α-Glycerophosphocholine in the Mental Recovery of Cerebral Ischemic Attacks

An Italian Multicenter Clinical Trial

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INTRODUCTION

Patients affected by acute ischemic cerebral event (TIA, p-TIA, stroke) may develop a syndrome characterized by sensitive-motor and, often, cognitive deficit, depending on the type of occlusion and individual response.[1,2]

Cerebrovascular disease is commonly considered to be the second cause of dementia, and stroke in particular accounts for 20–25%.[3] The term "dementia" implies a change in the mental state, from one level of mental functioning to a lower one over time. The explanation of the elevated risk of dementia following stroke is not yet fully understood: injury of different and multiple brain regions, each specific for certain cognitive functions, might lead to dementia simply on an additive basis, or a multiplicative mechanism may apply with the cumulative effect of several lesions. Many drugs, have been clinically tested in order to assess their role in the functional recovery of these patients.

Among these, α-glycerophosphocholine (α-GPC), a new molecule belonging to a class of choline donors, has shown a very promising profile on the basis of pharmacokinetics and pharmacological studies: in animals it has shown to exert an integrated neuronal function[4] and to facilitate learning and memory in a dose-related way.[5,6] Once α-GPC crosses the blood-brain barrier, it directly increases the synthesis and the release of acethylcholine, and serves as a precursor for membrane phospholipids, improving the functionality of neuronal membranes.[7–9] In healthy human volunteers, it has been possible to prevent the memory deficit produced by scopolamine.[10] And both in open and controlled clinical studies[11–14] on a substantial number of patients,[15] it has shown a good therapeutic effect on the outcome of dementia regardless of its etiology.

The aim of the present study was to assess α-GPC efficacy and tolerability in the treatment of neuropsychic symptoms following acute stroke.

MATERIAL AND METHODS

Experimental Design

The present study was an open multicenter uncontrolled trial involving 176 centers of internal medicine, geriatrics, and neurology spread all over Italy.

TABLE 1. Clinical Assessment and Evaluation Time

	First Part		Second Part	
	Baseline	1st Month	3rd Month	6th Month
Demography and run-in assessment	X			
SYS/DIAS BP and HR	X	X	X	X
Mathew Scale	X	X		
MMSE		X	X	X
GDS		X	X	X
Crichton Rat. Scale		X	X	X
Blood Analyses	X		X	X
α-GPC therapy	1000 mg/day im		3 × 400 mg/day orally	

The study was carried out in two phases that lasted 6 months altogether: during the first part (which lasted from day 1 to day 28, generally in hospital), the patients were treated parenterally with α-GPC at the dosage of 1000 mg/day, and in the second part (which lasted from day 29 to the end of the 6th month), the patients were treated orally with α-GPC at a dosage of 1200 mg/day, at a regimen of 400 mg three times a day.

The clinical assessments were made at the admission visit (baseline), at the end of the first part, and after 3 and 6 months from the beginning.

TABLE 1 reports the list of the clinical assessments and the checking times.

First part (baseline, 28th day): the clinical assessments consisted of patient's medical history (only at baseline), physical and neurological examination, arterial blood pressure and heart rate control, Mathew Scale and blood analyses.

Second part (28th day or secondary baseline, 3rd month, 6th month): the clinical assessments consisted of physical and neurological examination, Minimental State Test, Crichton Rating Scale, Global Deterioration Scale, arterial blood pressure and heart rate control, blood analyses (only at the 6th month).

Experimental Sample

The study population consisted of 2058 patients 45–85 years of age, with diagnosis of cerebral ischemic attacks (stroke or TIA), within the previous 10 days.

The exclusion criteria were patients with a baseline Mathew score <35, or presenting consciousness deficit such that no cooperation was possible in performing the assessment tools requested by the protocol, or those receiving pharmacological therapy with psychotropic or nootropic drugs, or with short life expectancy, or with previous psychiatric and neurologic diseases, or with severe renal, liver, or heart diseases and neoplasms. Furthermore those patients with hemorragic infarction, head injury, or intracerebral or subarachnoid hemorrage, as well as alcohol and/or drug addictions, were not considered eligible for the study.

Concomitant Treatments

Conventional treatment for stroke was accepted; concomitant treatments with other brain-related drugs were excluded. Possible concomitant treatments for other diseases had to be kept as stable as possible during the six months of the study. The

short half-life anxiolitics were accepted only at doses already stabilized for 30 days, and they had to be recorded on the patients' case report forms.

Treatment Discontinuation and Adverse Effects

Investigators could discontinue the treatment at any time, and were asked to report this information on the patient's form, especially if the discontinuation was due to an adverse effect reported by the patient or detected by the investigator that could be related to the drug in study.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). The statistical analyses were performed by Medical Statistics Service (Castellanza, VA, Italy); for the analysis of continuous variables parametric tests were used, and nonparametric tests were used to assess the efficacy of the drug (Friedman test, χ^2 approximation).

