Stroke

Articles

Treatment of Acute Ischemic Stroke With Piracetam

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Next Section

Abstract

Background and Purpose Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients.

Methods Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as

assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n=927) and in an “early treatment” population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n=452).

Results In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; *P*=.15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; *P*=.07) and Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; *P*=.02). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score <55), showed significant improvement on piracetam in both outcomes (*P*<.02).

Conclusions Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

Key Words:

- cerebral ischemia
- neuroprotection
- clinical trials
- piracetam

Previous SectionNext Section

Introduction

Classes of drug under investigation for the treatment of acute ischemic stroke include those that promote early cerebral reperfusion, neuroprotective agents, and drugs to reduce cerebral edema. Controlled trials have not yet provided unequivocal or repeated evidence of improved survival or morbidity with any agent. Early thrombolytic therapy remains under scrutiny because the cost of a better outcome has so far been an increase in mortality or morbidity, mostly from intracranial hemorrhage, and only one study[1] has so far shown improved function and survival. Benefit from

antithrombotic therapy also remains unproven although one recent pilot study with low-molecular-weight heparin reported improved outcome.[2]

We describe a clinical trial with piracetam, a drug reported to increase compromised regional cerebral blood flow[3] and depressed glucose metabolism in infarcted and adjacent tissue.[4] Improved outcome relative to placebo was found in two pilot studies in acute stroke in which high-dose piracetam was given intravenously 3–5 days after the onset of stroke.[3,5]

The mode of action of piracetam is unique and, although not entirely clear, may be explained by neuroprotective properties[6] mediated through effects on the cell membrane,[7,8] which are most marked in the presence of hypoxia.[6] Piracetam has been found to be present in the polar heads of phospholipid membrane models,[7] and this interaction has been shown to restore membrane fluidity.[8] This probably accounts for the maintenance or improvement of membrane-bound cell functions including ATP production,[9] neurotransmission,[10] and secondary messenger activity.[11] Piracetam has been shown in placebo-controlled studies to improve learning and memory,[12] vertigo,[13] cortical myoclonus,[14] and, as an adjunct to speech therapy, aphasia.[15,16]

The Piracetam Acute Stroke Study (PASS) tested the primary hypothesis that in acute ischemic supratentorial stroke, piracetam improves neurologic status at 4 weeks compared with placebo. Ability to perform activities of daily living at 12 weeks was the major secondary outcome parameter. Treatment was initiated within 12 hours of the onset of symptoms, and because therapy is more likely to be efficacious the sooner it is introduced, the protocol specified analysis in all randomized patients and in a subgroup treated within 6 hours of the onset of stroke.

Previous SectionNext Section

Subjects and Methods

Study Design and Procedures

The multicenter trial, which was placebo controlled and of double-blind parallel group design, required treatment for 12 weeks. Investigators were neurologists, internists, or gerontologists from 55 hospitals in 10 European countries. A project team liaised with centers directly and by monitoring investigators' meetings and study materials, including a videocassette of the Orgogozo scale assessment.[17] A pilot evaluation of blinded results in the first 79 patients allowed assessment of feasibility and study power assumptions.

Steering and safety committees supervised the trial. Members of the latter were otherwise unconnected with the project, and their functions included review of deaths and serious adverse events and, in the event of untoward findings, termination of the trial. The study was performed according to European Community Guidelines for Good Clinical Practice[18] after approval of the protocol by relevant ethics committees.

Patients

Patients aged 40 to 85 years admitted with a clinical diagnosis of acute ischemic supratentorial stroke were randomized and treated if they were arousable and if symptoms occurring within the preceding 12 hours were disabling as defined by an Orgogozo scale score of >5 and <70. Onset 2

hours after going to bed was arbitrarily assumed in those who awoke with stroke-related symptoms (n=83). The diagnosis was confirmed by CT; a scan performed within 24 hours of onset and, if necessary, repeated within 8 days had to show evidence of a nonlacunar supratentorial infarct (>1 cm^2) consistent with the clinical deficit. CT criteria for exclusion were evidence of cerebral hemorrhage and a mass effect with a midline shift (≥0.5 cm) on the early scan. Other exclusion criteria were stupor or coma defined as a score of <5 on the Glasgow Coma Scale,[19] previous stroke with clinical sequelae, and confounding neurologic or systemic illness. Patients or relatives provided written informed consent.

