Acta Psychiatr Scand 1996: 94: 404–410
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ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

A double-blind randomized placebo-controlled study of the efficacy and safety of pirlindole, a reversible monoamine oxidase A inhibitor, in the treatment of depression

De Wilde JE, Geerts S, Van Dorpe J, Bruhwyler J, Géczy J. A double-blind randomized placebo-controlled study of the efficacy and safety of pirlindole, a reversible monoamine oxidase A inhibitor, in the treatment of depression.
Acta Psychiatr Scand 1996: 94: 404–410. © Munksgaard 1996.

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The efficacy and safety of pirlindole (300 mg/day), a new reversible inhibitor of monoamine oxidase A, have been evaluated in a multicentre placebo-controlled double-blind randomized trial in 103 in-patients suffering from unipolar major depression (DSM-III-R 296.2, 296.3) over a 42-day period after a run-in placebo period of 6 days. Pirlindole produced a significantly greater decrease than placebo in the Hamilton depression score (from day 28), the Hamilton anxiety score (from day 28) and the Montgomery-Asberg depression score (on day 42). On day 42, the Hamilton depression score was ≤ 7, ≥ 8 and ≤ 15, or ≥ 16 in 21%, 45% and 34%, respectively, in the placebo group compared to 72%, 24% and 3.4%, respectively, in the pirlindole group ($P < 0.001$). The differences between the two groups in terms of tolerance and safety were not statistically significant.

Key words: major depression; antidepressant; monoamine oxidase inhibitor

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Accepted for publication March 30, 1996

Introduction

Depression is a major public health problem causing subjective distress, impaired functional capacity, secondary mental and somatic complications, and increased mortality (1).

Until recently, monoamine oxidase inhibitors (MAOIs) were regarded as 'secondary drugs' relative to the tricyclic antidepressants, for three main reasons. First, hepatotoxicity was a problem with the early MAOIs, such as iproniazid. Secondly, and probably most important of all, was the cheese effect, the interaction between MAOIs and foods rich in tyramine, leading to hypertensive episodes, with eventual serious consequences, including cerebral haemorrhage or even death. Thirdly, in true depressions, MAOIs were considered to be less efficacious than tricyclic antidepressants (2). During the 1980s, controlled studies provided evidence that MAOIs are very effective in the treatment of so-called therapy-resistant depressions, atypical depressions, phobias, panic disorders and anxiety states (3, 4). In addition, factors such as low cardiotoxicity, absence of anticholinergic side-effects and mood-activating properties may represent advantages of MAOIs over tricyclic antidepressants (5).

Recently, selective reversible inhibitors of MAO A (RIMAs) have become available, among which moclobemide has been the most extensively studied (6, 7). When a patient has been treated with a RIMA, MAO B can continue to metabolize ingested tyramine, thus reducing the risk of a potentially dangerous rise in blood pressure (8). The efficacy and safety of moclobemide have mainly been demonstrated in placebo-controlled studies (2, 9) and in comparative trials vs. reference therapies (1, 2, 10, 11).

Pirlindole is a tetracyclic compound that has been characterized as a potential antidepressant drug in preclinical studies (12–14), and about which

interest has arisen due to its marked selectivity as a RIMA (15). In clinical trials, no significant differences were found between pirlindole and maprotiline (16), imipramine (17, 18), amitriptyline (18–20), desipramine (21) and mianserin (De Wilde, unpublished results) in terms of efficacy and safety. Recently, a therapeutic equivalence, in terms of efficacy and tolerability, between pirlindole and moclobemide has also been demonstrated (Tanghe et al., unpublished results). However, pirlindole has never been compared to placebo in a controlled clinical trial.

The present study was undertaken in accordance with the 1988 European Consensus Conference on the Methodology of Clinical Trials of Antidepressants, which states that an antidepressant is 'a drug that has been shown, in comparison with placebo, to improve all characteristic symptoms of the depressive syndrome in at least a subgroup of patients with recognized depressive disorder of at least moderate severity' (22). It consisted of a double-blind randomized placebo-controlled trial designed to evaluate the efficacy and safety of pirlindole in the treatment of unipolar major depression with single episodes (DSM-III-R 296.2) or recurrent episodes (DSM-III-R 296.3).

