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Orodispersible Sublingual Piribedil to Abort OFF Episodes: A Single Dose Placebo-Controlled, Randomized, Double-Blind, Cross-Over Study

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Abstract: S90049, a novel sublingual formulation of the non-ergoline D_2-D_3 agonist piribedil, has a pharmacokinetic profile promising to provide rapid relief on motor signs in Parkinson's disease (PD). We assessed the efficacy and safety of S90049 in aborting OFF episodes responding to subcutaneous apomorphine in PD patients with motor fluctuations. This was a single-dose double-blind double-placebo 3 × 3 cross-over study. Optimal tested doses were determined during a previous open-label titration phase (S90049 median dose: 60 mg, apomorphine: 5 mg). Primary endpoint was the maximal change versus baseline in UPDRS motor score (ΔUPDRS III) assessed after drug administration following an overnight withdrawal of antiparkinsonian medications. Thirty patients (age: 60 ± 8 years, PD duration: 12 ± 6 years, UPDRS III OFF: 37 ± 15) participated. S90049 was superior to placebo on ΔUPDRS III (−13 ± 12 versus −7 ± 9 respectively; estimated difference −5.2, 95% Confidence Interval (CI)[−10.4;0.05], $P = 0.05$). This was also true for secondary outcomes: number of patients switching from OFF to ON (17 on S90049 vs. 8 on placebo, $P = 0.03$), time to turn ON ($P = 0.013$) and duration of the ON phase ($P = 0.03$). In the 17 patients who switched ON on S90049, ΔUPDRS III was similar on S90049 (−21.2 ± 10.1) and apomorphine (−23.6 ± 14.1) (estimated difference: 4.0 95% CI [−2.9;10.9]). S90049 was well tolerated: no serious or unexpected adverse event occurred. A single dose of up to 60 mg of S90049 given sublingually was superior to placebo in improving UPDRS III and aborting a practical OFF in patients with advanced PD. Testing greater doses might improve response rate. © 2010 Movement Disorder Society

Key words: Parkinson's disease; motor fluctuations; dopamine agonist; piribedil; S90049; apomorphine

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INTRODUCTION

Levodopa (L-dopa) chronic use in Parkinson's disease (PD) is associated with motor fluctuations and OFF episodes. Fluctuations can improve on L-dopa doses adjustments, oral dopamine agonists, COMT

inhibitors, or MAO-B inhibitors.[1,2] However, some patients must use subcutaneous (sc) apomorphine injections to abort OFF episodes resisting to orally active therapies.[3,4] Although efficacious,[5] such injections are not practical to manipulate, especially in akinetic patients. Attempts to develop other routes of administration for apomorphine (intra-nasal, sublingual, intrarectal, or others)[6] have been tested but none is currently approved for routine clinical practice.

Piribedil is a centrally acting non-ergoline D_2-D_3 dopamine agonist[7,8] used in the treatment of PD in the form of piribedil base for oral administration as monotherapy and as adjunct to L-dopa.[9–11] An orodispersible formulation of piribedil, S90049, has been developed for sublingual administration. Its pharmacokinetic profile after single and repeated (10 mg t.i.d) administrations in PD patients shows, from the first dose, an early (T_{max} = 20 minutes) and significant peak plasma level (corresponding to the clinically effective concentrations with intravenous administration).[12] This pharmacokinetic profile seems promising to provide a rapid relief of akinesia and other dopa-responsive symptoms in advanced PD.

The primary objective of this study was to assess the effect of a single dose of S90049 on a practically defined OFF stage (after 12-hour overnight wash-out of all other antiparkinsonian medications) in advanced PD patients with motor fluctuations responding to apomorphine subcutaneous injections.

METHODS

The study was conducted in six centers in France in accordance with the Good Clinical Practice guidelines and the declaration of Helsinki. The study was approved by the appropriate regulatory and ethical authorities before study initiation. All patients provided written informed consent before participation.

Patients

Patients were qualified if they had been diagnosed as suffering from PD according to the United Kingdom Parkinson's Disease Society Brain Bank,[13] if they had a score of II-IV (OFF state) on the Hoehn and Yahr scale,[14] and were L-dopa and apomorphine-responders with motor fluctuations. Antiparkinsonian treatment had to be stable for at least 2 weeks before inclusion. Patients with a history of hallucinations and/or episodes of confusion, with a history of neurosurgery for PD, uncontrolled high blood pressure or symptomatic postural hypotension, uncontrolled diabetes, renal or hepatic impairment, or any clinically significant abnormality on blood tests, and electrocardiography (ECG) could not be included.