Treatment

Patients were randomly assigned to treatment with piracetam or placebo from a computer-generated randomization schedule stratified by study center. Immediately after randomization, eligible patients received an intravenous bolus of 12 g of piracetam (Nootropil®) or matching placebo administered over 20 minutes followed by treatment for 12 weeks (12 g daily or placebo for 4 weeks and 4.8 g daily or placebo for 8 weeks) (Table 1⇓). UCB Pharma supplied and packaged all piracetam and matched placebo solutions and tablets.

Table 1.

Dosage Regimen of Piracetam and Placebo

	Treatment Period			
	On Admission	6 h After Bolus Injection Until Day 4	Day 5 Until Wk 4	Wk 5 Until Wk 12
Dose	12 g	12 g/d	12 g/d	4.8 g/d
Route of administration	Intravenous	Intravenous	Oral	Oral
Dosage form	Infusion	Ampoules	33% Solution	1200-mg tablets
Frequency of administration	Once Bolus over 20 min	3 g 6-hourly	4 g three times daily	2.4 g twice daily

Nonstudy medications allowed were calcium antagonists for hypertension or heart disease, osmotic diuretics for cerebral edema, and heparin in low dosage to prevent deep venous thrombosis and in full dosage after 48 hours to prevent embolism of cardiac origin. Although concomitant aspirin was not recommended for at least 24 hours after the start of treatment, its use before or immediately after the stroke was not a reason for exclusion. Dipyridamole and ticlopidine were prohibited during the first 4 weeks. Thrombolytic agents, hemodilution, and drugs acting on the cerebral vasculature were forbidden.

Assessments

Study assessments were performed 1 and 3 days and 1, 2, 4, 8, and 12 weeks after the start of treatment. Neurologic status evaluated by the Middle Cerebral Artery neurologic scale[17] after 4 weeks was the primary end point. Functional capacity for activities of daily living at 12 weeks assessed by the Barthel Index[20] was the major secondary outcome. Serial measurements of both indexes allowed evaluation of the clinical course.

The Orgogozo scale,[17] developed for clinical trial evaluation of middle cerebral artery strokes, has been validated[21] [22] and provides objective, reproducible ratings of high prognostic value even in the early hours after a stroke. The scale evaluates 10 items: vigilance, verbal communication, elevation of the arm, finger and thumb movements, arm tone, deviation of head and eyes, facial movements, elevation of the leg, dorsiflexion of the foot, and leg tone. Weighted scores for each item vary between 0 and 5 or 10 and 15 to provide a maximum score of 100.

The Barthel Index has been widely used to assess functional outcome or activities of daily living in the evaluation of stroke. Patients who can perform all specified activities unaided receive a score of 100 but may remain handicapped by neurologic impairments even though they are independent in daily activities. Patients who die cannot be rated. The Barthel Index was therefore modified so that patients scored as 100 and without neurologic abnormality (Orgogozo scale, 100) received a score of 110, and patients who died, a score of −10. Barthel Index responses were also grouped into six dependency classes to assess clinically relevant outcome[23] : death; score <40, needing constant care; 40 to 55, needing institutional care; 60 to 80, assisted independence; 85 to 100, nearly complete independence but with neurologic deficit; Barthel Index 100 and Orgogozo scale 100, complete recovery. The Barthel Index was first scored after 3 days as earlier measurements are not assessable in patients with moderate to severe deficits.

Statistics

Estimation of sample size was based on clinically relevant improvement in the Orgogozo scale, assuming that a mean difference of 3.5 points relative to placebo at 4 weeks is equivalent to a mean improvement of 10 points in 35% of patients. Computer simulations using Orgogozo scale measurements during the pilot phase of the trial indicated that using a level of $\alpha = .05$, 250 patients in each treatment group surviving for 4 weeks would yield a power of 0.80 to detect these changes. To allow for deaths and withdrawals, we planned to include 900 patients.