Material and methods

This study was a multicentre, double-blind, randomized trial conducted in 7 centres in Belgium (St Denijs-Westrem, Assebroek, Oudenaarde, Kortrijk, Munsterbilzen, Sint-Niklaas and Tielt). Throughout the study, a monitor regularly visited the investigators in order to verify adherence to the protocol, and the accuracy of the data was checked during the data-recording phase. The study was conducted according to the principles of the Helsinki Declaration amended in Tokyo, Venice and Hong Kong, and the study protocol was approved by the Ethical Committee of the Vrije Universiteit of Brussels.

A total of 103 in-patients were included in the study, which lasted for 48 days (a 6-day run-in period under placebo and a 42-day treatment period). Men and women aged between 20 and 60 years were included if they were suffering from a major unipolar depression with single episodes (DSM-III-R 296.2) or recurrent episodes (DSM-III-R 296.3). The depressive episode had to have started between 2 weeks and a maximum of 3 months previously. The score of depression on the Hamilton Depression Rating Scale (HDRS) (21 items) had to be >18 and the score on the Montgomery-Asberg Depression Rating Scale (MADRS) had to be >25. In addition, the total score on the depression rating scale of Raskin had to be higher than the total score on the anxiety scale of Covi. Patients had to provide written or oral consent (in the latter case before an informed witness). Patients suffering from depression with psychotic characteristics (DSM-III-R 296.24 and 296.34) as well as those suffering from bipolar disorders (DSM-III-R 296.4, 296.5 and 296.6) were excluded from the study. Suicidally inclined patients and those who were agitated, with a disturbed mood, between two depressive episodes and/or unresponsive to at least two other antidepressive treatments prescribed over a period of at least 21 days, were also excluded. The other exclusion criteria were as follows: electroconvulsive therapy during the last 6 months, known drug addiction, chronic alcohol abuse in the last 6 months, brain organic or vascular disorders or pheochromocytoma, repeated hyperglycaemia in excess of 1.3 g l^{-1} or diabetes, acute hepatitis in the previous 3 months, disturbed hepatic tests, epilepsy, glaucoma, renal insufficiency, pregnancy, lactation or absence of efficient contraception, intake of lithium during the previous 4 weeks, or intake of glucocorticoids, central antihypertensive drugs, guanethidine or sympathicomimetics. If, after the wash-out placebo run-in period of 6 days, the patient showed an improvement in his or her depression (a decrease of ≥25% of the initial HDRS or MADRS score), he or she was excluded (tardive exclusion) from the study.

Placebo and pirlindole (75 mg) were supplied as identical tablets. During the wash-out placebo run-in period of 6 days, the dosage was 2 tablets daily (one in the morning and one in the evening). During the 42-day treatment period, the dosage was 2 tablets daily (one in the morning and one in the evening) on days 1 and 2, then 3 tablets daily (two in the morning and one in the evening) from days 3 to 6, and 4 tablets daily (two in the morning and two in the evening) from days 7 to 42. Patients who presented with sleep disturbances during the course of the study could be given lormetazepam at a maximum daily dose of 2 mg. Other medical treatments for non-psychiatric conditions could be continued.

Complete assessments were made at baseline (6 days before the start of treatment) and on days 1, 7, 14, 21, 28 and 42 after the start of treatment. On day 35, only the compliance and any side-effects were recorded. If no therapeutic effect or aggravation was observed on day 21, the patient had to leave the study because of inefficacy of the treatment (premature discontinuation). On day 28, the patient could leave the hospital, depending on his or her state of health. The following variables were recorded: HDRS (17 and 21 items), Hamilton Anxiety Rating Scale (HARS), MADRS, therapeutic index, compliance (judged to be satisfactory when at least 80% of the tablets had been taken),

medical check-up, laboratory analyses and ECG (only at baseline and after 21 and 42 days of treatment).

The therapeutic index was a 16-point scale that combined an evaluation by the doctor of both the therapeutic effect (4-point scale: excellent, good, poor or no effect) and the adverse effects (4-point scale: none, mild, important, or side-effect nullifying the therapeutic benefit). This scale could either be analysed globally, or the therapeutic and adverse event subscales could be taken into account separately.

