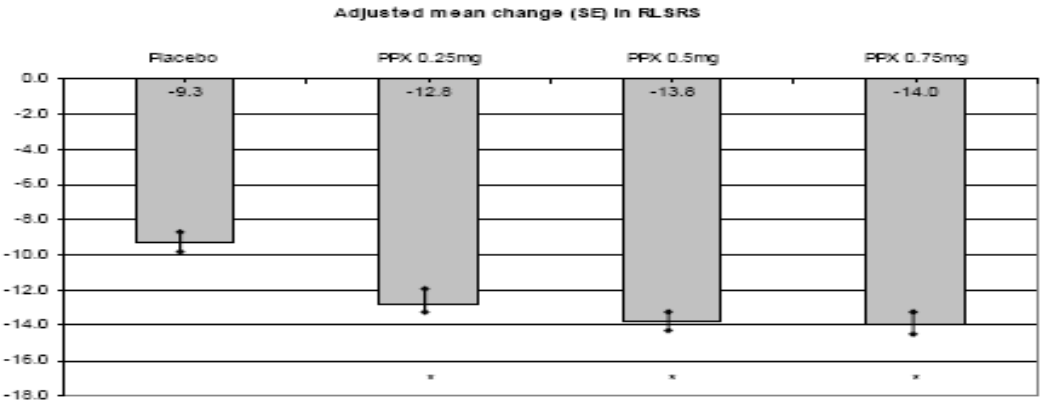
Primary endpoint - Reduction in RLSRS

At Week 12, the adjusted mean changes in RLSRS total score (p-value vs. placebo) were -9.3 (placebo), -12.8 (0.25 mg, p=0.0086), -13.8 (0.5 mg, p=0.0011), and -14.0 (0.75 mg, p=0.0005).

Table 11.4.1.1.1: 2 Analysis of covariance per randomized treatment groups for RLSRS score change from baseline at final visit (12 weeks) / FAS

RLSRS Total Score	Placebo	Pramipexole 0.25 mg	Pramipexole 0.5 mg	Pramipexole 0.75 mg
Number of Patients	85	88	79	87
Baseline				
Mean (SD)	23.5 (5.2)	23.4 (4.9)	22.9 (5.1)	24.1 (5.2)
Treatment phase				
Mean (SD)	14.1 (9.2)	10.3 (8.8)	9.5 (8.7)	9.6 (9.5)
Change from baseline				
Mean (SD)	-9.4 (9.1)	-13.1 (9.5)	-13.4 (9.7)	-14.4 (9.0)
Adjusted mean* (SE)	-9.3 (1.0)	-12.8 (1.0)	-13.8 (1.0)	-14.0 (1.0)
Difference from Placebo				
Adjusted mean* (SE)		-3.6 (1.3)	-4.6 (1.4)	-4.7 (1.3)
95% confidence interval		[-6.2, -0.9]	[-7.3, -1.8]	[-7.4, -2.1]
p-value	-	0.0086	0.0011	0.0005

* Analysis of covariance with factors treatment and pooled centre, covariates age and baseline RLSRS
Source data: Chapter 15, Table 15.2.1:1, Appendix 16.1.9.2, Statdoc 6.1.1.3



* indicates significant at the 5% level vs. placebo.

Figure 11.4.1.1.1: 1 Adjusted RLSRS mean change (SE) from baseline at final visit (12 weeks) / FAS

The MAH stratified the treatment response with regard to baseline RLSRS score.

Table 3.3.3: 1 Treatment response in RLSRS total score by baseline RLSRS severity in studies 248.515 (period 1), 248.520 (period 1), 248.543 / FAS

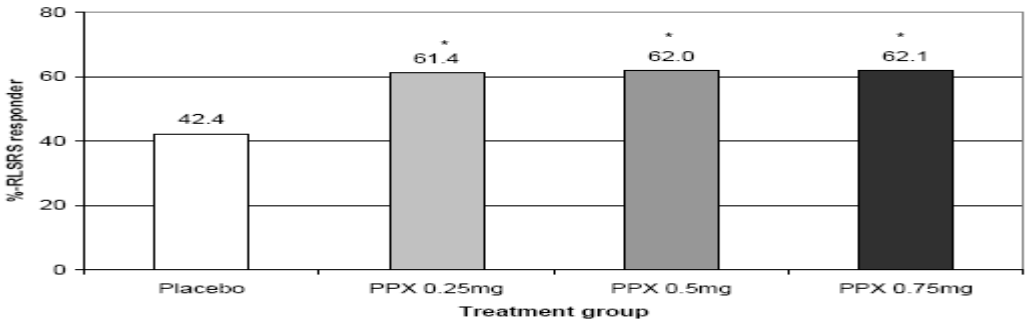
RLSRS at baseline	248.515 *		248.520 **		248.543 ***	
	PBO	PPX	PBO	PPX	PBO	PPX
Moderate RLS (11-20)						
Number of Patients	6	26	31	50	28	84
Adjusted mean change from baseline (SE) °	-1.3 (2.0)	-10.9 (1.0)	-4.3 (1.4)	-8.2 (1.2)	-6.9 (1.5)	-9.3 (0.9)
Adjusted mean difference to placebo (SE) °		-9.6 (2.3)		-3.9 (1.7)		-2.4 (1.8)
95% CI		(-14.3, -5.0)		(-7.4, -0.5)		(-5.9, 1.1)
p-value		0.0002		0.0274		0.1784
Severe RLS (21-30)						
Number of Patients	13	58	66	146	51	144
Adjusted mean change from baseline (SE) °	-9.3 (2.0)	-16.9 (0.9)	-6.7 (1.2)	-12.3 (0.8)	-9.6 (1.4)	-14.8 (0.8)
Adjusted mean difference to placebo (SE) °		-7.5 (2.2)		-5.6 (1.4)		-5.1 (1.6)
95% CI		(-11.9, -3.1)		(-8.3, -2.8)		(-8.2, -2.1)
p-value		0.0011		<.0001		0.0012
Very severe RLS (31-40)						
Number of Patients	2	2	17	28	6	26
Adjusted mean change from baseline (SE) °	N/A	N/A	-3.0 (2.9)	-20.6 (2.2)	-19.9 (7.0)	-16.0 (2.7)
Adjusted mean difference to placebo (SE) °		N/A		-17.7 (3.9)		4.0 (8.5)
95% CI		N/A		(-25.5, -9.8)		(-15.3, 23.2)
p-value		N/A		<.0001		0.6536

* After 3 weeks of double-blind treatment, secondary endpoint.
** After 6 weeks of double-blind treatment, co-primary endpoint.
*** After 12 weeks of double-blind treatment, co-primary endpoint.
° Adjusted (ANCOVA with treatment, pooled centre) for baseline, age

Table 11.4.1.2.1: 3 Analysis of RLSRS Response at final visit / FAS

RLSRS Response	Placebo N (%)	PPX 0.25 mg N (%)	PPX 0.5 mg N (%)	PPX 0.75 mg N (%)	PPX Total N (%)	Total N (%)
Total	85 (100.0)	88 (100.0)	79 (100.0)	87 (100.0)	254 (100.0)	339 (100.0)
Non-Responder	49 (57.6)	34 (38.6)	30 (38.0)	33 (37.9)	97 (38.2)	146 (43.1)
Responder	36 (42.4)	54 (61.4)	49 (62.0)	54 (62.1)	157 (61.8)	193 (56.9)
p-value for CMH comp. to placebo*	-	0.0075	0.0124	0.0135	0.0019	-

* Cochran-Mantel-Haenszel test with pooled centre stratification
Source data: Table 15.2.1: 3



* indicates significant at the 5% level vs. placebo

Figure 11.4.1.2.1: 1 RLSRS Response after 12 weeks / FAS, LOCF

Stratified analysis of response in relation to RLSRS at baseline showed that the efficacy of treatment (with regard to RLSRS reduction) increased with increasing RLSRS at baseline. The highest effect was found in patients with high baseline RLSRS (Severe/very severe RLS). A difference of only -2.4 in RLSRS found in patients with moderate RLS further emphasise this. The CHMP considered that there was a significant reduction in RLSRS for both placebo and pramipexole treated patients. However, the difference in RLSRS response between placebo and pramipexole is of doubtful clinical relevance in light of the high placebo response.

The MAH responded that in published literature an adjusted treatment difference of -2.5 and -3.0 points on the RLSRS scale is described as clinically relevant in two studies using a flexible dose design. In light of the achieved treatment difference of -4.3 points in a fixed dose trial this can be regarded as a clinically relevant result. Due to the fixed dose design in study 248.543, individual patients may not have received optimal treatment, whereas the flexible dose design allows for individual dose optimisation and hence increased efficacy. This is confirmed in the 6-week double-blind period of Study248.520 where a flexible dose design was used. Following the MAH's responses the CHMP considered that the efficacy of pramipexole is in line with products with similar modes of action.

The CHMP questioned the robustness of the study as the results are changed in the direction of the effect size (in favour of placebo for very severe RLS). The MAH responded that the adjusted mean effect size (SE) for placebo treated patients in RLSRS of -19.9 (7.0) is exceptional, but that this result is based on a small subgroup of 6 patients only, showing a large standard error and is therefore considered not to be conclusive, as well as that the change from baseline in RLSRS score in severe and very severe RLS patients is similar (-14.8, -16.0, respectively). Following the MAH's responses the CHMP considered that the exceptionally high placebo response observed for very severe RLS (and thus the change of direction of the effect size) may be due to small sample size.

