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Impact of chisan® (ADAPT-232) on the quality-of-life and its efficacy as an adjuvant in the treatment of acute non-specific pneumonia

M. Narimanian[a], M. Badalyan[a], V. Panosyan[a], E. Gabrielyan[b], A. Panossian[b,*], G. Wikman[c], H. Wagner[d]

[a]*Department of Family Medicine, Yerevan State Medical University, Yerevan, Armenia*
[b]*Armenian Drug and Medical Technology Agency, Yerevan, Armenia*
[c]*Swedish Herbal Institute, Viktor Rydbergsgatan 10, SE-411 32, Gothenburg, Sweden*
[d]*Centre of Pharma-Research, Pharmaceutical Biology, Butenandtstr. 5-13, University of Munich, D-81377 Munich, Germany*

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Abstract

A double-blind, placebo-controlled, randomised (simple randomisation), pilot (phase III) study of Chisan® (ADAPT-232; a standardised fixed combination of extracts of *Rhodiola rosea* L., *Schisandra chinensis* Turcz. Baill., and *Eleutherococcus senticosus* Maxim) was carried out on two parallel groups of patients suffering from acute non-specific pneumonia. Sixty patients (males and females; 18–65 years old) received a standard treatment with cephazoline, bromhexine, and theophylline: in addition, one group of 30 patients was given Chisan mixture, whilst the second group of 30 patients received a placebo, each medication being taken twice daily from the beginning of the study for 10–15 days. The primary outcome measurements were the duration of antibiotic therapy associated with the clinical manifestations of the acute phase of the disease, together with an evaluation of mental performance in a psychometric test and the self-evaluation of quality-of-life (QOL) (WHOQOL-Bref questionnaires) before treatment and on the first and fifth days after clinical convalescence. The mean duration of treatment with antibiotics required to bring about recovery from the acute phase of the disease was 2 days shorter in patients treated with Chisan compared with those in the placebo group. With respect to all QOL domains (physical, psychological, social and ecological), patients in the Chisan group scored higher at the beginning of the rehabilitation period, and significantly higher on the fifth day after clinical convalescence, than patients in the control group. Clearly, adjuvant therapy with ADAPT-232 has a positive effect on the recovery of patients by decreasing the duration of the acute phase of the illness, by increasing mental performance of patients in the rehabilitation period, and by improving their QOL. Both the clinical and laboratory results of the present study suggest that Chisan (ADAPT-232) can be recommended in the standard treatment of patients with acute non-specific pneumonia as an adjuvant to increase the QOL and to expedite the recovery of patients.

Keywords: Adaptogens; *Eleutherococcus senticosus*; *Rhodiola rosea*; *Schisandra chinensis*; Chisan®; ADAPT 232; Mental performance; Quality-of-life; Placebo-controlled parallel-group clinical trials

*Corresponding author.
E-mail address: ap@shi.se (A. Panossian).

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Introduction

Our comprehension of the profound importance and significance of "quality-of-life" (QOL) began to develop only during the last 25 years. According to the WHO (World Health Organization, 1993; Cramer and Spilker, 1998) QOL may be defined in general terms as an individual's perception of their position in life within the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns. A good healthcare-related definition was given by Schipper (1990) who stated that "QOL represents the functional effect of illness and its consequent therapy upon a patient as perceived by the patient. Four broad domains contribute to the overall effect: physical and occupational function; psychological state; social interaction; and somatic sensation". In the last decade or so, consideration of the influence of a therapy, with respect to its clinical efficacy and safety, on the QOL has started to receive increased attention.

It has been proposed (Panossian, 2004) that the group of herbal medicines known as adaptogens could be used as a remedy for improving the QOL in any population of patients or healthy subjects. Members of this group of medications are innocuous agents which non-specifically increase the resistance of an individual against physical, chemical or biological factors ("stressors") by normalising their effect independent of the nature of pathologic state (Brekhman and Dardymov, 1968). The adaptogens are, in fact, natural bio-regulators which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et al., 1999; Panossian, 2004). Currently, only three plant species (*Eleutherococcus senticosus*, *Schisandra chinensis* and *Rhodiola rosea*) are recognised to meet the strict criteria required to be considered adaptogens. A number of studies have demonstrated the efficacy of these adaptogens in stress-induced disorders of the central nervous, cardiovascular and immune systems, and they have been used as adjuvants to other medicines in enhancing curative effect in, e.g., chronic pneumonia, chronic tuberculosis, vascular dystonia, and cancer (reduction of metastasis), and in reducing the debilitating effects of radiotherapy and chemotherapy (Panossian, 2004). It is anticipated, therefore, that adaptogens may have a direct impact on most facets of physical health and psychological state and, moreover, may indirectly improve aspects of social and environmental domains.

