



BRIEF REPORT

# Enhancement of Retinal Function and of Neural Conduction Along the Visual Pathway Induced by Treatment with Citicoline Eye Drops in Liposomal Formulation in Open Angle Glaucoma: A Pilot Electrofunctional Study

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Received: December 13, 2018 / Published online: February 21, 2019  
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## ABSTRACT

**Introduction:** To evaluate the retinal function and the relative neural conduction along the visual pathway after treatment with citicoline in liposomal formulation (CLF) eye drops in patients with open angle glaucoma (OAG).

**Methods:** Twelve OAG patients (mean age  $\pm$  standard deviation  $52.58 \pm 11.39$  years, intraocular pressure  $< 18$  mmHg under topical hypotensive treatment, Humphrey field analyzer mean deviation  $-4.49 \pm 2.46$  dB) were enrolled. Only one eye of studied patients was treated with CLF eye drops (OMK1-LF<sup>®</sup>, Omikron Italia, 3 drops/day) (CLF group, 12 eyes) over a period of 4 months. In CLF eyes, pattern electroretinogram (PERG), visual evoked potentials (VEP), and visual field test were assessed at baseline and at the end of treatment (month 4).

**Results:** After treatment with CLF eye drops, a significant increase of PERG P50–N95 amplitude and a significant shortening of VEP P100 implicit time were found. In CLF eyes, the shortening of VEP P100 implicit time was significantly correlated with the increase of PERG P50–N95 amplitude.

**Conclusion:** Data from this pilot study suggest that treatment with CLF eye drops induces an enhancement of the retinal bioelectrical responses (increase of PERG amplitude) with a consequent improvement of the bioelectrical activity of the visual cortex (shortening of VEP implicit time).

**Funding:** Omikron Italia S.r.l. and Opko Health Europe.

**Keywords:** Citicoline; Glaucoma; Ophthalmology; PERG; VEP

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## INTRODUCTION

Patients with open angle glaucoma (OAG) present functional impairment of the different elements forming the visual pathway that can be detected by electrophysiological methods. In OAG, abnormal flash or multifocal electroretinogram (ERG) responses may reflect dysfunction of retinal preganglionic elements [1, 2], abnormal pattern ERG (PERG) and reduced photopic negative response (PhNR) indicate dysfunction of retinal ganglion cells

(RGCs) and their fibers [3–8], and delayed or reduced visual evoked potential (VEP) signals suggest an abnormal neural conduction along the visual pathway [6, 9, 10]. An improvement of PERG responses may be obtained after lowering the intraocular pressure (IOP) with beta-blockers or acetazolamide [11–15] and after treatment with nicergoline [16], or with coenzyme Q<sub>10</sub> in conjunction with vitamin E [17].

Since 1996, we found that, after intramuscular or oral treatment with citicoline, OAG patients showed an improvement of the RGCs function and of the neural conduction along the visual pathway [18–20]. This approach was similar to that used in different brain disorders due to vascular, traumatic, or degenerative processes [21]. In accordance with our results [18–20], Chang and Goldberg [22] suggested that citicoline might have a neuroenhancing effect. This is consistent with the amelioration of the glaucomatous perimetric condition [23] and the reduction of the progression of visual field defects, as recently reported in glaucomatous eyes (by using 500 mg of citicoline in oral solution) [24].

Since 2012, citicoline is available also for topical treatment. By high-performance liquid chromatography assessment, it has been documented in an animal experimental model that a topical ocular solution composed by citicoline and sodium hyaluronate (containing also benzalkonium chloride) can reach the vitreous [25]. In OAG patients, treatment with citicoline eye drops may induce a stabilization of cell membranes, rebounding into an increase of the RGCs function (increase in PERG amplitude) with related improvement of the neural conduction along the visual pathway (shortening in VEP implicit time) and consequent amelioration of the perimetric condition [26].

More recently, a new preservative-free eye drop formulation, containing a liposomal system as a carrier for citicoline, has been developed.

