Document title	**Clinical Study Report Synopsis**
Study title	**Effect of 3 doses (20, 40 and 60 mg) of a sublingual formulation of piribedil (S 90049) in combination with levodopa on end-of-dose fluctuations in advanced Parkinson's disease patients after a 14 -day treatment-period (one administration t.i.d.).** **A randomised, double- blind study consisting of 3 cross-over: 40 mg versus placebo, 20 mg versus 60 mg and 40 mg versus 20 mg.**
Study drug	**S 90049 - Piribedil orodispersible tablet**
Studied Indication	**Parkinson's disease**
Development phase	**Phase II**
Protocol code	**SC2-90049-003**
Study initiation date	**30 May 2005**
Study completion date	**17 July 2007**
Main coordinator	[redacted] **France**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50rue Carnot** **92284 Suresnes Cedex- France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 18 July 2008**

~~CONFIDENTIAL~~

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 on/y)*
Name of Finished Product: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

Effect of 3 doses (20, 40 and 60 mg) of a sublingual formulation of piribedil (S 90049) in combination with levodopa on end-of-dose fluctuations in advanced Parkinson's disease patients after a 14-day treatment-period (one administration t.i.d.). A randomised, double-blind study consisting of 3 cross-over: 40 mg versus placebo, 20 mg versus 60 mg and 40 mg versus 20 mg.
Protocol n° SC2-90049-003

Coordinator:
[redacted] rance

Study centres: *Multicentre study*
- Total number of countries: 4
- Total number of centres having included at least 1 patient: 20 centres
- Number of centres/country: FRA: 10; DEU: 5; POR: 1; SPA: 4
- Number ofrandomized patients/country FRA: 60; DEU: 10; POR: 3; SPA: 16

Publication (reference): NA

Studied period: Initiation date: 30 May 2005 Completion date: 17 July 2007	Phase of development of the study: II

Objectives:
Main objective: The main objective of this trial was to assess the effect of 3 different doses (20, 40 and 60 mg) of a sublingual new formulation of piribedil in combination with L-dopa on end-of-dose fluctuations in advanced Parkinson's disease patients after a 14-day treatment period. The main objective was to assess the effect of the 40 mg dose versus placebo. The two other comparisons especially the 20 versus 60 mg comparison, aimed at demonstrating a possible dose-effect.
Secondary objective: To assess the local (sublingual) and general acceptability of the different doses of S 90049 (one sublingual administration t.i.d. for 14 days).

Methodology:
This is a phase II, multicentre, international study without direct individual benefit. It is a randomised, double-blind study consisting of 3 (2 x 2) cross-over (CO): 40 mg versus placebo (COl), 20 mg versus 60 mg (C02), and 40 mg versus 20 mg (C03).
After inclusion, there was a 3 to 5 days phase of dopamine agonists withdrawal and then 2 treatment periods of 14 days separated by a 3-day wash-out interval. The effect of S 90049 in combination with levodopa was assessed during a standardized "OFF" episode achieved by a 9-hour withholding of the usual antiparkinsonian treatment. The main end-points were the latency to the best "ON" state and the duration of the "ON" period. UPDRS motor score and dyskinesia score were recorded every 30 minutes for 5 hours (3 hours if no switch to "ON"). Additional UPDRS III and dyskinesia scores were recorded at the time of the switch "OFF-ON" and of the switch "ON-OFF". The patient was asked to write down the time at which he feels the beginning of the "tum on" and report it to the investigator (amendment 2).
Assessment tests were performed at the end of each treatment period.
The baseline test (without study treatments) was carried out 10 ± 3 days after the end of the second treatment period.
A home diary, kept for the 3 days preceding the visits, allowed to record the "OFF" phase duration, dyskinesia and doses oflevodopa.

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 on/y)*
Name of Finished Product: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

Number of patients:
Planned:
Total: 80 patients included to obtain at least 64 completed and fully documented observations.
Total for each cross-over: 32 patients for the cross-over 40 mg versus placebo (cross-over n° 1),
16 patients for the cross-over 20 mg versus 60 mg (cross-over n° 2),
16 patients for the cross-over 40 mg versus 20 mg (cross-over n° 3).

Included:
Total: 92 patients were included, 89 patients randomised and 79 completed the study.
Total for each cross-over: 45 patients for the cross-over 40 mg versus placebo (cross-over n° 1),
22 patients for the cross-over 20 mg versus 60 mg (cross-over n° 2),
22 patients for the cross-over 40 mg versus 20 mg (cross-over n° 3).

Diagnosis and main criteria for inclusion :
Patients were men or women, aged 35 to 80 years, with idiopathie Parkinson's disease at the stage III or IV in "OFF" state according to the modified Hoehn and Yahr classification, with fluctuating responses to L-Dopa (end-of-dose akinesia).
The following treatments were prohibited during the study: Apomorphine, Dopamine Agonists and Neuroleptics.

