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SINGLE DOSE BIOAVAILABILITY AND PHARMACOKINETIC STUDY OF A INNOVATIVE FORMULATION OF α -LIPOIC ACID (ALA600) IN HEALTHY VOLUNTEERS

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E D I Z I O N I · M I N E R V A · M E D I C A

Single dose bioavailability and pharmacokinetic study of a innovative formulation of α -lipoic acid (ALA600) in healthy volunteers

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Aim. α -Lipoic acid is an important micronutrient with several pharmacological as well as antioxidant properties. The present study was aimed to examine the human bioavailability, pharmacokinetics (PK) and tolerability of an innovative oral formulation (ALA600) containing racemic α -lipoic acid 600 mg.

Methods. After a single 600-mg oral administration in healthy volunteers, blood samples were collected up to 8 hours post dosing, and plasma α -lipoic acid concentrations were determined by Liquid Chromatography-Mass Spectrometry (LC-MS) detection.

Results. The PK data revealed a short time to reach plasma peak concentrations (50.8 ± 4.2 min) with a C_{max} of 6.86 ± 1.29 $\mu\text{g/mL}$. The C_{max} implying that the new pharmaceutical form positively influences absorption and absorption time. The AUC value of 5.65 ± 0.79 $\mu\text{g/mL} \cdot \text{h}$ is the more reliable measure of new formulation bioavailability. The half-life and MRT values further show that new formulation is absorbed consistently and rapidly and is eliminated efficiently. These PK data appear

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to promote further refinement of present formulation. Should the authors compare the obtained data with the recent published data, the new formulation of α -lipoic acid tends to show an improvement of C_{max} value (2.5-5.4 times) and AUC (1.8 times).

Conclusion. ALA600 formulation is characterized by rapid absorption, high bioavailability, brief half-life and low toxicity. These PK parameters could significantly increase clinical use of lipoic acid with improvement of the therapeutic effects at the cellular level and might also prove to be the most suitable formulation for chronic administration such as peripheral neuropathies.

Key words: Lipoid acid - Pharmacokinetics - Biological availability - Healthy volunteers.

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Conflicts of interest.—Authors disclose any commercial associations that might pose a conflict of interest in connection with the submitted manuscript such as employment, consultancies, paid lecturing, financial involvement, patent ownership, etc.

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Alpha-lipoic acid (1,2-dithiolane-3-valeric acid) (ALA), also known as thioctic acid, was discovered in 1937. Unlike other vitamins, ALA exerts an antioxidant activity both in the reduced and oxidated forms. The reduced form of dihydrolipoic acid (6,8-dimercaptocaproic acid) can directly

regenerate ascorbate due to its low redox potential (-0.32 V), and is able to regenerate endogenous thiols involved in physiological redox antioxidant systems, such as cysteine and glutathione.

The redox couple α -lipoic/dihydrolipoic is covalently bound to a lysine residue, forming an essential lipoamide, which functions as a co-enzyme for the E₂ subunit of four multi-enzymatic mitochondrial complexes, for example pyruvate dehydrogenase.¹⁻⁶ After administration, ALA is reduced at the intracellular level by various enzymes and released into the extracellular environment as its principal metabolite, dihydrolipoic acid (DHLA).^{7, 8}

The racemic form of ALA is used as a nutraceutical, but in many countries it is a registered pharmaceutical product. A daily dose of 600 mg of lipoic acid for three months can significantly reduce the formation of lipid hydroperoxides, increasing cytosolic glutathione and levels of vitamins C and E, as well as preventing the toxicity associated with the loss of these vitamins.⁹ ALA directly neutralises the free radicals formed following the ionic action of transition metals (*e.g.*, iron and copper).¹⁰ Treatment with lipoic acid reduces oxidative stress in healthy subjects¹¹ and diabetic patients,¹² and induces the expression of cellular antioxidants and phase 2 enzymes including catalase, glutathione reductase, glutathione-S-transferase and nicotinamide adenine dinucleotide phosphate (NADPH).^{8, 13} An increasing amount of data demonstrate that ALA interacts specifically with the mechanisms of cytoprotective cellular signalling.¹⁴

Pharmacologically, ALA improves glycaemic control,¹⁵ alleviates complications of diabetes mellitus¹⁶⁻¹⁹, improves symptoms of peripheral neuropathy and effectively mitigates the toxicity of heavy metals.²⁰

The goal of the present study was to evaluate the human bioavailability, pharmacokinetics (PK) and tolerability of a new oral formulation containing α -lipoic acid (600 mg) in healthy volunteers after administration of one dose (1 tablet) of ALA600.