Antiparkinsonian treatments including L-dopa, dopamine agonists, COMT, or MAO-B inhibitors, and amantadine were allowed but withheld 12 hours before each test. Anticholinergics and neuroleptics were prohibited. Domperidone (60 mg/day, orally) was given starting 4 days before the titration phase and throughout the duration of the study to prevent potential side effects of tested medications.

Study Design

This was a placebo-controlled, randomized, double-blind, double-dummy, 3 × 3 cross-over phase IIA study, using apomorphine as an internal active reference drug (Fig. 1). All patients were assessed in the morning practically defined OFF condition after an overnight wash-out of all Antiparkinsonian medications. An open-label titration phase preceded the double-blind evaluation phase to identify the optimal dose of sc apomorphine (1–9 mg) and S90049 (10–60 mg) switching patients OFF to ON, to be assessed in the subsequent blinded phase, and to exclude patients who were not responding to apomorphine. Patients who did not respond to 60 mg of S90049 were still eligible and enrolled in the double-blind assessment phase. Study products (piribedil, apomorphine, and their placebo) and randomization (per center by blocs of six corresponding to the six sequences of the 3 × 3 cross-over design) were provided by IRIS-Servier, Courbevoie, France. Apomorphine treatment was prepared by a pharmacist independent from the study to ensure the blind.

The primary outcome was the maximal improvement of UPDRS motor score (Part III) from baseline, after investigational drug administration.[15] UPDRS III was measured at baseline (before drug intake), every 15 minutes for the first hour after drug intake, and then every 30 minutes for the subsequent 5 hours. Testing was interrupted if the patient did not switch OFF–ON within a 3-hour interval, or if the patient returned to an OFF state within the 6-hour interval after an initial switch OFF–ON. Patients were evaluated and scored by the same investigator throughout the study.

Secondary criteria for efficacy assessment were: number of patients who switched OFF–ON (responders), time to switch OFF–ON and duration of the ON state. The fact that a patient switched from OFF to ON, and the time when this occurred was defined sub-

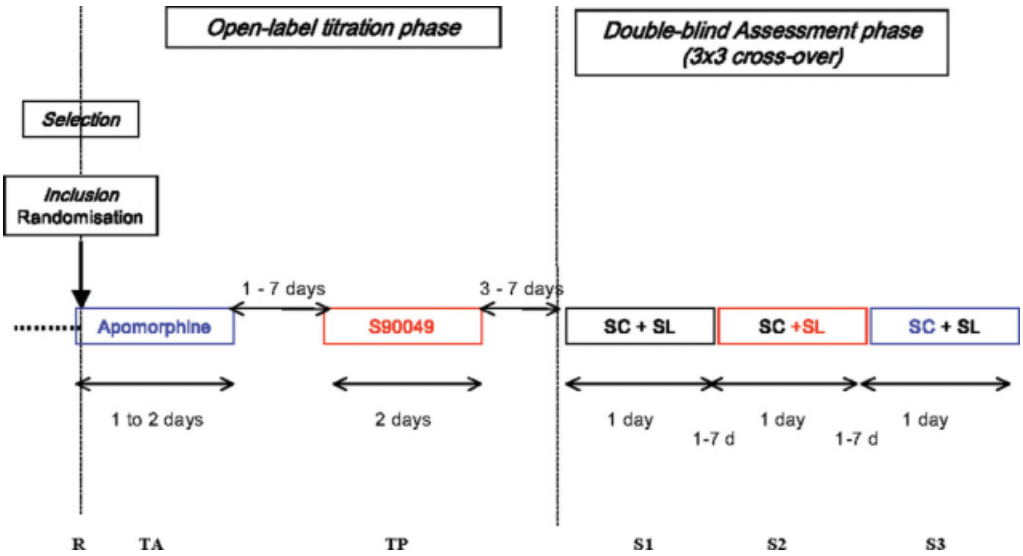

FIG. 1. Study plan. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

jectively upon common agreement between the patient and the investigator.

Adverse events (including dyskinesias) were to be reported spontaneously. Examination of the oral (sublingual) mucosa was systematically performed at each assessment session. Blood pressure and heart rate was measured every hour during assessment sessions. Clinical examination, ECG, biochemistry, hematology were performed at inclusion and follow-up visits.

