2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Trivastal® 50 mg LP	**Volume:**	
Name of Active Ingredient: Piribedil (S4200)	**Page:**	

Title of study: Early treatment of Idiopathic Parkinson's Disease (IPD) with dopaminergic agonist piribedil in monotherapy (adaptation of the daily dose from 150 to 300 mg per day per os). A 2-year randomised, parallel group, placebo controlled study in IPD "de novo" patients.

A planned short-term assessment of the initial 7 months of treatment.

Protocol No.: CL3-04200-006

Main coordinator:

[redacted]

Study centres:

52 active centres in 7 countries (10 in Argentina, 6 in India, 6 in France, 5 in Mexico, 7 in South Africa, 14 in Spain and 4 in Portugal).

Publications (reference):

Lees A *et al.* Piribedil efficacy in monotherapy (150-300 mg/day) in de novo parkinsonian patients: a 6-month planned intermediate analysis of the 2-year Parkinson-REGAIN study. Neurology 2004;62 (Suppl. 5):A399.

Rascol O *et al.* Piribedil efficacy in monotherapy (150-300 mg/day) in de novo parkinsonian patients: a 6-month planned intermediate analysis of the 2-year parkinson REGAIN study. Movement Disorders 2004;19(Suppl. 9):603.

Studied period:	**Phase of development of the study:**
Initiation date: 10 May 2001 (first selection visit) Cut off date: 15 May 2003 (last visit in short-term assessment)	III

Objectives:

To compare the therapeutic effect of piribedil to placebo in L-dopa naïve out-patients with motor symptoms of early stage (Hoehn and Yahr Stage 1 to 3) IPD:

- Short-term evaluation (7 months): To demonstrate the superiority of piribedil to placebo as measured by change from baseline to last post-baseline visit in UPDRS III total score in monotherapy;
- Long-term evaluation (24 months): To demonstrate the superiority of piribedil to placebo as measured by (1) the time to develop and (2) the number of patients developing "dyskinesia" or other motor complications, irrespective of the addition of L-dopa.

This report presents the results of the 7-month short-term evaluation.

Methodology:

This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study to assess the therapeutic effect of S 4200 (piribedil) on *de novo* patients with IPD. Randomisation was stratified by centre.

Number of patients:

Planned: 400 (200 per group); Treated: 405 (205 placebo / 200 piribedil)

405 included patients: Argentina–72; India–96; France–14; Mexico–59; South Africa–47; Spain–91; Portugal–26.

Diagnosis and main criteria for inclusion:

Male or female patients aged between 30 and 77 years, who were out-patients with diagnosed IPD (defined by UK PD Society Brain Bank), without any other known or suspected cause of parkinsonism, Hoehn and Yahr Stage 1 to 3, *de novo* or completely naïve to L-dopa (< 6 weeks previous treatment) and no more than 3 months previous dopamine agonist treatment.

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Study drug:
Piribedil 50 mg tablets, orally administered with placebo as 2 tablets tid (to preserve blind) for 7 months as follows:
- Day 0 to Day 7: 50 mg.
- Day 8 to Day 14: 100 mg.
- Day 15 to Day 28: 150 mg.
- Day 28 to Day 42: 150 or 200 mg.
- Day 42 to Month 4: 150, 200 or 250 mg.
- Month 4 to Month 7: 150, 200, 250 or 300 mg.

Up or down titration was done by 50 mg steps.
Batch No: K01674, K03580, J12519, J10657, H12598, H06585

Reference product:
Placebo orally administered as 2 tablets tid at dummy daily-dose levels
Batch No: H1522, H1680, J02622, J03613, J09630, J12575, K03579, J10656, H06584, H12597, H12596

L-dopa rescue treatment: Immediate-release form, 3 oral administrations per day at a dose determined by physician. Rescue treatment is authorised for both treatment groups by Day 42 in case of therapeutic failure.

Additional compound: Domperidone (Motilium®), 6 tablets per day, 60 mg/day from 48 hours prior to inclusion day up to Day 42 Thereafter the daily dose could be adapted.
Batch No: K06620, H09641

Duration of treatment:
All patients underwent a run-in period, receiving placebo for at least 28 days (21 days for completely treatment-naïve patients, 60 days for patients previously treated by selegiline) before randomisation. This was followed by:
- A titration period (receiving either placebo or piribedil) from Day 0 to Day 28.
- An adaptative period (receiving either placebo or piribedil) from Day 28 to Day 42.