Materials and methods

Ethics

The trial protocol, informed consent form (ICF) and subject recruitment procedures were approved by the Independent Ethical Committee (IEC) Università di Camerino – Azienda ASUR Marche ZT-10 of Camerino. Before signing the ICF the volunteers were informed about the study in detail by a physician and given ample time to ask questions. Each ICF was signed by the informing physician and the volunteer. The study was conducted in accordance with the Declaration of Helsinki in its revised edition, the Guidelines of Good Clinical Practice (CPMP/ICH/135/95) and the Directives 2001/20/EC and 2005/28/EC and with international and local regulatory requirements.

Inclusion and exclusion criteria

No formal sample size calculation was performed. However, a sample size of 18 subjects was considered adequate to accurately assess the bioavailability and the PK of the investigational drug.

Healthy volunteers, aged between 18 and 55 years; body mass index (BMI) between 20 to 30 kg/m²; normal findings in the physical examination and vital signs: blood pressure (BP) between 100-140/45-90 mmHg, heart rate (HR) between 40-99 beats/minute, both measured after three minutes sitting, and temperature between 35.8 °C and 37.5 °C; normal laboratory values, unless the investigator did not consider abnormalities to be clinically significant; negative test for hepatitis Bs-antigen, hepatitis C antibodies and HIV I and II antibodies; written ICF.

Presence of cardiac, pulmonary, gastrointestinal, endocrine, musculoskeletal, neurological, haematological, hepatic or renal disease, unless deemed not clinically significant by the investigator; presence of any significant physical or organ abnormality; history or evidence of psychiatric or psychological disease (including depression) unless deemed not clinically significant by

the investigator; any clinically significant illness during the four weeks before this study; pregnancy, lactation; smoking; history of alcohol or drug abuse; known history of hypersensitivity to α -lipoic acid or to other sulphur molecules; use of any prescription medication in the 14 days preceding this study; use of over-the-counter (OTC), homeopathic or herbal medicines in the 14 days preceding this study; use of preparations containing α -lipoic acid in the 30 days preceding this study; participation in a clinical trial with an investigational drug in the 6 months preceding this study; blood donation in the month preceding this study; participation as a plasma donor in a plasmapheresis programme in the 7 days preceding this study; subjects who are unable or unwilling to adhere to the protocol procedures; withdrawal of ICF.

Two populations were considered: the "Per Protocol" population defined as all subjects who took investigational product and provided blood samples at all time points; this population was used to calculate the PK endpoints; and the "safety population" defined as all subjects who took the investigational product and provided at least one post-treatment safety assessment. Statistical analyses were performed using the commercially available computer programme Origin (version 7.0). All data are presented as mean \pm standard error (SE). Descriptive statistics were used for the concentration-time data for α -lipoic acid.

Treatments

The ALA600, kindly provided by Alfa Wassermann (Bologna, Italy), is a new oral formulation of α -lipoic acid (600 mg) and vitamins of the B complex (B₁ 2.1 mg, B₂ 2.4 mg, B₃ 9 mg and B₆ 3 mg). This patented oral formulation (EP 1401405 B1 Giellesi) was developed to improve the bioavailability of active ingredients added to the amphiphilic matrix, which are poorly absorbed *via* the oral route due to high variability of absorption in the gastrointestinal tract. This technology, which was originally used to deliver drug substances, has been applied

in other fields, such as alimentary supply to obtain prompt-release and fast-absorption, and to enhance the bioavailability of lipoic acid.

Subjects were administered a single dose of 600 mg of α -lipoic acid (ALA600) in the fasted state with 150 mL of water in the presence of the Research Physician.