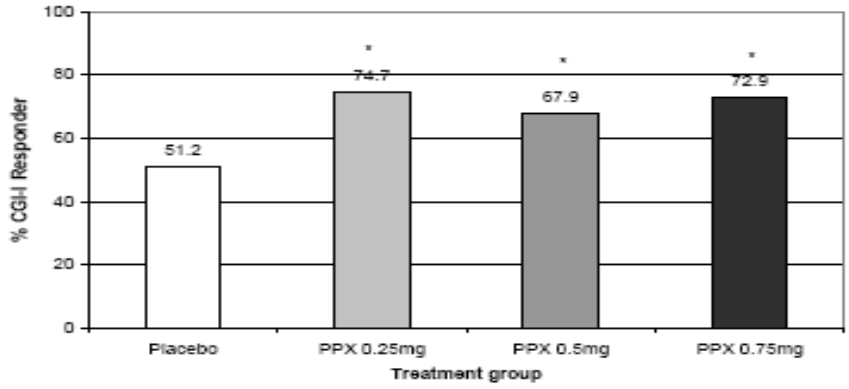
Primary endpoint - Proportions of CGI-I responders

The proportions of CGI-I responders (p-value vs. placebo) were 51.2% (placebo), 74.7% (0.25 mg, p=0.0005), 67.9% (0.5 mg, p=0.0484), 72.9% (0.75 mg, p=0.0038). At the final visit, the RLSRS-responder rates were (p-value vs. placebo): 42.4% (placebo), 61.4% (0.25 mg, p=0.0075), 62.0% (0.5 mg, p=0.0124), and 62.1% (0.75 mg, p=0.0135).

Table 11.4.1.1.4: 1 Analysis of CGI-Improvement at final visit (12 weeks) / FAS

CGI-Improvement	Placebo N (%)	PPX 0.25 mg N (%)	PPX 0.5 mg N (%)	PPX 0.75 mg N (%)	PPX Total N (%)
Total	84 (100.0)	87 (100.0)	78 (100.0)	85 (100.0)	250 (100.0)
Non-Responder	41 (48.8)	22 (25.3)	25 (32.1)	23 (27.1)	70 (28.0)
Responder	43 (51.2)	65 (74.7)	53 (67.9)	62 (72.9)	180 (72.0)
p-value for CMH comp. to placebo*	-	0.0005	0.0484	0.0038	0.0005

* Cochran-Mantel-Haenszel test with pooled centre stratification
Source data: Table 15.2.1: 9-10



* indicates significant at the 5% level vs. placebo

Figure 11.4.1.1.4: 1 Proportion of responders in Clinical Global Impressions - Global Improvement at final visit (12 weeks) / FAS

The CHMP considered that improvement in CGI-I was correlated with RLSRS. The responder rate is characterized by a high responder rate in placebo treated patients.

Primary endpoint - Time course in 'the change in RLSRS total score'

Assessment of the time course of the primary endpoint, 'the change in RLSRS total score' was analysed at Weeks 4, 6 and 12 using data of those patients, who provided an assessment after 4 weeks, which was extended, if necessary by LOCF. After 4 weeks the treatment difference compared to placebo of -6 points was highly significant ($p<0.0001$). This was confirmed after 6 weeks (0.25mg: $p<0.0005$; 0.5mg: $p<0.0001$; 0.75mg: $p<0.0001$). Due to the analysis approach of using the last

retrievable value, after 12 weeks the minimal treatment effect was -3.6 points, but still all doses were significant. Similar observations were also seen in the PPS population analysis.

Table 11.4.1.2.1: 1 RLSRS mean change from baseline over time / FAS (LOCF)

RLSRS total score	Placebo	PPX 0.25 mg	PPX 0.5 mg	PPX 0.75 mg	PPX Total	Total
Baseline						
N	83	87	76	85	248	331
Mean	23.5	23.4	22.9	24.1	23.5	23.5
SD	5.3	4.8	5.2	5.2	5.1	5.1
Median	23.0	23.0	22.5	24.0	23.0	23.0
After 4 weeks (V6)						
N	83	87	76	85	248	331
Mean	14.8	8.3	9.2	10.0	9.1	10.6
SD	8.7	8.4	8.1	9.8	8.8	9.1
Median	14.0	8.0	8.0	9.0	8.0	10.0
Change from baseline (V6)						
N	83	87	76	85	248	331
Mean	-8.6	-15.1	-13.7	-14.1	-14.4	-12.9
SD	8.4	9.3	8.8	10.1	9.4	9.5
Median	-8.0	-16.0	-14.0	-15.0	-15.0	-13.0
p-value vs. placebo	-	<0.0001	<0.0001	<0.0001	<0.0001	-
After 6 weeks (V7)						
N	83	87	76	85	248	331
Mean	14.0	9.3	8.4	9.0	8.9	10.2
SD	8.5	8.4	8.0	9.3	8.6	8.8
Median	13.0	9.0	6.5	8.0	8.0	10.0
Change from baseline (V7)						
N	83	87	76	85	248	331
Mean	-9.5	-14.2	-14.5	-15.1	-14.6	-13.3
SD	8.1	9.0	9.2	9.2	9.1	9.1
Median	-8.0	-16.0	-15.5	-16.0	-16.0	-14.0
p-value vs. placebo	-	0.0005	<0.0001	<0.0001	<0.0001	-
After 12 weeks (V9)						
N	83	87	76	85	248	331
Mean	13.9	10.2	9.1	9.4	9.6	10.7
SD	9.2	8.9	8.6	9.5	9.0	9.2
Median	13.0	9.0	7.5	8.0	8.0	9.0
Change from baseline (V9)						
N	83	87	76	85	248	331
Mean	-9.6	-13.2	-13.8	-14.6	-13.9	-12.8
SD	9.1	9.5	9.6	9.1	9.3	9.4
Median	-8.0	-14.0	-15.0	-14.0	-14.0	-13.0
p-value vs. placebo	-	0.0124	0.0009	0.0008	0.0002	-

Source data: Appendix 16.1.9.2, Table 6.1.1.2, Statdoc 6.1.1.4

The CHMP considered that the efficacy of pramipexole seems to ware off with time (difference being -6 points after 4 weeks, dropping to -3.6 points, after 12 weeks). This warrants further assessments of efficacy in long-term trials i.e. 6 – 12 months double blind trials as suggested by the CHMP. The explanation previously provided by the MAH for not conducting a study of this length (not feasible due to expected high dropout-rate in the placebo group) was not considered valid in light of current experience with pramipexole. The CHMP considered that the Study 248.546 did not provide evidence for maintained efficacy over 9 months of treatment. Under all circumstances the wearing off of treatment effect is not assessed in this study design (no placebo group for comparison within the first 6 months of treatment). Study **248.546 (Pivotal study)** cannot be used to assess whether the effect of pramipexole in RLS wears off with trial duration (no placebo group for comparison in the first 6 moths). In the 12-week **pivotal Study 248.543** there is a 25% reduction in efficacy over the last 8 weeks of treatment. Comparisons across studies **248.543, 248.515 and 248.520** indicate decreased efficacy with trial duration. The data indicate that efficacy of pramipexole compared to placebo is wearing off with trial duration. Thus, the MAH was requested to provide stopping rules for continued treatment beyond 3 months since the effect compared to placebo wears off with treatment duration, which should be mentioned in the SPC.

Secondary endpoint

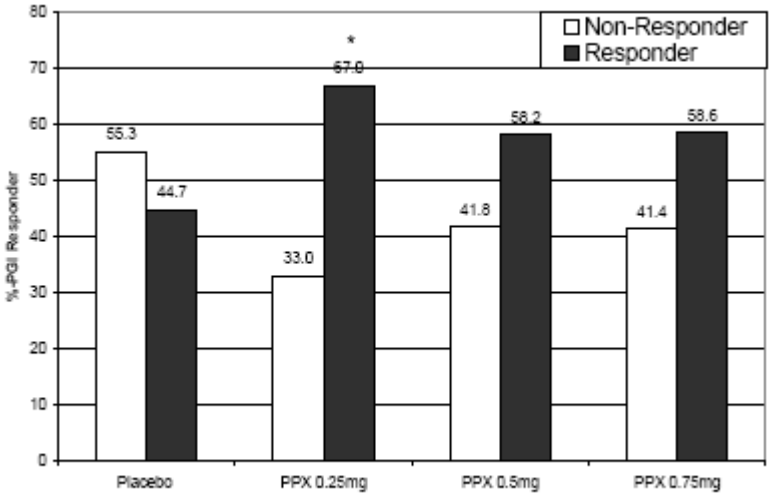
Secondary endpoint - Patient Global Impression (PGI) after 12 weeks

In the pramipexole total group, 61.4% of patients were PGI responders after 12 weeks compared with 44.7% in the placebo group. The Cochran-Mantel-Haenszel test with stratification by pooled centre showed a significant difference in favour of pramipexole total (p=0.0056). The pramipexole 0.25 mg group revealed significance, while the other treatment groups were not significantly different than placebo.

Table 11.4.1.2.3: 1 Analysis of PGI at final visit (12 weeks) / FAS, LOCF

PGI-Improvement	Placebo N (%)	PPX 0.25mg N (%)	PPX 0.5mg N (%)	PPX 0.75mg N (%)	PPX Total N (%)	Total N (%)
Total	85 (100.0)	88 (100.0)	79 (100.0)	87 (100.0)	254 (100.0)	339 (100.0)
Non-Responder	47 (55.3)	29 (33.0)	33 (41.8)	36 (41.4)	98 (38.6)	145 (42.8)
Responder	38 (44.7)	59 (67.0)	46 (58.2)	51 (58.6)	156 (61.4)	194 (57.2)
p-value for comp. to placebo*	-	0.0023	0.0867	0.0680	0.0056	-

* Cochran-Mantel-Haenszel test with pooled centre stratification
Source data: Table 15.2.2: 14-15