A stabilisation and adjustment period (receiving either placebo or piribedil) from Day 42 to Month 7 for the short-term assessment.

Criteria for evaluation: Efficacy variables
The primary efficacy variable was the UPDRS III total score. The main expression was the change from baseline to the last visit in true monotherapy conditions. The secondary expressions of the main criterion were:
- Percentage change in UPDRS III total score in true monotherapy conditions.
- Response to treatment (decrease in UPDRS III total score of at least 30%) in true monotherapy conditions.

Secondary efficacy variables included:
- UPDRS III subscores in true monotherapy conditions.
- UPDRS II (Activities of Daily Living [ADL]) in true monotherapy conditions.
- Time to therapeutic failure (introduction of L-dopa).
- Percentage of patients requiring treatment with L-dopa.
- L-dopa daily dose.
- UPDRS IV (dyskinesia and clinical fluctuation score) in true monotherapy conditions.
- UPDRS V (Hoehn and Yahr) in true monotherapy conditions.
- UPDRS VI (Schwab and England) in true monotherapy conditions.
- Dyskinesia subjective rating scale in true monotherapy conditions.
- Depressive symptoms (Montgomery and Asberg Depression Rating Scale [MADRS] and Becks Depression Inventory [BDI]) in true monotherapy conditions.
- Quality of life (Parkinson's Disease Quality of Life [PDQL] questionnaire) in true monotherapy conditions.

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Safety variables:

- All adverse events (AEs), emergent adverse events (EAEs) and serious adverse events (SAEs) occurring up to Month 7.
- Change from baseline to last visit in haematology and biochemistry parameters.
- Changes from baseline in vital signs (weight, blood pressure and heart rate).

Statistical methods:

- The Randomised Set (RS) consisted of all included and randomised patients (by IVRS).
- The Full Analysis Set (FAS) consisted of patients from the RS who received at least 1 dose of trial medication, who have a baseline and at least 1 post-baseline value for UPDRS III.
- The Per Protocol Set (PPS) consisted of patients in the FAS who followed the study until Month 7 and had no protocol deviation that might interfere with the main efficacy criteria.
- The Safety Set (SS) consisted of all included patients who received at least 1 dose of trial medication.
- The Cognitive Wis Per Protocol Set (CPPSM7-W) consisted of patients in the FAS, with no missing values and who had good protocol compliance for at least 1 baseline test and 1 post-baseline Wisconsin test, with no protocol deviations and MADRS score < 30 at D0 and had Wisconsin test data at Month 7.
- The Cognitive SVDR Per Protocol Set (CPPSM7-SVDR) consisted of patients in the FAS, with no missing values and who had good protocol compliance for at least 3 baseline tests and 3 post-baseline tests, with no protocol deviations and MADRS score < 30 at D0 and had Stroop, verbal fluency, digit ordering and "reverse form" of digit symbol test data at Month 7.