The aim of the present double-blind, parallel-group, randomised (simple randomisation), pilot study was to evaluate the efficacy as an adjuvant therapy of the adaptogen Chisan® (ADAPT-232; a standardised fixed combination of extracts of *R. rosea*, L., *S. chinensis* Turcz. Baill., and *E. senticosus* Maxim) as measured in terms of improvement of the QOL and recovery period of patients suffering from acute non-specific pneumonia and receiving a standard treatment.

Materials and methods

Study design

This was a double-blind, placebo-controlled, randomised (simple randomisation), pilot (phase III) study of 60 patients carried out at the Department of Family Medicine at the Armenian State Medical Institute between April and December 2003. The protocols of the study were reviewed and approved by the Ethics Committee of the Armenian Drug and Medical Technology Agency of the Ministry of Health of the Republic of Armenia. Study subjects were randomised according to the order of first contact with a doctor on day 0. The identification number of each patient and the drug code number (randomly encoded in a drug-list) were both recorded in a protocol and in the patient's journal to allow subsequent identification. Information concerning the placebo and the verum became known to the investigators and volunteers only after completion of the study and final statistical analysis of the results.

Study drugs

The test medication was manufactured in liquid form according to Good Manufacturing Practice (GMP) by the Swedish Herbal Institute (Gothenburg, Sweden). Chisan mixture (batch 2384) was a fixed combination of extracts from roots of *R. rosea* L. (Golden Root; 27.6%), from berries of *S. chinensis* Turcz. Baill. (Schisandra; 51.0%), and from roots of *E. senticosus* Maxim (Siberian ginseng; 24.4%) that had been standardised to contain salidroside (0.068 mg/ml), rosavin, (0.141 mg/ml), shisandrin (0.177 mg/ml), γ-shisandrin (0.105 mg/ml), and eleutherosides B and E (0.011 and 0.027 mg/ml). The placebo, and the liquid matrix for the verum, contained syrup, sorbitol, caramel aroma, methyl parahydroxybenzoate, orange oil, polysorbate, propyl parahydroxybenzoate and water. The medications were provided in dark glass bottles with a cap, sealing ring and a measuring dosage cup (graduated 5, 10, 15 and 20 ml) and were labelled "Chisan/Placebo A" (for the verum) or "Chisan/Placebo B" (for the placebo) followed by "120 ml, code number (sequential from 1 to 30), shake before use". The appearance, the organoleptic characteristics and the packaging of the placebo and the verum were similar such that they could not be distinguished one from another.

All patients received a standard treatment with an antibiotic (injections each of 1 g of sterile cephazoline

sodium salt; Help Ltd., Greece), an antitussive agent (bromhexine coated tablets each containing 8 mg of bromhexine hydrochloride and inactive excipients; Berlin-Chemie Ltd., Germany), and a broncholytic medication (Teotard capsules (300 mg) each containing 200 mg of theophylline propionate and inactive excipients; KRKA Ltd., Slovenia).

All drugs employed were stored separately at room temperature in a secure location so as to prevent their use for purposes other than the described study.

Patients

Patients of either gender diagnosed as suffering from acute non-specific pneumonia were selected to take part in the trial to investigate the impact of adjuvant therapy with Chisan mixture on the improvement of the QOL and on the recovery period offered by a standard treatment. For the purposes of diagnosis, prior to consideration for inclusion in the study, volunteers underwent the following examinations and analyses: physical examination by a physician (compilation of anamnesis, detailed chest auscultation and percussion, thermometry), chest X-ray, and general blood and urine analysis. An investigator completed a baseline questionnaire for each patient in order to obtain details concerning age, smoking habits and history of illness, and a physician assisted with the completion of a WHOQOL-Bref questionnaire (World Health Organization, 1993, 1996).