* indicates significance at the 5% level vs. placebo

Table 11.4.1.2.3: 2 PGI – Improvement after 1, 4, 6 and 12 weeks / FAS, LOCF

PGI – Global Improvement -ALL CENTRES-	Placebo N (%)	PPX 0.25 mg N (%)	PPX 0.5 mg N (%)	PPX 0.75 mg N (%)	PPX Total N (%)	Total N (%)
Number of patients	85 (100.0)	88 (100.0)	79 (100.0)	87 (100.0)	254 (100.0)	339 (100.0)
After 1 week (V3)						
Non-responder	73 (85.9)	47 (53.4)	45 (57.0)	54 (62.1)	146 (57.5)	219 (64.6)
Responder	12 (14.1)	41 (46.6)	34 (43.0)	33 (37.9)	108 (42.5)	120 (35.4)
p-value CMH for comp. to placebo	-	<.0001	<.0001	0.0003	<.0001	-
After 4 weeks (V6)						
Non-responder	54 (63.5)	28 (31.8)	32 (40.5)	34 (39.1)	94 (37.0)	148 (43.7)
Responder	31 (36.5)	60 (68.2)	47 (59.5)	53 (60.9)	160 (63.0)	191 (56.3)
p-value CMH for comp. to placebo	-	<0.0001	0.0035	0.0044	-	-
After 6 weeks (V7)						
Non-responder	45 (52.9)	30 (34.1)	30 (38.0)	27 (31.0)	87 (34.3)	132 (38.9)
Responder	40 (47.1)	58 (65.9)	49 (62.0)	60 (69.0)	167 (65.7)	207 (61.1)
p-value CMH for comp. to placebo	-	0.0104	0.0020	0.0371	-	-
After 12 weeks (V9)						
Non-responder	47 (55.3)	29 (33.0)	33 (41.8)	36 (41.4)	98 (38.6)	145 (42.8)
Responder	38 (44.7)	59 (67.0)	46 (58.2)	51 (58.6)	156 (61.4)	194 (57.2)
p-value CMH for comp. to placebo	-	0.0619	0.0864	0.2326	-	-

Source data: Table 15.2.2: 16-17, Appendix 16.1.9.2, Table 6.5.1.4

The CHMP considered that in the pramipexole total group, 61.4% of patients were PGI responders after 12 weeks compared with 44.7% in the placebo group, which was significant. However, when comparing the individual dosages, the difference was not significant. The effect (i.e. difference between treatment and placebo) did wear off with time. This parameter warrants further assessments of efficacy in long-term trials i.e. 6 – 12 months double blind trials as previously suggested by the CHMP.

Secondary endpoint - Visual Analogue Scales (VASs) for the assessment of RLS severity / FAS

The VASs used in this Study are a self-designed instrument that was not validated against any other assessment scale. Therefore, inferences from this scale to other scales for the assessment of RLS symptoms are very limited.

The CHMP considered that a significant effect on the VAS was identified and as such the results of the VAS are supportive. However as indicated by the MAH, the VAS scales have not been validated against any other assessment scale and therefore it is difficult to draw definite conclusions from these findings.

Secondary endpoint - Analysis of Epworth Sleepiness Scale

At baseline, the mean score (±SD) was 8.1 (±4.4) in the placebo group and 7.5 (±4.5) for the pramipexole total group. At week 12, both treatment groups showed a decrease in the mean ESS score to 6.6 (±3.9) in the placebo group and to 5.8 (±4.0) in the pramipexole total group. The mean reduction in the placebo group was 1.6 (±3.8) compared with 1.7 (±4.0) in the pramipexole total group, which was not significant.

Table 11.4.1.2.5: 1 Analysis of Epworth Sleepiness Scale at final visit mean (12 weeks), change from baseline, means with SD, adjusted means with SE, and 95% CI / FAS

Epworth Sleepiness Scale	Placebo	Pramipexole 0.25 mg	Pramipexole 0.5 mg	Pramipexole 0.75 mg	Pramipexole Total
Number of Patients	85	88	79	87	254
Baseline					
Mean (SD)	8.1 (4.4)	7.5 (4.7)	7.5 (3.8)	7.5 (4.9)	7.5 (4.5)
Treatment phase					
Mean (SD)	6.6 (3.9)	5.3 (3.5)	6.2 (4.4)	5.9 (4.2)	5.8 (4.0)
Change from baseline					
Mean (SD)	-1.6 (3.8)	-2.2 (4.4)	-1.3 (4.2)	-1.6 (3.3)	-1.7 (4.0)
Adjusted mean* (SE)	-1.4 (0.4)	-2.2 (0.4)	-1.4 (0.4)	-1.7 (0.4)	-1.8 (0.2)
Difference from Placebo					
Adjusted mean* (SE)		-0.9 (0.5)	-0.0 (0.5)	-0.3 (0.5)	-0.4 (0.4)
95% confidence interval		[-1.9, 0.1]	[-1.0, 1.0]	[-1.3, 0.7]	[-1.3, 0.4]
p-value	-	0.0800	0.9656	0.5023	0.3028

* Analysis of covariance with factors treatment and pooled centre, covariates age and baseline RLSRS
Source data: Table 15.2.2: 6, Appendix 16.1.9.2, Statdoc 6.4.1.5

The CHMP considered that the Epworth Sleepiness Scale (ESS) did not reveal a difference between pramipexole and placebo.

Secondary endpoint - Augmentation Severity Rating Scale

Augmentation is defined as the worsening of RLS symptoms attributable to a specific therapeutic intervention for RLS and exhibits a shift of RLS symptoms, which occur 2 or more hours earlier than the observed time of onset of symptoms during the initial course of stable treatment, or the state before treatment initiation. For assessment of this phenomenon, the definition that augmentation should be present for at least 1 week, for a minimum of 5 days per week, to meet diagnostic criteria was applied in this study using the Augmentation Severity Rating Scale (ASRS) for measurement at end of treatment (Week 12). The augmentation score interpreted the changes from baseline (without providing a baseline score) and varies from 0 (no augmentation) to 4 (maximal augmentation). The highest ASRS scores calculated per treatment group were found between 2.0 and 2.25, with a median of 0.25 (placebo) and 0.5 (pramipexole groups and total). As can be seen below there was no significant measurable augmentation observed in any pramipexole dose group relative to placebo.

Table 11.4.1.2.6: 1 Analysis of the Augmentation Severity Rating Scale (ASRS) at final visit (12 weeks) / FAS

Augmentation severity rating scale dose group	Placebo		Pramipexole 0.25 mg		Pramipexole 0.5 mg		Pramipexole 0.75 mg		Pramipexole Total	
	N	%	N	%	N	%	N	%	N	%
All	80	100.0	76	100.0	68	100.0	71	100.0	295	100.0
ASRS score = 0	30	37.5	23	30.3	18	26.5	26	36.6	97	32.9
ASRS score in 0.25-0.5	25	31.3	23	30.3	24	35.3	14	19.7	86	29.2
ASRS score in >0.5 -1.0	19	23.8	22	28.9	21	30.9	23	32.4	85	28.8
ASRS score > 1	6	7.5	8	10.5	5	7.4	8	11.3	27	9.2
p-value CMH vs. placebo		-		0.7176		0.4547		0.2089		-

Source data: Table 15.22: 21

The CHMP considered that the MAH has provided the results of a new scale for the assessment of augmentation, and the results of the comparison of placebo versus individual dosages. Following the MAH's responses the CHMP considered that it is agreed that the rating scale is non-validated and the clinical significance therefore is difficult to interpret. Moreover, the study was not powered to show a difference in augmentation. Although not statistically significant, the results indicate that augmentation may be more often found in patients treated with pramipexole (the frequency of ASRS>0.5 is 29% higher for pramipexole treated compared to placebo). The CHMP considered that the issue resolved, but the clinical significance of augmentation need further consideration.

Secondary endpoint - Johns Hopkins RLS Quality of Life Scale

The CHMP considered that there was a significant effect of pramipexole as measured by the Johns Hopkins RLS Quality of Life Scale. There was a minor increase in the QoL for placebo treated patients from week 6 to week 12, but otherwise the effect as measured on the Johns Hopkins RLS Quality of Life Scale is reassuring with regard to maintained effect of pramipexole in RLS. However, the LOCF method could lead to overestimation of the effect of pramipexole and therefore an analysis of the PPS would be supportive.

Table 11.4.1.2.7: 2 Johns Hopkins RLS Quality of Life Scale over time / FAS

Johns Hopkins RLS-QoL	Placebo	PPX 0.25 mg	PPX 0.5 mg	PPX 0.75 mg
After 6 weeks (V7)				
Number of Patients	82	87	77	85
Baseline				
Mean (SD)	69.1 (16.3)	69.3 (16.3)	70.4 (14.7)	67.9 (19.6)
Treatment phase				
Mean (SD)	81.9 (15.6)	89.5 (12.0)	90.2 (9.8)	88.0 (15.7)
Adjusted* mean change(SE)	12.9 (1.3)	20.1 (1.3)	20.6 (1.4)	19.6 (1.3)
p-value	-	<0.0001	<0.0001	0.0003
After 12 weeks (V9)				
Number of Patients	82	87	77	85
Baseline				
Mean (SD)	69.1 (16.3)	69.3 (16.3)	70.4 (14.7)	67.9 (19.6)
Treatment phase				
Mean (SD)	82.5 (17.8)	88.6 (12.5)	90.7 (10.5)	88.2 (14.8)
Adjusted* mean change(SE)	13.5 (1.4)	19.2 (1.4)	21.3 (1.5)	19.5 (1.4)
p-value	-	0.0041	0.0002	0.0029

* Analysis of covariance with factors treatment and pooled centre, covariates age and baseline RLS-QoL
Source data: Table 15.2.2: 21

The MAH provided analysis for the PPS population is shown in the below table and supports the results of the FAS analysis. The adjusted difference to placebo in the PPS analysis is even larger when compared to the pramipexole combined dose groups. These data confirm that the LOCF method used for the primary analysis did not lead to an overestimation of the pramipexole effect. The CHMP agreed that the analysis for the PPS population supports the results of the FAS analysis.