Pharmacokinetic assessment

Blood samples were taken at the following times: pre-dose (5 min before drug dosing); 5, 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6 and 8 hours post-dose. Blood samples were collected in plain plastic heparinised containers and centrifuged within 20 minutes at 2,000 rpm for 15 minutes. The plasma was divided into three aliquots of 1 mL. Plasma was shock frozen at -20 °C within one hour from blood withdrawal and stored at -80 °C until analysis. Concentrations of α -lipoic acid were determined by LC/MS/MS (Liquid Chromatography Mass Spectrometry), and the following PK parameters of α -lipoic acid were calculated: C_{max} (maximum plasma concentration), T_{max} (time of maximum plasma concentration), t_{1/2} (terminal half-life), AUC_t (Area Under the plasma concentration-time Curve from time zero to time t, where t is the last measurable (non-zero) concentration using the trapezoidal rule), AUC_{inf} (Area Under the plasma concentration-time Curve from time of dosing extrapolated to infinity using the trapezoidal rule), AUMC (Area Under the first Moment of the Curve), MRT (Mean Residence Time).

The actual sampling points were used with the computer programme Microsoft Office 2003 and OriginPro 7.0 (OriginLab). AUCs were computed using the Log Linear Method, trapezoidal when C_n>C_{n-1}.

The sponsor implemented and maintained quality assurance and quality control systems with written Standard Operating Procedures (SOP) in accordance with the Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95). Quality assurance was guaranteed by regular monitoring of the study by a qualified monitor.

TABLE I.—Demographic data and baseline characteristics. Results are reported as frequency and mean \pm standard deviation (min-max range between brackets) as appropriate.

Gender	10 males (50%)	10 females (50%)
Age (years)	38 \pm 6 (30-47)	32 \pm 9 (23-54)
Height (cm)	181 \pm 5 (174-188)	167 \pm 8 (155-180)
Body weight (kg)	81 \pm 13 (66-105)	57 \pm 6 (49-65)
Body Mass Index	24.8 \pm 2.7 (21.3-29.7)	20.5 \pm 2 (17.4-23.2)
Systolic blood pressure (mmHg)	123.8 \pm 7.7 (110-140)	111.2 \pm 5.7 (95-125)
Diastolic blood pressure (mmHg)	73 \pm 3.9 (60-80)	69.8 \pm 1.3 (60-80)
Heart rate (bpm)	75 \pm 8.8 (55-90)	71 \pm 4.4 (60-80)
Temperature ($^{\circ}$ C)	36.1 \pm 0.3 (35.5-36.9)	36.4 \pm 0.5 (35.5-37.0)

α -lipoic acid assay

The operating procedures were carried out according to International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline (Current Step 4 version. Complementary guideline on methodology dated 6 November 1996 incorporated in November 2005).

ALA plasma levels were determined by high-performance liquid chromatography (HPLC) (Agilent 1200 SL) equipped with triple quadrupole mass detector (Agilent 6410) and column Acquity UPLC BEH C18, 50 mm \times 2.1 mm \times 1.7 μ m.

The mobile phase was made up of 5 mM of ammonium acetate solution for LC/MS (0.3854 g/L) in water. The stock solutions of lipoic acid (SSLA, Sigma 117K0679) and internal standard (IS) were prepared in methanol. The internal reference was cyclohexanobutyric acid (Aldrich, 00105LA). Calibration curves were prepared for both solutions by spiking each plasma blank samples with proper volume of the standard solutions to obtain the calibration curve points of ALA. The standard calibra-

tion curves for ALA were constructed using the analyte/IS peak area ratios versus the nominal concentrations of the analytes. Chromatographic separations were carried out using acetonitrile as mobile phase and acetic acid 0.1% (pH 4.0 adjusted with ammonia solution) (65:35, v/v); the flow rate was 0.2 mL/min. The analytical column was kept at 30 $^{\circ}$ C and the effluent was connected to an electrospray ionization MS interface without splitting. Electrospray ionization was performed using nitrogen at 10 L/min flow rate, 40 psi nebulizing pressure, and 350 $^{\circ}$ C drying gas temperature. Capillary voltage was set at 3000 V. Fragment voltage was applied between the capillary outlet and the first skimmer-produced fragment ions by in-source collision-induced dissociation by nitrogen. 70 V optimum fragment voltage was selected (varying 50-150 V). The Limit of Determination (LoD) was 5 μ g/mL; the lower limit of quantitation (LLOQ) was 20 μ g/mL; the limit used for data certification was 50 μ g/mL.