For the purposes of the short-term assessment, last post-baseline visit was defined as the last non-missing value recorded after inclusion (up to Month 7). The last non-missing value in monotherapy was defined as the last non-missing value recorded after inclusion and before any introduction of L-dopa therapy (up to Month 7). A missing value at baseline was to be replaced by the value at the selection visit.
The main analysis of the primary efficacy variable (change in UPDRS III total score between baseline and last post-baseline visit in monotherapy) was performed using an ANCOVA (fixed effects: previous L-dopa, country; covariate: baseline UPDRS III total score) and a 2.5% level of significance (1-sided) to show superiority of piribedil in the FAS. Sensitivity analyses were also performed, taking into account centre as a random effect, and missing values on the RS (using Gould's method). As there is only 1 primary analysis, no adjustments for multiplicity were needed. Treatment response in monotherapy was analysed using logistic regression (independent variables: baseline, country and treatment).
All secondary efficacy variables were analysed descriptively at each visit and at each visit in monotherapy. Changes in UPDRS subscores from baseline to last visit in monotherapy were analysed using an ANCOVA (fixed effects: previous L-dopa, country; covariate: baseline UPDRS III subscore). Changes in UPDRS II (ADL) score from baseline to last visit in monotherapy were analysed using an ANCOVA (fixed effects: previous L-dopa, country; covariate: baseline UPDRS II [ADL score]). Time to therapeutic failure was analysed using Kaplan-Meier's method and Cox proportional hazards model (Likelihood ratio test; covariates: baseline Hoehn and Yahr stage, previous L-dopa, country). L-dopa dose was analysed as change from first to last prescribed dose. The final L-dopa dose was analysed using an ANOVA (fixed effects: previous L-dopa, Hoehn and Yahr stage). UPDRS V (Hoehn and Yahr) was analysed using an ANCOVA (fixed effect: country; covariate: baseline Hoehn and Yahr stage). Analyses of secondary efficacy variables were performed at a 5% level of significance (2-sided comparisons) using both the FAS and the PPS, except in the dyskinesia and clinical fluctuations scale, UPDRS V, UPDRS VI and the dyskinesia rating scale, all of which were performed on the FAS only. Descriptive statistics were presented for cognitive function (Stroop, verbal fluency, digit ordering and reverse form of digit symbols tests) and analysed by ANCOVA (adjusting for country [fixed effect] and baseline). A correlation analysis was also performed, using change from baseline to last post-baseline visit and age at selection, years of education, disease duration at selection, motor examination score, Hoehn and Yahr score and MADRS total score. In addition to the FAS, the analysis of the criteria for the Stroop test, verbal fluency, digit ordering and reverse form of digit symbol test was performed on the CPPSM7-SVDR. The analysis of the Wisconsin Card Sorting test was performed on the CPPSM7-W.

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Statistical methods (Cont'd):
All safety data were analysed by treatment group in the SS of patients and pooled for a description of AEs, SAEs and EAEs as well as by visit for descriptions of vital signs and biological parameters.

Summary – Conclusions:
Study population and outcome:

	Placebo	Piribedil	Whole population
Included	205	200	405
Randomised Set (RS)	204	197	401
Lost to Follow-up before Month 7 (n [%])	0	3 (1.5)	3 (0.7)
Withdrawn:	25 (12.3)	40 (20.3)	65(16.2)
due to adverse event (n [%])	5 (2.5)	15 (7.6)	20 (5.0)
due to non-medical reason (n [%])	13 (6.4)	13 (6.6)	26 (6.5)
due to protocol deviation (n [%])	0 (0.0)	6 (3.0)	6 (1.5)
due to lack of efficacy (n [%])	7 (3.4)	3 (1.5)	10 (2.5)
Completed Month7	179 (87.7)	157 (79.7)	336 (83.8)
Full Analysis Set (FAS) (n [%])	199 (97.5)	187 (94.9)	386 (96.3)
Per Protocol Set (PPS) (n [%])	154 (75.5)	136 (69.0)	290 (72.3)
Safety Set (SS) (n [%])	205 (100.5)	200 (101.5)	405 (101.0)

Main baseline characteristics of the RS:

		Placebo N = 204	Piribedil N = 197	Whole population N = 401
Age (years)	Mean (SD)	62.3 (10.3)	62.4 (9.5)	62.3 (9.9)
	Min - Max	32 - 78	30 - 77	30 - 78
Gender	Male n (%)	128 (62.7%)	116 (58.9%)	244 (60.8%)
Family history of PD	No n (%)	182 (89.2%)	176 (89.3%)	358 (89.3%)
PD duration (years)	Mean (SD)	1.97 (2.04)	1.99 (1.80)	1.98 (1.92)
Previous treatment for PD	No n (%)	125 (61.3%)	105 (53.3%)	230 (57.4%)
Dopamine agonists	N (%)	11 (5.4%)	18 (9.1%)	29 (7.2%)
Dopa and derivatives	N (%)	19 (9.3%)	30 (15.2%)	49 (12.2%)
Adamantane derivatives	N (%)	12 (5.9%)	24 (12.2%)	36 (9.0%)
Tertiary amines	N (%)	38 (18.6%)	36 (18.3%)	74 (18.5%)
Hoehn and Yahr	Mean (SD)	2 (0.5)	2.1 (0.5)	2 (0.5)
MADRS score	Mean (SD)	6.5 (7.2)	7.7 (7.2)	7.1 (7.2)
UPDRS III score	Mean (SD)	23.1 (11.5)	25.9 (11.7)	24.5 (11.7)

The mean study treatment duration was 203.0 ± 46.8 and 190.1 ± 60.3 days in placebo and piribedil groups, respectively.