In an animal model of diabetic retinopathy (DR), treatment with citicoline liposomal formulation (CLF) prevented glial cell activation and neural apoptosis [27], thus suggesting that it might be a new associated strategy for treating early DR.

Therefore, the aim of this pilot study was to evaluate, by means of PERG and VEP recordings, whether the treatment with CLF eye drops could have an effect on the retinal function and consequently on the neural conduction along the visual pathway in patients with OAG.

## METHODS

### Patients

Twelve eyes from 12 patients [mean age  $\pm$  standard deviation (SD) of  $52.58 \pm 11.39$  years, range 43–60 years) affected by OAG were recruited. OAG patients were selected from a larger population of 238 OAG patients based on the following inclusion criteria:

- Age between 20 and 60 years
- Diagnosis of OAG defined as a repeatable Humphrey field analyzer (HFA) 24-2 SITA standard visual field defect compatible with glaucoma; a mean deviation (MD) between  $-2$  and  $-6$  dB; typical glaucomatous optic nerve head damage
- Best corrected visual acuity  $\geq 5/10$  Snellen
- IOP  $< 18$  mmHg under topical hypotensive treatment (monotherapy as well as combined therapy)

The exclusion criteria were:

- Ocular surgery, including cataract surgery, in the last 3 months
- Cataract or macular diseases
- Argon laser trabeculoplasty in the last 6 months
- Hypersensitivity to the active ingredients used in the study
- Secondary ocular hypertension, including steroid-induced ocular hypertension
- Ocular or systemic diseases that could affect the outcome of the study
- Changes of systemic treatments that could affect IOP values
- Treatment with lutein, zeaxanthin, citicoline, docosahexaenoic acid, ubiquinone, coenzyme Q<sub>10</sub> in the last 3 months
- Pregnancy, breastfeeding
- Diabetes

- Systemic lupus erythematosus, rheumatoid arthritis, connectivitis
- Use of anticoagulants and lithium

### Study Design

This study has been designed as a pilot open-label, single-arm, before–after treatment.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

The study was not registered because it was a premarket study of the device, but the Italian Ministry of Health was notified. The study was approved by the local ethics committee (Comitato Etico Centrale Sezione IFO Bietti, Registro Sperimentazioni N.66/16/FB).

Upon recruitment, each patient was aware that he/she was being enrolled in a study to test a new ocular topical formulation containing citicoline and sodium hyaluronate in a liposomal formulation.

CLF eyes were those treated with CLF eye drops (citicoline 2%, phospholipids 2%, sodium hyaluronate 0.075%, phosphate buffer, and water, OMK1-LF<sup>®</sup>, Omikron Italia, Italy) 3 drops/day in addition to the topical hypotensive treatment for 4 months (CLF group, 12 eyes).

CLF patients were examined (electrophysiological examinations, HFA 24-2, and evaluation of side effects, see below) at baseline and after 4 months of treatment.

Compliance to eye drops administration was assessed through a questionnaire, which was distributed by the study personnel at each visit. As expected in a clinical study, reported adherence to treatment was high, and all patients rated their compliance as “good to very good” (regular use of the eye drops in at least 80% of the study period).

### Electrophysiological Examination

In CLF eyes, the electrophysiological examination was performed at baseline and after 4 months of treatment.

In agreement with previously published studies [5, 6, 17–20, 26, 28–31], simultaneous PERG and VEP recordings were performed.

### Evaluation of Side Effects

Throughout the entire period of treatment with CLF eye drops we assessed possible IOP increase > 18 mmHg, and the presence of conjunctival hyperemia, corneal microabrasions, conjunctival and corneal lesions, dry eye, reduced quality or quantity of tears by performing the break-up time and the Schirmer tests, respectively, were considered as adverse side effects.

### Statistics

To detect a difference of 28.13% or greater in PERG P50–N95 amplitude [26], a sample size of 11 patients was estimated, with a power of 90%, and an alpha error of 0.5%.

