

# THE EFFECT OF *cis*-9-CETYL MYRISTOLEATE (CMO) AND ADJUNCTIVE THERAPY ON THE COURSE OF ARTHRITIC EPISODES IN PATIENTS WITH VARIOUS AUTO-IMMUNE DISEASES CHARACTERIZED BY THE COMMON TERMINOLOGY, "ARTHRITIS" AND "PSORIASIS"

A Randomized Clinical Trial, Dr. H. Siemandsi, M.D., *et al*

**Objective.** Recent published reports offer anecdotal evidence that *cis*-9-cetyl myristoleate may provide significant amelioration of various arthritic conditions. We set out to perform controlled studies to determine if this material was efficacious, either in the short term, or in some measurable manner, over a much longer period.

**Methods.** A prospective, randomized study design was used to allocate patients to receive *cis*-9-cetyl myristoleate, *cis*-9-cetyl myristoleate plus glucosamine hydrochloride (GH), sea cucumber (SC) and hydrolyzed cartilage (HC) and a placebo.

**Results.** At the start of this study, the duration, severity, and pattern of arthritic episodes were found to be similar in the 3 treatment groups. At the end of the study it was found that the number of arthritic episodes was significantly reduced, and the duration of episode-free time was significantly prolonged, in the two *cis*-9-cetyl myristoleate groups compared with the placebo group.

**Conclusion.** *Cis*-9-cetyl myristoleate treatment and *cis*-9-cetyl myristoleate plus GH, SC & HC were demonstrated to offer significant benefits over the placebo in the prevention of arthritic episodes. It was further determined that these results could not be obtained with other standard arthritic therapies based upon exhaustive reviews of patient records prior to opening of the study. *Cis*-9-cetyl myristoleate and *cis*-9-cetyl myristoleate plus GH, SC & HC treatment also seems to permit some relief to autoimmune inflammatory diseases which may prove to be long-term. This finding could provide additional evidence for the theory, reflected by the earlier anecdotal evidence as well as some animal studies, that *cis*-9-cetyl myristoleate and *cis*-9-cetyl myristoleate plus GS, SC & HC may prove to be of major benefit in the future treatment of autoimmune diseases.

The terms arthritis and psoriasis have come to describe a series of conditions reflecting a wide range of symptoms, some permanent and some transient. Each condition, however, is typified by certain common elements such as some sort of inflammatory response with resulting pain, various forms of cellular degeneration and frequently, permanent loss of mobility and quality of life.

With the exception of osteoarthritis, most researchers are beginning to believe all arthritic conditions may have a common, albeit many-faceted, etiology - autoimmune dysfunction. Unfortunately the great number and complexity of immune system components and their diverse interplay has made this theory difficult to prove.

While it has not been proven, the original research done on *cis*-9-cetyl myristoleate at NIH indicates a direct connection between the observed effect of *cis*-9-cetyl myristoleate and some ability of *cis*-9-cetyl myristoleate to correct certain immune dysfunctions which may cause many arthritic conditions.

## PATIENTS AND METHODS

**Study design.** The study was a 32 week (8 week cycle, 4 in-hospital & 4 in follow-up), multicentric, double-blind, randomized, placebo-controlled parallel trial that compared the efficacy of *cis*-9-cetyl myristoleate alone, and *cis*-9-cetyl myristoleate plus GS, SC & HC, administered over a period of 30 days, with placebo, for the treatment of various forms of autoimmune diseases commonly characterized as arthritis and psoriasis. Out of a dose of 90 grams of total fatty acid esters, 18 grams constituted *cis*-9-cetyl myristoleate. Those study patients who received the support nutrients GS, SC, & HC were given a total dosage of 18 grams each of these nutrients.