All analyses reported were based on the intention to treat. Missing data were assigned the value of the last available assessment. Outcome was analyzed in all patients and in an “early treatment” subgroup planned in the study protocol to include those treated within 6 hours of stroke onset. The steering committee subsequently redefined this period as “less than 7 hours” after stroke onset for several reasons. The precise times of onset of stroke and to treatment are often uncertain and represent best estimates. They were frequently recorded to the nearest 15 minutes. In the total population, the steering committee therefore agreed to include patients treated less than 13 hours after stroke onset. Similarly, the early treatment subgroup was redefined to include patients treated less than 7 hours after stroke onset; the additional patients thereby included increased the power of the analysis. This subgroup analysis therefore differed slightly from that specified in the initial protocol.

We performed additional analyses in those patients in the early treatment subgroup with moderate and severe neurologic deficits, defined by baseline Orgogozo scale scores as less than 55. Patients with moderate to severe deficits at the onset of stroke have been shown to be more responsive to drug effect in previous trials.[24]

Characteristics at baseline were compared using χ^2, *t*, and Mann–Whitney tests. Mean differences in Orgogozo scale and Barthel Index scores were compared using the nonparametric Cochran–Mantel–Haenszel test; means and standard deviations were used in a descriptive sense. Results were analyzed in all patients with baseline Orgogozo scale measurements. Orgogozo scale analyses were performed after stratification according to baseline scores to minimize imbalance between groups in the initial severity of stroke. Deaths were scored with the last Orgogozo scale value carried forward. To compare the frequency with which patients reached each functional class derived from Barthel Index scores, we used survival analysis. Risk rates for death were estimated and compared using the Cochran–Mantel–Haenszel test after controlling for baseline Orgogozo scale scores. Logistic regression was used to determine which of many potential factors predicted mortality. Adverse events were compared using the χ^2 test. Tests were two tailed and assumed a significance level of $\alpha=.048$.[25] SAS software (statistical package 6.08) was used for all computations.

Interim Analysis of Efficacy and Safety

One planned interim analysis was performed on the results in the first 514 patients using significance levels of $\alpha=.005$ for efficacy and $\alpha=.05$ for safety parameters. This showed no differences between treatment groups deemed sufficient to stop the trial.

Previous SectionNext Section

Results

Of 927 patients enrolled and randomized between February 1992 and April 1995, 464 were allocated to treatment with piracetam and 463 to placebo. Treatment groups did not differ significantly in baseline characteristics (Table 2⇓) in blood pressure, in the number of patients receiving aspirin and/or heparin within the first 48 hours, or in risk factors for stroke present on admission.

Table 2.

Characteristics of Patients at Baseline According to Treatment Group (n=927)

	Piracetam (n=464)	Placebo (n=463)
Patients randomized		
Mean age±SD, y	69.9±11.1	70.9±10.7
Sex ratio (M/F)	1.08	1.06
Neurological status		
Glasgow Coma Scale, mean±SD	12.4±2.7	12.6±2.6
Orgogozo scale		
Mean±SD	37.2±15.9	38.6±16.8
Median	35	35
Time from stroke to start of treatment, h	7.2±3.5	7.1±3.5

All randomized patients were treated, their data were included in intention-to-treat analyses, and they were evaluated for safety. For the primary outcome, data were missing at baseline in four piracetam-treated patients (0.9%) and after 4 weeks in 39 (8.4%) and 38 patients (8.2%) in piracetam and placebo groups. Results in patients fulfilling protocol criteria did not differ significantly from those in the intention-to-treat population and are therefore not reported.

Of the intention-to-treat population, 255 patients did not meet at least one protocol requirement on admission or during the first 4 weeks of treatment (Table 3⇓). Most protocol violations occurred on study entry because of inappropriate CT scan findings in 148 patients. Evidence of primary hemorrhagic stroke was present in 31 patients (piracetam 15, placebo 16) on the first CT scan. Lacunar stroke (22), infratentorial stroke (20), and mass with midline shift (three) also led to exclusion. The second examination was considered normal in 65 patients (piracetam 40, placebo 25). No scan was performed in seven patients.

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Table 3.

Intention-to-Treat Population: Reasons for Failure to Meet Protocol Requirements During the First 4 Weeks of Treatment

Outcome

Efficacy

The primary end point, the mean Orgogozo scale score after 4 weeks, was similar in piracetam (57.7±31.7) (mean±SD) and placebo (57.6±31.5) groups (Table 4⇓) (Fig 1⇓). Functional ability for activities of daily living did not differ significantly between treatment groups: mean Barthel Index

scores after 12 weeks were slightly higher in patients given piracetam (piracetam, 55.8±43.8; placebo, 53.1±43.3; *P*=.33). (Table 4⇓) (Fig 2⇓).

