Title page

CLINICAL STUDY REPORT

INFLUENCE OF THE NON-ERGOT DOPAMINE AGONIST PIRIBEDIL ON VIGILANCE AND COGNITIVE FUNCTION IN PATIENTS WITH PARKINSON'S DISEASE COMPARED TO OTHER ORAL NON-ERGOT DOPAMINE AGONISTS (PIVICOG-PD)

PIR-007/K

EudraCT Number: 2009-012419-16

Investigational product:	Piribedil (Clarium®)
Clinical development phase:	III
Indication:	Parkinson's disease
Sponsor:	Desitin Arzneimittel GmbH Weg beim Jäger 214 22335 Hamburg, Germany
Coordinating investigator:	PD. Dr. Karla Eggert Klinik für Neurologie und Poliklinik der Philipps-Universität Marburg Baldingerstraße 35043 Marburg, Germany
Date of first patient enrolled:	02-Mar-2010
Date of last patient completed:	07-Dec-2011
Early termination:	Not applicable
Sponsor's signatory:	Dr. K. Kuhn and Dr. M. Wangemann Desitin Arzneimittel GmbH Weg beim Jäger 214 22335 Hamburg, Germany
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Report version and date:	Final 1.0 (02-Oct-2012)

1 Synopsis

Title of the study:
Influence of the non-ergot dopamine agonist piribedil on vigilance and cognitive function in patients with Parkinson's disease compared to other oral non-ergot dopamine agonists.

Principal investigators and study centers: 11 centers and investigators in Germany.

Coordinating investigator: Dr. Karla Eggert, Klinik für Neurologie und Poliklinik der Philipps-Universität Marburg, Baldingerstraße, 35043 Marburg, Germany

Publication (reference): not applicable

Studied period: 02-Mar-2010 (first patient in) to 07-Dec-2011 (last patient out)

Clinical phase: phase III

Objectives:
Primary objective
The primary objective of this study was to test whether piribedil is superior to continued pramipexole or ropinirole treatment regarding improvement of reduced vigilance in patients with Parkinson's disease (PD).

Secondary objectives
The secondary objectives of this study were:

- to evaluate the effects of piribedil on cognitive functions
- to evaluate the safety of piribedil
- to evaluate the tolerability of piribedil

Methodology:
This was a multi-center, randomized, rater-blinded, active-controlled phase III study with two treatment arms in patients with PD. The study consisted of a Screening visit (Visit 1, one to two weeks before randomization), a Baseline visit (randomization, Visit 2, Day 0), a titration period of three weeks (Visits 3, 4, and 5 on Days 7, 14, and 21), and a treatment period of eight weeks with stable dose. Patients randomized to the comparator group continued with their prior treatment regimen (pramipexole or ropinirole) without changing doses. Patients assigned to the piribedil treatment group switched overnight one day after Visit 2 (Baseline visit) to an equivalent dose of piribedil according to a defined equivalence scheme. During the titration period, dose adaptation of piribedil may have been performed at Visit 3 (Day 7) and Visit 4 (Day 14) based on motor symptoms assessed with the Clinical Global Impression of Change (CGI-C). Patients' motor symptoms were evaluated at the end of the titration period at

at Visit 5 (Day 21). During the treatment period, adverse events (AEs) and changes in the use of concomitant medications were recorded at Visit 6 (Day 49) and by telephone calls on Day 35 and Day 63. All efficacy and safety assessments performed at Screening and/or Baseline were repeated at the final Visit 7 (Day 77).

Number of patients (total and for each treatment) planned and analyzed:

- Planned: 62 evaluable patients (31 in each treatment group)
- Analyzed sets:

	Number of patients				
	Enrolled	FAS	SAF[a]	mFAS	PP set
Piribedil		44	45	37	29
Comparator		36	35	36	27
Total	92	80	80	73	56

[a] One patient randomized to the comparator group was treated with piribedil.
FAS = full analysis set (includes all patients as randomized), mFAS = modified full analysis set (includes all patients as randomized and successfully completed the piribedil titration period), PP = per-protocol (includes all patients as randomized and did not violate any major protocol criteria), SAF = safety analysis set (includes all patients as treated).