Table 19.1 Analysis of the Johns Hopkins Quality of life scale (FAS and PPS)

FAS analysis	Placebo	PPX 0.25mg	PPX 0.5mg	PPX 0.75mg	PPX total
N	83	88	78	87	253
Adj. mean change from baseline (SE)	13.5 (1.4)	19.3 (1.4)	21.1 (1.5)	19.4 (1.4)	19.9 (0.8)
Adj. mean change from placebo [95% CI]		5.8 [1.9;9.7]	7.6 [3.6;11.6]	5.9 [2.0;9.8]	6.4 [3.2;9.6]
p-value		0.0034	0.0002	0.0029	<0.0001
PPS analysis	**Placebo**	**PPX 0.25mg**	**PPX 0.5mg**	**PPX 0.75mg**	**PPX total**
N	61	70	55	65	190
Adj. mean change from baseline (SE)	14.0 (1.6)	20.6 (1.5)	21.8 (1.7)	19.5 (1.6)	20.6 (0.9)
Adj. mean change from placebo [95% CI]		6.6 [2.4;10.9]	7.8 [3.3;12.4]	5.5 [1.2; 9.8]	6.5 [3.0;10.1]
p-value		0.0023	0.0008	0.0124	0.0003

Source data: Attachment 7 (CTR App. 16.1.9.2, Statdocs 6.7.1.3, 6.7.2.3)

Study 248.546

Methods

The main objective of this study was the evaluation of long-term efficacy of pramipexole treatment compared to placebo in a randomised withdrawal design. During a 6-month open-label run-in phase, all patients received pramipexole (dose range 0.125 mg-0.75 mg). At month 6, responders based on RLSRS score and CGI-I were randomised to either continue on the same dose of pramipexole or to receive placebo under double-blind conditions. This study was performed at 13 centres in Germany and involved 224 patients of which 150 patients were randomised into the double-blind period.

The ***primary endpoint*** was time to a pre-defined target event (worsening of RLS as assessed by the CGI-I and the RLSRS score, RLSRS score > 15 and CGI-I at least 'minimally worse') during the second period of the study. In addition, in this study augmentation was evaluated using the Augmentation Severity Rating Scale. The ***secondary endpoints*** analysed during the FAS period 2 were CGI-severity of illness, CGI therapeutic effect, CGI-side effects, PGI, Johns Hopkins Quality of Life score, VASs, ESS, and ASRS.

In total, 224 patients were entered and treated with pramipexole in the open-label run-in phase (period 1). Of these, 41 patients (18.3%) discontinued prematurely in the open label phase. Overall, 150 patients were randomised in period 2 and 33 patients did not enter period 2. The second period of a nominal duration of 3 months was completed by 96 patients (64.0%) overall. With regard to treatment group, the frequency of premature discontinuations was much higher in the placebo group (65.3%) than in the pramipexole group (9.0%), as expected because of the randomised withdrawal design of period 2.

The CHMP considered that drugs with psychotropic effects are usually tapered off over a substantial period (usually weeks to months) to avoid the introduction of rebound phenomena and a rationale for not using a taper off in this trial should be provided. The MAH responded that in the current SPC for pramipexole tapering off is recommended from high doses to avoid possible symptoms suggestive of neuroleptic malignant syndrome which have been reported with abrupt withdrawal of dopaminergic therapy. However, tapering off is not recommended to avoid rebound phenomena. Parkinson's disease patients take their total daily dose in 3 equally divided doses, which leads to a very constant plasma level of pramipexole with a low peak/trough ratio. In contrast in RLS patients the peak/trough ratio of the plasma level is much higher compared to Parkinson's patients according to the once daily dosing. In study 248.546 the PK profile of pramipexole in RLS patients was investigated. The daily variation of PPX blood levels for 0.54 base (0.75mg of salt) is twice as high as the variation from trough to wash-out, and therefore the MAH considers it not necessary to taper off pramipexole in the indication RLS.

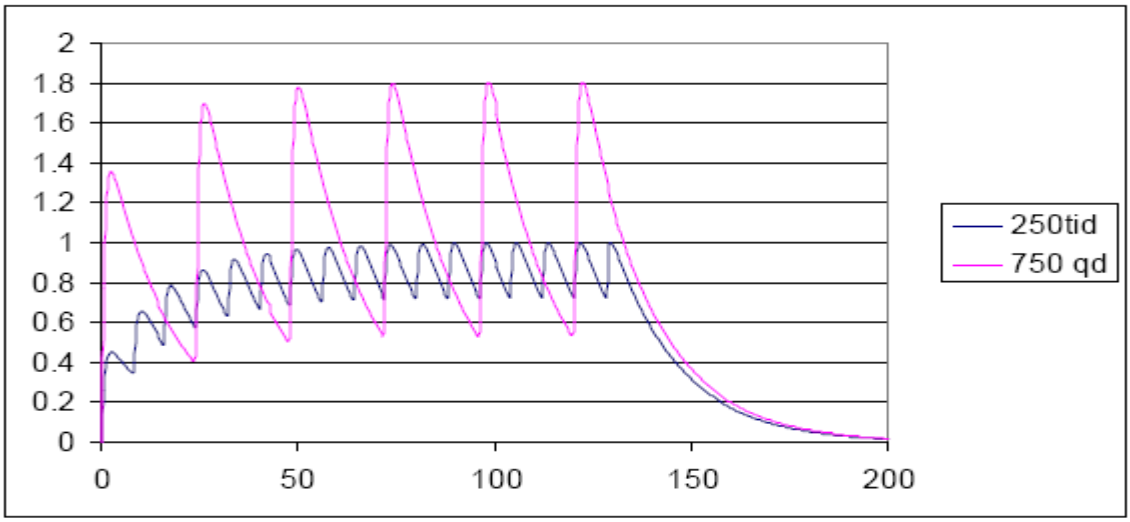


Figure 1: Simulated steady state plasma concentration time profiles after administration of 0.75 mg pramipexole q.d. (pink line) or 0.25 mg pramipexole t.i.d (blue line).

Following the MAH's responses the CHMP considered that the biological effect of pramipexole in RLS may well be present long after the blood concentration has reached low levels. The results presented do not provide evidence against the need to taper off pramipexole and do not exclude the possibility of rebound and need for taper off pramipexole in RLS. Rebound may be a problem after abrupt discontinuation, and should be reflected in the SPC. It was agreed to add the following sentence to section 4.2.2 of the SPC: "*Rebound (worsening of symptoms after abrupt discontinuation of treatment) can not be excluded.*"

Primary outcome - Time to target event was analysed with the Kaplan-Meier method

Below an overview of the occurrence of target events by treatment group and visit.

Table 11.4.1.1: 2 Kaplan-Meier estimates for the time to target event (by visits) in double-blind phase / FAS period 2

Kaplan-Meier analysis	Placebo At risk N (%)	Placebo Remaining N (%)	Placebo Survival estimate	Pramipexole At risk N (%)	Pramipexole Remaining N (%)	Pramipexole Survival estimate	Chi tes
Visit 10	69 (100.0)	69 (100.0)	1.0000	78 (100.0)	78 (100.0)	1.0000	
Visit 11	69 (100.0)	20 (29.0)	0.2899	78 (100.0)	70 (89.7)	0.9103	<0.
Visit 12	20 (29.0)	15 (21.7)	0.2174	70 (89.7)	67 (85.9)	0.8712	<0.
Visit 13	15 (21.7)	13 (18.8)	0.1884	67 (85.9)	65 (83.3)	0.8452	<0.
Visit 14	13 (18.8)	0 (0.0)	0.0761	65 (83.3)	0 (0.0)	0.7772	<0.
Log-Rank Test[2]					<0.0001		
First day of significant Fisher's exact test (p<0.05)					Day 2		

Source data: Table 15.2.1: 1
Relative to Visit 10, the following time windows were defined: Visit 11 = Day 3-10, Visit 12 = Day 11-28, Visit 13 = 29-53, Visit 14, Day >53
[1] Chi-Squared test is a comparison between treatment groups on cumulative counts of events
[2] Log-Rank test applies to non-categorised time to event

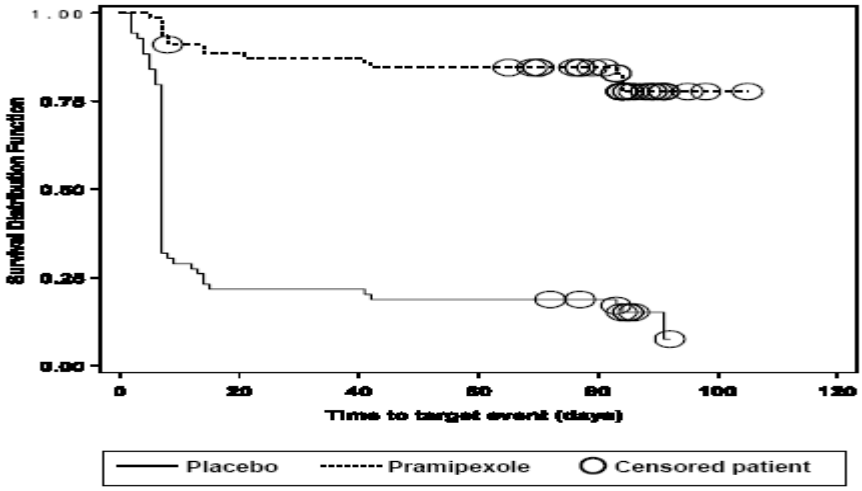


Figure 11.4.1.1: 1 Kaplan-Meier estimates of the time to target event (days) in the double-blind phase / FAS period 2

Table 11.4.1.1: 3 Analysis of the time to target event (days) in the double-blind phase / FAS period 2

Analysis of time to target event	Placebo	Pramipexole
Time taken to reach survival estimate of 0.85	5 days	42 days
Time taken to reach survival estimate of 0.50	7 days	>84 days [censored]

Source data: Table 15.2.1: 1

Table 11.4.1.2.1: 5 RLSRS total score, change from baseline period 2 (Visit 10) to final double-blind visit by treatment group; means with SD, adjusted means with SE, and 95% CI / FAS period 2

RLSRS total score		Placebo	Pramipexole
Number of patients		69	78
Baseline	Mean (SD)	10.01 (6.50)	8.72 (6.03)
Final DB visit	Mean (SD)	24.57 (11.06)	11.03 (9.13)
Change from baseline	Mean (SD)	14.55 (11.25)	2.31 (8.54)
	Adjusted mean* (SE)	14.86 (1.15)	2.03 (1.08)
Difference to placebo	Adjusted mean* (SE)		-12.83 (1.58)
	95% CI		[-15.96,-9.71]
	p-value		<0.0001

Source data: Table 15.2.2: 5
* Analysis of covariance with baseline RLSRS total score as a covariate