At baseline, in CLF eyes, test–retest data of PERG and VEP were expressed as the mean difference between two recordings obtained in two separate sessions  $\pm$  SD of this difference. A 95% confidence limit (CL, mean  $\pm$  2 SD) of test–retest variability in CLF eyes was established assuming a normal distribution.

In CLF eyes, at 4-month time point, changes in the PERG and VEP responses were compared to baseline and were evaluated by ANOVA for repeated measures. After treatment, PERG and VEP differences observed in individual CLF eyes with respect to the baseline values were calculated by performing a logarithmic transformation to better approximate a normal distribution. Pearson’s correlation was used to correlate the PERG and VEP individual changes (difference at 4 months minus baseline).

Also, changes in HFA 24-2 parameters [MD, pattern standard deviation (PSD) and mean sensitivity (MS)] from baseline were evaluated by paired *t* test analysis.

A *p* value lower than 0.05 was considered as statistically significant in all analyses.

## RESULTS

Figure 1 shows simultaneous PERG and VEP recordings and relative HFA performed on two representative OAG eyes at baseline and after 4 months of treatment with CLF eye drops in addition to hypotensive therapy.

Individual PERG and VEP changes observed in CLF eyes at 4 months compared to baseline are shown in Fig. 2a–c, respectively. Table 1 lists the number of individual changes expressed in absolute values and percentage with respect to the total number of eyes belonging to the CLF group at 4 months of follow-up.

Mean data of PERG and VEP parameters observed in the CLF group at baseline and after 4 months, and the relative statistical analyses are shown in Table 2.

Figure 2d presents the correlations found in CLF eyes between PERG P50–N95 amplitude differences and VEP P100 implicit time differences (4 months minus baseline).

When considering the individual changes concerning the 95% CL after 4 months of treatment with CLF eye drops, a large percentage of CLF eyes showed an increase of PERG P50–N95 amplitudes (83.33%) and a shortening of VEP implicit times (91.66%), while 58.33% of CLF eyes showed improved VEP N75–P100 amplitudes.

In CLF eyes, the improvement of PERG P50–N95 amplitudes was significantly ( $p < 0.05$ ) correlated with the shortening of VEP P100 implicit times (Fig. 2d).

Non-significant ( $p > 0.05$ ) correlations were observed between the differences of all electrophysiological parameters (PERG and VEP values) and age, time elapsed from the OAG diagnosis, IOP at the time of the first diagnosis of ocular hypertension, IOP at the time of electrophysiological examination, MD, and PSD.

On average, in the group of eyes after CLF treatment with respect to baseline, the mean values of PERG P50–N95 amplitude and VEP P100 implicit time were significantly ( $p < 0.05$ ) increased and reduced, respectively; those of VEP N75–P100 amplitude were increased

Fig. 1 Examples of simultaneous VEP and PERG recordings and Humphrey field analyzer (HFA) performed in two OAG eyes (CLF#3 and CLF#6) treated with hypotensive therapy plus CLF at baseline (baseline) and after 4 months of treatment (4 months). In comparison with the baseline condition, after treatment with CLF eye drops, an increase of PERG P50–N95 amplitude (up down arrow) and shortening of VEP P100 implicit time (rightwards arrow), together with changes of the visual field defects, can be observed

without reaching a significance level and HFA 24-2 parameters did not show statistically significant changes (MD  $-4.49 \pm 2.46$  vs  $-4.36 \pm 2.24$  dB,  $p = 0.58$ ; PSD  $6.05 \pm 3.36$  vs  $5.78 \pm 3.68$  dB,  $p = 0.43$ ; MS  $25.33 \pm 2.05$  vs  $25.51 \pm 1.82$  dB,  $p = 0.53$ ).