Diagnosis and criteria for inclusion:

- Male or female Caucasian patients aged 35 to 80 years
- Patients with idiopathic PD
- Hoehn & Yahr stages 1 to 4
- Stable therapy with anti-parkinson medication, including stable treatment with pramipexole or ropinirole, for at least four weeks prior to Screening
- Significant daytime sleepiness: Epworth Sleepiness Scale (ESS) score ≥11 under previous therapy with pramipexole or ropinirole
- Patients who had read and understood the patient information sheet and had provided a signed written informed consent form
- Patients considered to be compliant to the study regimen

Test product:

Piribedil, 100 to 300 mg/day (equivalent to the dose of pramipexole or ropinirole that the patient had currently taken at enrolment), oral tablets, batch numbers: 9003554 and 1004408.

Reference product:

The comparator was not provided by the sponsor and was not considered to be study medication. Patients continued their standard therapy with pramipexole or ropinirole. Dosing was done according to routine clinical practice following the product recommendations.

Duration of treatment: 11 weeks (3 weeks titration and 8 weeks stable dose)

Criteria for evaluation:

Primary variable

'Median reaction time during second 15 minutes (minutes 16-30)' of the subtest 'vigilance', visual test condition 'moving bar' of the Test battery for Attention Performance (TAP) at end of treatment (EoT).[1]

Secondary variables

- Other vigilance parameters of the TAP test
- Other neuropsychological tests:
  - Test of verbal fluency (RWT)
  - Verbal learning memory test (VLMT)
  - Stroop test (FWIT)
- ESS
- Parkinson's Disease Sleep Scale (PDSS-2)
- Unified Parkinson's Disease Rating Scale (UPDRS) subscores I to IV and total score
- Parkinson's disease questionnaire (PDQ-39)
- Beck Depression Inventory (BDI)
- Clinical Global Impressions (CGI) (except item 3.2)
- Patient Global Impression (PGI)

Statistical methods:

The primary efficacy variable was tested confirmatory for the modified full analysis set (mFAS; i.e.). All other analyses based on the full analysis set (FAS), mFAS, and per-protocol (PP) set were exploratory. The FAS included all patients who received the treatment to which they were randomized to (intention-to-treat procedure). The mFAS included all patients of the FAS who did not prematurely discontinue during the titration period or who did not have a CGI-C >4 ('minimally worse', 'much worse' or 'very much worse') at Visit 5. Statistical testing was 2-sided using a 5% significance level. The primary efficacy variable was analyzed using a Wilcoxon (Mann-Whitney) rank-sum test. In order to assess the robustness of the results, the primary efficacy variable was further analyzed using several sensitivity analyses (last observation carried forward analyses). Results of the neuropsychological tests, ESS, UPDRS, PDQ-39, BDI II, and PDSS-2 scores at EoT were compared between both treatment groups using a Wilcoxon (Mann-Whitney) rank-sum test. The CGI items (1, 2, and 3.1) and the PGI score were compared between both treatment groups using Fisher's exact test. Safety analyses were done descriptively.

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1 The primary efficacy variable was changed from "subtest 'vigilance', visual test condition 'moving bar' of the TAP" to "median reaction time during the second 15 minutes of the test (16-30) of TAP subtest 'vigilance', visual test condition 'moving bar' at end of treatment in Version 2.0 of the clinical study protocol.

SUMMARY - CONCLUSIONS

Patient disposition:

Of 92 patients screened, 80 patients were randomized to receive either piribedil (44 patients) or to continue with their prior treatment regimen (36 patients). One patient was randomized to the comparator group but was erroneously treated with piribedil[2]. A total of 10 patients in the piribedil and 5 patients in the comparator group prematurely discontinued the study. The remaining 65 patients completed the study as planned.