Statistical Analyses

Statistical Analyses, Tables and Graphs were Performed Using SAS for Windows, Version 8.2.

Descriptive statistics were performed for the demographic data and baseline characteristics and were expressed as counts and frequencies (n,%), means $\pm$ standard deviation (SD) or medians (minimum-maximum) according to the nature of the distributions analyzed.

The primary hypothesis was to prove that S90049 was superior to placebo at the 5% two-sided nominal alpha level in the Full Analysis Set (FAS) defined according to the Intent-To-Treat principle. As all patients selected in the trial were apomorphine-responders, differences between sc apomorphine and S90049 were a priori biased to the advantage of apomorphine, and, therefore, comparisons were not meaningful. Hence, no formal hypothesis tests for differences between apomorphine and S90049 were preplanned. Besides, comparison between apomorphine and placebo was performed to assess trial sensitivity. Since the only comparison of interest was between S90049 and placebo, there was no need to adjust for multiplicity.

The primary endpoint was analyzed as follows: UPDRS III change was set to zero in the patients who did not improve after drug intake. Pairwise treatment effects with their 95% confidence intervals (CI) were estimated as differences in adjusted means in a cross-over linear mixed model adjusting for direct treatments (placebo, S90049, apomorphine), periods and random subjects. Possible carry-over effects were tested in another model. Model assumptions were checked. Alternative robust non-parametric Wilcoxon analyses were systematically proposed as sensitivity analyses.

For secondary endpoints, the number of patients, who switched from OFF to ON, and the time to switch ON were respectively analyzed in a logistic regression mixed model and COX survival model adjusting for design factors. Time to ON and duration of ON were set to 180 and 0 minute respectively for patients who did not switch ON. Treatment differences were expressed as odds ratios (OR) or hazard ratios (HR), respectively. Survival curves were estimated using the Kaplan-Meier method. Duration of ON phase was analyzed like the primary efficacy endpoint.

Subgroup post-hoc descriptive statistical analyses were also performed to report quantitative responses in the group of responders to S90049. However, given the low sample size of this subgroup, results should be interpreted with caution.