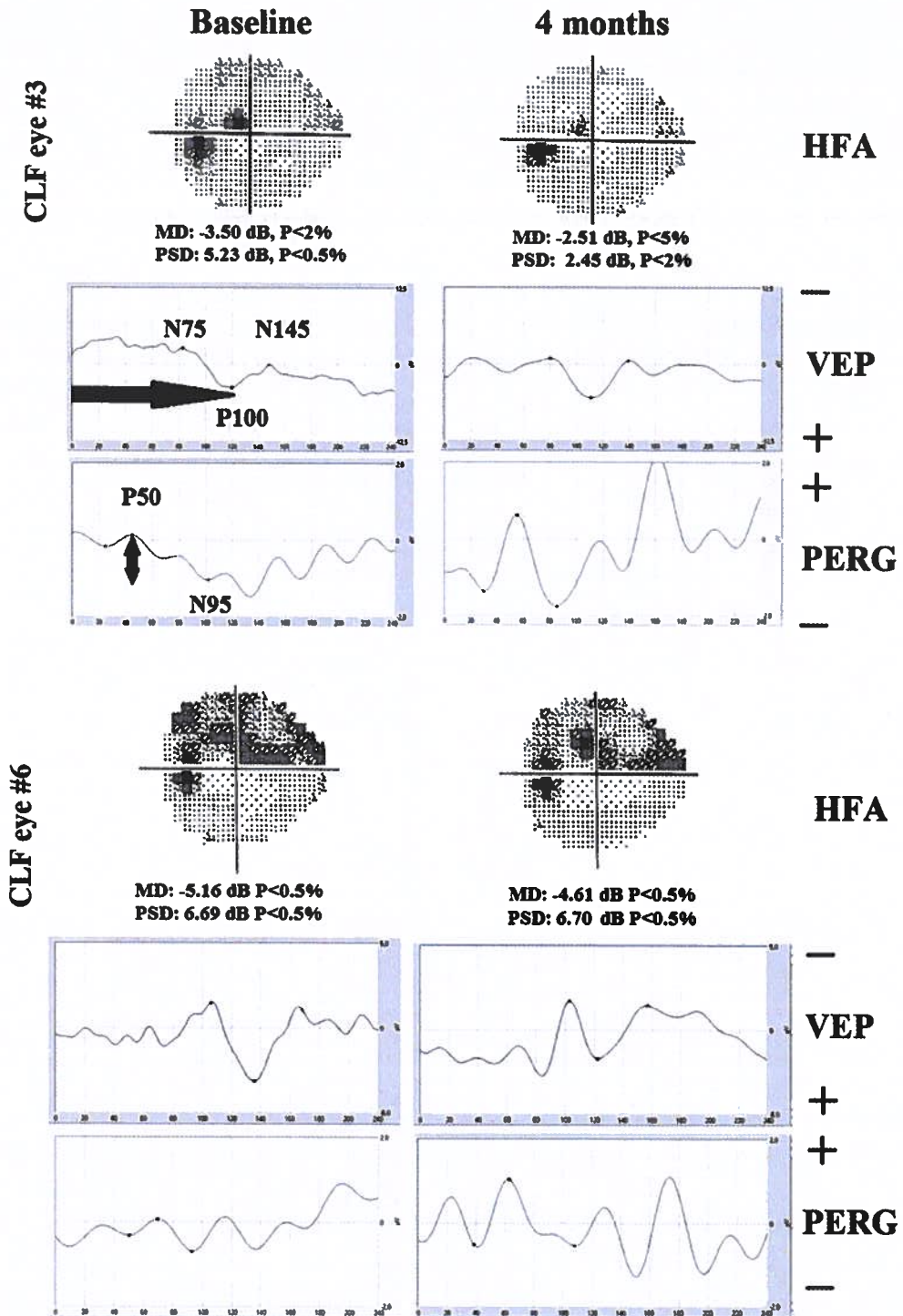
Nevertheless, 66.66% (8/12) of CLF eyes showed positive changes of HFA 24-2 MD and MS values and 50% of the eyes (6/12) showed positive change of PSD values.