RESULTS

Demographic Characteristics

A total of 2058 patients with diagnosis of ischemic attacks were recruited. Inclusion and exclusion criteria were not fulfilled by 14 patients, who were not considered in the statistical analysis for efficacy. The 14 patients were excluded on the grounds of age limits (2 patients), different diagnosis (2 patients), inappropriate dosage of the drug in study (1 patient), and for low scoring at the Mathew Scale (9 patients). Features of the 2044 remaining patients are reported in TABLE 2.

TABLE 2. Demographic Characteristics

Patients enrolled	2058	
Patients evaluated	2044	[a]
Gender:		
Males	1132	55.5%
Females	908	44.5%
Missing	4	
Mean age	70.3	±8.65
Patients aged 45–65	485	23.7%
Patients aged >65	1559	76.3%
Years of schooling:		
1–5	429	21.0%
5–8	965	47.2%
>8	397	19.4%
Missing	253	12.4%
Family history of cerebrovascular events	761	37.2%
Diagnosis: ischemic stroke	1152	56.4%
TIA	892	43.6%

[a] 14 drop out.

Males and females were equally represented, accounting for 55.5 and 44.5% respectively. The mean age was 70.3 years (485 patients, 23.7%, aged 45–65; 1559 patients, 76.3%, aged 66–85 years); nearly 50% of patients had 5–8 years schooling, and around 20% each had elementary or high school diplomas; 1152 patients (56.4%) suffered from an ischemic stroke, and 892 (43.9%) from transient ischemic attack (TIA).

Most of the patients enrolled had concomitant diseases, as shown in TABLE 3. In fact, 1781 patients (87.1%) had concurrent diseases, mainly related to the cardiovascular apparatus (72.4%) and metabolic disturbances (31.5%).

In parallel, concurrent therapies were recorded for 78.3% cases, and, likewise, drugs for the cardiovascular therapy were the majority (82.5%).

Efficacy

First Part of the Study (Days 1–28)

In order to assess the efficacy of α-GPC administered intramuscularly (im) during the 28 days of the first part of the study, which took place mainly in hospital, the Mathew Scale assessment was used; this scale scores 0 (clinical death) to 100

TABLE 3. Concomitant Diseases and Drugs

Patients with concomitant diseases	1721	87.1%
Patients without concomitant diseases	263	12.9%
Concomitant Disease:		
Cardiovascular	1290	72.4%
Metabolic/diabetes	561	31.5%
Concomitant drugs:		
Cardiac therapy	1470	82.5%
Antithrombotics	588	37.5%
Drugs for diabetes	308	19.5%

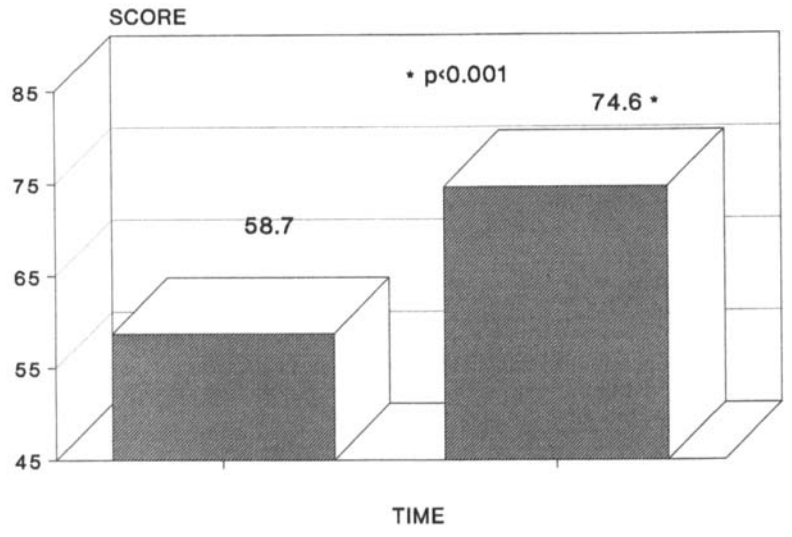
(patient with perfect consciousness).[16] A minimum score = 35 was chosen for enrollment, in order to have patients with a sufficient level of consciousness to cooperate in performing the psychometric tests.

FIGURE 1 and TABLE 4 show the trends and the mean values of the scoring to this scale at baseline and on the 28th day of treatment. The mean Mathew scale value increases from 58.7 to 74.6 corresponding to 15.9 points ($p < 0.001$).

In agreement with Gelmers,[17,18] the patients were furthermore divided into two classes: "more deteriorated" (score 35–65) and "less deteriorated" (score >65). A high percentage of patients improved their conditions at the end of the first phase of the trial, moving to the "less deteriorated" class. These changes were statistically significant ($p < 0.001$).

Second Part of the Study (Days 29–180)

In order to assess the efficacy of α-GPC during the second part of the study, in which 400 mg tid were administered orally to patients mainly discharged from hospital, the Crichton Rating Scale (CRS) and the Mini Mental State Test (MMST)



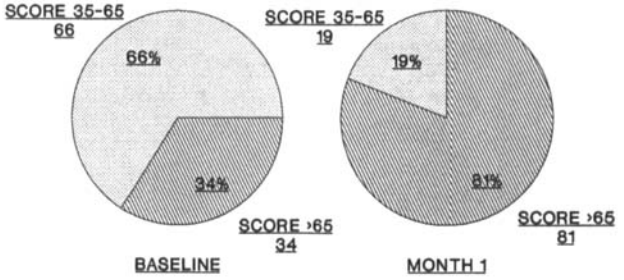


FIGURE 1. Top: Mean values of Mathew Scale in time. **Bottom:** Number and percentage in time of patients in the two classes of Mathew Scale score according to Gelmers.