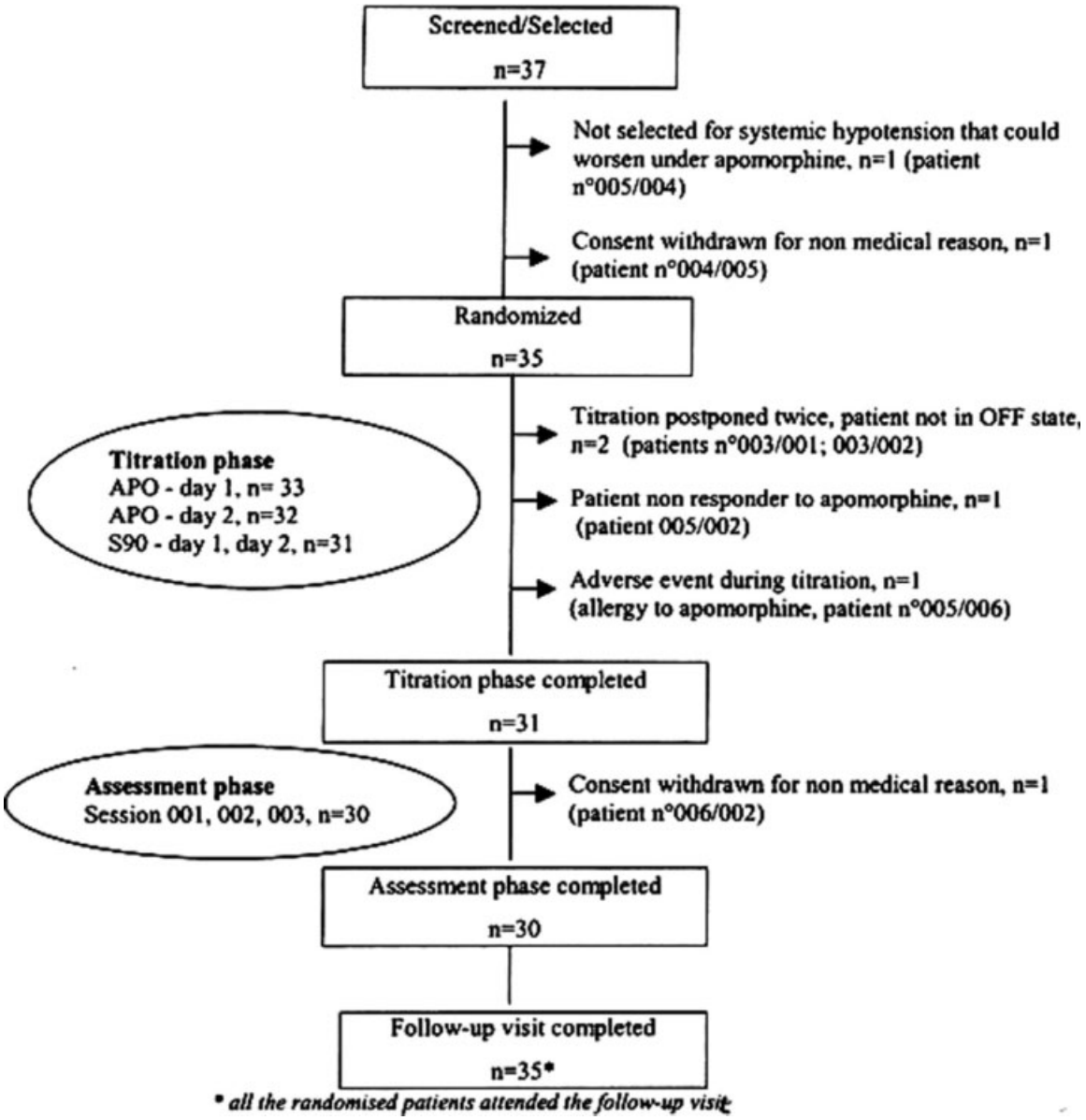

FIG. 2. Patients disposition in the study.

Descriptive Statistics were Performed for Clinical and Biological Safety Parameters.

Assuming a six points difference in the means of the UPDRS III maximal changes between placebo and S90049, a within subject variance of 58.4 (estimated from data of a previous PK/PD trial),[12] and a 5% two-sided nominal alpha level, 25 patients were needed to achieve a 80% power. Further, assuming a rate of drop-outs around 15%, at least 30 patients were to be included to get 25 complete and fully documented observations.

RESULTS

Thirty-five patients entered the trial and were randomized. Five patients did not enter the double-blind phase for local adverse reaction with apomorphine ($n = 1$), non-response to apomorphine ($n = 1$), OFF state not obtained ($n = 2$) and withdrawal of informed consent ($n = 1$) (see flow chart in Fig. 2). Therefore, the FAS cross-over population comprised 30 patients who all completed the double-blind phase. The baseline demographics and disease characteristics in these patients are presented in Table 1.

TABLE 1. *Demography and characteristics of Parkinson's disease at baseline—FAS*

Clinical characteristics	FAS Population $N = 30$
Age (years)	59.9 ± 8.3
Sex ratio (M/F)	22/8
Duration of the disease (years)	12.0 ± 5.5
Duration of levodopa treatment (years)	10.7 ± 4.8
Daily levodopa dose (mg/day)	1080.0 ± 758.4
Oral dopamine agonist *N* (%)	25 (83.3%)
Current treatment with apomorphine *N* (%)	7 (23%)
Hoehn & Yahr in OFF state *N* (%)	
Stage II	6 (20%)
Stage III	6 (20%)
Stage IV	18 (60%)
UPDRS III OFF	37.1 ± 14.6

Values are expressed as N (%) and means ± SD.

During the double-blind phase, apomorphine was administered at a median dose of 5 mg (min-max = 1–9 mg) and S90049 at a median dose of 60 mg (min-max = 10–60 mg), corresponding to the optimal doses determined at the end of titration phase. Baseline UPDRS motor scores were similar in each of the 3 treatment-groups (Table 2).

Efficacy

Analysis Performed in All 30 randomized Patients (Full Analysis Set)

The primary outcome (mean UPDRS III improvement from baseline) was significantly greater on S90049 than on placebo (treatment effect: −5.2, 95% CI [−10.4;0.05], $P = 0.05$, non-parametric test: $P = 0.005$) (Table 2-A). This was also true for apomorphine (−17.1, 95% CI [−22.3;−11.9], $P < 0.001$) using both parametric and non-parametric approaches, confirming the sensitivity of the study.