Efficacy Results:

Primary efficacy variable - UPDRS III total score (last post-baseline change in monotherapy):

	Placebo	Piribedil
FAS (n = 386)	199	187
Last change (mean [SD])	2.6 [8.9]	-4.9 [9.8]
ANCOVA : LS mean difference (95% CI)	7.26 (5.38, 9.14); p < 0.0001	
Sensitivity analysis (ANCOVA) LS mean difference (95% CI)	7.27 (5.45, 9.09); p < 0.0001	
PPS (n = 290)	154	136
Last change (mean [SD])	1.3 [8.5]	-5.6 [9.9]
ANCOVA : LS mean difference (95% CI)	6.77 (4.64, 8.89); p < 0.0001	

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Efficacy Results (Cont'd):

Secondary efficacy variables:

UPDRS III subscores changes in monotherapy:

A significantly greater improvement was observed with piribedil treatment compared with placebo in all subscores in true monotherapy conditions: tremor at rest ($p < 0.0001$), action or postural tremor ($p = 0.008$), rigidity ($p = 0.0002$), bradykinesia ($p < 0.0001$), and axial score ($p = 0.0002$).

Proportion of responders at the last visit in monotherapy (Logistic regression):

In the FAS, 42.2% (n = 79) of patients were responders to piribedil treatment compared with 13.6% (n = 27) to placebo treatment. The percentage of responders to piribedil reached 48.5% (n = 66) in PPS.

	Odds Ratio	**95% CI**	**p-value**
FAS (n = 386)	4.69	[2.82, 7.80]	< 0.001
PPS (n = 290)	4.56	[2.63, 7.91]	< 0.001

UPDRS II (ADL) total score change from baseline to last post-baseline visit in monotherapy:

	Placebo	**Piribedil**
FAS (n = 386)	199	187
Last change in monotherapy (mean [SD])	1.5 [4.4]	-1.2 [4.6]
ANCOVA: LS means difference (95% CI)	2.71 (1.80, 3.62); p < 0.0001	
PPS (n = 290)	154	136
Last change in monotherapy (mean [SD])	1 [4.4]	-1.8 [4.4]
ANCOVA: LS means difference (95% CI)	2.73 (1.71, 3.75); p < 0.0001	

Time to introduction of L-dopa:

A lower proportion of piribedil-treated patients (16.6%) than placebo-treated patients (40.2%) received L-dopa rescue treatment during the 7 months of treatment. The proportion of patients taking L-dopa was significantly higher in the placebo group, with an Odds ratio of 3.72 for the FAS ($p < 0.001$). This result was supported by analysis of the PPS (Odds ratio of 3.2, $p < 0.001$) The relative risk of the need to introduce L-dopa rescue treatment during 7 months of treatment was 3.02 in the FAS and 2.72 in the PPS for placebo *versus* piribedil.

Cox proportional Hazard Model	**Relative risk***	**95% CI**	**p-value**
FAS (n = 386)	3.02	[1.96, 4.65]	< 0.0001
PPS (n = 290)	2.72	[1.62, 4.58]	0.0002

** Relative risk = piribedil-placebo; Analysis adjusted for UPDRS III baseline and country*

Placebo patients generally received a significantly higher last prescribed L-dopa daily dose (139.1 mg in the placebo group and 57.0 mg in the piribedil group [$p < 0.0001$] in the FAS and 130.7 mg in the placebo group and 52.2 mg in the piribedil group [$p = 0.0004$] in the PPS).

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Efficacy Results (Cont'd):

Other secondary criteria:

During the first 7 months of treatment, a decrease in Hoehn and Yahr stage was seen with piribedil treatment, which was significantly different to placebo ($p < 0.008$, FAS).

While the MADRS score remained relatively stable in both groups over 7 months, a decrease of 1 point on the Beck depression inventory was demonstrated in the piribedil group and an increase of 1.2 points in the placebo group.

In general, the effects of piribedil on cognitive function from baseline to the last post-baseline visit did not appear to differ from placebo.