Safety assessment

Safety was assessed at screening (Visit 1) and at the end-of-study (Visit 3) by vital signs, a physical examination (general appearance, skin, eyes, ENT, chest/lungs, heart/cardiovascular, muscular-skeletal system, abdomen, kidney, lymph nodes, nervous system, genitourinary and endocrine system) and routine laboratory tests: haematology - erythrocytation rate (ESR), red blood cell count (RBC), white blood cells total and differential count (WBC), haemoglobin, haematocrit, platelet count, prothrombin time; clinical chemistry - plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (α -GT), lactate dehydrogenase (LDH), alkaline phosphatase (AP), glucose, creatinine, total serum proteins, sodium and potassium; and urinalysis - specific weight, pH, glucose, ketones, haemoglobin, protein, bilirubin, urobilinogen and nitrites. At screening (Visit 1) only: hepatitis B antigen (HBsAg), hepatitis C antibody (HCV-Ab), human immunodeficiency virus 1 and 2 antibodies (HIV 1 and 2-Ab) and a pre-

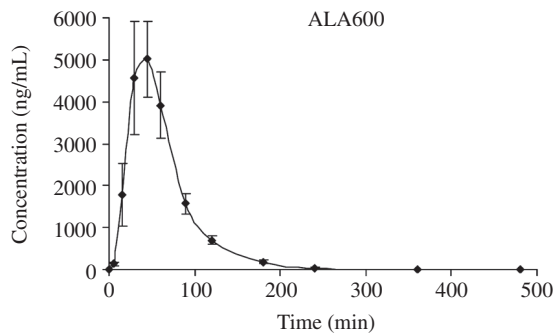


Figure 1.—Concentration/time curves of the new formulation of α -lipoic acid. Values are the mean \pm standard error.

gnancy test for females. Adverse events were monitored throughout the entire study.

Results

Demographic and other baseline characteristics

A total of 20 healthy volunteers (10 males and 10 females) were enrolled; 18 subjects completed the study (9 males and 9 females), one subject withdrew consent and one subject was lost to follow up. The age of the volunteers ranged from 23 to 54 years (mean

35), with a mean for males of 38 years (range 30-47) and of 32 years for females (range 23-54). Baseline data from all subjects enrolled in this study are summarised in Table I.

PK analysis

The α -lipoic acid concentration data were collected and the PK parameters calculated assuming the value 0 for the data below the LoD (50 ng/mL). The mean concentration of ALA600 in 18 healthy volunteers was calculated for each sampling point and the concentration curve was created (Figure 1). C_{max} was 6.86 ± 1.29 $\mu\text{g/mL}$; T_{max} was 50.8 ± 4.2 min; AUC_t was 5.65 ± 0.79 $\mu\text{g/mL}\cdot\text{h}$; the PK parameter AUC_{inf} was 5.94 ± 0.77 $\mu\text{g/mL}\cdot\text{h}$; AUMC was $21,922,429.1 \pm 8,731,254.13$ $\mu\text{g/mL}\cdot\text{h}$; MRT was 72.6 ± 25.81 min; while half-life was 39.4 ± 6.1 h (Table II).

Safety evaluation

All subjects had normal findings at screening for vital signs, physical examination and laboratory tests. There were no clinically relevant changes in any of these parameters in any subject during the study (Table III). No adverse events were experienced by any the volunteers during the study. No

TABLE II.—PK parameters of the new formulation of α -lipoic acid (ALA600) given at the single oral dose of 600 mg. Results are reported as mean \pm standard deviation.