S90049 and sc apomorphine were also superior to placebo on all secondary outcomes. More patients switched ON on S90049 (17/30, 57%) than on placebo (8/30, 27%) (OR = 3.5, 95% CI [1.1;11.1], $P = 0.033$). This was also true for apomorphine (29/30, 97%) (OR = 119.5, 95% CI [12.2; 1168.1], $P < 0.001$). Median time to ON was significantly shorter on S90049 than on placebo (HR = 2.4, 95% CI [1.0;5.5], $P = 0.044$). This was also true for apomorphine (HR=11.3, 95% CI [4.9;26.0]; $p < 0.001$). Median duration of the ON phase was significantly longer on S90049 andapomorphine than on placebo (non-parametric approach, $p = 0.03$ and $p = 0.0011$, respectively).

Subgroup Analysis Performed in the Patients who Switched ON on S90049

Seventeen patients switched ON with S90049 during the double-blind phase. These responders were less severe than patients, who did not switch ON with S90049, with shorter duration of PD (10.9 ± 4.9 versus 13.4 ± 6.0 years), shorter L-dopa-therapy duration (9.5 ± 4.3 versus 12.2 ± 5.2 years), lower daily L-dopa dose (894 ± 480

TABLE 2. *Motor response after a single dose of placebo, S90049 or apomorphine in the 30 patients who were randomized (A, full analysis set), and in the subgroup of patients who switched to ON in response to S90049 (B)*

	Placebo	S90049	Apomorphine
A: All patients (FAS population, $N = 30$ in each group)	$N = 30$	$N = 30$	$N = 30$
UPDRS III Basal score (mean ± SD)	37.6±16.6	38.1 ± 14.7	37.3 ± 16.0
Maximal improvement from baseline	−7.2 ± 9.0	−12.9 ± 12.3*	−24.3 ± 12.4***
% maximal UPDRS improvement	19 ± 21 %	36 ± 29 %	66 ± 23 %
Responders (Patients who switched ON in response to each treatment) (N, %)	8 (27%)	17 (57%)*	29 (97%)***
Latency to ON (minutes) [median (range)][a]	180 (15–189)	45 (13–194)*	16 (7–180)***
Duration of ON (minutes) [median (range)][a]	0.0 (0–312)	28 (0–348)*	54 (0–325)**
B: Patients who switched ON in response to S90049 (N = 17, 57% of the FAS population)	N = 17	N = 17	N = 17
UPDRS III Basal score (mean ± SD)	36.5 ± 16.3	37.4 ± 15.2	36.6 ± 16.1
Maximal improvement from baseline	−8.8 ± 11.1	−21.2 ± 10.1**	−23.6 ± 14.1***
% maximal UPDRS improvement	24 ± 26 %	58 ± 16 %	69 ± 20 %
Latency to ON (minutes) [median (range)][a]	181 (15–189)	30 (13–45)**	16 (7–180)***
Duration of ON (minutes) [median (range)][a]	0 (0–312)	60 (23–348)**	55 (0–325)**

UPDRS III = Unified Parkinson Disease Rating Scale Part III Motor Score. Values are expressed as N (%), means ± SD and medians (range).

[a]Statistics are given using censored values in patients who did not turn ON: 180 minutes (test duration in this case) for time to ON and 0 for duration of ON.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$. For maximal change in UPDRS III (primary endpoint), a cross-over mixed linear model was used (non-parametric tests confirmed the results in the FAs analysis with $P = 0.005$ and $P < 0.001$ respectively with S90049 and apomorphine). The number of patients who switched OFF–ON was analyzed using a logistic regression mixed model adjusting for cross-over factors. For the latency to ON, a COX survival model adjusting for cross-over factors was applied. For the duration of the ON phase, a non-parametric approach was used (hypothesis of normality not met).