Table 11.4.1.2.1: 6 CGI-I ratings (combined categories) at the end of double-blind phase (compared to baseline period 2) by treatment group / FAS period 2

CGI-I (combined categories)	Placebo N (%)	Pramipexole N (%)
Number of patients	69	78
Improved[1]	5 (7.2)	18 (23.1)
No change	12 (17.4)	47 (60.3)
Worse[2]	52 (75.4)	13 (16.7)
p-value Mantel-Haenszel test		<0.0001

Source data: Table 15.2.2: 7
[1] Improved = Very much/Much/Minimally improved
[2] Worse = Very much/Much/Minimally worse

The CHMP considered that it seems quite evident that patients with a response to pramipexole treatment who were randomised to continued pramipexole or placebo did better on continued pramipexole with regard to the primary outcome parameters (time to event/change in RLSRS and CGI-I). However, the nature of the trial design makes it difficult to interpret. The difference observed may be due to lack of efficacy among placebo treated patients but may also reflect rebound following treatment for 6 months with a psychoactive drug (no taper). In addition, since the placebo response is extensive this is not evidence of sustained efficacy of pramipexole beyond 6 months of treatment. The trial therefore provides questionable evidence for long-term efficacy of pramipexole in RLS. The MAH responded that the trial design of a randomised withdrawal study is used to investigate whether responders to active treatment stay responders when the treatment is switched to placebo or whether the treatment effect vanishes after randomisation to placebo. In general it cannot be assumed that placebo treated patients will immediately deteriorate in such a setting. This trial design served also to counterbalance possible placebo responses as only treatment responders were randomised to the double-blind period. The results of Study 248.546 demonstrate the long-term efficacy of pramipexole

up to 9 months. Placebo treated patients deteriorated considerably after discontinuation of pramipexole, whereas patients who stayed on pramipexole showed a continued benefit. To avoid any bias due to a 'rebound' phenomenon after abrupt discontinuation of pramipexole, the MAH excluded those patients from the analysis, who experienced an immediate deterioration after one day. In a further analysis excluding all patients who had reached the predefined target event within 1 week after randomisation a highly significant statistical difference in the primary endpoint (time to target event) was still shown between pramipexole and placebo. This supports the findings from the primary analyses that early deterioration after discontinuation of pramipexole treatment is not biasing the treatment effect in favour of pramipexole. The MAH considers the results of this study are strong evidence for long-term efficacy of pramipexole in RLS. Following the MAH's responses the CHMP considered that the biological effect of pramipexole may extend longer than 1 week, despite the low plasma levels. And it is not excluded that rebound may be present more than 1 week after discontinuation of pramipexole (almost all the effect is seen within the first 3 weeks after randomisation).

For the double-blind phase (period 2), the safety period 2 population comprised all patients who received at least one dose of the study drug in period 2 (N=150). The FAS period 2 was formed by all patients in the safety period 2 population who provided Visit-10 RLSRS data and had at least one post-randomisation assessment of RLSRS / CGI-I, and who took at least 2 doses of randomised study medication on 2 consecutive days (N=147). The per-protocol set (PPS) period 2 was defined as all patients from the FAS period 2 without important protocol deviations (N=109). Overall, 39 patients were not included in the PPS period 2 due to important protocol deviations (38 patients from FAS period 2 plus patient 1262). The PPS period 2 thus represented 72.7% of the safety period 2 population

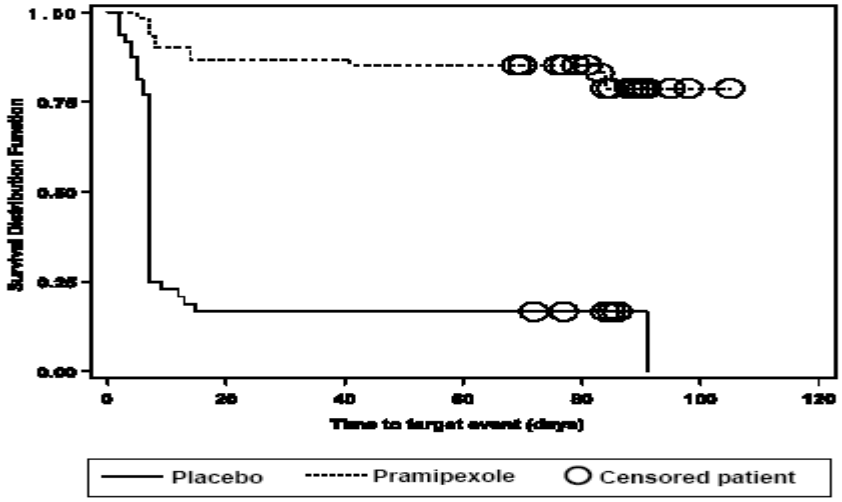


Figure 11.4.1.2.1: 1 Kaplan-Meier estimates of time to target event (days) in double-blind phase / PPS period 2

Source data: Figure 15.2.2: 1

There were a total of 39 protocol violations in the study (39/150 = 26%) after randomisation, most of which were found in the placebo group. The MAH responded that according to the clinical trial report of Study 248.546, the number of patients with protocol violations (PV) in the placebo group as 22 (30.6%) and in the pramipexole group 17 (21.8%) was higher in the placebo group compared to the pramipexole group.

The category 'Non-responder' covers all patients randomised without having fulfilled the responder criteria at the end of the 6-month open label period. The category 'No full compliance' covers all patients who did not take the trial drug continuously. The category 'Prohibited medication use' covers those patients who did not only take trial drug but also other RLS medications, which was not allowed due to the study protocol. These PVs were not linked to adverse events. Furthermore, the results within the PPS population, where patients with important PVs were excluded, confirm the results of the primary efficacy analyses performed in the FAS population. Following the MAH's responses the CHMP considered that as stated by the MAH the protocol violations does not reflect adverse events (RSL symptoms/augmentation).

Secondary endpoints

The CHMP considered that the secondary endpoints were in favour of pramipexole treatment, however shortcomings of the trial make the observations of limited value.

Secondary analysis - Assessment of efficacy in FAS Period 1

At the end of period 1, overall substantial improvements were observed for the following endpoints: RLSRS total score (mean change from baseline ˜15.7), RLSRS responder rate (76.6% full or partial responders), CGI-I (78.9% 'much / very much improved'), CGI severity of illness (51.8% sufficiently improved), CGI-therapeutic effect (80.3% sufficiently improved), PGI (80.2% improved), RLS-VASs (median changes from baseline were ˜41.0 mm [RLS severity while getting to sleep], ˜52.0 mm [RLS severity in the course of the night], ˜10.0 mm [RLS severity in the course of the day], and ˜39.0 mm [satisfaction with sleep]), and Johns Hopkins Quality of Life (median change from baseline +17.5). Few patients (6.0%) reported a significant interference of side effects with their function. Daytime sleepiness assessed by the ESS did not increase but showed some improvement (mean change from baseline ˜1.6). Substantial improvements were evident already after 1 to 2 weeks of treatment demonstrating the rapid onset of pramipexole treatment effects.

Table 11.4.1.2.3: 2 RLSRS response at the end of open-label phase (compared to baseline period 1) by final dose in open-label phase / FAS period 1

RLSRS Responder*	PPX 0.125mg N(%)	PPX 0.25mg N(%)	PPX 0.5mg N(%)	PPX 0.75mg N(%)	Total N(%)
Number of patients	13	61	68	80	222
Non-responders	3 (23.1)	10 (16.4)	13 (19.1)	26 (32.5)	52 (23.4)
Partial responders	1 (7.7)	14 (23.0)	6 (8.8)	9 (11.3)	30 (13.5)
Responders	9 (69.2)	37 (60.7)	49 (72.1)	45 (56.3)	140 (63.1)

Source data: Appendix 16.1.9.2, Table 6.4.1.3

* Non-responder = decrease of < 30% or increase in RLSRS since baseline, partial responder = decrease of 30% to <50% in RLSRS since baseline, responder = decrease of ≥50% in RLSRS since baseline

The CHMP concluded that the overall response rate (>50% reduction) in RLSRS was 63.1% in the 6 months open-label phase of the trial (Period 1), which compares to a response rate of 61.8% in Study 248.543. However, one would expect a higher response in an open trial with flexible titration (248.546) compared to a placebo-controlled trial with fixed dosages (Study 248.543). The MAH responded that open label trials cannot be compared with data from randomised controlled trials without introducing methodological flaws. However, the trial population in Study 248.543 had a baseline mean (SD) RLSRS total score of 23.5 (5.1) while in 248.546 the mean was 5 points higher with 28.5 (5.6), representing a more severely affected RLS population, as well as the number of patients already experienced in RLS treatment was higher in Study 248.546 (58.9%) compared to Study 248.543 (24.6%), which explains why the response rate in the populations meeting these two criteria is different. The data over time from Study 248.546 period 1 confirm that no wearing off was observed.

The CGI-I scale was applied only at the end of the open label phase prior to randomisation and cannot provide further insight. Following the MAH's responses the CHMP agreed with the conclusions reached by the MAH. However, since no placebo group was included in this trial, it is difficult to draw definite conclusions with regard to maintained efficacy.

Study 248.515

Methods

The main objective of the single centre study was to evaluate the short-term efficacy and safety (over 3 weeks) of different doses of pramipexole design (0.125 mg, 0.25 mg, 0.5 mg,0.75 mg) compared to placebo on periodic limb movements (PLM) and sleep parameters in patients with idiopathic restless legs syndrome (RLS).

The study performed in Finland involving 109 treated patients comprised of 2 periods was a randomised, placebo-controlled, double-blind, fixed-dose period of 3 weeks followed by 1 week of wash-out and an open-label flexible-dose period of 26 weeks. In period 1, patients were randomised to receive once daily either placebo or 0.125 mg, 0.25 mg, 0.5 mg, or 0.75 mg pramipexole for 3 weeks. All patients in the pramipexole groups started on 0.125 mg/day. For the higher dose groups, the dose was increased stepwise; the final dose was reached on Day 5 (0.25 mg), Day 9 (0.5 mg), and Day 13 (0.75 mg).

