UCB reference No.: RXCE06E1660

Approved by UCB 07-Sep-2007

Clinical Study Summary

DEV/CCM/02567.2007

CT Registry ID#: NCT00567060
Study No.: N01001

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.

Based on Clinical Study Report document reference code: RRCE03M0204

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Nootropil® Tablets	Piracetam	Mild cognitive impairment (MCI)

Name of Sponsor/Company: UCB Pharma SA

Title of Study:
A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 9600 and 4800 mg/day piracetam (oral 800 mg tablets, b.i.d.) taken for 12 months by subjects suffering from mild cognitive impairment (MCI)

Investigator(s) (number only): 69

Study Center(s) (number only): 69

Length of Study:
Date first patient enrolled: 18-May-2000
Date last patient completed: 21-Jan-2004

Phase of Development: Phase IV/III (therapeutic confirmatory registered in a cognitive indication/other countries)

Abstract:
The primary objective of this study was to assess the superiority of 1 or 2 doses of piracetam (PIR 4800 mg/day or PIR 9600 mg/day) over placebo (PBO) on the cognitive functions of subjects suffering from MCI over a 52-week period, using the Cognitive Battery Composite Score (CBCS), with support from the Clinician's Interview Based Impression of Change – Plus, Activities of Daily Living Inventory – Mild Cognitive Impairment version, Mini-Mental State Examination, Brief Symptoms Inventory, and Global Deterioration Scale. Subjects were male or female, aged between 50 and 89 years inclusive, with MCI and a ≥ 3 month history of symptomatic memory problems, a score of 0.5 on the Clinical Dementia Rating scale, and a score of <18 on the Hamilton Depression Scale. Subjects received either PIR 2400 mg or 4800 mg twice daily (b.i.d.) (4800 mg or 9600 mg total daily dose) or PBO b.i.d. The study consisted of a 2-week single-blind PBO run-in period followed by a 52-week double-blind treatment period. The primary efficacy parameter was the CBCS containing the items from 8 tests: New York University paragraph recall test (delayed recall); Alzheimer's Disease Cooperative Study cancellation test; symbol-digit modalities test; color trails test – form A (trial 2); letter number sequence test from the Wechsler Memory Scale III; free and cued selective reminding task; block design from the Wechsler Adult Intelligence Scale – revised, vocabulary subtest; and the semantic category fluency: animals and food. A linear mixed model for longitudinal data was used to assess the superiority of PIR over PBO with respect to the change from baseline in the CBCS to the 12-month evaluation. The model included baseline value, gender and age as prognostic factors, and was performed at the α=0.05 level of significance (2-sided). Safety assessments were based upon the recording of adverse events (AEs), laboratory tests, electrocardiogram (ECG), physical and neurological exams, vital signs and body weight.

Number of Subjects:	**PBO**	**PIR 4800 mg/day**	**PIR 9600 mg/day**
Planned, N:	200	200	200
Randomized, N:	225	227	224
Intent-To-Treat population, N	225	226	224
Completed, n (%):	171 (76.0)	164 (72.6)	177 (79.0)
Number of Subjects Withdrawn, n (%):	54 (24.0)	62 (27.4)	47 (21.0)
Withdrawn due to Adverse Events, n (%):	26 (11.6)	29 (12.8)	17 (7.6)
Withdrawn for Other Reasons, n (%):	28 (12.4)	33 (14.6)	30 (13.4)

CT Registry ID#: NCT00567060
Study No.: N01001

Demography:	**PBO (N=225)**	**PIR 4800 mg/day (N=226)**	**PIR 9600 mg/day (N=224)**
Gender (Females/Males):	124/101	111/115	111/113
Age (years), mean (SD):	67.83 (8.37)	68.82 (8.47)	68.85 (8.69)
Race, n (%)			
Caucasian	255 (100)	226 (100)	223 (99.6)
Other/mixed race	0	0	1 (0.4)

Safety Outcomes:

– Summary of treatment-emergent adverse events, deaths, other serious adverse events and certain other significant adverse events:

Overall, 163 subjects (72.1%) in the PIR 4800 mg/day group, 153 subjects (68.3%) in the PIR 9600 mg/day group, and 171 subjects (76.0%) in the PBO group experienced at least 1 treatment-emergent (TE)AE. The most frequently reported TEAEs were infections and infestations, which were experienced by 28.8% of subjects in the PIR 4800 mg/day group, 29.5% in the PIR 9600 mg/day group and 32.9% in the PBO group; nervous system disorders, which were experienced by 23.0% of subjects in the PIR 4800 mg/day group, 16.5% in the PIR 9600 mg/day group and 20.9% in the PBO group; and gastrointestinal disorders, which were experienced by 22.1% of subjects in the PIR 4800 mg/day group, 21.0% in the PIR 9600 mg/day group and 24.4% in the PBO group. There were 59 subjects with serious (S)AEs: 22 in the PIR 4800 mg/day group; 16 in the PIR 9600 mg/day group; and 21 in the PBO group. Four subjects died during the study: 3 in the PIR 4800 mg/day group (pleura cancer, cerebral hemorrhage, pulmonary fibrosis); and 1 in the PBO group (lung cancer metastatic). No fatality was considered by the investigator as drug-related. Two SAEs were considered by the investigator as possibly related to the study drug: 1 in the PIR 9600 mg/day group (cardiac failure) and 1 in the PBO group (cerebrovascular accident). AEs leading to permanent discontinuation of the study drug were recorded for 12.8%, 7.1%, and 11.1% of the subjects in the PIR 4800 mg/day, PIR 9600 mg/day, and PBO groups, respectively. A close review of the abnormal hepatic values, as well as the AEs in relation to the liver function and parameters, was not suggestive of a possible influence of the study drug; baseline concomitant conditions and/or concomitant drugs revealed alternative causes. No clinically significant changes in vital signs were observed. Close inspection of the ECGs did not reveal any additional safety concerns.
The one year exposure with high doses of piracetam confirms its excellent safety profile. No difference between PBO and the 2 piracetam groups have been observed during the study.

Treatment-Emergent AEs:	**PBO (N=225)**	**PIR 4800 mg/day (N=226)**	**PIR 9600 mg/day (N=224)**
Subjects with at least 1 TEAE, n (%):	171 (76.0)	163 (72.1)	153 (68.3)
MedDRA Primary System Organ Class with an incidence of ≥ 10%	*n (%) [n considered drug-related by the Investigator]*		
Gastrointestinal disorders	55 (24.4) [22]	50 (22.1) [22]	47 (21.0) [25]
General disorders and administration site conditions	25 (11.1) [8]	20 (8.8) [6]	19 (8.5) [4]
Infections and infestations	74 (32.9) [2]	65 (28.8) [0]	66 (29.5) [0]
Injury, poisoning and procedural complications	16 (7.1) [0]	19 (8.4) [0]	23 (10.3) [0]
Musculoskeletal and connective tissue disorders	39 (17.3) [2]	42 (18.6) [1]	32 (14.3) [1]
Nervous system disorders	47 (20.9) [15]	52 (23.0) [15]	37 (16.5) [11]
Psychiatric disorders	43 (19.1) [14]	25 (11.1) [11]	34 (15.2) [9]
Death, other SAEs:	**PBO (N=225)**	**PIR 4800 mg/day (N=226)**	**PIR 9600 mg/day (N=224)**
Death, n (%):	1 (0.4)	3 (1.3)	0
Subjects with SAEs, n (%):	21 (9.3)	22 (9.7)	16 (7.1)
MedDRA Primary System Organ Class with an incidence of ≥ 1%	*n (%) [n considered drug-related by the Investigator]*		
Cardiac disorders	5 (2.2) [0]	6 (2.7) [0]	3 (1.3) [1]
Gastrointestinal disorders	0	3 (1.3) [0]	2 (0.9) [0]
General disorders and administration site	3 (1.3) [0]	0	1 (0.4) [0]

CT Registry ID#: NCT00567060 **Study No.:** N01001			
conditions			
Infections and infestations	4 (1.8) [0]	1 (0.4) [0]	2 (0.9) [0]
Injury, poisoning and procedural complications	2 (0.9) [0]	1 (0.4) [0]	3 (1.3) [0]
Neoplasm benign, malignant and unspecified (including cysts and polyps)	4 (1.8) [0]	6 (2.7) [0]	1 (0.4) [0]
Nervous system disorders	3 (1.3) [1]	2 (0.9) [0]	2 (0.9) [0]
Respiratory, thoracic and mediastinal disorders	3 (1.3) [0]	2 (0.9) [0]	0
Primary Outcomes: For PIR 4800 mg versus placebo there is a difference of -0.291 [95% CI: -0.787, 0.206] at month 12 on the CBCS and a p-value of 0.251 for the Intent-To-Treat (ITT) population. For PIR 9600 mg versus PBO there is a difference of -0.298 [95% CI: -0.790, 0.193] at month 12 on the CBCS and a p-value of 0.234 for the ITT population.			
Publication Reference(s) based on the study: Jelic et al. – J Neurol Neurosurg Psychiatry 2006; 77: 429-438			
Date of report: 7-Sep-2007			