2 SYNOPSIS

Name of Sponsor: Gedeon Richter Plc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Cavinton Forte tablet (Richter)	Volume:	
Name of Active Ingredient: 10.0 mg vinpocetin / tablet	Page:	

Title of the study:	**Multicenter, open-label study to investigate the efficacy and safety of Cavinton Forte (vinpocetine) tablet in patients with mild cognitive impairment (MCI)**	
Investigator:	*Principal Investigator:* [redacted]	
Study centres:	[redacted]	
Time of clinical part:	First subject in: 25th Apr 2007 Last subject out: 3rd Dec 2009	**Phase of development:** Phase 4
Objective:	*Primary objective:* To investigate the efficacy of Cavinton Forte tablets administered for 18 months in patients with MCI. *Secondary objective:* To investigate the long term safety and tolerability of the study medication.	
Methodology (study design):	Multicenter, open-label, efficacy and safety study.	
Number of subjects:	Enrolled : 53 Safety population: 53 ITT population 53 PP population: 48 drop-outs / withdrawals: 5 replacements: 0 completed as per protocol: 48	

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Diagnosis and main criteria for inclusion:	Patients who meet the diagnostic criteria of mild cognitive impairement (MCI, Mayo criteria), with total score of MMSE between 24-28, between 35 and 70 years old (both males and females), 18 kg/m2 ≤ BMI ≤ 35 kg/m2 (and the minimal body weight is 40 kg).	
Test1 drug	Cavinton Forte tablet (10.0 mg vinpocetine, Richter)	
Reference drug	None	
Duration of the study:	Screening period: up to 21 days before the 'baseline' visit (V1) Treatment period: 18 months Follow-up: none Whole study period: 24 months	
Efficacy assessments:	ADAS-Cog and ADAS-Noncog tests CGIC-PGIC (Clinical Global Impression of Change - Patient Global Impresion of Change) ADL (Activity of Daily Living) MMSE (Mini Mental State Examination). Hamilton Depression Scale (HDS).	

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Criteria for evaluation:	***Efficacy:*** Efficacy was investigated with: • ADAS-Cog, a performance-based scale which included 11 items to assess cognitive function, e.g. memory and orientation. • ADAS-Noncog with 10 items assessed cognitive function, e.g. memory and orientation. • CGIC-PGIC (Clinical Global Impression of Change - Patient Global Impresion of Change). The CGIC consisted of an evaluation by the clinician of the patient's overall change since the beginning of the study. The PGIC consisted of a self-evaluation by the patient of his or her overall change since the beginning of the study. • ADL (Activity of Daily Living), measured the capacity to perform routine daily activities. • MMSE (Mini Mental State Examination)was a brief, quantitative measure of cognitive status in adults. • Hamilton Depression Scale (HDS) was a test measuring the severity of depressive symptoms in individuals. ***Safety:*** Descriptive statistics was performed for safety analysis.	

Statistical methods:	***Efficacy parameters:*** All statistical analyses and summaries of the clinical data were carried out by the Biostatistical Group of the Medical Affairs of Gedeon Richter Plc. using SAS System for Windows (Release 9.2 TS Level 2M3, Statistical Analysis System, SAS – Institute USA). Within all statistical analyses the p-value were rounded to three decimal places, expect in output from SAS statistical procedures. All statistical analyses were two-tailed, significance was tested at the 0.05 level. Descriptive statistics were calculated for all demographic and baseline parameters. Categorical data were described by frequency and percentage; continuous data by mean, median, standard deviation, minimum and maximum. The efficacy parameters were analysed by paired t-test (or nonapametric Wilcoxon test), additionally by reapeted measures ANOVA (using centre fix effect). To determine the presence of normality, Shapiro- Wilk test was carried out. ***Safety parameters:*** Safety investigations included: physical examination, ECG, blood tests, urine analysis, pregnancy test and collection and assessment of adverse events. To detect whether there was any significant difference between screening and the last visit for the continuous variables, paired test (parametric or nonparametric test) was performed, and for the dichotom variables McNemar test was performed. .

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Primary efficacy parameters

Table 1. Statistical evaluation of primary efficacy parameter.