The criteria for patient inclusion were: males or females between 18 and 65 years diagnosed as suffering from acute non-specific pneumonia. The criteria for exclusion were: patients with allergic reactions to herbal products or to bitterness, patients with contraindications and hypersensitivity to cephazoline, bromhexine or Teotard, patients who had become tolerant to the antibiotic cephazoline, pregnant patients or those attempting to become pregnant, breast-feeding mothers, patients with unstable psychological conditions, patients of deficient or excessive weight (i.e. outside the range 40–100 kg), patients with other organic disorders/diseases, patients receiving therapy (other than the medications under study), persons known to have problems with abuse of medications, narcotics or alcohol, persons with heavy smoking habits (>20 cigarettes per day).

Following selection for inclusion in the trial, written informed consent was obtained from each patient in accordance with the revised declaration of Helsinki (World Medical Association Declaration of Helsinki, 2000).

Methods

Selected patients were assigned to two groups using a simple randomisation procedure. Group A received Chisan mixture as an adjuvant to a standard treatment with cephazoline–bromhexine–Teotard, whilst the placebo group (group B; negative control group) received placebo plus a standard treatment with cephazoline–bromhexine–Teotard. Patients in both groups were provided with four or five bottles of Chisan/Placebo A or B containing 120 ml of liquid, 20 ml of which was to be taken twice a day for 10–15 days as required. Each bottle was given a sequential number with the code concealed from the investigator: the sequential numbers were matched with the order of arrival of the patients. Patient identification numbers were noted in a protocol and on the bottles in order to allow subsequent identification after completion of the study. The identity of the medication received by an individual became known to the investigators only after completion of the study and after the statistical analyses had been performed.

After being grouped, the patients were given a psychometric test, completed a WHOQOL-Bref questionnaire with the help of a physician, and commenced the double-blind treatment. During the acute phase of the disease only, each patient received, in addition to Chisan/Placebo, a standard anti-pneumonia treatment consisting of cephazoline sodium (1 g twice a day; intramuscular injection), bromhexine hydrochloride (8 mg three times a day; orally), and theophylline propionate (200 mg twice a day; orally). On the day of recovery from the acute phase of the disease (as determined by the absence of febrility for 2 days, absence of symptoms of auscultation and a control chest X-ray) patients individually completed a WHOQOL-Bref questionnaire with the help of a physician and were given a psychometric test. During the following rehabilitation period, patients received either Chisan mixture or placebo (as described above), and at the end of this time a further questionnaire was completed and a psychometric test applied. The efficacy of the treatment was evaluated with respect to the duration of the antibiotic therapy associated with clinical manifestations of the acute phase of the disease, the results of the questionnaires and of the psychometric tests.

The psychometric test employed (“arrangement of numbers”) permitted the evaluation of the state of functional components of mental activity such as the capacity of short-term memory, attention (stability and intensity), and the speed of mental performance. Tests were conducted using forms of the type shown in Fig. 1. Participants were set the task of filling in with a pencil the 25 empty cells in the blank square by arranging, in increasing order of magnitude, the numbers presented

74	47	95	32	89
68	49	51	25	71
19	62	80	86	42
34	60	79	58	30
5	84	93	26	10

Fig. 1. A sample form employed for the psychometric test (''arrangement of numbers'').

5	10	19	25	26
30	32	34	42	47
49	51	58	60	62
68	71	74	79	80
84	86	89	93	95

Fig. 2. Answer key employed to evaluate the results of the psychometric test shown in Fig. 1.

randomly in the completed square. A strict time limit of 2 min (measured using a stop-watch) was allowed for completion of the test. At the start of the test, subjects signed their forms and were given the following instructions: ''You will work with a form that has two squares. (A sample form or a form drawn on a class-board was exhibited.) One- and two-digit numbers are filled into 25 cells of the left square at random. The right square has 25 empty cells. On the command START you must write the numbers of the left square in the cells of the right square in increasing order beginning with the smallest number. The cells of the right square must be filled in line after line: first, the 5 cells (from left to right) of the top line, then the 5 cells of the second line, etc. No marks are to be made in the left square. If you find that you have omitted a number, do not cross anything out. Write down the number that you have missed out into the next empty cell and circle it. You will have 2 min for this task. You must arrange the maximum possible numbers in the correct order. Please, do not make mistakes. Do you have any questions? (Questions were answered at this point). GET READY. START.'' The stop-watch was started concomitantly with the order to commence the test. After the allotted time the command ''FINISH'' was given and it was required that all subjects stopped working simultaneously and placed their pencils on the table immediately. The results were checked with the help of a key (Fig. 2), and the total of numbers arranged correctly in the right square (productivity) and the total of omitted numbers (errors) were counted.