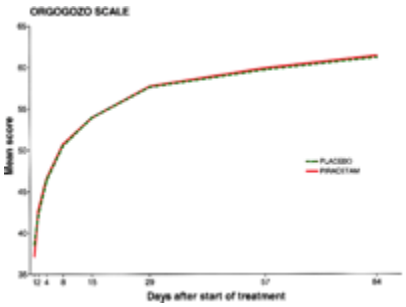

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Figure 1.

Mean Orgogozo scale scores in both treatment groups from baseline until 12 weeks' treatment.

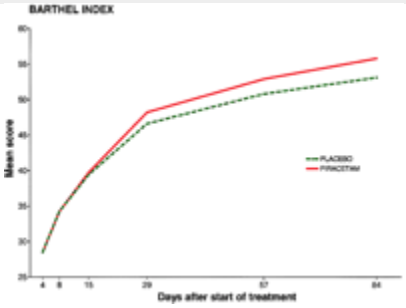

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Figure 2.

Mean Barthel Index responses in both treatment groups from 4 days' until 12 weeks' treatment.

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Table 4.

Results of Primary and Secondary Outcomes: Orgogozo Scale Scores at 4 Weeks and Barthel Index at 12 Weeks (Mean±SD)

Mortality

Death within 12 weeks occurred more often in the piracetam group than with placebo. Mortality within 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) on placebo. The difference was not significant (*P*=.15). The relative risk was 1.24 (95% CI, 0.97 to 1.59). Of six factors that contributed significantly to death when potential risk and prognostic and treatment-related factors were examined using logistic regression, the two most important were initial severity of stroke and age. The conditional relative mortality risk with an initial Orgogozo scale score below the median value (35 in each treatment group) was 6.01 (95% CI, 3.25 to 11.09), and with patients aged 72 years or more it was 3.51 (95% CI, 1.89 to 6.51). No significant contribution toward death was found for treatment, time to initiation of treatment, or interaction between treatment and any other factor.

The initial score for the Orgogozo scale was <35 in 214 piracetam-treated patients compared with 195 in the placebo group, a difference of 19. Mortality in these patients was similar in each group (piracetam, 36% 77/214; placebo, 33% 64/195). Age distribution was similar in each group.

Safety

Adverse events, regardless of cause and including those considered serious, occurred with similar frequency in each group and caused withdrawal from the study in 10 piracetam-treated patients and six who had received placebo. Symptomatic hemorrhagic transformation of the infarct, which occurred in 17 piracetam-treated and 16 placebo-treated patients, was fatal in four patients given piracetam and in three given placebo. After 12 weeks, three of 15 patients admitted with primary hemorrhagic stroke and receiving piracetam had died compared with six of 16 receiving placebo. In these patients, stroke was more severe at baseline in the piracetam group (mean Orgogozo scale score: piracetam, 28.7±25.0; placebo, 38.4±37.5).

Post Hoc Subgroup Analyses

Early Treatment Subgroup

The early treatment population consisted of 452 patients (224 piracetam, 228 placebo) whose baseline characteristics were similar in each group and differed in no significant respect from the total population. Mortality within 12 weeks was similar in both treatment groups: piracetam, 19.6% (44/180); placebo, 19.7% (45/183). We found differences in neurologic outcome favoring piracetam in this subgroup. The mean Orgogozo scale score after 4 weeks was 5.5 points greater in the piracetam (60.4±32.0) than in the placebo group (54.9±32.4), a difference approaching significance (*P*=.07).

The mean Barthel Index score at 12 weeks was significantly higher in the active group (58.6±42.8) compared with placebo (49.4±43.2) (*P*=.02). When the numbers of patients reaching each Barthel dependency class were compared, more patients recovered completely in the piracetam group

(18.8%) than on placebo (13.6%), and in contrast, a level of function requiring constant care was more frequent on placebo (25.0%) than on piracetam (19.6%). These differences were not significant.