The ***primary endpoint*** was the change from baseline to Week 3 in the periodic limb movements during time in bed index (PLMI) representing the hourly rate of periodic limb movements. ***Secondary endpoints*** were the change in RLSRS total score and the clinical global impression scale for improvement (CGI-I), sleep parameters, and quality of life (SF-36).

Results

Primary endpoint - Periodic limb movements during time in bed index (PLMI)

The CHMP concluded that there was a significant reduction in periodic limb movements during sleep.

Secondary endpoint - RLSRS total score and percentage of patients with very much improved or much improved CGI-I

The CHMP considered that although reduction in RLSRS was a secondary outcome measure, a significant reduction in RLSRS was found in this very short study. Similar positive results were found for CGI-I. The MAH chose to compare the efficacy in terms of RSLRS change across studies.

Table 3.2.2.2: 1 RLSRS total score by treatment (PBO / PPX) in the 248.515, 248.520, 248.543 studies, and overall, at baseline and study end; means with SD, medians, mean and median changes from baseline, adjusted mean changes from baseline, differences to placebo / FAS

	248.515 *		248.520 **		248.543 ***		Total	
	PBO	PPX	PBO	PPX	PBO	PPX	PBO	PPX
Number of Patients	21	86	114	224	85	254	220	564
Baseline								
Mean (SD)	22.9 (4.2)	22.7 (4.1)	24.9 (5.4)	24.7 (5.2)	23.5 (5.2)	23.4 (5.1)	24.2 (5.3)	23.8 (5.0)
Median	24.0	23.0	25.0	24.5	23.0	23.0	24.0	24.0
Study end								
Mean (SD)	16.7 (6.5)	7.7 (7.3)	18.8 (10.0)	12.3 (9.3)	14.1 (9.2)	9.8 (9.0)	16.8 (9.6)	10.5 (9.0)
Median	16.0	7.0	20.0	12.0	13.0	9.0	18.0	9.0
Change from baseline								
Mean (SD)	−6.2 (6.5)	−15.0 (7.8)	−6.1 (9.0)	-12.4 (10.1)	−9.4 (9.1)	−13.6 (9.4)	−7.4 (8.9)	−13.4 (9.5)
Median	−8.0	−15.0	−4.0	−12.5	−8.0	−14.0	−6.0	−14.0
Adjusted mean° (SE)	−5.9 (1.5)	−15.1 (0.8)	−5.7 (0.9)	−12.3 (0.6)	−9.3 (1.0)	−13.5 (0.6)	-	-
Difference to placebo								
Adjusted mean° (SE)		−9.2 (1.7)		−6.6 (1.1)		−4.3 (1.1)	-	-
95% CI	-	(−12.6, −5.8)	-	(−8.6, −4.5)	-	(−6.4, −2.1)	-	-
p-value °°	-	<.0001	-	0.0001	-	<.0001	-	-

* After 3 weeks of double-blind, fixed-dose treatment, RLSRS was secondary endpoint.
** After 6 weeks of double-blind, flexible-dose treatment, RLSRS was primary endpoint.
*** After 12 weeks of double-blind, fixed-dose treatment, RLSRS was primary endpoint.
° Adjusted (ANCOVA with treatment, pooled centre) for baseline and age.
°° p-value for difference between placebo and pramipexole within studies.

The CHMP considered that although not a primary outcome, in Study 248.515 there was a significant reduction in RLSRS after 3 weeks of double blind fixed dose treatment. The pooling of data from studies with different duration is questionable because of differences in design (flexible versus fixed dose) and since the efficacy of RLSRS wears off with duration of treatment within the pivotal Study 248.543. However, comparing efficacy across studies shows a consistent reduction in efficacy with

increased trial duration. The results warrant further assessment in long term, placebo controlled trials (6-12 months).

Following the MAH's responses the CHMP considered that comparisons of results between trials with different populations and design should always be cautioned – and consequently the reasons provided by the MAH (single centre versus multi centre and selected population (a PLMS index> 5/h at baseline) may well be involved. However they do not exclude or contradict that the differences may be related to trial duration. The explanations provided by the MAH do not exclude that the observed differences between the studies are related to trial duration

Trial no.	Duration	Difference in RLSRS (pramipexole versus placebo)
248.515	3 weeks	9.2
248.520	6 weeks	6.6
248.543	12 weeks	4.3

The efficacy of pramipexole was shown across studies for CGI.

Table 3.2.2.3.1: 1 CGI-I assessments (combined categories[#]) by treatment (PBO/PPX) for studies 248.515 248.520, 248.543, and overall / FAS

	248.515 * 3-week data		248.520 ** 6-week data		248.543 *** 12-week data		Total	
CGI-I (combined categories)	PBO N (%)	PPX N (%)	PBO N (%)	PPX N (%)	PBO N (%)	PPX N (%)	PBO N (%)	PPX N (%)
Total	21 (100.0)	86 (100.0)	114 (100.0)	224 (100.0)	84 (100.0)	250 (100.0)	219 (100.0)	560 (100.0)
Improved	9 (42.9)	65 (75.6)	37 (32.5)	141 (62.9)	43 (51.2)	180 (72.0)	89 (40.6)	386 (68.9)
Essentially unchanged	12 (57.1)	21 (24.4)	74 (64.9)	79 (35.3)	37 (44.0)	61 (24.4)	123 (56.2)	161 (28.8)
Worsened	0 (0.0)	0 (0.0)	3 (2.6)	4 (1.8)	4 (4.8)	9 (3.6)	7 (3.2)	13 (2.3)

* after 3 weeks of double-blind treatment, CGI-I was a secondary endpoint.
** after 6 weeks of double-blind treatment, CGI-I was a primary endpoint.
*** after 12 weeks of double-blind treatment, CGI-I was a primary endpoint.
[#] improved = 'very much improved' and 'much improved';
essentially unchanged = 'minimally improved', 'no change', and 'minimally worse';
worsened = 'much worse' and 'very much worse'

The CHMP considered that the Study 248.515 was not designed to show a difference in CGI-I. However, more patients improved with pramipexole on the CGI-I compared to placebo. As for the majority of other outcome parameters, a significant placebo response was observed. The pooling of data between studies with different design and duration is questionable, however, comparison across studies for CGI-I leaves the impression of a "wearing off effect" of pramipexole.

Secondary endpoint - Quality of life (SF 36)

The results of SF-36 standard physical component scale and standard mental component scale are shown below. The CHMP considered that no effect on quality of life as measured with SF36 standard physical component scale and standard mental component scale could be observed. Effects on quality of life may not be pronounced after short-term treatment.

Secondary endpoint - RLSRS total score during the open-label treatment (FAS period 2 population)

At baseline, all dose groups had similar mean RLSRS scores; the overall mean score was 23.0±4.3, indicating a population with moderate to severe RLS symptoms. At the end of week 30, reductions of the mean RLSRS scores were observed in all dose groups. Overall the mean reduction of the RLSRS score was 16.9±7.8.

Study 248.520

Methods

This study provided short-term (6 weeks) and long-term (46 weeks) data on efficacy and safety of pramipexole in a multi-centre flexible-dose design (dose range 0.125 mg-0.75 mg). The first 6 weeks were a randomised parallel-group double-blind study of pramipexole (flexible-dose) vs. placebo. The focus was on clinical parameters of RLS: The co-primary endpoints were the change in the RLSRS score from baseline and CGI-Global Improvement after 6 weeks of treatment. Patients who were responders after 6 weeks of treatment continued with double-blind medication for a further 46 weeks while patients who were non-responders received open-label pramipexole. Overall, 345 patients were treated in 37 centres in 5 European countries for 6 weeks.

The ***primary endpoints*** for efficacy were the change in RLSRS total score from baseline to week 6 and the proportion of CGI-I responders (much improved, very much improved) at week 6. ***Secondary endpoints*** were ESS, PGI, quality of life (SF-36) and VAS for RLS severity.

Results

The CHMP considered that a significant response for both primary outcome variables was observed in this short-term (6 weeks) FAS period of the trial, which was supported by several secondary outcome measures in period 1.

4.3 Clinical safety

A total of 889 patients with RLS received at least one dose of pramipexole and 295 patients at least one placebo dose in the course of the four studies. The planned pramipexole doses used in the RLS programme were 0.125, 0.25, 0.5, and 0.75 mg/day.

The main analysis of adverse events (AEs) was based on data from study grouping 2 (double-blind periods), where 575 patients were treated with pramipexole and 223 patients with placebo.

The CHMP considered that discontinuation in the study 248.543 due to adverse events was substantially higher for pramipexole than for placebo (11.6% in pramipexole and 5.8 % in placebo group).

Overall, the frequency of AEs in the double-blind periods of studies 248.515, 248.520, and 248.543 (study grouping 2) was higher in the pramipexole than in the placebo group, i.e., 419 (72.9%) patients in the pramipexole group and 141 (63.2%) in the placebo group experienced at least one AE. In both treatment groups, AEs most commonly belonged to the system organ class “nervous system disorders” (30.4% pramipexole and 26.0% placebo) or “gastointestinal disorders” (29.7% pramipexole and 13.9% placebo).

Nausea and somnolence were important adverse events – especially in the elderly population. These adverse events were found more frequently among patients treated with pramipexole. The risk of adverse events should be put in context of the modest efficacy of pramipexole. Nausea and fatigue decreased with duration of the trial, which is expected since the adverse events are probably dose related and therefore may lead to dose reduction (flexible dose) or discontinuation (fixed dose). The assumption made by the MAH that insomnia is an effect of disease rather than of the Study drug is probably correct, but it is disappointing that pramipexole did not have a positive effect on this parameter. The prevalence of insomnia remained almost constant throughout the study treatment. A similar trend was observed for insomnia in patients in the placebo group, suggesting this was an effect of the disease rather than of the study drug.