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The study was conducted under the auspices of the Joint European Hospital Studies Program. This study was designed by a committee, which consisted of rheumatologists and biostatisticians experienced in the development and execution of clinical trials. Oversight of the study was accomplished by an executive committee, composed of the primary researcher and primary statistician, selected participating investigators, consultants; and an independent oversight committee consisting of two experienced federally controlled, state health department rheumatologists and one state health department biostatistician.

**Eligibility criteria.** Patients were required to have inflammatory arthritis of at least one year duration in at least one peripheral joint, excluding the shoulders and hips. Included in this parameter, affected joints must have had joint tenderness and joint swelling of  $\geq 2$  on a four point scale and joint patient-physician overall assessment of involvement ranging from; none - mild - moderate - severe - very severe. The patients inducted into this trial for the purposes of psoriatic testing were chosen on generally the same criteria - involvement of epidermal involvement from; none - mild - moderate - severe - very severe.

Criteria for exclusion included unwillingness to stop the use of tobacco and caffeinated beverages, at least for the duration of the trial. Tobacco and caffeine use have been reported to greatly hamper the positive (if anecdotal) result of the use of *cis*-9-cetyl myristoleate. It also should be noted here that the use of any other medication in all forms of arthritis as well as psoriasis were not excluded as it was determined this would limit participation. It was also deemed advisable to approximate as much as possible, conditions that would be found in the average arthritic. One exception to this condition was the exclusion of patients showing sensitivity to salicylates or ibuprofen which were used as excipients in the placebo. Potential participants with other severe chronic conditions were excluded, as it was the opinion of the primary investigator that this type of participant would limit the potential successful completion of the study period.

All patients had failed to respond to therapy with therapeutic doses of one of the NSAIDs. All patients who took NSAIDs during the trial were required to be on stable dosages for one month prior to entry and throughout the trial. *No systemic or intrarticular steroids were allowed.*

**Informed consent.** The study protocol was reviewed and approved by the federally controlled state oversight committee. Prior to entry into this trial, each potential study participant was informed of the nature, duration, and purpose of the study to be administered, and all the potential benefits, inconveniences, and hazards that could reasonably be expected.

**Study medication.** Patients received either one-half litre of pleasantly flavored oral liquid containing 18 grams of *cis*-9-cetyl myristoleate or one-half litre of the same liquid *sans cis*-9-cetyl myristoleate. Both liquids were carefully compounded so as not to be able to be differentiated. Each patient was also given 180 capsules of the adjunctive medication containing a total each of 18 grams GL, SC and HC. Identical capsules containing the placebo compound were also distributed. The *cis*-9-cetyl myristoleate topical liquid was distributed as a 25% concentration in 60 cc. lightly scented lotion and an identical placebo lotion *sans cis*-9-cetyl myristoleate.

The oral liquid was used with meals in one teaspoon quantities, three times daily. Two capsules of GL, HC & SC were taken with each meal, three times daily. The topical lotion was used as needed and determined by each patient according to his or her own perceived requirement.

**Clinical assessment.** Outcome measures of disease activity and therapeutic efficacy were obtained at the time of screening (not more than four weeks before study entry), randomization at week zero, and thereafter at weeks: 1, 2, 3, and 4. Outcome measures included a variety of patient-reported, clinical, laboratory and radiographic assessments.

Patient self-assessment measures included morning stiffness, night pain, patient overall assessment and Mobility Functional Index as determined by this published procedure.

Clinician assessment measures included joint counts, dactylitis, Enthesopathy Index, Spondylitis Articular Index, chest expansion, modified Schober's test, finger-to floor test and physician overall assessment as detailed elsewhere in this paper. Additionally, the presence of symptomatic keratoderma, phalangeal and digital deformation as measured from a normal range of vertical protrusion at rest were measured. These tests, singularly and collectively were then compiled into a patient-by-patient qualitative scale as; none = 0, mild = 1, moderate = 2, severe = 3 and very severe = 4.