Patient compliance

Compliance was ensured by questioning the patients at the end of the study and by collecting the bottles used and any remaining content. The volume of unused liquid was measured and the lower limit for compliance was set at 98%.

Statistical methods

Each patient was identified by number and trial identification. The data were entered in the data-base (Microsoft™ Excel® 2000) patient by patient. The mean, standard error of the mean and standard deviation values for the duration of antibiotic therapy required, the scores in the psychometric tests and in the WHOQOL-Bref questionnaire domains were calculated according to standard methods. The significance of the difference in mean treatment times between groups A and B were determined using Student's *t*-test: the significance of the differences in QOL domain scores (on days 1 and 5 of rehabilitation) and of mean test scores between groups (both before and after treatment) were determined using one-way repeated ANOVA with Tukey's multiple comparison post-test. Data management and calculations were performed with GraphPad (San Diego, CA, USA) Prism software (version 3.03 for Windows).

Results

The study population consisted of 60 patients, 32 females (53.3%) and 28 males (46.7%) aged between 18 and 65 years (average 36.5 years). All of the selected patients completed the trial and none of them reported adverse reactions to the medication taken. At the conclusion of the study, the volume of medication returned by each participant was compared with the anticipated volume as calculated on the basis of the patient's statement of the duration of treatment. The correlation between the amount of unused medication and the information revealed by each patient concerning the number of days that medication had been used was extremely high, showing that all patients fulfilled the compliance criterion by taking 98% of the recommended dose.

Table 1 shows the QOL scores at the start of the trial for patients in the Chisan group (group A) and for those in the placebo group (group B). Table 2 indicates the mean duration of a standard treatment (days) required before patients were deemed to have recovered from the acute phase of the disease. Treatment times were significantly different between the two groups: those receiving Chisan mixture together with a standard

Table 1. QOL scores for patients in groups A and B before the start of treatment

WHOQOL-Bref questionnaire section	Chisan group A	Placebo group B
DOM1 Physical	10.80±1.72	11.10±2.58
DOM2 Psychological	11.25±1.71	11.98±1.73
DOM3 Social	11.58±1.73	12.40±2.12
DOM4 Ecological	13.62±2.44	13.51±2.49

Values shown are means±standard deviation ($n = 30$).

Table 2. Duration of standard treatment before patients were deemed to have recovered from the acute phase of the disease

	Chisan mixture group Group A	Placebo (control) group Group B
Number of participants	30	30
Mean duration of therapy (days)	5.67	7.53
Standard deviation	1.03	1.94
Standard error	0.19	0.35
Significance of difference between mean values (*t*-test)	$p<0.0001$	

treatment required shorter therapy with antibiotics (5.67 days) compared with those receiving the placebo with a standard treatment (7.53 days).

The mean scores of the psychometric test for the two groups measured at the beginning of the illness (before treatment began) and at the end of the treatment are shown in Fig. 3. It is clear that the mental performance of patients who had received standard treatment together with Chisan mixture adjuvant (group A) was significantly higher at the end of the treatment than of control patients (group B) who had received standard treatment and the placebo. For group A, both mental endurance (productivity; expressed as an increase in the total of correct number assignments) and mental efficacy (ability to concentrate; expressed as a decrease in errors made) after the treatment were significantly better than for group B.