Total score of ADAS-Cog/MCI (ITT Population)	N	Mean	Median	Minimum	Maximum	Std
Visit 1	53	8.6	9	4	13	2.4
Visit 2	53	7.7	8	4	13	2.2
Visit 3	53	6.3	6	2	13	2.4
Visit 4	53	5.7	5	1	13	2.8
VIsIt 5	53	5.2	5	1	12	2.5
Visit 6	53	5.1	5	1	12	2.7

This multicenter 24 months exploratoric study examined the efficacy and safety of Cavinton Forte tablet in patients with mild cognitive impairment. 53 patients were enrolled and randomized in the study. All of the randomised patients received study medication, so the safety population counted 53 patients. 5 patients were not eligible for the PP population. A total of 48 patients completed the study per protocol. The primary comparison was to assess the change between the baseline (Visit 1) and Visit 6 for efficacy parameters.

Based on p-value (< 0.0001) the mean difference of the ADAS-Cog/MCI scores (-3.585) was statistically significant between Visit 1 and Visit 6. There was significant differences regarding the change from baseline (visit 1) to visit 6 in case of the primary efficacy parameter.

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Safety:

Originally a total of 32 adverse event were recorded on the adverse event registration form in the CRF: 31 (96.88%) of them were initial and 1 (3.13%) was follow-up reports. However, one adverse event was recorded twice: first as initial type then again in the follow-up period. Since both records applied to the same adverse event (right radial head fracture that was healed) therefore the total number of adverse events was considered 31.

One patient experienced 2 SAEs (acute pancreatitis and pericardial effusion, NAAN), with the following seriousness criteria: "requires hospitalisation or prolongation of existing hospitalization" and "death". Intervention action was: conservative therapy, thoracotomy and pericardial drainage.

Two patients experienced single reported SAEs. One patient experienced 1 SAE (diabetes mellitus inadequate control, INFE) with the following seriousness criterion: "requires hospitalisation or prolongation of existing hospitalisation". Intervention action was medication and another patient experienced 1 SAE (rectal polyp, MAPÁ), with the same seriousness criterion: "requires hospitalisation or prolongation of existing hospitalisation", in which case intervention action was colonoscopy and polypectomia.

One patient died (2-1, NAAN), who had a pericardial fluid that required thoracotomy, pericardial draine and cardiac decompression with supportive therapy. Later cardiorespiratory insufficiency developed and the patient died (2008[redacted] in spite of resuscitations. It was considered as a serious, but not related AE.

Non serious AEs included lumbago acuta, insomnia, anxiety, vertebrobasilar insufficiency, radius fracture, blood pressure fluctuation, nausea, weight increased, hyperchlorhydria, haematuria, spinal osteoarthritis, enterocolitis, hiatus hernia, cardiomegaly, diabetes mellitus, dry mouth and eyes and petechiae.

These AEs were single case reports, except for acute lumbago, anxiety, vertebrobasilar insufficiency and diabetes mellitus, which were all experienced in 2 patients, respectively.

During the study one death occurred (due to pericardial fluid with cardiac compression, considered "not related" to the study drug according to the investigator).

Breakup of AEs/SAEs by seriousness and causality: 13 patients experienced non-serious, not related; 3 patients experienced non serious, possibly related; 3 patients experienced serious, not related and 1 patient experienced non serious, related AEs/SAEs.

Number of AEs/patient: 11 patients experienced 1 AE, 2 patients experienced 2 AEs, 2 patients experienced 3 AEs and 1 patient experienced 4 AEs

There were no significant differences in vital signs and ECG parameters.

Statistically significant difference could be found in case of the following parameters:

- Chloride (Clinical chemistry) (p=0.0339)
- Specific gravity (Urine) (p=0.0082)

Cavinton Forte was safe and had a good tolerability during the whole study period.

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Conclusion

The study was performed according to the study protocol.

There were significant differences regarding the change from baseline (visit 1) to visit 6 in case of all efficacy parameters. Significant improvement was detected in the psychometrical tests after the 18 months treatment period. The overall status of the patients improved significantly according both to the patient and the investigator. Also significant improvement was detected in daily activity. The complex improvement of the clinical symptoms affected the patients' mood positively.

Four SAEs (including one with fatal outcome) occurred during the study period that affected 8.32% of study population, however, none of them was related to study medication. The most frequent AEs were vertebrobasilar insufficiency (n=2, 6.45%, not related), acute lumbago (n=2, 6.45%, not related) and anxiety (n=2, 6.45%, possibly related).

Taken together, in this study Cavinton Forte was proved to be safe and well tolerated.