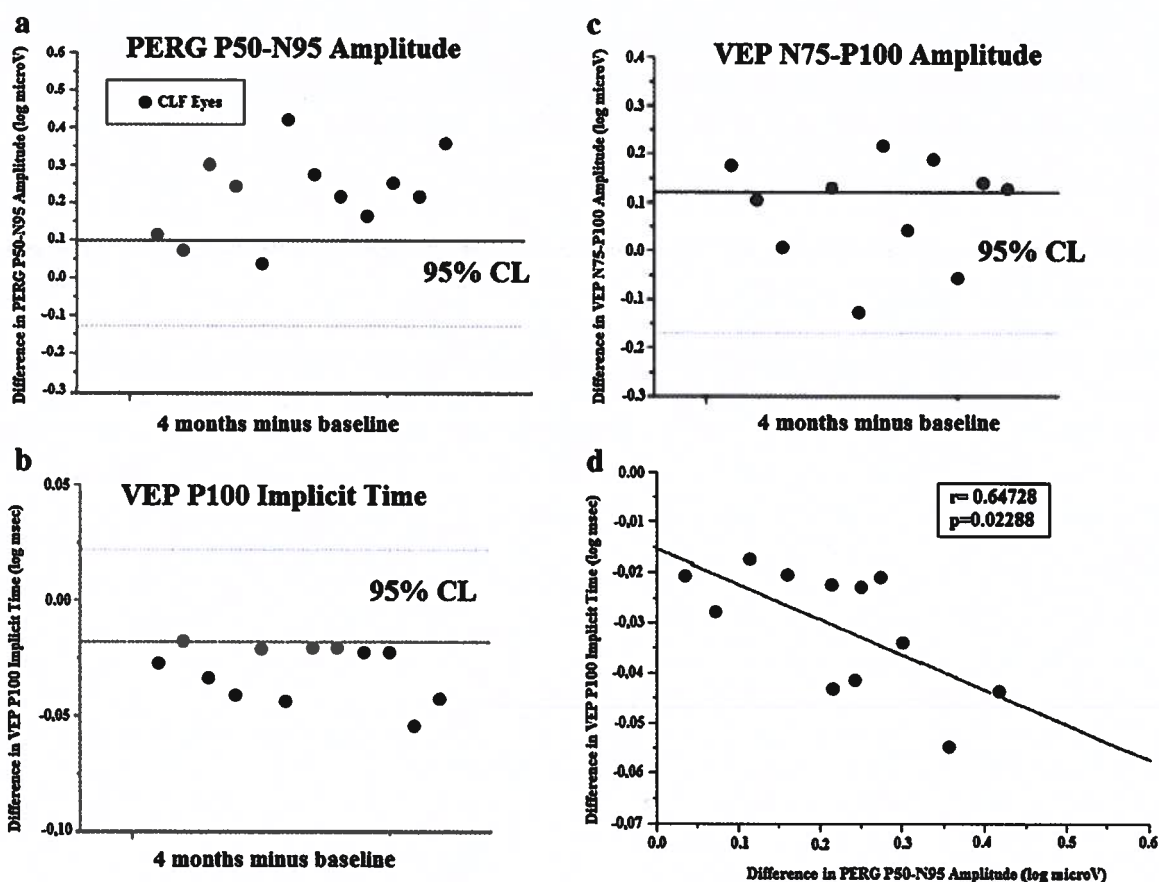
### Ocular or General Side Effects

Throughout the entire period of treatment with CLF eye drops, non-significant changes ( $p > 0.05$ ) of the IOP (baseline  $14.35 \pm 2.22$  mmHg, end of follow-up  $14.15 \pm 1.87$  mmHg) or in visual acuity were detected. In all CLF eyes, no ocular adverse side effects have been detected: presence of conjunctiva hyperemia, corneal microabrasions, conjunctiva and cornea lesions, dry eye, reduced quality or quantity of tears. In addition, non-significant changes ( $p > 0.05$ ) of the blood systolic pressure (baseline  $126.18 \pm 3.11$  mmHg, end of follow-up  $125.22 \pm 2.87$  mmHg) were found.

## DISCUSSION

The aim of our study was to evaluate whether the treatment with CLF eye drops could have any effect on the RGCs function and on the relative neural conduction along the visual pathway in OAG patients.