TABLE 4. Mathew Scale (0–100) (First Part of the Study)

(m ± SD)	Basal (58.7 ± 12.7)	28th Day (74.6 ± 10.3)
		$p < 0.001$
Number of patients with		
score 35–65	1348 (66%)	370 (18.5%)
score > 65	696 (34%)	1635 (81.5%)

were administered to the patients on the day in which the therapy route of administration was changed (28th day) and on the 3rd and 6th month. The Crichton Geriatric Rating Scale[19] score 1–10 is considered "normal," the score 11–20 "mild deterioration," 21–30 "moderate deterioration," and >30 "severe deterioration."

TABLE 5 and FIGURE 2 show the trend of the mean score value for the patients treated: they achieved a significant decrease (improvement) of 4.3 points, from 20.2 to 15.9, between the 28th day and the final visit. The lower part of FIGURE 2 shows the number of patients with the score corresponding to "mild deterioration": their number grows with time, increasing from 72.7% at the 3rd month to the 83.7% at the final visit (6th month).

Cognitive functions were assessed by the Mini Mental State Test in which score 0–23 is commonly considered as "abnormal deterioration" and score >23 as "normal."[20] The mean score values increased in time, showing an improvement of 2.2 points at the 3rd month ($p < 0.001$) and above the score of normality, and a further 1.1 points at the 6th month, up to 24.3. The trend of the mean values is reported in TABLE 6 and in FIGURE 3.

Moreover, the lower part of FIGURE 3 shows the percentage of patients who recovered from an abnormal to a normal score: it increases in time, moving from 40% at the 28th day to 55.8% at the 3rd month and to 65% at the 6th month.

TABLE 5. Crichton Geriatric Rating Scale (Second Part of the Study)

(m ± SD)	28th Day (20.2 ± 7.2)	3rd Month (17.8 ± 6.05)	6th Month (15.9 ± 5.35)
		$p < 0.001$	$p < 0.001$
Number of patients with deterioration			
Mild (<20)	1205 (59.8%)	1405 (72.7%)	1588 (83.7%)
Moderate (21–30)	613 (30.4%)	450 (23.3%)	271 (14.3%)
Severe (>30)	197 (9.8%)	77 (4%)	38 (2%)

The degree of global deterioration was assessed with the Global Deterioration Score (GDS),[21] in which the value 0 means normality and 7 means severe deterioration. TABLE 7 and FIGURE 4 report the trend of the mean values of GDS. The mean values decreased from 2.72 at the beginning of the second phase to 2.16 at the end of the trial; the difference between the mean scores was statistically significant ($p < 0.01$).

At the end of both parts of the study, investigators were requested to report their subjective opinions about the overall clinical efficacy and tolerability of α-GPC. FIGURE 5 shows the different percentages of the investigators' opinion at the end of each one of the two parts of the study.

A "very good"/"good" efficacy was reported by 68.9% (first part) and 77.6% (second part) of the investigators; a "moderate" efficacy was reported by 24.8% (first part) and 17.5% (second part) of investigators, and a "poor"/"none" efficacy was reported by 6.3% (first part) and 4.9% (second part) of the investigators.

Tolerability

Of the 2044 patients considered for the study, 140 (6.8%) withdrew from the treatment: 101 during the first part and 38 during the second part. The reasons for

