Document title	**Clinical Study Report Synopsis**
Study title	**Effects of Memantine 20 mg (Ebixa®) and Donepezil 5 mg (Aricept®) on motor cortex plasticity induced by paired associative stimulation using transcranial magnetic stimulation (TMS) in patients suffering from Mild Cognitive Impairment.** **A phase II monocentric, double-blind, randomised, placebo-controlled, parallel group study.**
Study drug	**Memantine and Donepezil**
Studied indication	**Alzheimer's disease**
Development phase	**Phase II**
Protocol code	**CL2-NEURO-005**
Study initiation date	**14 October 2010**
Study completion date	**14 June 2011**
Investigator	[redacted] **Italy (Sicily)**
Sponsor	**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 report	**Final version of 23 May 2012**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: ***Ebixa® and Aricept®***	**Volume:**	
Name of Active Ingredient: ***Memantine and Donepezil***	**Page:**	

Title of study: Effects of Memantine 20 mg (Ebixa®) and Donepezil 5 mg (Aricept®) on motor cortex plasticity induced by paired associative stimulation using transcranial magnetic stimulation (TMS) in patients suffering from Mild Cognitive Impairment.
A phase II monocentric, double-blind, randomised, placebo-controlled, parallel group study.
Protocol No.: CL2-NEURO-005

Investigator: [redacted] taly (Sicily).

Study centre: [redacted] Italy (Sicily).

Publication: None

Studied period: Initiation date: 14 October 2010 Completion date: 14 June 2011	**Phase of development of the study: II**

Objectives:
Primary objective: to assess the potential effects of one month of repeated administration of donepezil and memantine compared to placebo on motor cortex plasticity induced by paired associative stimulation using transcranial magnetic stimulation (TMS) in MCI patients.
Secondary objectives:
- To assess the potential effects of a single administration and one week of repeated administration of donepezil and memantine compared to placebo on motor cortex plasticity induced by paired associative stimulation using transcranial magnetic stimulation (TMS) in MCI patients.
- To assess the potential effects of donepezil and memantine compared to placebo on performances using a motor task in MCI patients.
- To compare at baseline motor cortex plasticity induced by paired associative stimulation using transcranial magnetic stimulation (TMS) and performances in motor test in elderly healthy volunteers and MCI patients.

Methodology:
Phase II, monocentre, randomised, double-blind, placebo-controlled study with 3 parallel groups in MCI patients. A control group of non-treated elderly healthy volunteers was to be assessed at baseline (D0) only.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 45 MCI patients (15 by group) and 15 elderly healthy volunteers.
Included: 6 MCI patients (1 in the memantine group, 2 in the donepezil group and 3 in the placebo group).
3 elderly healthy volunteers.

Diagnosis and main criteria for inclusion:
Male or female MCI patients or healthy volunteers, aged 60-80 years inclusive, with a MMSE score ≥ 26.

Study drug:
Memantine (Ebixa®): 10 mg/day during the first 2 days, then 20 mg/day, 1 capsule once a day in the morning.
Donepezil (Aricept®): 5 mg/day, 1 capsule once a day in the morning.
Batch No.:
- Memantine: L0030973, L0035967, L0030969, L0036127.
- Donepezil : L0031079, L0035741.

Reference product:
Placebo: 1 capsule once a day in the morning.

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Duration of treatment:

- 1-to-4-week run-in period without treatment (from ASSE to D0).
- 4-week double-blind treatment period (from D0 to D28).
- 2-to-3-week run-out period without treatment at the end of the 4-week double-blind period, or in case of premature withdrawal (end-of-study visit).

Criteria for evaluation:

The following criteria were assessed in elderly healthy volunteers at selection and/or on D0 only.

Pharmacodynamic measurements:

- TMS (Paired Associative Stimulation - PAS): Motor Evoked Potential (MEP) on D0, D1, D7 and D28. The primary criterion was the MEP amplitude+ (% of baseline) after 28 days of study drug treatment in MCI patients.
- Motor task: On D0, D1, D7 and D28.

Safety measurements:

- Adverse events: at each visit
- Physical examination: at selection visit (including body weight and height), on D0, D1, D7 and D28, and at the end of the study visit.
- Vital signs: Systolic (SBP) and Diastolic Blood Pressure (DBP) and Heart Rate (HR) measured in lying position, after 10 minutes rest, at selection visit, on D0, D1, D7 and D28, and at the end of the study visit.