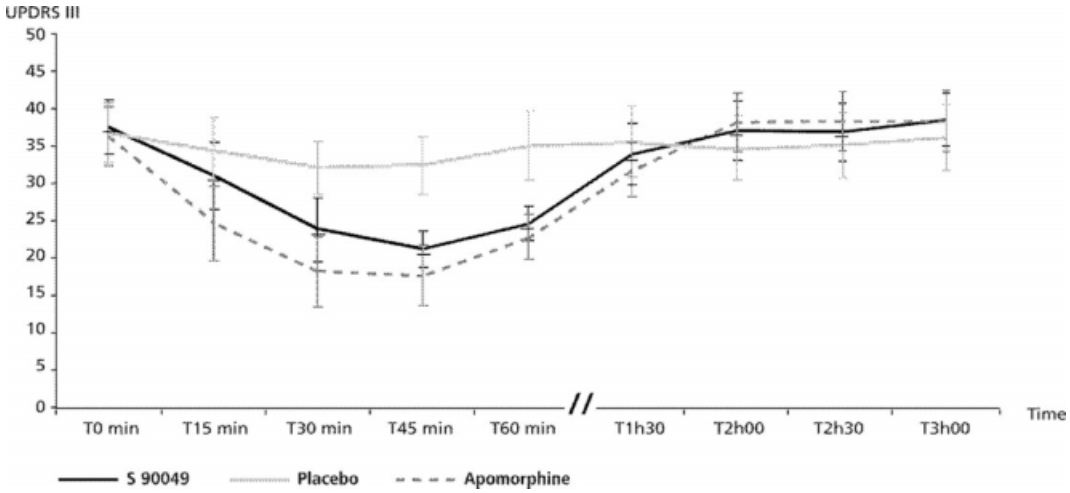

FIG. 3. Evolution of UPDRS motor score—Patients responders to S90049.

versus 1323 ± 985 mg/d) and a smaller percentage of current sc apomorphine use [1/17 (6%) versus 6/13 (46%)]. (Table 2-B) Five out of the 17 S90049-responders also responded to placebo and 16 to apomorphine. The maximal improvement of UPDRS III was significantly superior on S90049 than placebo (treatment effect: −11.08 95% CI [−18.7;−5.0], $P < 0.01$) as it was on apomorphine (−15.9 95% CI [−22.6;−9.2], $P < 0.001$). The estimated difference between S90049 and apomorphine was 4.0[−2.9;11.0]. The median latency to ON was significantly shorter on S90049 than placebo (HR 4.8 95% CI [1.74;13.47], $P < 0.01$) as on apomorphine (HR 14.1 95% CI [4.54;43.98], $P < 0.0001$). The median time to ON was shorter with apomorphine than with S90049 (HR = 0.34, 95% CI [0.14;0.82]). In these patients, although the motor improvement was more rapid with apomorphine, the evolution profile of UPDRS III with S90049 paralleled that of SC apomorphine (Fig. 3).

Placebo-responders

Eight patients (27% of the FAS population) switched ON following placebo intake. In these placebo-responders, the mean maximal UPDRS improvement was −16.9 ± 11.4 (−43 ± 26%), with a median latency to switching ON of 29 minutes (range 15–45).

Safety

No death nor serious adverse events were reported. During the double-blind phase, adverse events were reported in eight patients with placebo and S90049, and nine patients with apomorphine (Table 3). Only one patient reported a local adverse event related to the sublingual administration of S90049 (oral dysaesthesia). Most systemic adverse events reported with S90049 and apomorphine were nervous system disorders (dizziness, somnolence, headache), vascular disorders (orthostatic hypotension, hypotension), and gastro-intestinal disorders (nausea), as expected with dopamine agonists. Dyskinesia were experienced by 47% of patients who turned ON with S90049 (8/17), as compared with 76% with apomorphine (22/29).Vital signs did not significantly change during the assessment of S90049, placebo and apomorphine. No emergent clinically relevant change in ECG as well as in

TABLE 3. *Adverse events recorded during the cross-over double-blind phase (N = 30)*

	Placebo		S90049		Apomorphine	
	AE	Patients *N*(%)	AE	Patients *N*(%)	AE	Patients*N*(%)
Any emergent Adverse event (AE)	8	8 (26.6%)	10	8 (30%)	9	9 (30%)
AE leading to study withdrawal or SAE	0	-	0	-	0	-
Most frequent AE (≥ 5% in one group)						
Nausea/vomiting	1	1 (3.3%)	2	2 (6.6%)	1	1 (3.3%)
Orthostatic hypotension	1	1 (3.3%)	0	-	2	2 (6.6%)
Dizziness	0	-	0	-	2	2 (6.6%)
Parkinson's disease aggravated	2	2 (6.6%)	0	-	0	-

biochemistry or hematology parameters was detected, except in 1 patient (elevated liver enzymes ALAT, normal at inclusion and gamma GT, already present at inclusion).