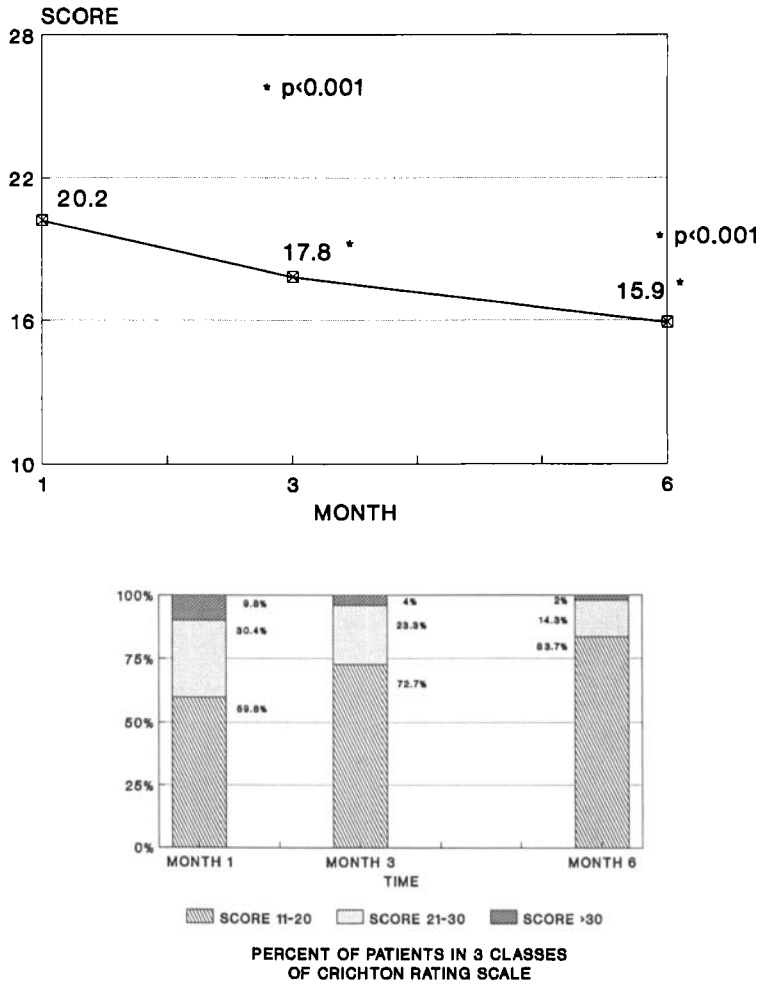
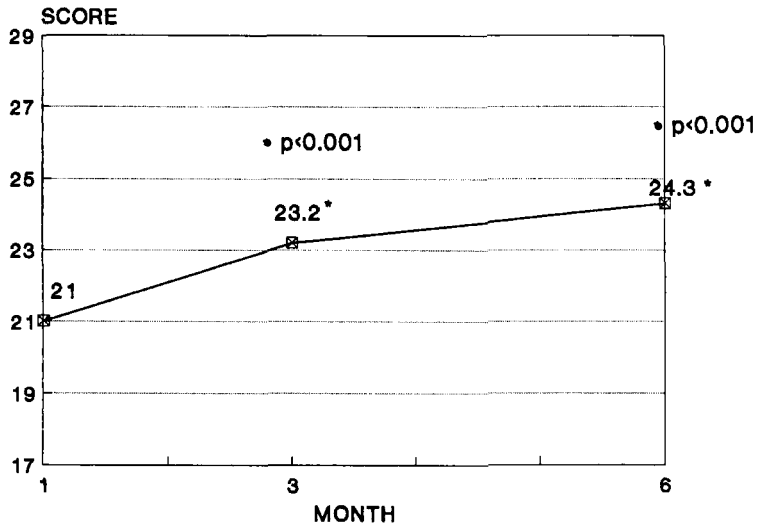


FIGURE 2. Top: Mean values of Crichton Geriatric Rating Scale in time. **Bottom:** Number and percentage in time of patients in the deterioration classes of Crichton Geriatric Rating Scale.

TABLE 6. Minimental State Test (Second Part of the Study)

(m ± SD)	28th Day (21.0 ± 6.1)	3rd Month (23.2 ± 5.4)	6th Month (24.3 ± 5.1)
		$p < 0.001$	$p < 0.001$
Number of patients with score			
0–23	1204 (60%)	851 (44.2%)	665 (35%)
> 23	803 (40%)	1074 (55.8%)	1234 (65%)



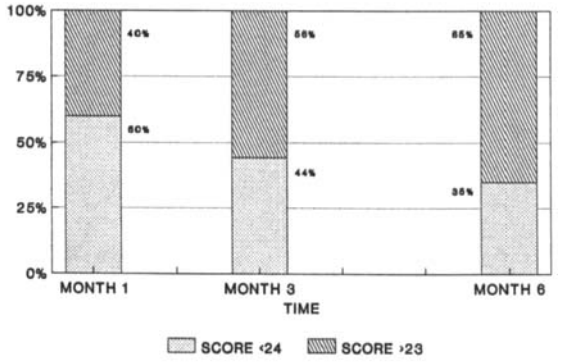


FIGURE 3. Top: Mean values of Mini Mental State Test in time. **Bottom:** Number and percentage in time of patients in the two deterioration classes of the Mini Mental State Test.

TABLE 7. Global Deterioration Scale (Second Part of the Study)

