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:	Single center, exploratoric, double-blind, placebo controlled study to investigate the efficacy and tolerability of vinpocetine in patients with non-proliferative diabetic retinopathy	
Investigators:	*Principal Investigator:* [redacted] *Sub-Investigators:* none	
Study centre:	[redacted]	
Time of clinical part:	First subject in: 15th Sept 2009 Last subject out: 25th May 2011	**Phase of development:** Phase 4
Objective:	*Primary objective:* To investigate the efficacy of Cavinton Forte (vinpocetine) tablet in patients with non-proliferative diabetic retinopathy. *Secondary objective:* To investigate the safety and tolerability of Cavinton Forte (vinpocetine) tablet.	
Methodology (study design):	Single center, exploratoric, double-blind, placebo controlled study.	
Number of subjects:	planned for randomisation: 30 screened: 36 screen failure 4 randomized: 32 drop-outs / withdrawals: 5 replacements: 0 completed as per protocol: 27	

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Diagnosis and main criteria for inclusion:	Patients with Type 2 diabetes mellitus with mild or moderate or severe non-proliferative diabetic retinopathy (NPDR), treated with diet and/or oral antidiabetics: sulphonylurea, biguanid, thiazolidindion, acarbose and/or insulin. Age between 30 and 80 years (both males and females), 18 $kg/m^2 \leq BMI \leq 35$ kg/m^2 (and the minimal body weight is 40 kg), patient's HgbA1c ≤ 10%.	
Test1 drug	Cavinton Forte tablet (10.0 mg vinpocetine, Richter)	
Reference drug	Placebo (Richter)	
Duration of the study:	Screening period: 3 weeks Each treatment periods: 24 weeks Follow-up: 4 weeks (About 28 weeks in total)	
Efficacy assessments:	The efficacy investigations (ETDRS chart, IOP measurement, fundus photography, fluorescein angiography, OCT, VEP, PERG, ERG) were performed at visit 1, 3, 4 and at follow-up as well.	

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Criteria for evaluation:	***Efficacy:*** Efficacy is planned to be investigated with: • Early Treatment Diabetic Retinopathy study chart for visual acuity testing (ETDRS), • Intra Ocular Pressure measurement (IOP), • Fundus photography to document the health of the optic nerve, vitreous, macula, retina and its blood vessels • Fluorescein angiography for examining the circulation of the retina using the dye tracing method, • Optical Coherence Tomography, an interferometric, non-invasive imaging technique (OCT), • Visual Evoked Potential using an electroencephalograph (VEP), • Pattern Electroretinogram Electroretinograph for the investigation of the electrical potentials generated within the retina (PERG). ***Safety:*** Descriptive statistics was performed for safety analysis.
Statistical methods:	***Efficacy parameters:*** Descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum) were presented by visit and treatment group for all efficacy parameters. All analyses were based on both ITT and PP populations. Validity of the normality assumption was checked with the Shapiro-Wilk test. If normality of the data was rejected at the 5% significance level, nonparametric Wilcoxon rank-sum test was performed to test the change from baseline (recorded at Visit 1) to Visit 4 between groups.If the data was normal distribution the between-treatment group comparisons for change from Visit 1 to Visit 4 were performed by means of an analysis of covariance (ANCOVA) model with treatment group as factor and baseline values measured at Visit 1 as the covariate.In case of dichotom efficacy parameters the between-treatment group comparisons for change from Visit 1 to Visit 4 were tested with Chi2 test (if the assumption of chi2 test was not confirmed Fisher exact test was performed). All statistical tests were two-tailed and only probability values $p<0.05$ were considered to indicate statistical significance. ***Safety parameters:*** To detect whether there is any significant difference between screening and the follow-up for the continuous variables, paired test (parametric or non-parametric test) was performed, and for the dichotomic variables, McNemar test was performed.

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Table 1. Statistical evaluation of primary efficacy parameters. Change from baseline to Visit 4.