Study drug:
S 90049: orodispersible tablets containing 20 or 40 mg of piribedil base micronized for sublingual administration (20, 40 or 60 mg, 3 times a day for 14 days in 2 tablets).
Batch No: N02021 and P11014.

Reference product:
Placebo of S 90049: orodispersible tablets identical to the 20 and 40 mg piribedil tablets for sublingual administration
Additional compounds:
- Domperidone: 1 or 2 tablets t.i.d., started 3 days before the frrst treatment administration and maintained throughout the duration of the study,
- Dispersible Modopar: administered at 3 patient morning levodopa dose (as needed throughout the day), if necessary, for the whole duration of the study.

Duration of treatment:
Active treatment period: 2 treatment periods of 14 days each.
Wash-out: 3 days before each treatment period.

Criteria for evaluation:
Efficacy measurements
- Primary end-points: duration of the "ON" phase and time to turn to best "ON"
- Secondary end-points: percentage of patients with relative decrease in UDPRS motor score 30 % at 30 min, time to the beginning of ON, maximal improvement of the UPDRS motor score, percentage of maximal improvement (ratio of the best score during the "ON" period to the basal score), area under the curve of the evolution of the UDPRS motor score, indirect parameter for evaluating the magnitude and the duration ofthe effect, dyskinesia score and the percentage ofawaking time OFF (patient diary).

Safety measurements
- patients' spontaneous report of adverse events, throughout the study,
- blood pressure and heart rate during the assessment tests,
- local acceptability (sublingual examination) before and after S 90049 administration,
- laboratory tests and physical examination including ECG.

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 on/y)*
Name of Finished Product: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

Statistical methods:

Efficacy analysis

The primary analysis was performed in the Full Analysis Set. The primary hypothesis was to prove the superiority of 40 mg over placebo. Secondary comparisons of 60 mg vs. 20 mg and 40 mg vs. 20 mg assessed the possible difference between doses. The 60 mg vs. 20 mg contrast was tested frrst and then, if this contrast was significant, the 40 mg vs. 20 mg contrast was tested in a hierarchical step-down procedure. There was no need to adjust for comparison multiplicity since statistical tests were performed in a hierarchical way using the conventional 2.5 % one-sided type 1error at each step. Comparisons of 20 mg vs. placebo, 60 mg vs. placebo and 20 mg vs. 40 mg were also investigated but relied on between-subject contrasts and were not powered a priori.

For each cross-over and criteria, ANOVA using a linear rnixed model with the treatrnent and period effects as fixed effects and subject effect considered as a random effect was performed. Adjusted Least square means together with the 95 %confidence interval, were estimated for each treatrnent and for all pair-wise differences between treatrnents. The possible carry-over effect was investigated using a separate model. A non parametric (Exact Wilcoxon rank sum test) approach was also used to test treatrnent effects. Parametric procedure (ANOVA) using Linear Mixed Model was used for the additional comparisons based on the 3 cross-over.

The Kaplan-Meier method for estimating survival curves was performed for time to ON and time to return to an OFF state (duration of ON). A Cox model adjusted for period, treatrnent and subject was also used for the time to turn ON and the time to beginning of ON.

Safety analysis

Descriptive statistics were performed on the safety set.

SUMMARY-CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 102 patients were screened to enter this study, 89 patients were randornized (45 in COl, 22 in C02 and 22 in C03), 88 patients (Safety Analysis Set) received at least one dose of the study treatrnent, and 10 patients were withdrawn before completing the study. The FAS included 83 advanced PD patients (52 men and 31 women), with a mean age 61.4 ± 8.8 years, who completed at least one evaluation of the study Disposition of patients per cross-over and per treatrnent, as well as main characteristics of the disease at baseline are detailed in the following tables.

Patients disposition - Cross-over

Status		COl *(N=45l)*	C02 *(N=22l)*	C03 *(N=22l)*	Total *(N=89l)*
Screened					102
Randomized		45 (100%)	22 (100%)	22 (100%)	89 (100%)
Withdrawn		7 (15.5%)	2 (9.1%)	1 (4.5%)	10 (11.2%)
dueto	Adverse event	6 (13.3%)	2 (9.1%)	1 (4.5%)	9(10.1%)
	Non-medical reason	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Com leted		38 (84.4%	20 (90.9%	21 (95.5%	79 (88.7%

Patients disposition per treatment

	Placebo	20mg*	40mg*	60mg
Randomized Set	45	44	67	22
SafeSet	41	44	64	21
Full Anal!sis Set (FAS}	41	42	62	21

**patients from 2 different cross-over*

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: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