**Laboratory assessment.** Laboratory evaluation included a urinalysis and complete blood cell count, with leukocyte differential and reticulocyte count. Chemical surveys and a Westergren erythrocyte sedimentation rate (ESR) determination were done at every visit by secondary researchers daily in the two hospital settings. The C-reactive protein (CRP) level was evaluated at the first and last day of the hospital stay. At the screening times, blood was drawn for HLA-B27 typing and RF and ANA determinations.

**Radiology assessment.** At the screening visit, all patients had the following radiographs performed: anteroposterior views of the pelvis and oblique views of the sacroiliac joints.

**Adverse drug reactions (ADR's).** Patients were screened for ADR's at every secondary researcher's visit. Patients were withdrawn from the study medication if any of the following were found; WBC less than 3000/mm<sup>3</sup>, absolute polymorphonuclear count less than 10000/mm<sup>3</sup>, acute or progressive decrease in hemoglobin or hematocrit, proteinuria less than 500 mg. for 24 hours, drug fever or significant rash.

**Compliance.** The patients were queried at each secondary researcher's visit regarding the dietary supplement or topical lotion they had used. A capsule count for the trial medication was done at each consultation to monitor compliance.

**Biostatistical considerations.** Each patient was classified as a treatment responder or nonresponder based on the following definition. Assessment measures were selected *a priori*, and criteria for clinical improvement and worsening were defined for each patient self-assessment and physician assessment (improvement = decrease by 1 category; worsening = increase by 1 category); joint pain/tenderness score and joint swelling score (improvement = decrease by 30%; worsening = increase by 30%). Treatment response was then defined as improvement in at least 2 of these 4 measures, one of which must be joint pain/tenderness or swelling, and ITO worsening in any of the 4 measures. The study was designated with a 90% power for detecting a placebo response rate of 30% compared with a *cis-9-cetyl* myristoleate and *cis-9-cetyl* myristoleate plus GS, SC & HC response rate of 50%, assuming a 10% withdrawal rate. This resulted in a target sample size of 431 patients with an actual sample size of 382.

In short, the analytical method was the change in primary and secondary outcome measures from baselines to the last available follow-ups analyzed using *t*-tests for continuous data and chi-square tests for ordinal and categorical data. Mixed-model analyses were done to characterize the response patterns over time using SAS PROC MIXED for continuous data and a program named MIXOR for categorical and ordinal data. All other analyses were conducted using SAS version 6.08. All statistical tests were two-sided and  $P \leq 0.05$  was the criterion for statistical significance.

## RESULTS

**Patient population.** Four hundred thirty-one patients entered the study. Of these, 106 were randomized to receive *cis-9-cetyl* myristoleate, 84 were randomized to receive *cis-9-cetyl* myristoleate plus GS, SC & HC; 226 received a placebo. Fifteen psoriatics received *cis-9-cetyl* myristoleate plus GS, SC & HC, plus CM-25% concentration topical at a 3X quantity ratio. Even though the study was sponsored by the owners of the respective private hospitals, recruitment was not limited to the typical fee-paying patients. Approximately 27% of the patients were actively recruited in the respective local area. Despite a prolonged accrual period and careful screening, the loss of approximately 11% of the starting participants occurred largely because of the inability to stop the use of tobacco and/or caffeinated beverages. Fulfillment of the final parameter of study size was accomplished by the substantial excess of volunteers wanting to enter the study - this coupled with the relatively short testing period required to validate the effects of *cis-9-cetyl* myristoleate and

*cis-9-cetyl* myristoleate plus GS, SC & HC.

Statistical Chart 1 outlines the baseline demographic, clinical, and laboratory variables. The duration of disease was 12 years. The Westergren ESR and CRP levels were mildly elevated. There were no statistically significant differences in any of these baseline parameters between the patients taking *cis-9-cetyl* myristoleate and *cis-9-cetyl* myristoleate plus GS, SC & HC and those taking placebo.