C_{max} ($\mu\text{g/mL}$)	T_{max} (min)	AUC_t ($\mu\text{g/mL}\cdot\text{h}$)	AUC_{inf} ($\mu\text{g/mL}\cdot\text{h}$)	Half-life (min)	MRT (min)
6.86 ± 1.29	50.8 ± 4.2	5.65 ± 0.79	5.94 ± 0.77	39.4 ± 6.1	72.6 ± 25.81

TABLE III.—Vital signs. Results are reported as frequency and mean \pm standard deviation (min-max range between brackets) as appropriate.

Parameter	Mean
Systolic Pressure (mmHg; normal: <130)	Screening 117.1 ± 11.5 (95-140)
	End of study 116.9 ± 8.9 (100-140)
Diastolic Pressure (mmHg; normal: <85)	Screening 70.8 ± 4.5 (60-80)
	End of study 72.5 ± 3.5 (70-80)
Heart rate (bpm; normal: 60-100)	Screening 70.7 ± 7.5 (55-80)
	End of study 73.3 ± 7.3 (53-80)
Temperature ($^{\circ}\text{C}$; normal: ≤ 37)	Screening 36.1 ± 0.5 (35.5-37.0)
	End of study 36.2 ± 0.5 (35.6-36.9)

TABLE IV.—PK parameters of different formulations of α -lipoic acid 600 mg. *The values expressed in original paper were $\mu\text{g/g}$. Assuming that the plasma specific weight is average considered as 1.025 g, the values of C_{max} and AUC_t reported in this table were increased by 2.5%.

References	C_{max} ($\mu\text{g/mL}$)	T_{max} (min)	AUC_t ($\mu\text{g/mL}\cdot\text{h}$)
High release lipoic acid 600 mg (drug) ^{29*}	1.27 \pm 0.2	88.1 \pm 33.6	3.27 \pm 0.37
High release lipoic acid 600 mg ^{29*}	2.29 \pm 0.3	64.3 \pm 10.2	2.93 \pm 0.45
Quick release lipoic acid 600 mg ^{29*}	2.26 \pm 0.4	34.3 \pm 4.3	3.14 \pm 0.33
Retard Lipoic acid 3 \times 200 mg ^{29*}	1.40 \pm 0.1	180	3.19 \pm 0.15
Lipoic acid N. 600 mg ²⁷	1.22 \pm 0.6	120	3.56 \pm 1.4

subject left the study due to adverse events or the investigator's decision.

Discussion

The correlation between PK parameters and therapeutic efficacy makes it possible to acquire important information which is useful for designing preclinical and clinical studies. The PK data revealed a short T_{max} (50.8 \pm 4.2 min) following administration of a single tablet of new formulation of racemic α -lipoic acid. The corresponding mean C_{max} was 6.86 \pm 1.29 $\mu\text{g/mL}$. The good C_{max} implying that pharmaceutical form affect in a positive manner the absorption and absorption time. Some authors reported that the rate of absorption of lipoic acid is not substantially influenced by the time of gastric emptying, as demonstrated in studies in insulin-dependent diabetics, in which no important influence on ALA bioavailability was observed.²¹ In addition, the data obtained in this study (C_{max} 6.86 $\mu\text{g/mL}$) are consistent with those reported by authors who found that the maximum plasma concentration (7.04 $\mu\text{g/mL}$) of bisnorlipoic acid, a product derived from the α -oxidation of lipoic acid, was observed 189 minutes after oral administration of 1 g of R-lipoic acid in male volunteers.²²

The AUC value of new formulation (5.65 \pm 0.79 $\mu\text{g/mL}\cdot\text{h}$) is the most reliable measure of its bioavailability since is directly related to the total amount of non modified drug which achieve the systemic circulation. The blood samples collection marked in this study allowed a careful as-

say and a complete observation of the drug elimination. Some studies report that the average plasma concentrations at which lipoic acid therapeutic effects begin to be seen correspond to C_{max} and AUC values equivalent to 4-5 $\mu\text{g/mL}$ and 2.85 $\mu\text{g/mL}\cdot\text{h}$, respectively.²³⁻²⁶ Nevertheless, a clear relationship between bioavailability and the antioxidative pharmacological effects has not yet been established.

The dose independent half-life and MRT values, correlated to the general conditions of the organs and systems, further show that new formulation is absorbed consistently and rapidly and is eliminated efficiently.