Characteristics of the disease at baseline - FAS

Clinical characteristics	COl N=41	C02 N=21	C03 N=21	AH N=83
Duration of the disease (years)	9.2±4.6	11.1 ± 5.3	9.6 ±4.0	9.8 ±4.6
Duration of levodopa (years)	8.5 ± 4.7	9.3 ± 4.8	8.3 ± 4.0	8.7 ±4.5
Daily levodopa dose (mg/day)	760.3 ± 338.5	788.5 ± 381.1	776.6 ± 380.4	746.2 ± 358.3
Levodopa intakes per day	5.1±1.4	5.0 ± 1.5	5.3 ± 1.5	5.1±1.5
Awaking time OFF per day (hours)	5.9 ± 2.7	5.8 ± 2.6	5.3 ± 2.5	5.7 ±2.6
Previous treatment with do amine agonists	31 {76%}	14 {67%}	19 {91%}	64 {77%}

Results are expressed as N (%),and means ±SD

EFFICACY RESULTS

- Descriptive statistics

Main efficacy data - Descriptive statistics - FAS

	Placebo N=41	Piribedil 20 mg N=41*	Piribedil 40 mg N=59*	Piribedil 60 mg N=21
Time to best ON (min)	68 ±44.7	60 ± 41.7	44 ± 22.3	44± 22.9
Time to beginning of ON	55 ± 45.3	48 ±42.8	35 ± 18.8	34± 17.4
Duration of ON (min)	90 ± 61.0	98 ± 54.8	137± 72.2	162 ± 64.8
Basal UPDRS III	38 ± 11.2	38 ± 11.4	37 ± 13.0	34 ± 11.5
UPDRS III maximal improvement (%)	61 ± 20.9	60 ± 18.0	68 ± 13.5	68 ± 12.1
Time OFF (hours per day)	6.7 ± 3.2	6.4 ± 3.7	4.9 ± 3.4	3.8 ± 2.1
% awaking time OFF	45 ± 19.8	40± 20.7	31 ± 21.4	25 ± 14.2

**patients from 2 cross-over. Results expressed as means ±SD*

- Primary efficacy criteria: duration of ON state and time to best ON

Primary efficacy criteria: Duration of ON and Time to best ON – FAS

	Treatment effect*	Standard Error	-value**
Duration o[ON			
Piribedil40 mg vs placebo (COl)	+65.9	10.3	P<0.001
Piribedil 60 mg vs 20 mg (C02)	+56.6	15.5	P=0.002
Piribedil 40 mg vs 20 mg (C03)	+16.3	12.8	P=0.22 (NS)
Piribedil 60 mg vs placebo	+80.9	16.2	P<0.001
Piribedil 20 mg vs placebo	+24.5	13.2	P=0.06 (NS)
Piribedil 60 g vs 40 mg	+24.3	15.0	P=0.11 (NS}
Time to Best ON (min1			
Piribedil40 mg vs placebo (COl)	-24.2	7.5	P=0.003
Piribedil 60 mg vs 20 mg (C02)	-24.1	8.8	P=0.013
Piribedil 40 mg vs 20 mg (C03)	-8.4	10.4	P=0.43 (NS)
Piribedil 60 mg vs placebo	-26.0	9.3	P=0.006
Piribedil 20 mg vs placebo	-8.8	7.7	P=0.25 (NS)
Piribedil 60 g vs 40 mg	-2.0	10.4	P=0.82 (NS)

**Differences in the adjusted means estimated in the ANOVA mode/ (minutes)*

*** ANOVA mixed mode/ adjustingfor treatment, period and random subject.*

Results using Exact Wilcoxon rank sum test for the 3 cross-over analyses were consistent with ANOVA

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: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

ln combination witb levodopa during a standardized OFF episode, a statistically significant increase in ON duration and decrease in the time to best ON were observed:

- between piribedil 40 mg and placebo with a 66-minute increase in ON duration and a 24-minute decrease intime to best ON ($p < 0.001$ and $p=0.003$ respectively).
- between piribedil 60 mg and piribedil 20 mg with a 56-minute increase in ON duration and a 24-minute decrease intime to best ON ($p = 0.002$ and p=O.Ol3 respectively).
- between piribedil 60 mg and placebo with a 81-minute increase in ON duration and a 26-minute decrease intime to best ON ($p < 0.001$ and $p=0.006$ respectively).

A trend in favor of tbe 20 mg dose versus placebo was observed for ON duration but not for time to best ON. No statistically significant difference was observed between tbe 40 and 20 mg doses and between the 40 and 60 mg doses for botb parameters.

- Secondary efficacy criteria

Secondary criteria from the combined levodopa challenge

In combination with levodopa during a standardized OFF episode, maximal improvement of UPDRS motor score was found to be:

- significantly higher with piribedil40 mg than with placebo ($p = 0.013$),
- significantly higher with piribedil40 mg than with piribedil 20 mg ($p= 0.035$),
- not significantly different with piribedil 60 mg and piribedil 20 mg.