In the pramipexole group in study grouping 2, female patients had a higher incidence of AEs than male patients (77.8% of 370 females vs. 63.9% of 205 males). AEs of the system organ class “gastrointestinal disorders” were more frequent in female (34.6%) than male patients (21.0%), whereas the frequencies of AEs in the system organ class “nervous system disorders” were similar (31.9% females and 27.8% males). In the pramipexole group, AEs that were more frequently reported in female patients were nausea (20.8% females vs. 6.3% males) and fatigue (10.5% females vs. 5.4% males). Both AEs were also reported more frequently in the placebo group for females compared to males (nausea in placebo group: 6.7% females vs. 2.7% males; fatigue in placebo group: 7.3% females

vs. 6.8% males). The CHMP considered that frequencies of adverse events (fatigue and nausea) should be described in the SPC in relation to gender. The following text will be included in section 4.8 of the SPC: "*Nausea and fatigue were more often reported in female patients treated with SIFROL (20.8% and 10.5% respectively) compared to males (6.7 % and 7.3% respectively).*"

The ***dose relationship of AEs*** was evaluated for the fixed-dose, double-blind periods of studies 248.515 (3-week treatment period) and 248.543 (12-week treatment period), analysed by randomised treatment group. The overall incidence of AEs in the different dose groups was similar, i.e., 17/21 (81.0%) patients experienced an AE with 0.125 mg compared to 85/110 (77.3%) with 0.25 mg, 81/102 (79.4%) with 0.5 mg, and 86/112 (76.8%) with 0.75 mg pramipexole. A dose relationship for AEs belonging to the system organ class "gastrointestinal disorders" and psychiatric disorders was observed. The CHMP concluded that the frequency of most adverse events was related to drug dose. This confirms that the adverse events are related to pramipexole and not an effect of disease.

Twenty-nine of 889 patients (3.3%) treated with pramipexole in the four clinical studies reported at least one ***SAE***. All SAEs were considered unrelated to the Study drug by the investigator. With the exception of the two fatal cases, and of two patients whose SAEs had not resolved at the close of the trial, all patients recovered from their episodes. Four of 295 patients (1.4%) treated with placebo reported at least one SAE in the four clinical studies. The CHMP considered that serious adverse events were more frequent among pramipexole treated patients (3.3%) compared to placebo (1.4%), but all were considered to be unrelated to drug. Further assessment in long-term placebo controlled trials would give a possibility to assess this issue in detail.

Clinical Laboratory Evaluations

The following parameters were evaluated: Haematology: Haematocrit, haemoglobin, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count, platelets, neutrophils, poly segment neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Coagulation: Prothrombin time (PT), Prothrombin time-international normalised ratio´(PT-INR), and activated partial thromboplastin time (APTT). Enzymes: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyltransferase (GGT), cholinesterase, lactate dehydrogenase (LDH), amylase, lipase. Substrates: Glucose, total cholesterol, blood urea nitrogen, creatinine, creatinine clearance, total bilirubin, direct bilirubin, triglycerides, uric acid, total protein, and albumin. Electrolytes: Sodium, potassium, calcium, chloride, and phosphate. Urinalysis: Protein, nitrite, glucose, ketone, RBC, WBC, blood, and pH, and further microscopic evaluations if the dip-stick test revealed any findings. Other: Ferritin, iron, thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Across all studies (Study grouping 1), there was no – or only marginal – change in median values from baseline to last assessment for any laboratory parameter in the pramipexole and placebo groups. The CHMP considered that clinical laboratory evaluation does not give rise to concern with regard to safety.

Vital signs

Overall, there were no clinically relevant changes in ***systolic blood pressure*** in both treatment groups. The CHMP considered that the effect on ***orthostatic reaction*** and pulse rate has not been sufficiently evaluated in this population. In general, there were no clinically relevant changes in the pulse rate in both treatment groups and based on frequency of adverse event reporting and the relatively low dose of pramipexole used in the RLS population, orthostatic reactions does not seem to constitute a major problem.

In general, there were no differences between the pramipexole and placebo groups with respect to ***physical examination*** findings. The CHMP considered that physical examination is a rough measure of adverse events – probably not sufficiently sensitive to pick up minor changes in the patients overall physical condition.

Dermatological examinations

Of a total of 316 patients treated with pramipexole in these studies undergoing dermatological examination, no case of melanoma was identified. The CHMP considered that as the studies were all short term trials, they probably were being too short to pick up any sign relating to the development of skin melanoma, however it is reassuring that no cases of melanoma occurred.

The MAH will continue to monitor the occurrence of melanoma as part of their post marketing surveillance and discuss respective findings in the forthcoming PSURs.

Safety in special populations: Children

All studies were performed in adults, and therefore no safety data are available on the use of pramipexole in paediatric patients with RLS.

Safety in special populations: Hepatically impaired patients

The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. However, because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment is not expected to have a significant effect on pramipexole elimination.

Safety in special populations: Renally impaired patients

The safety of pramipexole in renally impaired patients was assessed as part of the Parkinson's disease development programme, during which it was determined that pramipexole clearance correlates well with creatinine clearance in patients with varying degrees of renal impairment. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance (P98-7305). No patients with renal impairment (defined as having significant renal disease or creatinine clearance lower than 50 mL/minute) were included in the RLS clinical studies.

Safety in special populations: Elderly patients

In the RLS clinical studies, AEs were analysed by subgroups according to the age groups <65 years and >65 years in study grouping 2 and 4, to assess whether or not age influences the AE profile of pramipexole in RLS patients. One AE of specific interest in the elderly, based on data from the Parkinson's disease programme, was hallucination. The two patients who reported hallucination (one pramipexole, one placebo) in the RLS clinical programme were both <65 years of age.

Safety in special populations: Race

Approximately 99% of the patients included in the four clinical studies of the RLS development programme were Caucasian. The number of patients from different race groups was too small to draw any conclusions about the influence of race on the safety profile of pramipexole.

Safety in special populations: Pregnancy

One pregnancy occurred in the clinical trial with RLS (0,75 mg). The drug was stopped after the woman tested positive. After a normal pregnancy the child was born healthy.

Drug interactions

No new information with regard to drug interactions has been presented.

Overdose

In the RLS clinical studies, no event of overdose was reported.

Drug abuse

Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. The potential for drug abuse in the RLS population may be different from the Parkinson population, which is known to have a low abuse potential. Moreover, pramipexole is administered in a much lower daily dose in the RLS indication compared to Parkinson's disease. However, the MAH will monitor the abuse potential as part of their post marketing surveillance and will discuss respective findings in the forthcoming PSURs.

Withdrawal and rebound

In Study 248.520, there were considerable more patients who experienced RLS symptoms worse compared to baseline among patients treated with pramipexole (43.6%) compared to placebo (8.7%). This clearly show that rebound may be a phenomena associated with stopping pramipexole therapy. This has important implication for the interpretation of Study 248.546, since it is suspected that the effect shown in this study was related to withdrawal and rebound. The CHMP considered that withdrawal and rebound should be described in the SPC.

The MAH considered that the risk of rebound is minimal in this dose range. In addition, in most chronic diseases withdrawal of an efficacious treatment is followed by a worsening of symptoms (i.e. pain in rheumatoid arthritis, blood pressure etc.) and as this is no specific feature of pramipexole in the indication RLS, the MAH does not consider it necessary to specifically mention this in the SPC. The CHMP however still considered that rebound may be a problem after abrupt discontinuation. Thus, the following text will be added to section 4.2 of the SPC: *"Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded"*.

5. Pharmacovigilance

Risk Management Plan (RMP)

The MAH submitted a risk management plan.

Table: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks		
Hypotension, orthostatic reaction	Routine pharmacovigilance	Already included in section 4.8 of the SPC
Sudden onset of sleep	Routine pharmacovigilance	Already included in sections 4.4 and 4.8 of the SPC
Abnormal behaviours	Planned study to address these issue	
Abnormal dreams	Routine pharmacovigilance	
Delusions	Routine pharmacovigilance	
Paranoia	Routine pharmacovigilance	
Weight increase/eating disorder	Routine pharmacovigilance	
Hyperkinesia	Routine pharmacovigilance	
Potential risks		
Skin melanoma	Routine pharmacovigilance	
Retinal degeneration	Routine pharmacovigilance To be evaluated in ongoing Study 248.538 - Ophthalmological safety study of pramipexole vs. ropinerole in early4 Parkinson's disease patients (finalisation Q4/2009)	
Pulmonary fibrosis	Routine pharmacovigilance	
Substance abuse	Routine pharmacovigilance	
Embryotoxicity	Routine pharmacovigilance	
Leidig cell hyperplasia and adenomas	Routine pharmacovigilance	
Hyperreflexia	Routine pharmacovigilance	
Dystonia	Routine pharmcovigilance	
Photopsia	Routine pharmcovigilance	
Diplopia	Routine pharmcovigilance	

Missing information		
Augmentation and rebound	Planned double blind study of 6-12 months duration including assessment of augmentation and rebound. Augmentation, post treatment worsening and rebound in patients with RLS should be monitored and discussed in the forthcoming PSURs.	Already included in section 4.4 of the SPC
Overdose	Routine pharmcovigilance	Already included in section 4.9 of the SPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

PSUR cycle

In view of the extension of indication to RLS, the PSURs will be submitted every six months during two years, once a year for the following two years and thereafter at three-yearly intervals.

6. Changes to product information

Section 4.1 of the SPC

"4.1.2 SIFROL tablets are indicated for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 0.54 mg of base (0.75 mg of salt) (See section 4.2.2)."

Section 4.2 of the SPC

"4.2.2 Restless Legs Syndrome

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

The recommended starting dose of SIFROL is 0.088 mg of base (0.125 mg of salt) taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days to a maximum of 0.54 mg of base (0.75 mg of salt) per day (as shown in the table below).

Dose Schedule of SIFROL		
Titration Step	*Once Daily Evening Dose (mg of base)*	*Once Daily Evening Dose (mg of salt)*
1	*0.088*	*0.125*
*2**	*0.18*	*0.25*
*3**	*0.35*	*0.50*
*4**	*0.54*	*0.75*
** if needed*		

As long-term efficacy of SIFROL in the treatment of RLS has not been sufficiently tested, patient's response should be evaluated after 3 months treatment and treatment continuation

should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Treatment discontinuation

Since daily dose for the treatment of Restless Legs Syndrome will not exceed 0.54 mg of base (0.75 mg of salt) SIFROL can be discontinued without tapering off. Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded."