	28th Day	6th Month
m ± SD	2.72 ± 1.3	2.16 ± 1.1 $p < 0.01$

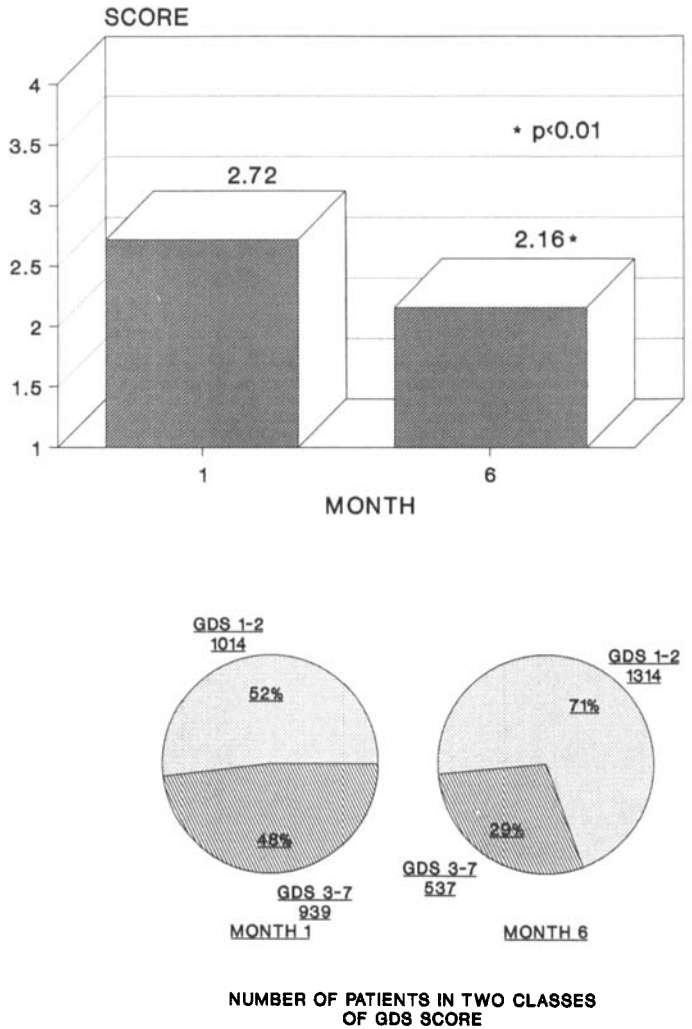


FIGURE 4. Top: Mean values of Global Deterioration Scale in time. **Bottom:** Number and percentage in time of patients in the classes of Global Deterioration Scale.

withdrawal are reported in TABLE 8; 41 patients died; the investigator related all the deaths to a worsening of the underlying pathology; none to the drug treatment.

Systemic tolerability was also controlled by monitoring arterial blood pressure, heart rate and blood analyses (full blood count and renal, liver functionality).

The patients were also observed for adverse events which were recorded at each control visit. TABLE 9 shows the mean values of blood pressure and heart rate: no changes occurred during all the treatment period.

No abnormal values were observed in the blood analyses as well as in the other monitoring records during the trial.

Unwanted Events

In total, 51 unwanted effects were reported by 44 out of the 2058 enrolled patients (2.14%). TABLE 10 lists all the unwanted effects complained of by the patients enrolled into the trial. Of the 2058 treated patients, 14 (0.68%) had to withdraw from the therapy with α-GPC for concomitant events: 10 in part I and 4 in part II. The reason for withdrawal were: 4 heartburn (3 in part I and 1 in part II), 2 nausea/vomit (in part I), 2 excitation/insomnia (in part I), 2 diarrhea (1 in part I, 1 in part II), 1 dizziness, 1 skin rash (in part II), 1 confusion, 1 repeated drop attacks (in part I). All the other events complained of did not result in a therapy withdrawal, and were of light or mild severity.

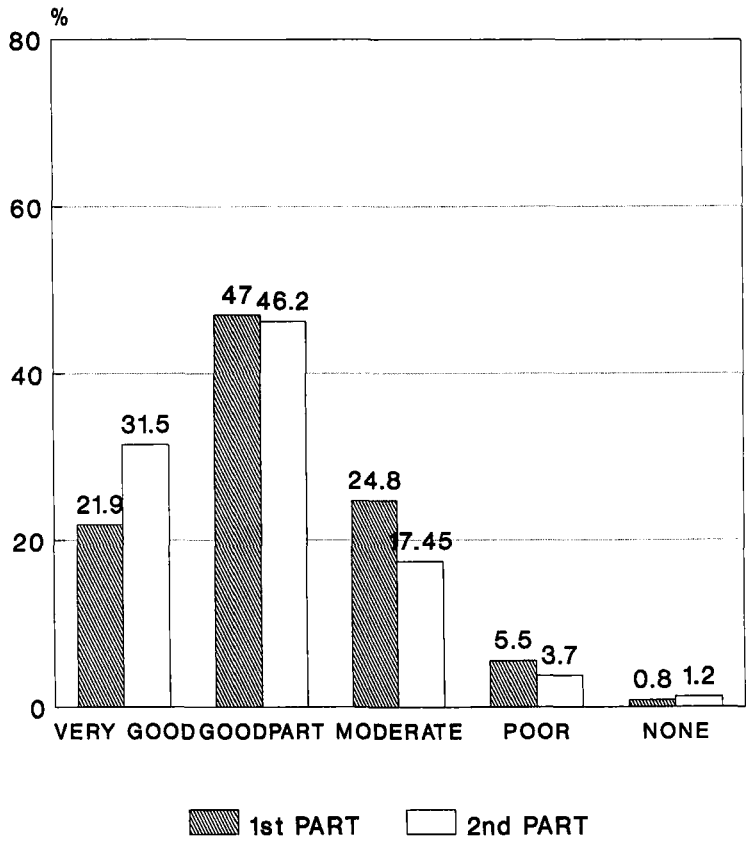


FIGURE 5. Overall clinical impression of efficacy reported by the investigators at the end of each of the two parts of the study.