All observed and reported adverse events were recorded. Events were graded using a 3-point scale (mild, moderate or severe), the relationship to the treatment was assessed on a 4-point scale (possible, probable, definite or unknown), and the action taken by the doctor was also assessed on a 4-point scale (none, reduction of the dosage, concomitant therapy or medication stopped).

The comparability of the two groups after randomization was assessed on day 1 using the Chi-square test for discrete variables and Student's *t*-test for continuous variables. The effects of placebo and pirlindole on continuous variables such as HDRS, HARS and MADRS scores were compared using an analysis of variance for repeated measurements, using the factors 'treatment', 'time' and the interaction 'time × treatment' as classification criteria. The same analysis was used for all visits taken together and for each visit compared to baseline (day 1). When the interaction was significant, *post hoc* intra-group comparisons were made using paired *t*-tests and inter-group comparisons were made using independent *t*-tests. The effects of placebo and pirlindole on discrete variables, such as the therapeutic index and side-effects percentages, were compared using the Chi-square test or the Mann–Whitney test. A probability of less than 5% was regarded as indicative of statistical signifi-cance. Calculations were performed using the SPSS statistical package.

Results

A total of 103 patients were included in the study. Five patients were either lost to follow-up or belatedly excluded after the placebo run-in period. The 98 remaining patients were assigned blindly to the placebo group ($n=49$) or the pirlindole group ($n=49$). In all, 59 patients completed the 6-week treatment period (30 placebo-treated and 29 pirlindole-treated). The treatment groups were well-matched for both demographic and illness characteristics (Table 1).

There were 19 (39%) premature discontinuations in the placebo group and 20 (41%) such discontinuations in the pirlindole group. The reasons for premature termination in the placebo group were disappearance of depressive symptoms (2), side-effects (3), poor response or aggravation (14). In the pirlindole group the reasons were disappearance of depressive symptoms (2), side-effects (3), poor response or aggravation (15). The differences between the two groups were not statistically significant ($P>0.05$).

Table 1. Demographic and illness characteristics (mean values ± SD) of the two treatment groups at baseline (day 1) after a placebo run-in period of 6 days

	Placebo ($n=49$)	Pirlindole ($n=49$)
Age (years)	47.5 ± 11.9	44.7 ± 12.7
Male sex	34.7%	26.5%
HDRS score	25.0 ± 5.3	25.7 ± 5.5
HARS score	19.9 ± 6.6	21.3 ± 6.7
MADRS score	31.9 ± 5.6	33.7 ± 6.1
Covi score	4.7 ± 1.9	5.0 ± 2.2
Raskin score	8.5 ± 1.4	8.8 ± 1.4

At the beginning of the study, 67% of the patients in the placebo group and 82% of the patients in the pirlindole group were taking lormetazepam ($P>0.05$). After 42 days of treatment, 72% of the patients were still taking lormetazepam in both groups. There were no significant weight changes during the study, and the mean blood pressure readings within each treatment group did not change significantly. Compliance was judged to be satisfactory for all of the patients remaining in the trial up until their last medical visit.

Efficacy

The mean HDRS, HARS and MADRS scores in the two groups were comparable at baseline (day 1). A significant 'time × treatment' interaction was detected for the three scores from day 28 (HDRS, $P<0.001$; HARS, $P<0.01$; MADRS, $P=0.01$) and was amplified by day 42 (HDRS, $P<0.001$; HARS, $P=0.001$; MADRS, $P=0.001$), regardless of whether all patients evaluable for efficacy were taken into account (intent-to-treat analysis, comparison between each visit and the baseline) (Figs 1–3), or only those who completed the 6-week study period (standard analysis, comparison of all visits simultaneously; $P<0.001$). This means that the change in the scores was significantly different in the two groups from day 28. Intra-group paired comparisons revealed significant ($P<0.001$) decreases in both groups between day 7 and the end of the study. Inter-group comparisons revealed significant differences between day 28 ($P<0.05$) and day 42 ($P<0.01$) for HDRS and HARS, and

