Document Title	**Clinical Study Report Synopsis**
Study title	**Assessment of the acceptability of a sublingual formulation of piribedil (S 90049), 10 to 30 mg given on request (maximum 5 times a day) on the top of L-dopa and a dopamine agonist in advanced Parkinson Disease patients with motor fluctuations: a 4-week open label pilot study.**
Study drug	**S 90049 - Piribedil orodispersible**
Studied indication	**Parkinson disease**
Development phase	**Phase III**
Protocol code	**SC3-90049-001**
Study initiation date	**2 December 2005**
Study completion date	**19 September 2006**
Main coordinator	[redacted] **France**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue 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 final report	**Final version of 09 January 2008**

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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: **NA**	**Volume:**	
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Title of study:
Assessment of the acceptability of a sublingual formulation of piribedil (S 90049), 10 to 30 mg given on request (maximum 5 times a day) on the top of L-dopa and a dopamine agonist in advanced Parkinson Disease patients with motor fluctuations: a 4-week open label pilot study.
Protocol No. SC3-90049-001

Coordinator: [redacted]

Study centres:
Total number of countries = 2
Total number of centres having included at least 1 participant = 8
Number of centres/country: FRA = 6, DEU = 3
Number of included participants/country: FRA = 15, DEU = 19

Publication (reference): NA

Studied period:	**Phase of development of the study:**
Initiation date: 02 December 2005 Completion date: 19 September 2006	III

Objective(s): The main objective of this pilot trial was to assess the acceptability of a sublingual new formulation of piribedil given on request on the top of L-dopa and a dopamine agonist in advanced Parkinson's disease patients with motor fluctuations.

Methodology:
This was an open pilot phase III, international multicentre study with direct individual benefit.

After a 1 to 3 weeks selection period, the trial was divided into 2 phases:

- an inpatient phase (1 to 3 days named H1, H2 and H3) in order to determine the dose necessary to obtain a rapid switch "OFF-ON" within 30 minutes. A dose titration was performed on spontaneous "OFF" episodes, S 90049 being given on the top of the other antiparkinsonian treatment.
- An outpatient phase of 4 weeks (Day 1 to Day 28). During this phase S 90049 was first administered at the dose determined during the hospitalisation. The study treatment was taken at most 5 times a day on request on the top of the other antiparkinsonian medications. During this period, an intermediate visit was planned at Day 7.

The 3 days preceding the visits (Day 7 and Day 28 at the end of the study), a home diary was to be completed by the patient which allowed to record the changes in L-dopa and dopamine agonist, the "OFF" phase duration and the latency to "ON" state after each study treatment intake.

In French centres, for patients wishing to continue the study drug treatment an optional additional 3 months study period was suggested. During these three additional months, the patients continued the study drug intake at the dose defined during the principal study phase. Three study visits took place (one visit each month). Only safety data were recorded.

Number of participants:
Planned: 60 completed and fully documented observations.
Included in principal study phase: 34 patients, 26 patients completed the study
Included in extension study phase: 6 patients included and completed

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Diagnosis and main criteria for inclusion:

Patients were men or women, aged 35 to 75 years, with idiopathic Parkinson's disease at the stage I to III in "ON" state according to the modified Hoehn and Yahr classification, treated with L-dopa and a dopamine agonist, with fluctuating responses to L-Dopa (end-of-dose akinesia).

The following treatments were prohibited during the study: Apomorphine, dispersible Modopar and Neuroleptics.

Study drug:

S 90049: orodispersible tablets containing 10 mg of piribedil base micronized for sublingual administration (1 to 3 tablets separated by an interval of maximum 5 minutes for each administration) - administration at request maximally five times / day respecting a minimal time interval of 2 hours between 2 intakes

Batch number
Principal study phase: L0007759
Additional optional study phase: L0007759

Associated treatment:

Domperidone: 1 or 2 tablets t.i.d., was to be started 3 days before the dose finding phase and maintained throughout the duration of the study in order to avoid possible side effects of S 90049

Batch number
Principal study phase: L0007959
Additional optional study phase: L0010087

Reference product: N.A.

Duration of treatment:

Principal study phase:
Dose finding phase (hospitalisation): 1 to 3 days
Outpatient phase: 4 weeks

Additional optional study phase for French centres: 3 months (90 days)

Criteria for evaluation:

Principal study phase
Safety measurements:

- Patients' spontaneous report of adverse events, throughout the study,
- clinical events due to dopamine agonists (orthostatic hypotension, hallucination, confusion, vigilance disorders),
- disabling dyskinesia,
- blood pressure and heart rate at each visit,
- local acceptability (sublingual examination) before and after S 90049 administration,
- physical examination.