TABLE 8. Discontinuation of the Trial

Reason	First Part	Second Part	Total
Drop out	52	21	73 (3.55%)
Exitus	30	11	41 (1.99%)
Unwanted events	10	4	14 (0.68%)
Improved	5	2	7 (0.34%)
Inefficacy	4	1	5 (0.24%)
	101	39	140 (6.8%)

The most frequent reported side effects were: heartburn (14), excitation-insomnia (9), nausea (8) and headache (4).

CONCLUSIONS

The present results collected from a large patient population diagnosed for acute ischemic cerebral attacks confirm the efficacy of α-GPC on the mental recovery after stroke.

At the end of the first part of the study, after 1 month of parenteral therapy with α-GPC, the results were very good both in tolerability and in efficacy: Mathew Scale reached a mean score equivalent to a less deteriorated neurological condition (> 65) and the tolerability was good: 34 events (1.66%) and 10 withdrawals (0.49%).

The improvement was maintained in time during the following 5 months of oral therapy, and a further improvement in cognitive functions (by the Minimental State Test), in behavioral functions (by the Crichton Geriatric Rating Scale), and in medical conditions related to cognitive decline (by the GDS) was statistically evaluable.

Tolerability was very good also in the second part: 17 events (0.33%) and 4 withdrawals (0.2%).

These data confirm in a large patient population the efficacy and the therapeutic role of α-GPC on the cognitive enhancement of patients with an acute cerebrovascular attacks (stroke and/or TIA): the very low incidence of adverse events confirms that α-GPC can be safely administered also for a long period after the occurrence of stroke.

TABLE 9. Arterial Blood Pressure and Heart Rate (Mean, Standard Deviation, Range)

	First Part		Second Part	
	Basal	28th Day	3rd Month	6th Month
Systolic (mean ± SD)	159 ± 23	149 ± 17	149.5 ± 15	149 ± 14.6
Range	100–240	100–200	100–200	100–205
Diastolic (mean ± SD)	90 ± 12	85 ± 9	85 ± 8	85 ± 8
Range	50–140	50–170	60–150	60–150
Heart rate (mean ± SD)	81.5 ± 12	78.5 ± 8.5	78.7 ± 8	78.6 ± 7
Range	45–152	50–120	45–165	56–110

TABLE 10. List of the 51 Adverse Events[a]

	Total	First Part	Second Part
Heartburn	14	10 (3)	4 (1)
Nausea-vomit	10	9 (2)	1
Excitation-insomnia	9	5 (2)	4
Headache	4	3	1
Diarrhea	3	2 (1)	1 (1)
Dizziness	2		2 (1)
Skin rash	2	1	1 (1)
Gastric bleeding	1		1
Increased γ-GT	1		1
Increased ALAT/ASAT	1		1
Confusion	1	1 (1)	
Anemia and low vit. B12	1	1	
Supraventricular arrhythmia	1	1	
Repeated drop attacks	1	1 (1)	

[a]The number in parenthesis indicates number of drop-out patients.

SUMMARY

The clinical efficacy and the tolerability of α-glycerophosphocholine (α-GPC), a drug able to provide high levels of choline for the nervous cells of the brain and to protect their cell walls, have been tested in a clinical open multicenter trial on 2044 patients suffering from recent stroke or transient ischemic attacks. α-GPC was administered after the attack at the daily dose of 1000 mg im for 28 days and orally at the dose of 400 mg tid during the following 5 months after the first phase.

The evaluation of the efficacy on the psychic recovery was done by the Mathew Scale (MS) during the period of im drug administration, and using the Mini Mental State Test (MMST), the Crichton Rating Scale (CRS), and the Global Deterioration Scale (GDS) during the following period of oral administration.

The MS mean increased 15.9 points in 28 days in a statistically significant way ($p < 0.001$) from 58.7 to 74.6. At the end of the 5 month oral administration, the CRS mean significantly decreased 4.3 points, from 20.2 to 15.9 ($p < 0.001$); the MMST mean significantly increased ($p < 0.001$) from 21 to 24.3 at the end of the trial, reaching the "normality" score at the 3rd month assessment. The GDS score at the end of the trial corresponded to "no cognitive decline" or "forgetfulness" in 71% of the patients. Adverse events were complained of by 44 patients (2.14%); in 14 (0.7%) the investigator preferred to discontinue therapy.

The most frequent complaints were heartburn (0.7%), nausea-vomit (0.5%), insomnia-excitation (0.4%), and headache (0.2%).

The trial confirms the therapeutic role of α-GPC on the cognitive recovery of patients with acute stroke or TIA, and the low percentage of adverse events confirms its excellent tolerability.