**Fig. 2** Pattern electroretinogram (PERG) P50–N95 amplitude (a), VEP P100 implicit time (b), and VEP N75–P100 amplitude (c) individual changes (4 months of treatment minus baseline) observed in OAG eyes treated with hypotensive therapy plus CLF (CLF group,  $N = 12$  eyes). The percentage of unmodified eyes (within the 95% confidence test–retest limit, CL) and percentage of eyes

with improvement (values over the CL for PERG and VEP amplitudes or under the CL for VEP implicit time—solid line) are reported in Table 1. **d** Individual differences of PERG P50–N95 amplitude plotted as a function of the corresponding differences of VEP P100 implicit time. Pearson's test was used for regression analysis and correlations

### Retinal Function (PERG Data)

In this study, we found that the group of OAG patients treated over a 4-month period with topical CLF drops showed an improvement of retinal function as suggested by the increase of PERG amplitudes. A similar enhancement has been previously observed by using both oral and intramuscular treatments with citicoline [18–20].

Our results are in agreement with those presented in a brief report [25] and in a randomized masked study [26] whereby PERG

amplitude changes were detected in OAG patients after 2 months [25] or 4 months [26] of citicoline eye drops treatment.

Citicoline acts as an intermediary in the synthesis of phosphatidylcholine (a major phospholipid) through the activation of the biosynthesis of structural phospholipids in neuronal membranes [32–35]. Recently, Matteucci et al. [36] reported remarkable data on the administration of citicoline in retinal cultures treated with glutamate or high glucose (a model of neurodegeneration) with consequent

**Table 1** Changes of electrophysiological parameters (PERG P50–N95 amplitudes, VEP P100 implicit times, and VEP N75–P100 amplitudes) after 4 months of treatment with respect to the baseline condition observed in OAG eyes treated with hypotensive therapy plus CLF (CLF group, *N* = 12 eyes)

	CLF group (12 eyes)					
	Unmodified		Improvement		Worsening	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Difference 4 months minus baseline						
PERG P50–N95 A	2	16.66	10	83.33	0	0
VEP P100 IT	1	8.34	11	91.66	0	0
VEP N75–P100 A	5	41.67	7	58.33	0	0

*Unmodified* within the 95% confidence test–retest limit, *improvement* values of increase in amplitudes (A) and shortening in implicit times (IT) that exceeded the 95% confidence test–retest limit, *worsening* values of reduction in amplitudes (A) and increase in implicit times (IT) that exceeded the 95% confidence test–retest limit. *N* number of eyes

**Table 2** Mean values of PERG P50–N95 amplitudes, VEP P100 implicit times, and VEP N75–P100 amplitudes detected at baseline and after 4 months in OAG eyes treated with hypotensive therapy plus CLF (CLF group, *N* = 12 eyes)

Group	<i>N</i>	Time	Mean	SD	ANOVA vs baseline	
					<i>f</i>	<i>p</i>
PERG P50–N95 amplitude (μV)						
CLF	12	Baseline	1.16	0.340		
CLF	12	4 months	1.94	0.587	(1,23) = 16.0	0.0006
VEP P100 implicit time (ms)						
CLF	12	Baseline	122.7	9.17		
CLF	12	4 months	114.2	7.11	(1,23) = 6.44	0.018
VEP N75–P100 amplitude (μV)						
CLF	12	Baseline	6.84	2.43		
CLF	12	4 months	8.71	3.72	(1,23) = 2.11	0.160

*ANOVA* statistical evaluation by a one-way analysis of variance

decreased pro-apoptotic effects and a reduced synaptic loss.

Thus, the effect of topical citicoline on the RGCs function that we observed in this study could be ascribed to the stabilization of RGCs membrane with consequent improving of their function as demonstrated by PERG amplitude improvement.

The action of citicoline eye drop administration is likely related to the stabilization of the

RGCs membrane [36] with consequent increase of their function (increase of PERG amplitude) leading to the increase of the observed neural conduction along the visual pathways as found in this study and in previous study [26].