Efficacy measurements:

outpatient phase: patient home diary to be completed the 3 days preceding a visit. The data recorded allowed to determine the awaking time OFF, the number of "OFF" episodes per day, the time to "ON", the number of S 90049 intakes per day and antiparkinsonian medications.

Additional optional study phase
Only Safety measurements were performed.

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Statistical methods:

Safety analysis: The acceptability of S 90049 was primarily assessed by the occurrence of Adverse Events (AE) and Serious Adverse Events (SAE) throughout the study. Dopaminergic AEs that were expected were particularly studied.

The efficacy of S 90049 was assessed by a descriptive analysis performed at each scheduled visit for the parameters recorded in the home diary. Changes from baseline were also summarized. Number of S 90049 intakes per day and time to "ON" was analyzed.

Safety analysis were performed in the ITT Safety set (definition see below).

Efficacy analysis were carried out in the Efficacy sets (definition see below).

Regarding the additional study phase, no efficacy analysis was performed.

All analysis were purely descriptive.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

The **ITT Safety Set (N = 34)** was defined as all included patients receiving at least one dose of the studied drug during the titration phase (**ITT SS**). The Safety Set covered all included patients.

The ITT Efficacy Set was defined as all included patients receiving at least one dose of the studied drug and with available efficacy data during the assessment phase (**ITT ES**).
The ITT Efficacy Set consisted of 30 patients (88,2% of the ITT Safety Set). 4 patients were excluded from the **ITT ES** due to withdrawal from the study.

Completer Efficacy Set
This covered all included patients who completed the four weeks of treatment **(CES)**.
The Completer Efficacy Set consisted of 26 patients (76.5% of the ITT Safety Set).
8 patients were excluded from the **CES**.

	Whole population
Included	34
Lost to Follow-up	N.A.
Withdrawn	8
due to adverse event	3
due to non-medical reason	1
due to lack of efficacy	4
Completed	26
ITT Safety Set	34
ITT Efficacy Set	30
Completer Efficacy Set	26

Demographic data and baseline characteristics were described for the **ITT Safety Set (N = 34).**

The ITT Safety Set included 34 patients, 19 males / 15 women, of mean age 64.4 ± 8.3 years and mean BMI 25.3 ± 5.2.

The mean duration of Parkinson's disease prior to inclusion in the study was 10.1 ± 4.6 years.

All patients presented wearing OFF and no patient presented ON - OFF fluctuations.

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All patients were L-Dopa responders, the mean duration of treatment with L-Dopa was 9.0 ± 4.7 years.

The mean UPDRS III motor score was 32.4 ± 9.1 in patients examined in OFF state (n=7) and 15.0 ± 9.1 in patients examined in ON state (n=27).

In "ON" period, 44.1% of the patients were in stage 2 of Hoehn and Yahr whereas 48.4% of the patients were in stage 4 in "OFF" period.

Except one patient, all patients were treated with one or two dopamine agonists.

The mean patients' treatment duration during the principal study phase was 27.6 ± 7.8 days. The dose/intake of study treatment decided at V2 (corresponding to the optimal dose determined at the end of the titration phase) was 10mg for 16.1% of the patients, 20mg for 48.4% and 30mg for 35.5% of the patients. The mean daily dose of Piribedil taken during the whole assessment phase (between V2 and V4) was 70.2mg ± 32.2mg per day with a mean daily number of intakes of 3.1 ± 1.2 .

Six patients were willing to participate in the optional additional study phase. All six patients completed the 3 months follow up period. All patients were treated with L-Dopa and one or two Dopamine Agonists. The mean daily dose of Piribedil taken during the 3 months was 66.4 mg/day ± 32.4 mg per day with a mean number of 2.6 ± 1 intakes per day.

EFFICACY RESULTS

The following table displays the main efficacy results for the Completer Efficacy Set (26 patients) deriving from analysis of the patients' home diary completed 3 consecutive days preceding the corresponding study visits:

	Mean awaking time OFF Median (hours)	**Percentage of awaking time OFF Median (%)**	**Mean number of OFF episodes Median (n)**	**Percentage of episodes aborted in 30/45 min (%)**
V2 – selection phase / dose finding visit	7.0]3.7 - 11.8]	42.7]21.2 - 66.0]	4.0]2.7 - 6.3]	
V3 – day 7 of study treatment	5.0]1.2 - 9.3]	29.8]7.2 - 52.5]	3.3]0.7 - 5.3]	62.3 / 74.9
V4 – day 28 of study treatment	5.2]0.8 - 18.0]	31.3]4.6- 100.0]	3.3]1.0 - 6.0]	59.3 / 68.8
Whole assessment phase				60.8 / 71.8

As described by the patient home diary, a decrease of 2h (CES) in the mean awaking time OFF per day was observed after approximately a seven day treatment period and this effect was practically maintained during the study with a decrease of 1.8h after approximately 4 weeks of study treatment intake.