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APPENDIX

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Bonincontro C.	Ospedale Civile Vasto (CH)
Bosi L.	Arcispedale S. Anna Ferrara
Cafagna D.	Ospedale Cattinara Trieste
Calcara G.	Ospedale S. Marta e. S. Venera Acireale (CT)
Camardella G.	Ospedale Civile Rieti
Cassani P.	Ospedale S. Biagio Domodossola (NO)
Castiglione R.	Ospedale Villa Sofia Palermo
Cataliotti C.	Ospedale S. Giovanni Di Dio e Isidoro Giarre (CT)
Cella L.	Ospedale S. Francesco Barga (LU)
Cerini G.	Ospedale M. Sarcone Terlizzi (BA)
Cerri C.	Ospedale Trabattoni Ronzoni Seregno (MI)
Cesareo E.	Ospedale A. Tortora Pagani (SA)
Ciannella L.	Ospedale G. Rummo Benevento
Clivati A.	Ospedale Citta' Di Sesto S. Giovanni (MI)
Codeluppi P.	Ospedale Civile I. Caffi Poggiorusco (MN)
Conti A.	Ospedale San Luca Firenze
Cortesi P.P.	Ospedale Pierantoni Forli'
Curti A.	Ospedale S. Giovanni Decoll. Andosilla Civitacastellana (VT)
Cusumano V.	Ospedale Civile Vittorio Emanuele III Monselice (PD)
D'Agnolo B.	Ospedale Cattinara Trieste
D'Angelo D.	Ospedale Generale Provinciale Giulianova (TE)
D'Auria N.	Fond. Praxis S. Maria a Vico (CE)
D'Avanzo A.	Ospedale Civile Avellino
De Angelis A.	Fond. Praxis S. Maria a Vico (CE)
De Falco F.A.	Ospedale Loreto Mare (NA)
Del Papa M.	Ospedale Civile Civitanova Marche (MC)
Di Taranto A.	Ospedale F. Lastaria Lucera (FG)
Fabriani P. Favilla A.	Ospedale F. Lotti Pontedera (PI)
Fabrizi De Biani G.	Ospedale Serristori Figline Valdarno (FI)
Fabrizi G.	Ospedale P. Burresi Poggibonsi (SI)
Facchini G.	Ospedale Del Comprensorio Lugo (RA)

Faggi L. Aimone G.	Ospedale Maggiore Lodi
Ferrari E.	Ospedale S. Margherita Pavia
Ferrari L.	Ospedale Civile Umberto I Enna
Ferrini L.	Ospedale Della Misericordia Montegranaro (AP)
Finocchiaro S.	Presidio Ospedaliero Ferrarotto Alessi Catania
Fiorina L.	Ospedale Civile Castellamonte (TO)
Galanti F.	Ospedale San Giovanni Roma
Galbiati G. Galli G.C.	Ospedale Di Lecco (CO)
Galeone F.	Ospedale Della Val Di Nievole Pescia (PT)
Galvanini G.T.	Presidio Ospedaliero Di Villafranca e Verona (VR)
Galzio R.	Ospedali Ed Istituti Riuniti Teramo
Ganga A.	Universita' Degli Studi Sassari
Gelarda G.	Ospedale Civico e Benfratelli Palermo
Gentile M.	Policlinico Umberto I Roma
Giamundo A.	II Policlinico Napoli
Giorgetti C.	Ospedale S. Chiara Pisa
Gorgone G.	Ospedale M. Raimondi S. Cataldo (CL)
Guerrieri G.	Ospedale Maggiore Modica (RG)
Gugliucci N.	Ospedale Civile Oliveto Citra (SA)
Guideri R.	Ospedale S. Andrea Massa Marittima (SI)
Guizzardi G.	Casa Di Cura De Cesaris Spoltore (PE)
Guizzaro A.	I Policlinico Napoli
Gurioli L. Desiderato P.	Ospedale Civile Cuorgne' (TO)
Gusmaroli V.	Ospedale Agnelli Pinerolo (TO)
Jorini G.M. Bazzani M.	Ospedale Civile Asola (MN)
Italiano F.	Ospedale Martini Nuovo Torino
La Rosa G.	Ospedale Regina Margherita Messina
Lagana' G.	Ospedale Morelli Reggio Calabria
Lai M.	Casa Di Cura Tomasini Ierzu (NU)
Laperuta A.	Ospedale A.Tortora Pagani (SA)
Lavitola G.	Ospedale Dell'Annunziata Cosenza
Leo F.	Ospedale G. Panico Tricase (LE)
Lipizer A.	Stabilimento Ospedaliero Gorizia
Loni G.	Ospedali Riuniti Livorno
Losi F.	Casa Di Cura S. Antonino Piacenza
Maffei R.	Ospedale S. Maria Della Pieta' Nola (NA)
Maffini S.	Ospedale Civile Cortemaggiore Piacenza
Maggi S.	Ospedale Civile Modugno (BA)
Magoni M.	Universita' Degli Studi Brescia
Manca P.	Ospedale Civile Sondrio
Mancini M. Bompani R.	Ospedale G. Stuard Parma
Mandarini A.	Ospedale Cardarelli Napoli
Mansoldo G.	Centro Ospedaliero S. Chiara Trento
Marangolo M.	Ospedale G. Garibaldi Catania
Marano R.	Policlinico Bari
Marchesi D.	Ospedale Domus Salutis Brescia
Mariella F.	Ospedale Civile Martina Franca (TA)
Marinangeli B.	Casa Di Cura Stella Maris S. Benedetto D. Tronto (AP)
Mengoli M.	Ospedale Civile S. Sebastiano Correggio (RE)
Molinari E.	Policlinico San Matteo Pavia
Morbelli E.	Casa Di Cura Societa' Esercizio Cesano Boscone (MI)
Morino U	Ospedale Martini Nuovo Torino
Munari L.	Ospedale Civile Padova
Murgia B.	Ospedale S. Francesco Nuoro
Musco A.	Ospedale Basso Ragusa Militello In Val Di Catania (CT)
Napoli S.	Ospedali Riuniti Sanremo e Bussana Sanremo (IM)