Statistical methods:

This study was prematurely stopped due to budget arbitration. Considering that very few participants were included (6/45 MCI patients planned, and 3/15 elderly healthy volunteers), no statistical analysis was performed. Only data listings were provided. These listings are appended in Section 4.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of participants

	MCI Patients				Elderly healthy volunteers
	Memantine 20 mg	**Donepezil 5 mg**	**Placebo**	**All patients**	
Included (randomised)	1	2	3	6	3
Completed	1	2	3	6	3

In all, 12 participants were screened. Of them, 3 were not selected (consent withdrawal, forbidden treatment (atenolol + venlafaxine, and aged > 80 years), and 6 patients and 3 elderly healthy volunteers were selected then included. All of them completed the study.

Demographic data and baseline characteristics at selection are described by treatment group and by type of participants in Table below. Ranges in the whole population are described hereafter.

The whole population was constituted of 4 male and 5 female participants. They were aged between 62 to 74 years. Their weight ranged between 60 and 86 kg. Their height ranged between 150 and 178 cm. Their BMI ranged between 22.6 and 32.9 kg/m². In all, they had an educational level ranging from 5 to 23 years including 5 participants with 5 years. All patients had a diagnosis of MCI.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Baseline characteristics at selection were as follows:

- MMSE score ranged between 27 to 32.
- Beck score ranged between 0 and 5 including 2 participants with 5, *i.e.* with a mild depression (corresponding to score between 4 and 7).
- Cognitive test scores:
  - Raven test corrected score ranged between 25.5 and 31.5.
  - Short story corrected score ranged between 3.5 and 17.0.
  - Verbal span corrected score ranged between 4.0 and 6.8.
  - Spacial span corrected score ranged between 4.3 and 6.5.
  - Rey's complex figure test:
    - Copy corrected score ranged between 28.8 and 38.4.
    - Immediate reproduction corrected score ranged between 9.4 and 31.5.
    - Delayed reproduction corrected score ranged between 9.7 and 25.7.
  - Verbal fluency test:
    - Semantic corrected score ranged between 8.3 and 14.5.
    - Lexical corrected score ranged between 17.9 and 34.3.
  - Token corrected score ranged between 27.8 and 34.0.
  - Benton line orientation corrected score ranged between 23 and 30.
  - Stroop test:
    - Corrected number for card ranged between 21.5 and 44.5.
    - Corrected number for coloured word ranged between 11.6 and 26.1.
  - Instrumental Activities of Daily Life (IADL) score ranged between 8 and 12.

The most frequent medical history was hypertension in 4 patients and 2 elderly healthy volunteers, followed by hypercholesterolemia in 1 patient and 2 elderly healthy volunteers, then cholecystitis in 2 patients. In a consistent way, the most frequent concomitant treatment at selection was agents acting on the renin-angiotensin system in 4 patients and 2 elderly healthy volunteers, and lipid modifying agents in 2 patients and 2 elderly healthy volunteers.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Demographic data and baseline characteristics at selection: range by treatment group and by type of participants

	MCI Patients				Elderly healthy volunteers
	Memantine 20 mg (N = 1)	Donepezil 5 mg (N = 2)	Placebo (N = 3)	All patients (N = 6)	(N = 3)
Gender	1M	1M/1F	1M/2F	3M/3F	1M/2F
Age (years)	74	72 ; 73	62 ; 72	62 ; 74	62 ; 70
Weight (kg)	85	60 ; 80	65 ; 77	60 ; 85	70 ; 86
Height (cm)	172	163 ; 170	156 ; 178	156 ; 178	150 ; 165
BMI (kg/m²)	28.7	22.6 ; 27.7	24.3 ; 28.8	22.6 ; 28.8	31.1 ; 32.9
Educational level (years)	5	5	5 ; 17	5 ; 17	5 ; 23
MMSE	27	30 ; 32	27 ; 30	27 ; 32	29 ; 31
Beck score	5	0 ; 3	0 ; 5	0 ; 5	0 ; 2
Cognitive tests corrected scores					
Raven test	25.5	30.5 ; 31.5	27.2 ; 31.4	25.5 ; 31.5	26.9 ; 29.8
Short story	7.0	6.5	3.5 ; 5.5	3.5 ; 7.0	9.0 ; 17.0
Verbal span	4.5	4.5 ; 5.5	4.0 ; 5.5	4.0 ; 5.5	5.3 ; 6.8
Spacial span	4.5	4.5 ; 6.5	4.3 ; 5.8	4.3 ; 6.5	4.5 ; 5.5
Rey's copy	28.8	35.8 ; 37.8	34.4 ; 37.5	28.8 ; 37.8	35.7 ; 38.4
Rey's immediate reproduction	9.4	11.4 ; 22.5	12.3 ; 28.1	9.4 ; 28.1	20.5 ; 31.5
Rey's delayed reproduction	9.7	10.7 ; 21.2	10.4 ; 25.7	9.7 ; 25.7	16.8 ; 19.1
Verbal fluency semantic	10.5	10.3 ; 10.8	8.3 ; 10.0	8.3 ; 10.8	11.3 ; 14.5
Verbal fluency lexical	24.6	24.6 ; 29.6	22.2 ; 24.5	22.2 ; 29.6	17.9 ; 34.3
Token	27.8	30.8	28.5 ; 34.0	27.8 ; 34.0	28.5 ; 34.0
Benton line orientation	23	25 ; 26	26 ; 28	23 ; 28	28 ; 30
Stroop number for card	21.5	28.5 ; 33.0	28.0 ; 35.4	21.5 ; 35.4	30.9 ; 44.5
Stroop number for coloured word	17.6	15.2 ; 17.6	11.6 ; 20.9	11.6 ; 20.9	20.8 ; 26.1
IADL score	9	8 ; 12	9 ; 12	8 ; 12	9 ; 12