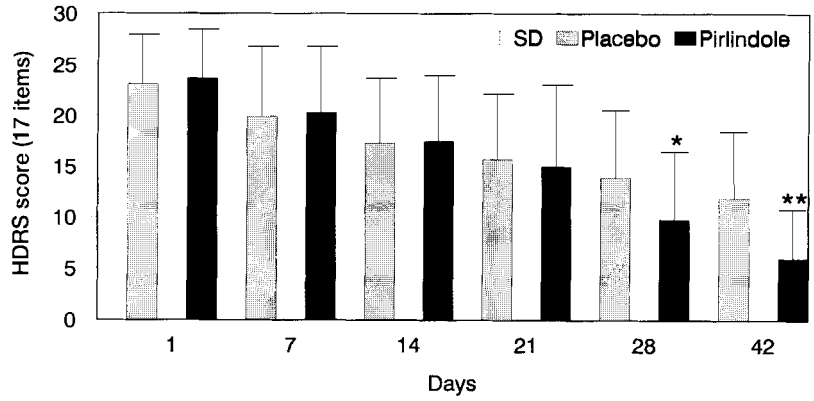

Fig. 1. Change in the mean (±SD) HDRS (17 items) score as a function of duration of treatment and as a function of the medication. Intention-to-treat analysis: $n = 49, 48, 48, 44, 32$ and 29 for the placebo group and $n = 49, 49, 48, 44, 31$ and 29 for the pirlindole group for days 1, 7, 14, 21, 28 and 42, respectively. $^{*}P < 0.05$, $^{**}P < 0.01$, *post hoc* tests when the analysis of variance for repeated measures gave a significant 'time × treatment' interaction.

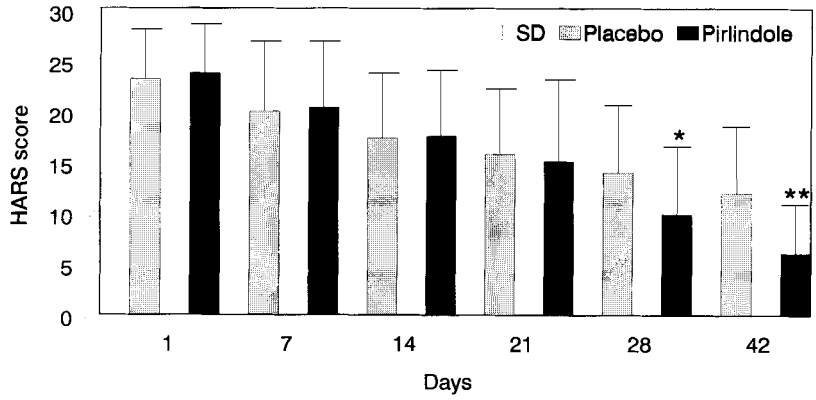

Fig. 2. Change in the mean (±SD) HARS score as a function of duration of treatment and as a function of the medication. Intention-to-treat analysis: $n = 49, 49, 49, 45, 33$ and 30 for the placebo group and $n = 49, 49, 48, 44, 31$ and 29 for the pirlindole group for days 1, 7, 14, 21, 28 and 42, respectively. $^{*}P < 0.05$, $^{**}P < 0.01$, *post hoc* tests when the analysis of variance for repeated measures gave a significant 'time × treatment' interaction.

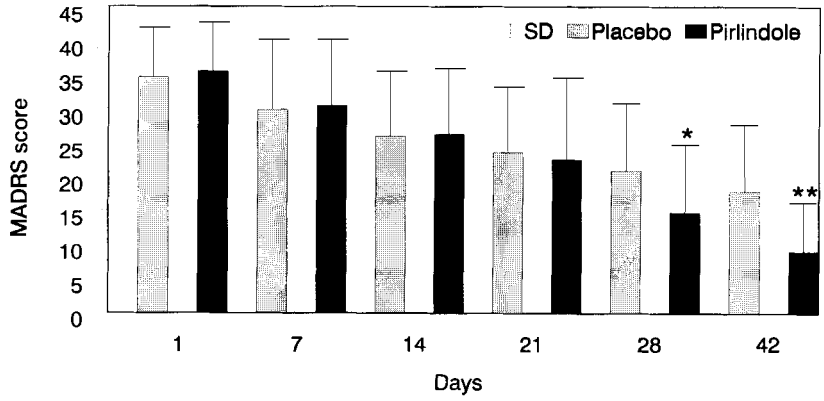

Fig. 3. Change in the mean (±SD) MADRS score as a function of duration of treatment and as a function of the medication. Intention-to-treat analysis: $n = 49, 49, 49, 45, 33$ and 30 for the placebo group and $n = 49, 49, 48, 44, 31$ and 29 for the pirlindole group for days 1, 7, 14, 21, 28 and 42, respectively. $^{**}P < 0.01$, *post hoc* tests when the analysis of variance for repeated measures gave a significant 'time × treatment' interaction.