The analysis of the whole assessment phase for the Completer Efficacy Set confirms that a rapid switch from the OFF to the ON state is obtained in the majority of the episodes. Indeed, 60.8% of the episodes are aborted within 30 minutes and 71.8% of the episodes are aborted within 45 minutes.

The significance of these efficacy results is restricted by the study design (open, exploratory) and the number of patients included as well as by the difficulties of interpreting data issued in the patient's home diary.

SAFETY RESULTS

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Referring to the principal study phase, overall 34 patients were included in the ITT Safety Set during the titration phase.

No serious nor significant adverse event (AE) was reported during the study.

Adverse events were either classified as *potentially dopamine agonist related* adverse events or as *other* adverse events:

Twenty six AEs potentially related to dopamine agonists appeared, most of them were of mild intensity (61.5%), 9 AEs (34.6%) were of moderate intensity and 1 AE (3.8%) was of severe intensity. The relationship to the study drug was established for all of them.

A total of 15 other AEs, 14 being emergent adverse events, was reported by seven patients. The relationship to treatment was established for three AEs (20.0%): "disabling dyskinesia", "increase of dyskinesia" and "dyspepsia".

The following table is a summary of all AEs observed that were classified as potentially related to the study drug.

Emergent adverse events possibly related to the study drug
Safety Set (n= 34)

	AE	Patient	%
Nervous System Disorders	**13**	**9**	**26%**
Dyskinesia	5	5	15%
Somnolence	3	3	9%
Headache	2	2	6%
Paraesthesia	2	2	6%
Disturbance in attention	1	1	3%
General Disorders And Administration Site Conditions	**7**	**6**	**18%**
Fatigue	6	5	15%
Malaise	1	1	3%
Gastrointestinal Disorders	**6**	**5**	**15%**
Nausea	3	2	6%
Dyspeptia	2	2	6%
Flatulence	1	1	3%
Psychiatric disorders	**3**	**2**	**6%**
Hallucinations	1	1	3%
Irritability	1	1	3%
Psychomotor hyperactivity	1	1	3%

These AEs included nervous system disorders (as dyskinesia, somnolence ...), general disorders and administration site conditions (fatigue and malaise), gastrointestinal disorders (as nausea) and psychiatric disorders.

Five AEs led to drug withdrawal of 3 patients.

Most of the AEs potentially related to the study drug are common side effects of most dopaminergic agents. No increase in frequency of these adverse events was observed.

During the whole part of the principal study phase, no patient showed any abnormality regarding sublingual examination.

No clinically relevant change in mean values of vital signs (supine, standing blood pressure and heart rate) was

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detected during the titration and assessment phase.

Extension study phase

Eight (8) adverse events of mild or moderate intensity were experienced by 4 patients.

A relationship to the study drug was established for 2 AEs.

No AE led to a withdrawal from the study drug or to a change in the study treatment dose.

No serious AE was reported during this optional extension study phase.

CONCLUSION

The ***main objective*** of this pilot trial was to assess the acceptability of a sublingual new formulation of piribedil given on request on the top of L-dopa and a dopamine agonist in advanced Parkinson's disease patients with motor fluctuations.

The primary end-point was the acceptability – based on the occurrence of adverse events – of S 90049 10 to 30 mg administered at most 5 times daily during 4 weeks on the top of the other antiparkinsonian medications.

Thirty-four (34) patients suffering for 10.1 ± 4.6 years from Parkinson disease and treated with L-Dopa and one or two dopamine agonists were included and 26 patients completed the principal study phase.

Even though, efficacy was only a secondary criteria in this study and analysis purely descriptive, the results obtained confirm the interest of orodispersible Piribedil for sublingual use in the treatment of fluctuating Parkinson's disease. The implication of these results is restricted by the study design (open, exploratory) and the number of patients included.

Concerning the main objective of this pilot study, that was to assess the acceptability, it can be concluded, that the sublingual administration of Piribedil orodispersible, 10 to 30 mg given on request on the top of L-dopa and a dopamine agonist in advanced Parkinson Disease showed a safe and well tolerated profile in this study. The number and nature of adverse events occurred did not reveal any elevated risk and corresponds to the frequency that is usually observed under dopamine agonist drug therapy. No application site reactions (sublingual examination) were observed.

To conclude, the results of this pilot trial showed that the administration of S 90049 together with Levodopa and one or two other dopamine agonists did not increase the occurrence of dopaminergic adverse events such as orthostatic hypotension, hallucinations, vigilance disorders, confusion, as well as the incidence of disabling dyskinesia.

Therefore, repeated administrations of S 90049 in combination with all the other antiparkinsonian treatments is safe and can be used in further studies.

Date of the report: 9 January 2008