M male ; F female

At inclusion, in both MCI patients and elderly healthy volunteers, supine SBP, DBP and HR were within the reference range (see Table below). In MCI patients, there were no ECG abnormality, and all ECG parameters were normal at selection (see Table below).

As regards laboratory tests at selection, one patient randomised in the placebo group was included with a potentially clinically significant abnormal GGT value (5.6 ULN), the other liver parameters being within the normal range.

Supine blood pressures and heart rate at inclusion, and ECG parameters at selection: range by treatment group and by type of participants

	MCI Patients				Elderly healthy volunteers
	Memantine 20 mg (N = 1)	Donepezil 5 mg (N = 2)	Placebo (N = 3)	All patients (N = 6)	(N = 3)
SBP (mmHg)	120	120 ; 130	130 ; 135	120 ; 135	130 ; 140
DBP (mmHg)	80	70 ; 75	75 ; 85	70 ; 85	80 ; 90
HR (bpm)	60	62 ; 70	64 ; 75	60 ; 75	74 ; 78
QT interval (ms)	382	378 ; 400	400 ; 440	378 ; 440	NP
QTc interval (ms)	441	420 ; 436	380 ; 410	380 ; 441	NP
QTc Bazett interval (ms)	441	423 ; 436	383 ; 425	383 ; 441	NP
PQ interval (ms)	188	164 ; 168	120 ; 160	120 ; 188	NP
QRS duration (ms)	110	96 ; 112	80 ; 100	80 ; 112	NP

NP not planned in the protocol

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

All patients received the treatment during 28 days except for one donepezil-treated patient who had a 27-day treatment period, and one placebo-treated patient who had a 29-day treatment period.

No new concomitant treatment was taken during the study.

PHARMACODYNAMIC RESULTS

No data available.

SAFETY RESULTS

- **Adverse events**

No adverse event was reported during the study.

- **Vital signs**

During the treatment intake supine blood pressures and heart rate were within the reference ranges in all treated patients as follows:

- SBP ranged between 120 and 135 mmHg.
- DBP ranged between 75 and 85 mmHg.
- HR ranged between 64 and 78 bpm.

The changes between the inclusion and the maximum or minimum values on treatment did not exceed ± 10 mmHg for the SBP, ± 5 mmHg for the DBP, and + 14 bpm for the HR except for one donepezil-treated patient for DBP on D7 and D28 (+ 15 mmHg and + 10 mmHg), and for one memantine-treated patient for HR on D28 (+ 16 bpm).

CONCLUSION

This phase II, monocentre, randomised, double-blind, placebo-controlled study with 3 parallel groups (memantine 20 mg/day, donepezil 5 mg/day and placebo) in MCI patients treated for 28 days, and a control group of non-treated elderly healthy volunteers (assessed at baseline only) was prematurely stopped due to budget arbitration. Considering that very few participants were included (6/45 MCI patients planned, and 3/15 elderly healthy volunteers), only data listings were provided. Baseline characteristics of the patients and healthy volunteers included were in accordance with the inclusion criteria of the study. During the study, no adverse event was reported, and no relevant change in supine blood pressures and heart rate was observed on treatment.

Date of the report: 23 May 2012