The PK parameters evaluated in similar published studies, conducted on various formulations of lipoic acid are presented in Table IV. Taking differences between studies into account, but considering that all studies were performed in healthy volunteers and that the study methods and doses used were essentially similar, the PK data obtained with new formulation appear to be a progress for clinical use. Should the authors compare the present data with the literature data,²⁷⁻²⁹ the new formulation show a significant improvement of C_{max} (2.5-5.4 times) and AUC (1.8 times) values.

The PK characteristics of a compound can significantly limit its clinical use if pharmacologically active concentrations are not reached and/or are not maintained for the time necessary to evoke therapeutic effects. Since it is not possible to correlate the PK and pharmacodynamics of ALA,²⁵ the therapeutic effects depend preponderantly on the C_{max} and AUC values rather than on the values of time to reach maximum concen-

tration (T_{max}), elimination half-life ($t_{1/2}$) or MRT. This opinion is supported by PK studies conducted in patients with multiple sclerosis, which demonstrated that therapeutic response is positively correlated to the C_{max} value.^{4, 30-32}

The antioxidant capacity of ALA depends fundamentally on the induction of regeneration of glutathione at the cellular level. The increase of glutathione after ALA administration is probably due to an adaptive cellular response induced by improved employment of the cysteine accumulated in the cell.³¹ It has recently been reported that the cellular kinetics of ALA are proportional to the plasma kinetics of the compound.²⁹

Considering the time needed to regenerate cellular glutathione after administration of ALA, ALA600 could prove to be a formulation able to reach its target quickly at active concentrations and could serve as an excellent point of departure for pursuing further interesting pharmacological and therapeutical development.

Riassunto

Studio su farmacocinetica e biodisponibilità di una dose singola di un'innovativa formulazione dell'acido alfa lipoico (ALA600) in volontari sani

Obiettivo. L'acido alfa lipoico è un importante micronutriente con numerose proprietà farmacologiche e antiossidanti. Il presente studio ha esaminato la biodisponibilità nell'uomo, la farmacocinetica e la tollerabilità di un'innovativa formulazione orale (ALA600) contenente 600 mg di acido alfa-lipoico racemico.

Metodi. A seguito di una singola somministrazione orale da 600 mg in volontari sani, sono stati raccolti campioni ematici fino a 8 ore dopo il dosaggio e sono state determinate le concentrazioni plasmatiche di acido alfa-lipoico tramite rilevazione con cromatografia liquida-spettrometria di massa (LC-MS).

Risultati. I dati farmacocinetici hanno rivelato un breve tempo di raggiungimento delle concentrazioni di picco nel plasma ($50,8 \pm 4,2$ min) con un C_{max} di $6,86 \pm 1,29$ $\mu\text{g/mL}$. Il C_{max} implica che la nuova forma farmaceutica influenza positivamente l'assorbimento e il tempo di assorbimento. Il valore di AUC di $5,65 \pm 0,79$ $\mu\text{g/mL}\cdot\text{h}$ è la misura più affidabile della biodisponibilità della nuova formulazione. L'emivita e i valori del tempo medio di permanenza in circolo (MRT) dimostrano ulteriormente che la nuova formulazione è assorbita in maniera co-

stante e rapida ed è eliminata in maniera efficiente. Questi dati farmacocinetici sembrano promuovere ulteriormente il perfezionamento della presente formulazione. Se gli autori dovessero confrontare i dati ottenuti con dati pubblicati di recente, la nuova formulazione di acido alfa-lipoico tende a mostrare un miglioramento del valore di C_{max} (2,5-5,4 volte) e di AUC (1,8 volte).

Conclusione. La formulazione ALA600 è caratterizzata da rapido assorbimento, elevata biodisponibilità, breve emivita e bassa tossicità. Tali parametri farmacocinetici possono aumentare in maniera significativa l'utilizzo clinico dell'acido lipoico con un miglioramento degli effetti terapeutici a livello cellulare e potrebbero anche dimostrare di essere la formulazione più adatta per la somministrazione cronica come nelle neuropatie periferiche.

Parole chiave: Acido lipoico - Farmacocinetica - Biodisponibilità - Volontari sani.

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