Variable	p-value
IOP Left Eye	0.5851
IOP Right Eye	0.2631
ETDRS Left Eye	0.2996
ETDRS Right Eye	0.7983
No. of bleedings Left Eye	0.6168
No. of bleeding Right Eye	0.3750
No. of microaneurysms Left Eye	0.5053
No of microaneurysms Right Eye	0.8603
Severity level on ICDRDSS Left Eye	1.000
Severity level on ICDRDSS Right Eye	1.000
Venous beading Left Eye	0.3000
Venous beading Right Eye	0.3158
Ischemia Left Eye	NA*
Ischemia Right Eye	NA*

*NA: there were no changes between visits

This single centre 12 months exploratoric study examined 31 patients with non-proliferative diabetic retinopathy under 24 weeks treatment with Cavinton Forte tablet and Placebo.

The aim of the study was to investigate the efficacy of Vinpocetine Forte tablet compared to Placebo. The primary comparison was to assess the change between the baseline (Visit 1) and Visit 4 for all efficacy parameters. In the secondary comparisons the difference between the arms in changes among the visits was measured.

There were no significant differences between the Cavinton Forte group and Placebo group regarding the change from baseline (visit 1) to visit 4 in case of all efficacy parameters. Change between visits comparison among the two arms were also non-significant for all efficacy parameters.

Changes of laboratory values between Screening and Visit 4 were analyzed. Statistically significant changes detected in case of MCV, MCHC, Phosphate and SGOT (ASAT) values.

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Table 2. Statistical evaluation of changes in efficacy parameters between visits

Variable	p-value				
	V3 vs. V1	FU vs. V1	V4 vs. V3	FU vs. V3	FU vs. V4
IOP Left Eye	0.132 (0.403)+	0.802	0.633	0.601	0.784
IOP Right Eye	0.437 (0.528)+	1.000	0.178	0.752	0.539
ETDRS Left Eye	1.000	0.500	1.000	0.813	0.656
ETDRS Right Eye	0.504	0.594	0.914	0.617	0.313
No. of bleedings Left Eye	0.573 (0.509)+	0.630	0.255	0.413	0.781
No. of bleeding Right Eye	0.130 (0.151)+	0.169	0.887	0.803	0.674
No. of microaneurysms Left Eye	0.778 (0.943)+	0.910	0.339	0.088	0.951
No of microaneurysms Right Eye	0.462 (0.576)+	0.227	0.838	0.638	0.297
Severity level on ICDRDSS Left Eye	1.000	NA*	1.000	NA*	NA*
Severity level on ICDRDSS Right Eye	0.5211 (1.000)+	1.000	1.000	NA*	NA*
Venous beading Left Eye	0.3333 (0.300)+	0.3158	NA*	NA*	NA*
Venous beading Right Eye	NA*	0.3333	0.3333	0.3478	NA*
Ischemia Left Eye	NA*	NA*	NA*	NA*	NA*
Ischemia Right Eye	NA*	NA*	NA*	NA*	NA*

*NA: there were no changes between visits, + different p-value in PP population

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Safety:

21 adverse events occurred during the study. There were 19 adverse events in the Cavinton Forte group and 2 adverse events in the Placebo group. The adverse events were assessed as mild in 10 cases, moderate in 9 cases and severe in 2 cases in intensity. There were 2 serious adverse events in the Cavinton Forte group and 1 serious adverse event in the Placebo group. The causal relation to the study drug was assessed as not related in all cases.

Conclusion

The study was performed according to the study protocol.

There were no significant differences between the Cavinton Forte group and Placebo group regarding the change from baseline (visit 1) to visit 4 in case of all efficacy parameters.

Change between visits comparison among the two arms were also non-significant for all efficacy parameters.

The study does not detect any differences between the Cavinton Forte and the Placebo in patients with non-proliferative diabetic retinopathy.