In piribedil-treated patients, the PDQL total score increased 5.0 points from baseline to last post-baseline visit, compared with a decrease from baseline to last post-baseline visit of 6.1 points in placebo-treated patients.

Safety Results:

Emergent adverse events:

Overall, 63.0% of patients in the SS experienced at least 1 EAE (57.1% in the placebo and 69.0% in the piribedil treatment group). These were analysed by preferred term as follows:

Preferred term	Placebo (N = 205)			Piribedil (N = 200)			All (N = 405)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%
Nausea	8	8	3.9	24	24	12.0	32	32	7.9
Hypertension	10	9	4.4	20	19	9.5	30	28	6.9
Dizziness	10	9	4.4	17	15	7.5	27	24	5.9
Anxiety	9	9	4.4	13	13	6.5	22	22	5.4
Hypotension postural	8	8	3.9	13	13	6.5	21	21	5.2
Insomnia	6	6	2.9	15	13	6.5	21	19	4.7
Constipation	6	6	2.9	13	13	6.5	19	19	4.7
Depression	12	12	5.9	7	7	3.5	19	19	4.7
Somnolence	6	6	2.9	12	12	6.0	18	18	4.4
Back pain	8	8	3.9	11	9	4.5	19	17	4.2
Oedema peripheral	7	7	3.4	11	10	5.0	18	17	4.2
Dyspepsia	8	7	3.4	10	9	4.5	18	16	4.0
Abdominal pain	4	4	2.0	12	12	6.0	16	16	4.0

Only data experienced by ≥ 4% of patients are presented
NEAE: Number of emergent adverse events; N: total number of exposed patients in the considered treatment group
*n: Number of patients affected; % = n/N*100*

While no action was taken for 44.0% of these patients (38.0% in placebo and 50.0% in piribedil groups), medication was stopped in 19 (4.7%) of these patients (2.0% in placebo and 7.5% in piribedil groups).

Treatment-related emergent adverse events:

Overall, 34.1% of patients in the SS experienced at least 1 treatment-related EAE (25.4% in the placebo and 43.0% in the piribedil treatment group).

Severe emergent adverse events

Overall, 10.4% of patients in the SS experienced at least 1 severe EAE (6.3% in the placebo and 14.5% in the piribedil treatment group).

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Safety Results (Cont'd):

Serious emergent adverse events:

Ten patients (4.9%) in placebo group and 17 patients (8.5%) in piribedil group experienced at least 1 SEAE as follows:

System organ class	Placebo (N = 205)			Piribedil (N = 200)			All (N = 405)		
	NSEAE	n	%	NSEAE	n	%	NSEAE	n	%
Gastro-intestinal system disorders	**1**	**1**	**0.5**	**3**	**3**	**1.5**	**4**	**4**	**1.0**
Abdominal pain	0	0	0	1	1	0.5	1	1	0.2
Gastritis	0	0	0	1	1	0.5	1	1	0.2
Nausea	1	1	0.5	0	0	0	1	1	0.2
Pancreatitis	0	0	0	1	1	0.5	1	1	0.2
Body as a whole – general disorders	**3**	**3**	**1.5**	**1**	**1**	**0.5**	**4**	**4**	**1.0**
Asthenia	1	1	0.5	0	0	0	1	1	0.2
Chest pain	1	1	0.5	0	0	0	1	1	0.2
Hernia NOS	1	1	0.5	0	0	0	1	1	0.2
Syncope	0	0	0	1	1	0.5	1	1	0.2
Musculo-skeletal system pain	**0**	**0**	**0**	**4**	**4**	**2.0**	**4**	**4**	**1.0**
Back pain	0	0	0	2	2	1.0	2	2	0.5
Fracture pathological	0	0	0	1	1	0.5	1	1	0.2
Skeletal pain	0	0	0	1	1	0.5	1	1	0.2
Vascular (extracardiac) disorders	**1**	**1**	**0.5**	**2**	**2**	**1.0**	**3**	**3**	**0.7**
Cerebrovascular disorders	0	0	0	1	1	0.5	1	1	0.2
Haemorrhage intracranial	0	0	0	1	1	0.5	1	1	0.2
Transient ischaemic attack	1	1	0.5	0	0	0	1	1	0.2
Secondary terms	**1**	**1**	**0.5**	**2**	**2**	**1.0**	**3**	**3**	**0.7**
Inflicted injury	1	1	0.5	1	1	0.5	2	2	0.5
Prostatic specific antigen increased	0	0	0	1	1	0.5	1	1	0.2
Liver and biliary system disorders	**1**	**1**	**0.5**	**2**	**2**	**1.0**	**3**	**3**	**0.7**
Cholelithiasis	0	0	0	1	1	0.5	1	1	0.2
Hepatitis cholestatic	1	1	0.5	0	0	0	1	1	0.2
Jaundice	0	0	0	1	1	0.5	1	1	0.2
Central and peripheral nervous system disorders	**1**	**1**	**0.5**	**1**	**1**	**0.5**	**2**	**2**	**0.5**
Paresis	1	1	0.5	0	0	0	1	1	0.2
Parkinsonism aggravated	0	0	0	1	1	0.5	1	1	0.2
Psychiatric disorders	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Hallucinations	0	0	0	1	1	0.5	1	1	0.2
Cardiovascular disorders, general	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Cardiac failure left	0	0	0	1	1	0.5	1	1	0.2
Autonomic nervous system	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Syncope	0	0	0	1	1	0.5	1	1	0.2
Metabolic and nutritional disorders	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Coma hypoglycaemic	0	0	0	1	1	0.5	1	1	0.2
Myo endo pericardial and valve disorders	**0**	**0**	**0**	**2**	**2**	**1.0**	**2**	**2**	**0.5**
Myocardial infarction	0	0	0	1	1	0.5	1	1	0.2
Myocardial ischemia	0	0	0	1	1	0.5	1	1	0.2
Neoplasm	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Colon carcinoma	0	0	0	1	1	0.5	1	1	0.2
Resistance mechanism disorders	**1**	**1**	**0.5**	**0**	**0**	**0**	**1**	**1**	**0.2**
Sepsis	1	1	0.5	0	0	0	1	1	0.2
Respiratory system disorders	**0**	**0**	**0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Pneumonia	0	0	0	1	1	0.5	1	1	0.2
White cell and res disorders	**1**	**1**	**0.5**	**0**	**0**	**0**	**1**	**1**	**0.2**
Leukaemia lymphocytic	1	1	0.5	0	0	0	1	1	0.2

(1) Number of serious emergent adverse events in a given system organ class or preferred term

(2) Number of patients with at least 1 serious emergent adverse event in a given system organ class or preferred term

*(3) Percentage of patients with at least 1 serious emergent adverse event in a given system organ class or preferred term (n/N)*100 (N: number of patients per group)*

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Safety Results (Cont'd) :

Withdrawals

Sixty-five patients (16.2%) withdrew from the study (25 patients [12.3%] in the placebo group and 40 patients [20.3%] in the piribedil group). Overall, 20 patients (5.0%) withdrew from the study as a result of AEs (5 patients [2.5%] in the placebo group and 15 patients [7.6%] in the piribedil group).

Status	Placebo N = 204	Piribedil N = 197	All N = 401
Withdrawn due to:	**25 (12.3%)**	**40 (20.3%)**	**65 (16.2%)**
adverse event	5 (2.5%)	15 (7.6%)	20 (5.0%)
lack of efficacy	7 (3.4%)	3 (1.5%)	10 (2.5%)
non-medical reason	13 (6.4%)	13 (6.6%)	26 (6.5%)
protocol deviation	0 (0.0%)	6 (3.0%)	6 (1.5%)
lost to follow-up	0 (0.0%)	3 (1.5%)	3 (0.7%)

Overall, treatment was stopped in 19 patients (4.7%) due to an EAE, as follows:

System organ class	Placebo (N = 205)			Piribedil (N = 200)			All (N = 405)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%
All events	**6**	**4**	**2.0**	**17**	**15**	**7.5**	**23**	**19**	**4.7**
Gastrointestinal system disorders	**0**	**0**	**0.0**	**6**	**5**	**2.5**	**6**	**5**	**1.2**
Abdominal pain	0	0	0.0	1	1	0.5	1	1	0.2
Dyspepsia	0	0	0.0	1	1	0.5	1	1	0.2
Nausea	0	0	0.0	1	1	0.5	1	1	0.2
Pancreatitis	0	0	0.0	1	1	0.5	1	1	0.2
Vomiting	0	0	0.0	2	2	1.0	2	2	0.5
Psychiatric disorders	**0**	**0**	**0.0**	**5**	**5**	**2.5**	**5**	**5**	**1.2**
Hallucination	0	0	0.0	4	4	2.0	4	4	1.0
Psychosis	0	0	0.0	1	1	0.5	1	1	0.2
Cardiovascular disorders, general	**0**	**0**	**0.0**	**2**	**2**	**1.0**	**2**	**2**	**0.5**
Cardiac failure left	0	0	0.0	1	1	0.5	1	1	0.2
Hypotension postural	0	0	0.0	1	1	0.5	1	1	0.2
Central and peripheral nervous system disorders	**4**	**2**	**1.0**	**0**	**0**	**0.0**	**4**	**2**	**0.5**
Hypokinesia	1	1	0.5	0	0	0.0	1	1	0.2
Parkinsonism aggravated	2	2	1.0	0	0	0.0	2	2	0.5
Tremor	1	1	0.5	0	0	0.0	1	1	0.2
Liver and biliary system disorders	**1**	**1**	**0.5**	**1**	**1**	**0.5**	**2**	**2**	**0.5**
Hepatitis cholestatic	1	1	0.5	0	0	0.0	1	1	0.2
Jaundice	0	0	0.0	1	1	0.5	1	1	0.2
Myo endo pericardial and valve disorders	**0**	**0**	**0.0**	**2**	**2**	**1.0**	**2**	**2**	**0.5**
Myocardial infarction	0	0	0.0	1	1	0.5	1	1	0.2
Myocardial ischaemia	0	0	0.0	1	1	0.5	1	1	0.2
Body as a whole – general disorders	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**1**	**1**	**0.2**
Asthenia	0	0	0.0	1	1	0.5	1	1	0.2
Resistance mechanism disorders	**1**	**1**	**0.5**	**0**	**0**	**0.0**	**1**	**1**	**0.2**
Sepsis	1	1	0.5	0	0	0.0	1	1	0.2

NEAE: number of emergent adverse events
N: total number of exposed patients in the considered treatment group
n: number of patients affected
*% = n/N*100*

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: Trivastal® 50 mg LP	**Volume:**	
Name of Active Ingredient: Piribedil (S4200)	**Page:**	

Conclusion:

Over a 7-month period, piribedil (150 to 300 mg/day) proved to be effective in reducing motor symptoms in *de novo* parkinsonian patients (mean UPDRS III total score changes from baseline to last post-baseline visit in monotherapy of piribedil *versus* placebo in the FAS; least squares [LS] mean difference [and 95% CI] of 7.26 [5.38, 9.14]; $p < 0.0001$). There was a 42.2% response rate with piribedil *versus* 13.6% with placebo (Odds ratio = 4.69, $p < 0.0001$). This beneficial effect was also demonstrated by changes in UPDRS II (ADL) for piribedil *versus* placebo (LS mean difference [and 95% CI] of 2.71 [1.80, 3.62]; $p < 0.0001$).

Although the number of patients remaining in the study at 7 months was similar in both groups, the number of patients receiving L-dopa rescue treatment was lower for the piribedil-treated group (relative risk = 3.02, $p < 0.0001$).

Piribedil was associated with a safety profile consistent with other dopamine agonists including nausea, insomnia, hypertension, dizziness, orthostatic hypotension, hallucinations and somnolence. The number of reported AEs was higher in piribedil-treated patients, especially gastrointestinal disorders. The percentage of emergent psychiatric events was comparable between piribedil-treated patients (23.0%) and placebo-treated patients (17.6%).

There were no notable mean changes from baseline to Month 7 in any biochemistry or haematology parameters. Potentially clinically significant changes were not experienced by more than 10 patients for any given biochemistry or haematology parameter.

Results of this large randomised, double blind, placebo controlled study confirm good efficacy of piribedil on all motor symptoms in *de novo* patients with Parkinson's disease, in true monotherapy conditions. These results support the use of the dopamine agonist piribedil as an effective initial therapeutic option, also able to significantly delay the need for an L-dopa adjunct.

Date of report: **10 August 2005**