Fig 3⇓ shows the evolution of mean scores for the Orgogozo scale and Barthel Index in both treatment groups. For both measures, consistent differences favored piracetam. For the Orgogozo scale, these differences appeared within 24 hours. For the Barthel Index, the difference increased with time and was greatest (9.2 points, P=.02) at 12 weeks.

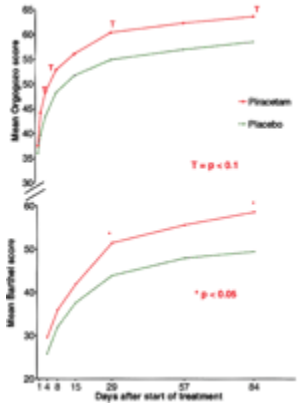

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Figure 3.

Post hoc analyses in early treatment subgroup. Mean scores until 12 weeks' treatment (top) from baseline for the Orgogozo scale and (bottom) from 4 days for the Barthel Index.

Because patients with mild stroke have a high rate of spontaneous recovery, a ceiling effect occurs in responses measured by neurological scales. Thus, when outcomes in the early treatment subgroup were related to the initial severity of stroke, differences favoring piracetam were confined to patients with moderate and marked neurologic impairment defined by an Orgogozo scale score <55 and were minimal in the presence of milder deficits (baseline Orgogozo scale, ≥55). (Fig 4⇓). Exploratory analyses were performed in 360 such patients, approximately 80% of the early treatment subgroup.

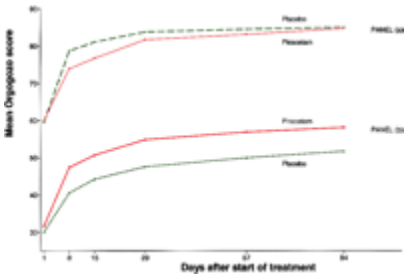

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Figure 4.

Post hoc analyses in early treatment subgroup. Mean Orgogozo scale scores during the study period (panel a) in patients with baseline scores ≥55 and (panel b) in patients with baseline scores <55.

The baseline characteristics of both these treatment subgroups were similar. We found significant improvement in patients on active treatment. The mean Orgogozo scale score at 4 weeks was more than 7 points greater in the piracetam group (54.9±31.9) than on placebo (47.6±30.4) (P<.02). At 12 weeks, the mean Barthel Index score in piracetam-treated patients (52.1±42.6) exceeded that on placebo (41.1±41.3) by 11 points (P<.02). For the number of patients reaching each Barthel dependency class, complete recovery occurred in 15.8% of piracetam-treated patients compared with 8.2% in the placebo group. Conversely, the need for constant care was more frequent in patients treated with placebo (29.7%) than piracetam (24.1%). These differences were not significant. There was no difference in mortality: piracetam, 23.0% (41/137); placebo, 23.1% (42/140).

Previous SectionNext Section

Discussion

Piracetam did not significantly improve neurologic or functional outcome in patients treated within 12 hours of the onset of acute ischemic stroke. Critical to success in limiting potentially reversible ischemic damage is initiation of treatment soon after the onset of stroke. Although time windows of 6, and even 3, hours were proposed when this trial was planned, confirmation of time window validity has not been consistent in clinical trials. We therefore included patients treated within 12 hours of onset and also planned a subgroup analysis in patients treated until 6 hours after the onset of stroke, a period subsequently redefined as less than 7 hours. An initial bolus injection was intended to provide a rapid therapeutic effect, and treatment was continued throughout the trial because as an adjunct to speech therapy, piracetam has been shown to improve aphasia after the acute phase of stroke.[15] [16]

Contrary to our prior hypothesis, the power of the study proved insufficient. Retrospective calculation indicated that the power to show the required difference of 3.5 points between groups in the Orgogozo scale at 4 weeks was 44%. The probability of a false-negative result in the study sample was thus 56%.

Piracetam is known to possess an unusually benign safety profile. Adverse events have been occasional and mild, and there has not been evidence of organ toxicity (A. Delaere, unpublished data, 1997). Tolerance was good in this trial as in other studies in acute stroke[3] [5] and cortical myoclonus,[14] which employed daily dosage with ≥12 g of piracetam. Importantly, hemorrhagic transformation of the infarct occurred with similar frequency in each treatment group. In addition, of those included with primary hemorrhagic stroke, fewer piracetam-treated patients died. This

suggests that piracetam could be administered acutely, before hospital admission and CT scanning, to patients presenting clinically with stroke.