Demography and baseline characteristics:

The demographic data were comparable between the treatment groups. All patients were Caucasian and the median age was 68 years. Approximately one third of patients in both treatment groups were female. There were no differences in disease stage and cognitive function between the treatment groups at Screening. Patients randomized to the piribedil group switched from their routine anti-parkinson medication to piribedil according to the equivalence scheme. The mean total daily dose of piribedil at Baseline was 192.2 mg (standard deviation: 65.7 mg). About two thirds of the patients in the comparator group were using pramipexole and one third of patients were treated with ropinirole.

Results - efficacy:

Primary efficacy variable

The median reaction time during the second 15 minutes of the TAP subtest 'vigilance' at EoT was comparable between the treatment groups in the mFAS and PP population.

Secondary efficacy variables

Results of the secondary efficacy variables in the FAS population are summarized in Table 2 (page 9).

Median reaction time during the TAP subtest 'vigilance': There was no difference between the treatment groups in the FAS, mFAS, and PP population in the median reaction time during the first 15 minutes and the entire 30 minutes of the TAP subtest 'vigilance' at EoT.

Number of omissions during the TAP subtest 'vigilance': The number of omissions during the second 15 minutes and the entire 30 minutes of the TAP test had increased in the comparator group and had decreased or had remained unchanged in the piribedil group. In the FAS population, differences between the treatment groups were not statistically significant. Between-treatment differences were more pronounced in the mFAS and PP population. A

[2] The investigator did not open the randomization envelope and treated the patient with piribedil.

statistically significant difference between the treatments was seen in favor of piribedil during the second 15 minutes of the TAP subtest 'vigilance' in the PP population, where the number of omissions had decreased by a median of 1.0 and had increased by a median of 1.0 in the comparator group ($p = 0.0459$).

Number of errors during the TAP subtest 'vigilance': In the FAS population, the number of errors during the TAP subtest 'vigilance' had decreased in both treatment groups from Baseline to EoT, with greater decreases for the mean values in the piribedil group than in the comparator group. The between-treatment difference was not statistically significant. Similar results were obtained in the mFAS and the PP population.

ESS: The median ESS score was 14.0 at Baseline in both treatment groups. The score decreased from Baseline to EoT from 14.0 to 10.0 following treatment with piribedil and to 12.0 following treatment with pramipexole or ropinirole (comparator group). In the FAS population, the median ESS score at EoT was significantly lower in the piribedil group than in the comparator group ($p = 0.0141$). Between-treatment differences were also significant in the mFAS and PP population in favor of piribedil.

Neuropsychological tests: Data analysis according to the statistical analysis plan showed nearly no changes in the Stroop test, verbal fluency test (RWT), verbal learning memory test (VLMT), and PDSS-2 from Baseline to EoT in any analysis population. None of the between-treatment differences at EoT was statistically significant. It is planned to further analyze the neuropsychological tests adjusted for age.

UPDRS: In the FAS population, there were almost no changes in UPDRS total score and subscores from Baseline to EoT in both treatment groups. Differences between treatments at EoT were not statistically significant. Similar results were obtained in the mFAS and the PP population.

Post-hoc analyses of clinically meaningful changes (>5 points) in UPDRS III scores showed that a higher proportion of patients in the piribedil group presented with an improvement in UPDRS III scores from Baseline to EoT than in the comparator group (Table 1; 26.8% versus 9.4%).

Table 1: Changes in UPDRS III scores - post-hoc analyses (FAS, N = 73[a])

	Number (%) of patients				Treatment difference
	Piribedil N = 41		Comparator N = 32		p-value[b]
Significantly better	11	(26.8)	3	(9.4)	
Better	5	(12.2)	12	(37.5)	
Unchanged	18	(43.9)	10	(31.2)	
Worse	2	(4.9)	5	(15.6)	
Significantly worse	5	(12.2)	2	(6.2)	**0.023**

Categorization: unchanged (change of -2 to 2), mildly worsened (change of 3 to 5), significantly worsened (change of more than 5), mildly improved (change of -3 to -5), and significantly improved (change of more than -5).