It is worth noting that in our previous study [26], functional enhancement of both RGC and visual pathways contributed to an amelioration of visual field defects.

We also correlated the differences of all electrophysiological parameters (PERG and VEP values) with several other parameters (age, time elapsed from the diagnosis of OAG, IOP at the time of the first diagnosis of ocular hypertension, IOP at the time of electrophysiological examination, MD, and PSD) and no correlations reached a statistically significant level, thereby leading to the conclusion that none of these parameters influences the improvement of the retinal function after CLF treatment.

#### Neural Conduction Along the Visual Pathways (VEP Data)

During a 4-month period, in CLF eyes, we observed a statistically significant improvement of the neural conduction along the visual pathway with respect to the baseline, as suggested by the increase of VEP amplitude and by the shortening of VEP implicit time. This result is in agreement with our previous studies performed with administration of intramuscular [18, 19], oral [20], or topical ocular [25, 26] citicoline.

VEP abnormalities in glaucoma reflect both dysfunction of the innermost retinal layers (RGCs and their fibers) and a delay in neural conduction along post-retinal visual pathways [6].

Furthermore, the morpho-functional changes occurring at the dorsal lateral geniculate nucleus (dLGN) level in OAG patients need to be considered. In fact, structural and functional damage of the dLGN in human or animals affected by glaucoma has been reported [37, 38].

When we used oral or intramuscular citicoline treatment [18–20] we found a VEP improvement, which was ascribed to a neuro-modulator effect of citicoline (“dopaminergic-like activity” [33]) at the dLGN level. This effect on VEP improvement is a direct consequence of better function of RGC.

It was particularly interesting to observe a significant correlation between the increase of PERG amplitude and the shortening of VEP P100 implicit time detected after topical treatment with CLF (Fig. 2d).

## CONCLUSIONS

The results of the present pilot study suggest that CLF eye drops may induce an enhancement of the RGC function (PERG improvement) with a consequent better neural conduction along the visual pathways (VEP improvement) in glaucomatous patients.

This study was designed on the assumption that citicoline may act directly on the retinal structures based on previous findings in animal models treated with the formulation of citicoline eye drops plus hyaluronic acid and benzalkonium chloride [25]. The PERG results observed in the present study corroborate the hypothesis that CLF eye drops may reach the vitreous body and may have an effect on the retinal structures.

When looking at the HFA 24-2 results, after 4 months of treatment with CLF eye drops, 66.66% of OAG eyes showed a positive change of both MD and MS values and 50% of OAG eyes showed a positive change of PSD values. However, since the power of this study was defined on the main electrophysiological parameter (PERG P50-N95 amplitude) and considering the HFA MD inter-individual variability at baseline, a larger cohort of OAG patients is needed to investigate the statistical significance of these changes.

Therefore, the limitation of the current pilot study is that we are not able to provide an adequate statistical analysis of the visual field changes. Furthermore, a longer follow-up period with a larger cohort of OAG patients would be required to confirm our findings (increase of retinal and visual pathway function after CLF eye drops treatment).

## ACKNOWLEDGEMENTS

We thank the participants of the study.

**Funding.** Research for this study was financially supported by the Italian Ministry of Health and Fondazione Roma. Sponsorship for this study and article processing charges were funded by Omikron Italia S.r.l. and Opko Health



Europe. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

**Other Assistance.** The authors acknowledge Dr. Valter Valli Fiore for his technical help in the electrophysiological evaluations and Dr. Francesca Berardo and Dr. Manuela Ferrazza for their technical help in performing other functional tests.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosures.** Vincenzo Parisi, Francesco Oddone, Gloria Roberti, Lucia Tanga, Carmela Carnevale, Lucia Ziccardi and Gianluca Manni have nothing to disclose.

**Compliance with Ethics Guidelines.** All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was not registered because it was a premarket study of the device, but the Italian Ministry of Health was notified. The study was approved by the local ethics committee (Comitato Etico Centrale Sezione IFO Bietti, Registro Sperimentazioni N.66/16/FB).

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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