The additional secondary comparisons showed a trend in favor of piribedil 60 mg vs placebo (p=0.08), and no statistically significant difference between piribedil 20 mg and placebo and between piribedil 60 and 40 mg. Similar results were observed for the evolution of UPDRS III changes over time (AUC). A dose-dependant effect was also observed for tbe number of patients with an at least 30% decrease in UPDRS motor score, which was 39, 44, 66 and 76% with placebo and piribedil 20, 40 and 60 mg respectively.

The percentage of patients experiencing dyskinesia while in ON state was not superior with piribedil tban with placebo.

Data from the patients home diaries

After 14 days of treatrnent (3 intakes per day), the percentage of awaking time OFF per day was significantly lower with piribedil 40 and 60 mg than with placebo with a benefit of more than 2 hours.

SAFETY RESULTS

- Emergent adverse events

Treatment Emergent Adverse Events (TEAEs) in the safety set

Adverse Events	Placebo		Piribedil					
			20mg		40mg		60mg	
	N=41		N=44		N=64		N=21	
	#	N{%}	#	N{%}	#	N{%}	#	N{%}
All TEAEs	27	14 (34.1)	36	25 (56.8)	60	29 (45.3)	28	15 (71.4)
TEAEs related to study drug*	9	7(17.1)	18	13 (29.5)	38	23 (35.9)	23	14 (66.7)
TEAEs leading to study withdrawal	1	1 (2.4)	3	3 (6.8)	*5*	4 (6.3)	0	-
Serious TEAEs	1	1 (2.4)	2	2 (4.5)	*5*	*5* (7.8)	0	-
Most frequent TEAE (5% in 1 group)								
Nausea	1	1 (2.4)	1	1 (2.3)	12	11 (17.2)	6	5 (23.8)
Vomiting	1	1 (2.4)	1	1 (2.3)	*5*	4 (6.3)	2	2 (9.5)
Somnolence	2	2 (4.9)	3	3 (6.8)	0	-	3	2 (9.5)
Dyskinesia	0	-	0	-	3	3 (4.7)	2	2 (9.5)
Hypotension	1	1 (2.4)	1	1 (2.3)	0	-	2	2 (9.5)
PD aggravated	1	1 (2.4)	4	4 (9.1)	3	2 (3.1)	1	1 (4.8)
Dystonia	0	-	3	3 (6.8)	1	1 (1.6)	0	-

#: number ofTEAEs- N (%): number and percentage of patients with at [east one TEAE

** Relationship assessed as probable, possible or doubtful*

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 on/y)*
Name of Finished Product: *NA*	Volume:	
Name of Active Ingredient: *Piribedil*	Page:	

Few serions Treatment Emergent Adverse Events (TEAE) were reported and few TEAE resulted in a study withdrawal. The most frequent TEAE were gastrointestinal and neuropsychiatrie disorders, as usually reported with dopamine agonists and their incidence increased with the dose.

- Laboratory tests, other safety evaluation

The biological and ECG survey did not evidence significant changes.

CONCLUSION

The objective of this trial was to assess the effect of 3 different doses (20, 40 and 60 mg) of a sublingual new formulation of piribedil in combination with L-dopa on end-of-dose fluctuations in advanced Parkinson's disease patients after a 14-day treatment period. The main evaluation criteria were the ON duration and the time to ON (best ON) assessed during a standardized OFF episode. The main comparison was the 40 mg dose versus placebo. The two other comparisons, especially the 60 mg versus 20 mg comparison, aimed at demonstrating a possible dose-effect.

Eighty nine (89) patients were randomized, 88 patients (Safety Analysis Set) received at least one dose of the study treatment, and 10 patients were withdrawn before completing the study. The FAS included 83 patients (52 men and 31 women, mean age 61.4 ± 8.8 years) who completed at least one study period. Patients were advanced Parkinson's Disease patients (mean duration of PD: 9.8 ± 4.6 years) with a mean awaking time OFF: 5.7 ± 2.6 hours despite a treatment with levodopa plus dopamine agonists (in 77% of the cases).

During a standardized OFF episode, orodispersible piribedil, in combination with levodopa, decreased the time to ON, prolonged the ON phase and increased the maximum improvement of UPDRS motor score in a dose-dependent manner in patients with Parkinson's disease and motor fluctuations. Piribedil 40 and 60 mg, 3 times a day for 14 days, also significantly decreased the percentage ofawaking time OFF.

The treatment was generally and locally well tolerated and there was no unexpected adverse event. Treatment-related adverse events were dose-dependent.

The interest of orodispersible piribedil in advanced Parkinson's Disease patients with motor fluctuations has to be confurned in long term studies.

Date of the report: 18 July 2008