[a] Patients with missing data at EoT were excluded from the analysis (no last-observation carried forward method was applied).

[b] 2-sided Fisher's exact test for between-treatment differences in change of UPDRS III.

EoT = end of treatment (final visit or premature discontinuation), FAS = full analysis set, N = number of patients, UPDRS = Unified Parkinson's Disease Rating Scale.

PDQ-39: In the FAS, the mean PDQ-39 scores of all subscales generally decreased (improved) in the piribedil group from Baseline to EoT, with the largest improvements in the subscales 'cognitions', 'communication', and 'mobility'. There was no consistent trend towards an increase or decrease in mean and median PDQ-39 scores in the comparator group. For none of the subscales a between-treatment difference was statistically significant at EoT. Similar results were seen in the mFAS and PP population. A statistically significant between-treatment difference in favor of piribedil was observed in the mFAS and the PP population for the subscale 'communication' (mFAS: $p = 0.0416$, PP: $p = 0.0322$).

Post-hoc analyses of the change in PDQ-39 subscale scores from Baseline to EoT showed a trend towards a greater improvement from Baseline to EoT in the piribedil group compared with the comparator for 'mobility' and 'communication' (FAS: $p = 0.0600$ and $p = 0.0198$, respectively).

BDI II: Patients with depressive symptoms (BDI score >16) were excluded from this study. Nevertheless, the mean BDI II score had slightly decreased from Screening to EoT in both treatment groups in the FAS population. Differences between treatments at EoT were not statistically significant. Similar results were obtained in the mFAS and the PP population.

CGI item 1 - severity of illness: The majority of investigators judged the severity of illness of the patients in the FAS as moderate at Baseline and EoT, without a statistically significant difference between the treatment groups. Results were similar in the mFAS and PP population.

CGI item 2 - global improvement: In the FAS, for the majority of patients in the comparator group (58.3%), no change regarding the global improvement from Baseline to EoT was

reported. In the piribedil group, 45.5% of the patients improved much or minimal, while for only 22.7% and 25.0% of the patients no change or a worsening (minimally worse, much worse, and very much worse) was reported, respectively. Differences between the treatment groups were statistically significant ($p = 0.0004$). Between-treatment differences were also significant in the mFAS and PP population.

A post-hoc analysis was performed for the FAS to compare the total CGI item 2 scores at EoT. Median CGI item 2 score at EoT was 4.0 ('no change') in both treatment groups ($p = 0.1321$; the total CGI score ranges from 1 to 7, with higher scores indicating a worse clinical global impression).

CGI item 3.1 - therapeutic effect: In the FAS, for the majority of patients (63.9%) in the comparator group, an unchanged or worse therapeutic effect was reported compared to Baseline and for none of the patients a marked improvement was reported. In the piribedil group, a marked and moderate improvement was reported for 6.8% and 31.8% of patients, respectively. Differences between the treatment groups were statistically significant ($p = 0.0442$). Between-treatment differences were also significant in the mFAS and PP population.

A post-hoc analysis was performed for the FAS to compare the total CGI item 3.1 scores at EoT. The CGI item 3.1 score at EoT was lower in the piribedil group (median: 2.0 ['minimal']) compared with the comparator group (median: 3.0; $p = 0.0060$).

PGI - self-rated global improvement: In the FAS, more patients in the piribedil group reported to feel better (very much better, much better, and little better) than in the comparator group. The proportion of patients that reported no change or reported to feel worse (very much worse, much worse, and little worse) was higher in the comparator group than in the piribedil group. The difference between the treatment groups was statistically significant ($p = 0.0107$). Between-treatment differences were also significant in the mFAS and PP population.