The WHOQOL-Bref questionnaire scores were determined separately within the physical, physiological, social, and ecological domains (Fig. 4A–D, respectively) at the termination of the acute phase of the disease and 5 days later (end of treatment). In all domains, mean QOL scores were statistically significantly higher for patients who had received Chisan mixture adjuvant (group A) than for those who had received placebo (group B): the difference in QOL scores was particularly noteworthy

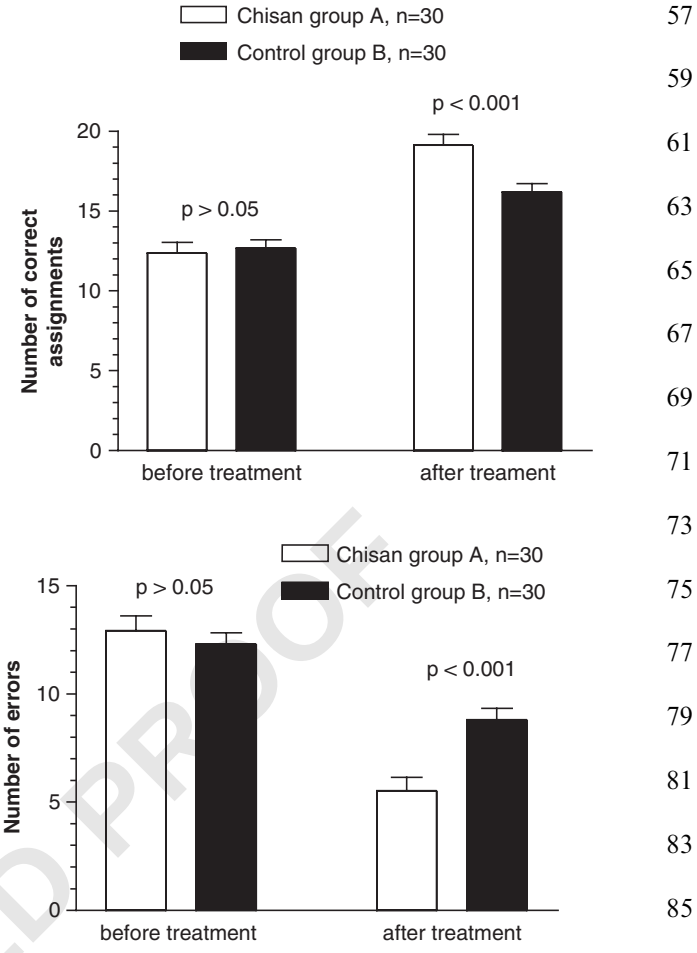

Fig. 3. Effect of adjuvant therapy with Chisan mixture versus placebo on the mental performance of patients undergoing a standard treatment for acute non-specific pneumonia. Mental endurance and efficacy were determined by application of a psychometric test (“arrangement of numbers”) at the beginning of the illness (before treatment) and at the end of treatment, which measured productivity (number of correct answers; top panel) and ability to concentrate (number of errors; bottom panel). The *p*-values shown indicate the significance (or otherwise) of the difference between the mean scores of groups A and B.

with respect to the physical state of these patients (Fig. 4A).

Discussion

Community-acquired pneumonia (CAP) together with influenza ranks as the sixth leading cause of death in the United States. The incidence of these related conditions has increased by almost 60% in the past 15 years, making CAP a rapidly growing health risk particularly amongst the elderly. Guidelines for the