on day 42 ($P < 0.01$) for MADRS, the decrease in the three scores being significantly greater in the pirlindole group (Figs 1–3). With regard to HDRS, a classification of patients who received the complete

treatment into three categories was established on day 42 according to their HDRS score as follows: ≤7, no depression; ≥8 and ≤15, minor depression; ≥16, major depression. In the placebo group the distribution into the three categories was 21%, 45% and 34%, respectively, and in the pirlindole group the distribution was 72%, 24% and 3.4%, respectively. The difference between the two groups was statistically significant ($P<0.001$).

A decrease of more than 50% in the HARS score was measured in 50% of the placebo patients, compared to 86% of the pirlindole patients ($P<0.01$). A decrease of more than 50% in the MADRS score was measured in 57% of the placebo patients, compared to 93% of the pirlindole patients ($P<0.01$). The same statistically significant superiority of pirlindole over placebo was demonstrated when statistical analyses were performed on the different items of the HDRS, considered in subgroups according to the Danish University Antidepressant Group (23) (items 1, 2, 3, depression/guilt; items 4, 5, 6, sleep disturbances; items 7, 8, retardation; items 9, 10, 11, anxiety/agitation; items 12, 13, somatic complaints) (data not shown).

Taking into account the efficacy subscale of the therapeutic index, a significant difference was detected between the two groups from day 28 of treatment ($P<0.05$), which increased until day 42 ($P<0.001$). On day 42, the efficacy of pirlindole was judged to be excellent or good in 97% of patients, compared to 63% in the placebo group (Table 2).

Table 2. Efficacy of the medication (expressed as percentage of patients) after 28 and 42 days of treatment

	Placebo		Pirlindole	
	Day 28 ($n=33$)	Day 42 ($n=30$)	Day 28 ($n=31$)	Day 42 ($n=29$)
No effect or aggravation	3.0	3.3	6.5	3.4
Poor efficacy	30.3	33.3	6.5	0
Good efficacy	54.5	40.0	58.1	34.5
Excellent efficacy	12.1	23.3	29.0	62.1

Table 3. Tolerability of the medication (expressed as percentage of patients) after 28 and 42 days of treatment

	Placebo		Pirlindole	
	Day 28 ($n=33$)	Day 42 ($n=30$)	Day 28 ($n=31$)	Day 42 ($n=29$)
No side-effects	84.8	90.0	80.7	89.7
Mild side-effects	15.2	10.0	16.1	6.9
Important side-effects	0	0	3.2	3.4
Side-effects cancelling the therapeutic benefit	0	0	0	0

Table 4. Most commonly reported and observed adverse events, expressed as number of side-effects, with percentage of patients displaying each side-effect shown in parentheses

Adverse event	Placebo ($n=49$)	Pirlindole ($n=49$)
Gastrointestinal symptoms	10 (20.4)	9 (18.4)
Weight changes	1 (2.0)	1 (2.0)
Anorexia	2 (4.0)	1 (2.0)
Insomnia	0 (0)	2 (4.0)
Confusion	1 (2.0)	0 (0)
Headache	3 (6.1)	5 (10.2)
Dizziness	1 (2.0)	2 (4.0)
Drowsiness	3 (6.1)	6 (12.2)
Agitation	1 (2.0)	3 (6.1)
Tremor	2 (4.0)	1 (2.0)
Dry mouth	5 (10.2)	1 (2.0)
Blurred vision	2 (4.0)	1 (2.0)
Sweating	0 (0)	1 (2.0)
Hypotension	1 (2.0)	0 (0)
Palpitations	1 (2.0)	0 (0)
Itching	0 (0)	2 (4.0)
Dermatitis	0 (0)	1 (2.0)
Other	8 (16.3)	6 (12.2)
Total	41	42

Tolerability

Taking into account the tolerance subscale of the therapeutic index, no significant differences were detected between the two groups during the whole study ($P>0.05$). On day 42, no side-effects were observed in 90% of the placebo patients and in 90% of the pirlindole patients (Table 3).