Between-treatment difference in the total PGI score at EoT was analyzed post-hoc for the FAS population. The median score for the patients' self-rated global improvement at EoT was significantly lower (greater improvement) in the piribedil group (3.0) than in the comparator group (4.0; $p = 0.0251$).

Table 2: Summary of secondary efficacy variables (FAS[a], N = 80)

Test	Subtest	Median (range) score at EoT		Difference
		Piribedil N = 44[b]	Comparator N = 36[c]	p-value[d]
TAP	Median reaction time (1st 15 min)	922 (721 -1507)	914 (655 - 2029)	0.8668
	Median reaction time (entire 30 min)	964 (753 - 1558)	943 (651 - 2015)	0.6286
	Change in no. of errors (1st part)	0.0 (-349 - 39)	-1.0 (-74 - 80)	0.2232
	Change in no. of errors (2nd part)	0.0 (-322 - 30)	0.0 (-113 - 86)	0.6724
	Change in no. of errors (entire 30 min)	0.0 (-671 - 69)	0.0 (-187 - 166)	0.5313
	Change in no. of omissions (1st part)	0.0 (-9 - 10)	0.0 (-13 - 5)	0.4311
	Change in no. of omissions (2nd part)	0.0 (-7 - 10)	1.0 (-9 - 10)	0.0622
	Change in no. of omissions (entire 30 min)	0.0 (-14 - 15)	1.0 (-22 - 14)	0.1509
	Change in no. of omissions (2nd part; PP)	-1.0 (-7 - 10)	1.0 (-9 - 10)	**0.0459**
ESS		10.0 (1 - 23)	12.0 (5 - 20)	**0.0141**
PDSS-2		13 (3 - 50)	14 (2 - 41)	0.4766
UPDRS	Total score	30.0 (8 - 89)	28.5 (7 - 75)	0.6527
	UPDRS I	1.0 (0 - 4)	1.0 (0 - 6)	0.8467
	UPDRS II	8.5 (1 - 26)	7.0 (1 - 25)	0.4671
	UPDRS III	17.0 (4 - 56)	17.5 (3 - 39)	0.8999
	UPDRS IV	1.0 (0 - 10)	1.0 (0 - 9)	0.6512
PDQ-39	Summary index	19.1 (2 - 96)	19.3 (1 - 47)	0.8808
	Communication	16.7 (0 - 100)	8.3 (0 - 58)	0.0993
	Mobility	10.0 (0 - 95)	15.0 (0 - 100)	0.3202
	Cognitions	37.5 (0 - 94)	34.4 (0 - 69)	0.9457
	Activities of daily living	16.7 (0 - 92)	18.8 (0 - 75)	1.0000
	Emotional well-being	16.7 (0 - 96)	18.8 (0 - 54)	0.7931
	Stigma	6.3 (0 - 94)	6.3 (0 - 50)	0.6667
	Social support	4.2 (0 - 100)	0.0 (0 - 42)	0.5430
	Bodily discomfort	33.3 (0 - 100)	29.2 (0 - 75)	0.3806
	Communication (PP)	16.7 (0 - 100)	0.0 (0 - 58)	**0.0322**
	Communication (mFAS)	16.7 (0 - 100)	8.3 (0 - 58)	**0.0416**
BDI II		6.5 (0 - 24)	7.0 (0 - 18)	0.9420
Post-hoc analyses:				
PDQ-39	Change in communication	0.0 (-42 - 50)	0.((-25 - 33)	**0.0198**
	Change in mobility	0.0 (-55 - 48)	0.((-23 - 45)	0.0600
CGI	Item 1 (severity of illness)	4.0 (2 - 5)	4.0 (2 - 5)	0.8369
	Item 2 (global improvement)	4.0 (2 - 7)	4.0 (3 - 5)	0.1321
	Item 3.1 (therapeutic effect)	2.0 (0 - 3)	3.0 (1 - 3)	**0.0060**
PGI		3.0 (1 - 7)	4.0 (2 - 7)	**0.0251**

See next page for footnotes.