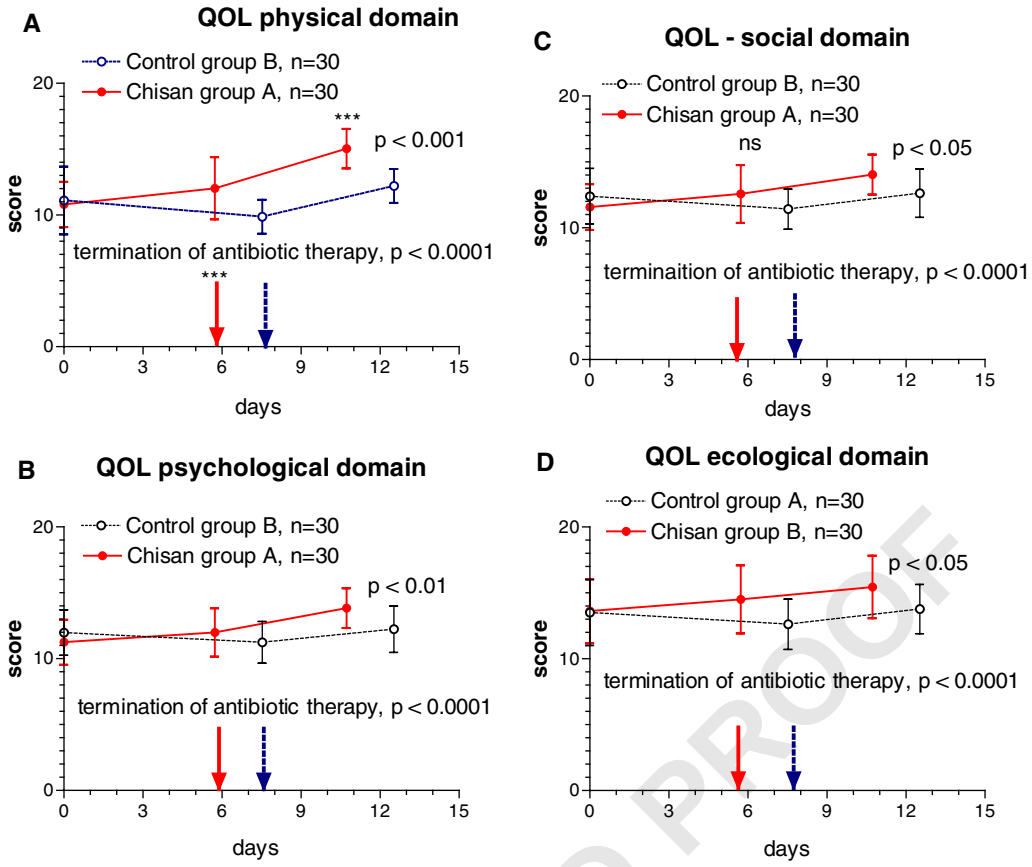

Fig. 4. WHOQOL-Bref questionnaire scores of patients undergoing a standard treatment for acute non-specific pneumonia and receiving either adjuvant therapy with Chisan mixture or placebo determined at the termination of acute phase of the disease and 5 days later (end of treatment). In each case, the arrows indicate the day of termination of antibiotic therapy (end of acute phase of disease) for the two treatment groups (see Table 2). The *p*-values shown indicate the significance (or otherwise) of the difference between the mean scores of groups A and B: highly significant differences are marked with the symbol ***.

empirical treatment of CAP continue to be updated (Niederman et al., 1993, 2001; Huchon et al., 1998). The Infectious Disease Society of America (IDSA) now recommends macrolides, doxycycline or fluoroquinolones for primary therapy, as each of these agents is effective against the primary pathogen and many others. Therapy for patients with severe pneumonia should include fluoroquinolones, erythromycin, supplemented with ceftriaxone or a beta-lactam inhibitor. Hospitalised patients may usually be switched from intravenous to oral therapy within 3 days. The total course of treatment for patients with CAP caused by *Streptococcus pneumoniae* is typically from 7 to 14 days (or until the patient has been afebrile for 72 h), whereas for patients with atypical pathogens, treatment often continues for 10–21 days. In severe cases, the additional use of drugs with immunomodulating activities may be indicated where the duration of CAP is of more than 4 weeks, the main symptoms of the disease persist, or the patient presents different forms of allergies (Spanish Thoracic Society, 1992). Independent of the treatment regime, the QOL of patients suffering from pneumonia is considerably impaired.

In the present study, we have used the herbal drug Chisan as an adjuvant therapy with a standard treatment for acute non-specific pneumonia. Chisan mixture is a fixed combination of extracts from the adaptogens *R. rosea* L., *S. chinensis* Turcz. Baill., *E. senticosus* Maxim, plants which are known to increase non-specific resistance of an organism to stress. The results obtained in this study clearly indicate that adjuvant treatment of pneumonia patients with Chisan (ADAPT-232) significantly decreases the period of antibiotic therapy required for recovery, decreasing the duration of the acute phase of the illness, and improves the mental performance of patients during the convalescence period with an accompanying improvement in the QOL.

In conclusion, this pilot clinical trial has demonstrated that plant adaptogens, particularly ADAPT 232, can be recommended for use with a standard treatment of patients with acute non-specific pneumonia as an

adjuvant in order to increase the QOL and expedite the recovery of patients.

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