Dosing in patients with renal impairment

The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 mL/min require no reduction in daily dose. The use of SIFROL has not been studied in hemodialysis patients, or in patients with severe renal impairment.

Dosing in patients with hepatic impairment

Dose adjustments in patients with hepatic failure is not required, as approx. 90% of adsorbed drug is excreted through the kidneys."

Section 4.4 of the SPC

"Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medications can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of SIFROL in patients with Restless Legs Syndrome were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of SIFROL and the appropriate management of these events have not been evaluated in controlled clinical trials."

Section 4.6 of the SPC

In the absence of human data, SIFROL should not be used during breast-feeding, ~~if possible.~~

Section 4.8 of the SPC

"The following side effects are expected under the use of SIFROL: confusional state, constipation, dizziness, dyskinesias, fatigue, hallucinations, headache, hypotension, insomnia, libido disorders, nausea, peripheral oedema, pathological gambling, somnolence, and sudden onset of sleep.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on SIFROL and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63 % of patients on SIFROL and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse reactions reported in these tables are those events that occurred in 1% or more of patients treated with SIFROL and were reported significantly more often in patients taking SIFROL than placebo, or where the event was considered clinically relevant. However, the majority of common adverse reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was continued.

Table 1: Very common Adverse Reactions (≥ 10%)

System organ class	*Adverse reaction*	*Pramipexole N= 1923 (%)*
Gastrointestinal disorders	*Nausea*	*17.2*
Psychiatric disorder	*Dyskinesia*	*12.9*

Table 2: Common Adverse Reactions (≥ 1% - < 10%)

System organ class	*Adverse reaction*	*Pramipexole N= 1923 (%)*
Gastrointestinal disorders	*Constipation*	*5.5*
General disorders and administration site conditions	*Fatigue* *Peripheral oedema*	*6.1* *1.2*
Nervous system disorders	*Headache*	*6.5*
	Somnolence	*8.6*
Psychiatric disorders	*Confusional state*	*3.0*
	Hallucination	*2.0*
	Hallucination visual	*4.6*
	Insomnia	*8.0*

SIFROL is associated with somnolence (8.6%) and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (0.1%). See also 4.4.

SIFROL may be associated with libido disorders (increased (0.1%) or decreased (0.4%)).

As described in literature for dopamine agonists used for treatment of Parkinson's disease, patients treated with SIFROL, especially at high doses, have been reported as showing pathological gambling, generally reversible upon treatment discontinuation.

The most commonly (≥ 5%) reported adverse reaction in patients with Parkinson's disease treated with Sifrol were dizziness, dyskinesia, somnolence, insomnia, hallucination, confusional state and constipation. The incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.2.1). More frequent adverse reactions in combination with levodopa were dyskinesias. Hypotension may occur at the beginning of treatment, especially if SIFROL is titrated too fast.

The most commonly (≥ 5%) reported adverse reaction in patients with Restless Legs Syndrome treated with Sifrol were nausea, headache and fatigue. Nausea and fatigue were more often reported in female patients treated with SIFROL (20.8% and 10.5%, respectively) compared to males (6.7 % and 7.3%, respectively).

Section 4.9 of the SPC

There is no clinical experience with massive overdosage. The expected adverse events would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, electrocardiogram monitoring and administration of activated charcoal.

Section 5.1 of the SPC

"The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

"~~Current evidence favours a disinhibition of normal CNS pacemakers, probably governed by multiple influences that may relate to PLM and disruptions in sleep and periodic leg movements.~~"

Clinical trials in Restless Legs Syndrome

The efficacy of SIFROL was evaluated in four placebo-controlled clinical trials in approximately 1000 patients with moderate to very severe idiopathic Restless Legs Syndrome. Efficacy was demonstrated in controlled trials in patients treated for up to 12 weeks. Maintenance of effect has not been sufficiently tested.

The mean change from baseline in the Restless Legs Syndrome Rating Scale (IRLS) and the Clinical Global Impression-Improvement (CGI-I) were the primary efficacy outcome measures. For both primary endpoints statistically significant differences have been observed for the pramipexole dose groups 0.25 mg, 0.5 mg and 0.75 mg in comparison to placebo. After 12 weeks of treatment the baseline IRLS score improved from 23.5 to 14.1 points for placebo and from 23.4 to 9.4 points for pramipexole (doses combined). The adjusted mean difference was -4.3 points (CI 95% -6.4; -2.1 points, p-value <0.0001). CGI-I responder rates (improved, very much improved) were 51.2% and 72.0 % for placebo and pramipexole respectively (difference 20% CI 95%: 8.1%; 31.8%, p<0.0005). Efficacy was observed with 0.088 mg of base (0.125 mg of salt) per day after the first week of treatment.

In a placebo-controlled polysomnography study over 3 weeks SIFROL significantly reduced the number of periodic limb movements during time in bed.

~~Compared to placebo, the patients treated with SIFROL reached statistically significant superiority in terms of sleep satisfaction, improvement in their condition while getting to sleep, during the night and day as measured by Visual Analogue Scales."~~

Section 1 of the PL

SIFROL 1.1 mg tablets are taken by patients to treat moderate to severe idiopathic Restless Legs Syndrome.

Section 2 of the PL

If you are treated for Restless Legs Syndrome and if you are taking or have recently taken any other medicines, even those not prescribed, in particular those which affect kidney function or are excreted by the kidneys, e.g. cimetidine, or drugs that may cause drowsiness (somnolence), or alcohol please inform your doctor or pharmacist.pharmacist.

Section 3 of the PL

"Sifrol tablets 0.088 mg tablets are only for adults and should not be taken by children and adolescents up to 18 years.

Always take Sifrol tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Swallow the tablets with a glass of water.

At the beginning of treatment you will start by taking one Sifrol 0.088 mg tablet once daily 2-3 hours before bedtime. If this dose is not sufficient to relieve symptoms, your doctor may recommend to increase the dose gradually every 4-7 days to 0.18 mg, 0.35 mg or 0.54 mg per day.

Response to treatment should be evaluated after 3 month treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated gradually as advised above.

If you have impaired kidney function, please inform your doctor or pharmacist.

If you have to stop taking this medicine, please inform your doctor or pharmacist.

Effects when treatment with Sifrol 0.088 mg tablets is stopped:

If the treatment with SIFROL is abruptly stopped, symptoms like fever, rigidity, increased heart rate and/or disturbance of consciousness can occur (see "Parkinson's disease").

In patients treated with doses up to 0.54 mg of pramipexole base or 0.75 mg of pramipexole salt for RLS SIFROL can be stopped without tapering off. However, worsening of symptoms after abrupt discontinuation of treatment may occur in isolated cases.

Readability test

According to Art. 59(3) and 61(1) of Directive 2001/83/EC, as amended, the MAH should provide the results of assessments carried out in cooperation with target patient groups on the PL ('user consultation') or give a justification for not performing such consultation. The MAH provided a justification for not providing a readability test based on the fact that the product has been on the market in the EU for 7.5 years and that during this time, no problems have been reported with the use of Sifrol or understanding of the PL. The MAH therefore did not see an immediate need for a readability test in RLS patients. The CHMP did not consider the MAH's justification for not performing a readability test acceptable, especially since the PL will now comprise of two different indications/populations. The MAH has committed to submit a readability test of the English PL post-authorisation.

7. Overall conclusions and benefit/risk assessment

Efficacy

Short-term (3 months) efficacy in the co-primary endpoints RLSRS total score and CGI-I response was shown in 4 randomised double-blind placebo controlled trials including approximately 1000 patients administered pramipexole up to 12 weeks for the treatment of moderate to severe RLS. The periodic limb movements during sleep and RLS severity at bedtime during night and day were reduced and the sleep measured by VAS improved during treatment.

As the efficacy varied with disease severity, being most pronounced in the severely affected, the benefit in the mildly affected population was questionable. The CHMP considered that the proposed indication be amended in the following way to apply to the restricted moderate to severe population: *"SIFROL tablets are indicated for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 0.54 mg of base (0.75 mg of salt)".*

Efficacy was shown to wear off with treatment duration. Moreover, efficacy was not seen with increased dose, whereas adverse events and drop-outs increased. Thus, the following text is added to section 4.2 of the SPC: *"As long-term efficacy of Sifrol in the treatment of RLS has not yet been sufficiently tested, patients' response should evaluated after 3 months treatment and the need for treatment continuation should be reconsidered"*.

Efficacy has not been shown in long-term trials. The open-label extensions of the placebo-controlled trials cannot be used to show long-term efficacy, but be regarded as supportive of the findings. The MAH has committed to perform a study of 6 months duration post-authorisation.

Safety

No new clinically meaningful safety issues could be identified in the RLS population in comparison to the adverse event profile of pramipexole in Parkinson's disease.

Nausea, fatigue and headache were reported most frequently and in higher frequencies with pramipexole compared to placebo. Nausea and fatigue were also more often reported in female patients (20.8% and 10.5% respectively) compared to males (6.7% and 7.3% respectively).

Augmentation /rebound following abrupt discontinuation of treatment cannot be excluded. However, no firm conclusions on the occurrence can be drawn given the methodological limitations of the used scale of the study duration. A general precautionary statement in the section 4.2 of the SPC clarifying that as with other dopamine agonists augmentation may occur with pramipexole is considered appropriate: *"Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded"*.

As part of the pharmacological action of dopamine agonists, the occurrence of hallucinations and orthostatic hypotension cannot be excluded for RLS. This also applied to sudden onset of sleep, where a respective warning has been included in the SPC.

Benefit/risk

The CHMP considered that the benefit risk profile for the use of pramipexole in moderate to severe RLS is considered positive, as therapeutic benefit was shown in the controlled trials with acceptable adverse events.

The CHMP considered that this variation to extend the indication to include *"SIFROL tablets are indicated for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 0.54 mg of base (0.75 mg of salt)"*, with consequential changes to the sections 4.2, 4.4, 4.8 and 5.1 of the SPC was acceptable.