Side-effects were observed in 38 patients (39%) in total — 20 (41%) members of the placebo group and 18 (37%) members of the pirlindole group. The difference between the frequency of side-effects in the two groups was not statistically significant. A total of 41 side-effects were recorded in the placebo group and 42 side-effects in the pirlindole group (Table 4). In the placebo group, the intensity of side-effects was mild (73%) or moderate (27%), while in the pirlindole group it was mild (38%), moderate (55%) or severe (7%). Severe side-effects had consequences in only one patient (weight changes), who stopped the medication; the other cases were related to the indication and not to the drug. In the placebo group the evoked cause was the drug in 53% of cases, compared to 38% of cases in the pirlindole group. The action taken by the doctor with regard to the placebo group was as follows: no action (45%), posology decrease (5%), use of concomitant drug (40%) or cessation of the medication (10%). In the pirlindole group the action was as follows: no action (50%), use of concomitant drug (39%) or cessation of the

medication (11%). All of these differences between the two groups were non-significant ($P > 0.05$).

Physical examination (including ECG, laboratory analysis of haematology and clinical chemistry variables, blood pressure, heart rate and body weight) did not appear to be affected by pirlindole or placebo.

Discussion

Previous double-blind and open studies with pirlindole have already led to the conclusion that it is an efficacious antidepressive drug, which shows no significant differences when compared to amitriptyline (18), imipramine (17), desipramine (21), maprotiline (16) and mianserin (De Wilde, unpublished results). The findings of the present study demonstrate that pirlindole is significantly superior to placebo in terms of efficacy from day 28 of treatment up until day 42. It is also interesting to note that pirlindole produced a significantly greater decrease in the HARS score than placebo, which attests to its efficacy with regard to the anxious components of depression. The relatively late onset of action of pirlindole (4 weeks) could be explained by the use of too low a dosage. However, this does not appear to be the case, since a therapeutic equivalence has recently been demonstrated between pirlindole and moclobemide using 225 to 300 mg daily and 450 to 600 mg daily, respectively (Tanghe et al., unpublished results). Another parameter that could account for such a delay in the onset of action is the time period scheduled in the protocol (7 days) to reach the final dose of 300 mg daily. The good level of tolerance of pirlindole should allow the treatment to begin directly with doses above 150 mg daily. Moreover, the demonstration of a statistically significant superiority of active treatment over placebo is largely dependent on the sample size. For example, the study by Versiani et al. (2) of more than 300 patients showed a statistically significant difference between moclobemide and placebo after 21 days of treatment, while other authors (24) did not find any significant difference between moclobemide and placebo up to the 28th day of treatment in a sample of 68 patients. The intermediate number of patients ($n = 98$) in the present study sample could explain the delay before a statistically significant difference between pirlindole and placebo was reached.

Pirlindole did not display the typical side-effects of non-selective irreversible MAOIs, or their complications, so the intake of food containing tyramine was not contraindicated. This view has been confirmed by a study in which tyramine was perfused in healthy volunteers taking pirlindole (25). In the present study, the total frequency of side-effects was comparable in the pirlindole (37%) and placebo (41%) groups. The percentage differences for each type of side-effect were non-significant ($P > 0.05$). Compared to the tolerability of tricyclic antidepressants (26), symptoms typical of anticholinergic side-effects, e.g. dry mouth, tremor, sweating and blurred vision, were markedly less frequent in patients treated with pirlindole.

In conclusion, this double-blind randomized placebo-controlled study clearly demonstrates the efficacy and safety of pirlindole in the treatment of major depression. The superior efficacy of pirlindole compared to placebo was evident and statistically significant from the fourth week of treatment until the end of the study. The tolerability of pirlindole was good, and did not differ significantly from that of placebo.

Acknowledgements

The authors are grateful to Drs F. Bruynhooghe, P. Daneels, E. De Bleecker, F. Demeulemeester, M. Dierick, K. Eeckhout, P. Elens, C. Mertens, F. Messoten, J. Raemdonck, L. Ruelens, S. Seghers, E. Spiers and G. Verdec for their participation as investigators in this clinical trial.

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