Neviani V.	Casa Di Cura Hesperia Modena
Nevola C.	Ospedale Civile Avellino
Nicolino A.	Fondaz. Clinica Del Lavoro Campoli Del Monte Taburno (BN)
Orefice G.	II Policlinico Napoli
Pacifici P.	Ospedale Civile S. Maria Dei Laici Amelia (TR)
Pagano S.	Casa Di Cura Orestano Palermo
Pagliano F.	Ospedale Generale Carate Brianza (MI)
Palermo F.	Ospedali Riuniti G. Melacrino e F. Bianchi Reggio Calabria
Papuzzo M.	Clinica S. Marco Latina
Pascalis L.	Ospedale S. Giovanni Di Dio Cagliari
Pedace C.	Ospedale S. Foiano Arezzo
Petroni A.	Clinica Di Lorenzo Avezzano (AQ)
Pipicelli G.	Ospedale Civile Soverato (CZ)
Pisani L.	Pio Albergo Trivulzio Milano
Pittera A.	Ospedale SS. Salvatore Paterno' (CT)
Platania S. Tringale G.	Ospedale Civile E Muscatello Augusta (SR)
Polizzi C.	Ospedale S. Biagio Marsala (TP)
Pomante P.	Clinica S. Anna Pomezia (ROMA)
Ponseveroni A.	Ospedale Misericordia e Dolce Prato (FI)
Porcellati C.	Ospedale Civile R. Silvestrini Perugia
Pozzuoli L.	Ospedale Civile Caserta
Principe M.	Ospedale S. Camillo De Lellis Manfredonia (FG)
Princi R.	Ospedale Civile Locri (RC)
Pumilia G.	Ospedale Civico e Benfratelli Palermo
Puoti F. Cotrufo R.	I Policlinico Napoli
Raganato G.	Ospedale S. Giuseppe Da Copertino Copertino (LE)
Rampino A.	Casa Di Cura Citta' Di Udine
Rapex G.	Ospedale M. Montessori Chiaravalle (AN)
Rascio L.	Ospedale S. Camillo Roma
Rastelli G.	Ospedale Civile Fidenza (PR)
Renzi D. Artese D.	Ospedale SS. Trinita' Popoli (PE)
Ricca M.	Ospedale Di Camerata Firenze
Rizzo D.	Ospedale Cardarelli Napoli
Rocchi G.	Stabilimento Ospedaliero Sacile (PN)
Rodari T.	Ospedali Riuniti Verbania e Pallanza Verbania (NO)
Rollandi M.	Ospedale Civile S. Andrea La Spezia
Rossini P.M.	Ospedale Fatebenefratelli Roma
Salvi P.	Ospedale Quarenghi S. Pellegrino (BG)
Sarapo G.	Ospedale Civile Villa D'Agri (PZ)
Sardi A.	Ospedale Civile Chivasso (TO)
Sarno A.	Ospedale Villa Camaldoli Napoli
Scarda G. Neri A.	Ospedale S. Filippo Neri Roma
Schioppa M.	Ospedale Vecchio Pellegrini Napoli
Schisano G.	Ospedale Nuovo Pellegrini Napoli
Sechi F. Molinu M. Testoni M.	Ospedale Presidente A. Segni Ozieri (SS)
Sesti A.G.	Casa Di Cura Villa Kraus Firenze
Sgro G.	Ospedale Dell'Annunziata Sulmona (AQ)
Simone P.	Casa Sollievo Della Sofferenza S. Giovanni Rotondo (FG)
Solinas F.	Ospedale Presidente A. Segni Ozieri (SS)
Spedo A.	Ospedale Civile Migliorini e Balzan Badia Polesine (RO)
Stella L.	Ospedale Cardarelli Napoli
Tagliabue P. Balbis E.	Ospedale S. Andrea Vercelli
Tavormina F.	Ospedale S. Antonio Abate Trapani

Tessitore A.	Ospedale Cardarelli Napoli
Timpanaro S.	Presidio Ospedaliero Vittorio Emanuele II Catania
Trampetti P.	Ospedale Civile Montefalco (PG)
Travaglini A.	Ospedale Civile S. Maria Terni
Tridico N.	Ospedale Civile Rossano (CS)
Venco A. Serena G.	Ospedale Di Circolo Varese
Vicari E.	Ospedale V. Cervello Palermo
Viglierchio P.	Ospedale San Paolo Savona
Vigna L.	Ospedale G. Ferrari Castrovillari (CS)
Vivalda L.	Ospedale Martini Nuovo Torino
Voglini C.	Ospedale S. Ambrogio Mortara (PV)
Volpe D.	Ospedale S. Raffaele Arcangelo e Fatebenefratelli Venezia
Zanardi M. Morena M. Rossi M.	Ospedale Civile Ge-Sampierdarena
Zito F.	Ospedale SS. Annunziata Taranto