Initial severity of stroke and age are the strongest predictors of mortality after stroke.[26] We confirmed this using logistic regression and could show no correlation between treatment-related factors and death. The higher mortality in piracetam-treated patients was not statistically significant and is mostly explained because the initial stroke was severe in more of these patients. Piracetam is therefore most unlikely to influence mortality in acute stroke.

Post hoc analyses in the early treatment subgroup showed a trend toward improvement in favor of pira-cetam. Since most patients with mild neurologic impairment after a stroke recover spontaneously, it is difficult to detect small differences due to treatment because of a ceiling effect on responses measured by neurologic scales.[24] We therefore performed additional analyses in patients with stroke of moderate and severe degree, which showed significant differences in favor of piracetam.

Piracetam and placebo did not differ significantly in effects on neurologic or functional status in patients treated within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that when given within 7 hours of onset, piracetam may be beneficial, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II), will soon begin.

Previous SectionNext Section

Appendix A1

The following principal investigators and clinical centers participated in the Piracetam in Acute Stroke Study (PASS):

Austria: E. Diabl (Linz); *Belgium:* E. Baeck (Antwerp), S. Blecic (Brussels), A. Capon (Brussels), H. Carton (Louvain), A. Catano (Montigny-le-Tilleul), M. Cornette (Seraing), P.P. De Deyn (Middelheim, Antwerp), I. Dehaene (Bruges), B. De Potter (Ghent), J.L. De Reuck (Ghent), H. De Vooght (St. Truiden), J. Janssens (Louvain), F. Piessens (Duffel), M. Vandewoude (St. Elisabeth, Antwerp); *France:* B. Dupuy (Cherbourg), H. Duclos (Pontoise), D. Joyeux (Valence), D. Milandre (Marseille), M. Salzman (Roanne), A. Setiey (Gleize), J.F. Savet (Macon), J.M. Warter (Strasbourg); *Germany:* W. Christe (Berlin), L. Harms (Berlin), G.H. Kessler (Greifswald), P. Marx (Berlin); *Greece:* I. Milonas (Thessaloniki); *Hungary:* A. Fazekas (Budapest), Z. Haflner (Budapest), P. Harczos (Budapest), J. Szanto (Zalaegerszeg Pòzna), L. Szegedy (Budapest), L. Vécsei (Szeged); *Netherlands:* J.A. Haas (Almelo), J.M. Minderhoud (Groningen), J. Swen (Delft), P. Raedts (Helmond), E. Sanders (Breda); *Portugal:* J. Ferro (Lisbon); *Spain:* J. Alvarez-Sabín (Barcelona), C. Hernández-Lahoz (Oviedo), C. Martinez-Parra (Sevilla), D. Mateo González (Madrid), M. Noya (Santiago de Compostella), M. Rebollo (Santander), J. Vilchez Padilla (Valencia); *United Kingdom:* D. Barer, M. Lye (Liverpool), M. Datta Chaudhury (Stockport), M. Finlay (Rochdale), J. George (Carlisle), M.A. Samad (Fulwood), A.K. Sharma (Liverpool), R.C. Tallis (Manchester), R.H. Taylor (Haslar).

Committees

Steering: P.P. De Deyn (Antwerp, Belgium), J.L. De Reuck (Ghent, Belgium), P. Marx (Berlin, Germany), J.M. Minderhoud (Groningen, The Netherlands), Z. Nagy (Budapest, Hungary), R.C. Tallis (Manchester, United Kingdom), UCB Pharma Participant: W. Deberdt (Braine-l'Alleud, Belgium); *Safety:* A. Dresse (Liege, Belgium), J-M. Orgogozo (Bordeaux, France), R. Vlietinck (Louvain, Belgium); *Monitoring & Data Management:* BRI International (Mechelen, Belgium); *Statistics:* M-P Derde, Data Investigation Company Europe (DICE) (Brussels, Belgium).

Previous SectionNext Section

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1. Top
2. Abstract
3. Subjects and Methods
4. Results
5. Discussion
6. Appendix A1
7. Acknowledgments
8. References

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