DISCUSSION

This proof-of-concept study demonstrated for the first time in a double-blind design that a single dose of S90049, a novel formulation of the orodispersible D2 dopamine agonist piribedil (median dose 60 mg) was superior to placebo in improving UPDRS III and in switching patients with advanced PD from the OFF to the ON condition. This finding supports our initial hypothesis.

When the 30 patients who participated into the trial were analyzed altogether (Full Analysis Set), S90049, although statistically superior to placebo on all primary and secondary endpoints, did not switch ON all patients and did not induce overall the same response as the reference drug, sc apomorphine. The two active treatments were not formally compared statistically (as predefined in the analysis plan) because all patients had been selected a priori to respond to apomorphine. Nevertheless, it is clear that apomorphine effects were quantitatively more robust than those of S90049 in this global analysis. This observation deserves further discussion however, because methodological issues related to study design and statistical analysis introduced a bias in favor of apomorphine. First, as already mentioned, inclusion criteria required patients to switch ON on apomorphine to enter into the trial, while those who did not were excluded. This was not true for S90049. Second, the maximal dose of S90049 was arbitrarily set at 60 mg, and it remains unknown at this stage if greater doses could have switched more patients ON. This hypothesis deserves further explorations, especially because patients who did not respond to S90049 had a more severe disorder than those who did. Third, imputation techniques chosen to analyze nonresponders in the FAS analysis worsened artificially a number of secondary outcomes, like for example time to switch ON that was arbitrarily censored at 180 minutes for patients who did not switch ON.

One can also consider the effects of S90049 in the 17 patients who responded to the drug (57% of the randomized population). In such patients, UPDRS changes indicated that an acute sublingual challenge with S90049 can induce substantial and relatively rapid relief of Parkinsonian symptoms in PD patients suffering from OFF episodes. This suggests that S90049 might be seen as a putative alternative to sc apomorphine to abort OFF episodes on demand. The amplitude of the response (minus 20 points in UPDRS III, that is a 60% improvement from baseline) was in the range of the apomorphine effect and comparable to previous reports in similar clinical experimental conditions with L-dopa[16,5,17] or apomorphine.[5] The mean time to switch ON with S90049 (27 minutes) was also shorter than that usually reported with standard L-dopa (44 to 51 minutes according to most studies),[16–18] and similar to that observed with dispersible L-dopa benzeraside.[19,20] This delay was however longer than that induced in the same patients by sc apomorphine (median time to ON 16 minutes on apomorphine versus 30 minutes on S90049). This is in line with previous reports showing that time to ON was also longer when apomorphine was administered sublingually (25–40 minutes).[21–23] However, 50% of the S90049 "responders" switched ON within 30 minutes, a delay that is of clinical interest and might improve if greater doses are to be tested in the future.

Another finding of this study refers to the placebo response. Overall, the mean maximal improvement of the UPDRS motor score reported on placebo in the entire population (FAS analysis) was 19% (range 0–85%). Similar values have already been reported elsewhere in similar experimental conditions with fluctuating patients with PD.[12,24] However, an unexpected high proportion of patients was considered as having switched ON following placebo administration (27%). This percentage is greater than what is generally assumed in studies using an acute challenge design and emphasizes the importance of using a randomized placebo-controlled double-blind design for proof-of-concept trials assessing new antiparkinsonian medications in acute challenge conditions. The definition that was used to assess if and when a patient switched ON was subjective and based on consensus between the patient and the investigator. Such placebo-responders did not present however marginal or borderline improvement, since their mean UPDRS score improved by more than 40%. This reinforces the notion that a substantial placebo effect is commonly observed in PD.[25] There is evidence for the involvement of reward (clinical benefit) mechanisms and activation of the nigrostriatal dopamine system in such a placebo response.[26,27]

In summary, this single-dose double-blind placebo-controlled study supports the hypothesis that S90049 used as an acute challenge monotherapy can abort a standardized OFF episode in patients with advanced PD and motor fluctuations. The reasons why some patients did not switch ON with S90049 requires further explorations. The fact that (i) nonresponders had

more severe clinical markers of PD and (ii) the drug was well tolerated up to the arbitrarily defined maximal tested dose (60 mg) suggests that the response to greater doses should be explored in future studies, although pharmacokinetic factors, such as possible saturation of sublingual absorption with higher dose, might limit the response to such higher doses. Future trials would help defining if this sublingual formulation of the dopamine agonist piribedil should be developed as a convenient alternative to subcutaneous injections of apomorphine.

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