Bolded numbers indicate statistical significance. Changes were calculated from Baseline to EoT.
[a] If not otherwise indicated.
[b] N = 1 missing for TAP, VLMT, ESS, PDSS-2, RWT; N = 4 missing for PGI and item 2 and 3.1 of the CGI.
[c] N = 1 missing for PDQ-39 subscales mobility, activity of daily living, and social support, N = 2 missing for ESS; N = 3 missing for PGI, PDQ-39 summary index, and item 2 and 3.1 of the CGI.
[d] 2-sided Wilcoxon test for between-treatment differences.
BDI = Beck Depression Inventory, CGI = Clinical Global Impression, EoT = end of treatment (final visit or premature discontinuation), FAS = full analysis set, mFAS = modified FAS, min = minutes, N = number of patients, no. = number, PDSS-2 = Parkinson's Disease Sleep Scale (version without questions on daytime sleepiness), PDQ-39 = Parkinson's disease questionnaire, PGI = Patient Global Impression, PP = per-protocol, TAP = Test battery for Attentional Performance, UPDRS = Unified Parkinson's Disease Rating Scale.

Results - safety:

Overall, 119 AEs were experienced by 41 patients. The number of AEs as well as the number and proportion of patients who experienced at least one AE was higher in the piribedil group compared with the comparator group, in which patients continued their existing treatment regimen: 103 AEs in 73.3% of patients in the piribedil group versus 16 AEs in 22.9% of patients in the comparator group. In the piribedil group, the majority of AEs were related to 'nervous system disorders', followed by 'gastrointestinal disorders' and 'psychiatric disorders'. In the comparator group most AEs were associated with 'musculoskeletal and connective tissue disorders'. The majority of AEs was judged to be mild or moderate. No severe AEs were experienced in the comparator group, while seven patients in the piribedil group experienced 10 AEs that were judged to be severe. Five of these severe AEs in two patients were judged to have a reasonably causal relationship to the treatment. All of the latter AEs occurred within the first four weeks after randomization (i.e. titration period plus one week).

Table 3: Overview of adverse events (SAF, N = 80)

	Piribedil N = 45	Comparator N = 35	Total N = 80
Number of			
AEs	103	16	119
Probably related AEs	16	2	18
Possibly related AEs	40	-	40
SAEs	3	1	4
Number (%) of pts with			
AEs	33 (73.3)	8 (22.9)	41 (51.3)
Probably related AEs	10 (22.2)	2 (5.7)	12 (15.0)
Possibly related AEs	21 (46.7)	-	21 (26.3)
SAEs	3 (6.7)	1 (2.9)	4 (5.0)

AE = adverse event, N = number of patients, pts = patients, SAE = serious adverse event, SAF = safety analysis set.

In general, the number of AEs per day as well as the number of AEs per patient was higher during the first four weeks after randomization (i.e. titration period plus one week) than

during the stable dosing period (0.051 versus 0.016 AEs per day and 1.378 versus 0.821 AEs per patient in the piribedil group and 0.009 versus 0.004 AEs per day and 0.229 versus 0.188 AEs per patient in the comparator group). Further, the number of AEs with a reasonably causal relationship in the piribedil group was notably lower during the treatment period compared with the titration period.

Table 4: Adverse events by onset time (SAF, N = 80)

	Start of the AE	
	within 4 weeks after randomization	**after 4 weeks after randomization**
Number (%)[a] of pts with AEs		
Piribedil	26 (57.8)	18 (40.0)
Comparator	6 (17.1)	3 (8.6)
Number of AEs		
Piribedil	62	32
Comparator	8	6
Number (%)[a] of pts with causally related[b] AEs		
Piribedil	21 (46.7)	9 (20.0)
Comparator	2 (5.7)	-
Number of causally related[b] AEs		
Piribedil	41	11
Comparator	2	-

The number of AEs during the first four weeks after randomization and the number of AEs thereafter do not add up to the total number of AEs: AEs with unknown start date (one AE in the comparator and six AEs in the piribedil group) as well as AEs which occurred before randomization (three AEs in the piribedil and one AE in the comparator group) are not presented in the table.
[a] Based on the total number of patients per treatment group. [b] Probably or possibly related AEs.
AE = adverse event, N = number of patients, obs. = observation, pts = patients, SAF = safety analysis set.

In the piribedil group, 46.7% of patients experienced AEs which were judged to be possibly related to the study medication and 22.2% of patients experienced AEs which were considered to be probably related to the study medication. The majority of these AEs occurred during the titration period. The most common causally related AEs which occurred within the first four weeks after randomization were nausea (9 AEs in 7 patients), dizziness, and worsening of PD (each 4 AEs in 4 patients). After the first four weeks of treatment only one AE with a reasonable causal relationship was documented twice, which was somnolence. The two causally related AEs in the comparator group occurred within the first four weeks after randomization (5.7% of patients)

Five serious AEs (SAEs) occurred during this study: bone pain, radicular syndrome, and pulmonary embolism in the piribedil group, intervertebral disc protrusion in the comparator group, and coronary artery disease in one non-randomized patient. All SAEs were judged to be not related to the study medication and had recovered at the end of the study.

Six patients in the piribedil group and one patient in the comparator group prematurely terminated the study due to an AE. All but one of these AEs was judged to have a reasonably causal relationship to the treatment.

Overall, only small changes in median values of hematology, biochemistry, and coagulation variables were observed without any apparent differences between the treatment groups.

In both treatment groups there were no or only minor changes in diastolic and systolic blood pressure and pulse rate. There was one patient in the piribedil group and seven patients in the comparator group with abnormal ECG findings at the end of the study. All abnormal findings in both treatment groups were judged to be not clinically significant.

Based on the investigators evaluation (CGI item 3.2), the majority of patients in both treatment groups were not impaired by side effects at all or reported that side effects did not significantly interfere with their daily activities; the proportion of patients with a significant impairment was higher in the comparator group than in the piribedil group (22.6% versus 14.3%).

Conclusions:

- There was no significant difference in the primary endpoint reaction time of the TAP subtest vigilance between piribedil and the comparator
- In the PP population, piribedil was significantly superior to the comparator regarding the number of omissions during the second half of the TAP subtest vigilance
- Piribedil reduced daytime sleepiness, with significantly lower ESS scores at end of treatment than the comparator
- A significantly higher therapeutic effect and improvement in disease status was seen in patients treated with piribedil compared with the comparator as judged by the investigator and more patients in the piribedil group reported to feel better (very much better, much better, and little better) than in the comparator group at the end of treatment
- A significantly higher proportion of patients in the piribedil group presented with a clinically relevant improvement in UPDRS III score from Baseline to EoT than in the comparator group
- In the mFAS and the PP population, piribedil was significantly superior to the comparator in the PDQ-39 subscale 'communication'
- Piribedil was safe and well tolerated

Date of report: 02-Oct-2012

Signatures

Study title:

Influence of the non-ergot dopamine agonist piribedil on vigilance and cognitive function in patients with Parkinson's disease compared to other oral non-ergot dopamine agonists.

Compound: Piribedil (Clarium®)

Protocol number: PIR-007/K

The undersigned has read this report (Version Final 1.0, 02-Oct-2012) and hereby confirms that, to the best of his knowledge, it accurately describes the conduct and the results of the study.

Coordinating investigator:

Dr. Karla Eggert

15.10.2012

date signature

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Sponsor's signatory:

Sponsor's Clinical Trial Manager
Dr. Martina Wangemann

15.10.12 (date) Martina Wangemann (signature)

Sponsor's Medical Expert
Dr. Katrin Kuhn

15.10.12 (date) Katrin Kuhn (signature)