**Compliance.** Compliance for both the *cis-9-cetyl* myristoleate and *cis-9-cetyl* myristoleate plus GS, SC & HC and placebo groups was quite high. There was a statistical trend toward those in the *cis-9-cetyl* myristoleate and *cis-9-cetyl* myristoleate plus GS, SC & HC group taking more tablets per day (96% compliance) than those in the placebo group (86% compliance) ( $P = 0.08$ ). The probability of this observation was due to the rapid response of pain relief in the *cetyl* myristoleate groups.

**Primary outcome measures.** The Oversight Committee defined response based on a decision rule as outlined in Patients and Methods. Statistical Chart 1 shows that based on that definition of treatment response, using the last-visit analysis, response rates were 63.3% in the *cis-9-cetyl* myristoleate group and 87.3% in the *cis-9-cetyl* myristoleate plus GS, SC & HC group and 14.5% in the placebo group. Trends favoring *cis-9-cetyl* myristoleate and *cis-9-cetyl* myristoleate plus GS, SC & HC groups were noted in components of the response definition. Physician overall assessment showed an improvement of 58.1% for the patients using *cis-9-cetyl* myristoleate alone and 84.2% for the patients using *cis-9-cetyl* myristoleate plus GS, SC & HC. Patients experiencing worsening or no reaction totaled 1.0% in all groups, compared with improvement of 13.9% in placebo group. Patient overall assessment demonstrated 59.2% improvement in the *cis-9-cetyl* myristoleate alone group and 88.2% in the *cis-9-cetyl* myristoleate plus GS, SC & HC. Patients experiencing worsening or no reaction totaled 1.0% in all groups, compared with improvement of 16.1% in placebo group. Joint swelling scores improved in 47.2% in patients using *cis-9-cetyl* myristoleate alone and 77.2% in patients using *cis-9-cetyl* myristoleate plus GS, SC & HC. Patients experiencing worsening or no reaction totaled 1.0% in all groups, compared with improvement of 21.1% in placebo group.

**Secondary and laboratory outcome measures.** Analysis of secondary outcome results (Statistical Chart 2) demonstrated a significant reduction in the Spondylitis Articular Index in the *cis-9-cetyl* myristoleate group and in the *cis-9-cetyl* myristoleate plus GS, SC & HC-treated patients. Trends favoring the *cis-9-cetyl* myristoleate group and in the *cis-9-cetyl* myristoleate plus GS, SC & HC group were also seen in a reduced duration of early stiffness and in an improvement in the fingers-to-floor result.

Laboratory outcome measures showed some statistically significant changes. Total neutrophils decreased in the *cis-9-cetyl* myristoleate group and in the *cis-9-cetyl* myristoleate plus GS, SC & HC group compared with the placebo group. The Westergren ESR significantly decreased in the *cis-9-cetyl* myristoleate group and in the *cis-9-cetyl* myristoleate plus GS, SC & HC groups compared with the placebo group. The CRP values were not significantly different and the values in ESR for the responders was not statistically significant from the nonresponders.

**Withdrawals and adverse drug reactions.** Statistical Chart 3 summarizes the data of patient exits from the study. Forty-nine patients withdrew from the study before completing the study, 16 from the *cis-9-cetyl* myristoleate and 10 from *cis-9-cetyl* myristoleate plus GS, SC & HC groups, 2 from the psoriatic group, and 21 from the placebo group. Follow-ups in all groups averaged approximately the same and these measurements were combined, combined average - (mean  $\pm$  SD 6.97  $\pm$  .264 months) ( $P = .06$ ). Withdrawal of consent was the most common reason for discontinuing the study. Seven patients withdrew because of no improvement or worsening disease. Two patients had to be with

drawn from the study because of concurrent illnesses requiring conflicting medication. The majority of withdrawals, however, was the result of patient addictions to nicotine, caffeine and alcohol and the patient inability to cease these activities during the study period.

#### STATISTICAL DATA SUMMARY

Statistical chart 2 displays the percentages of study patients showing improvement in the primary outcome variables (columns 1-3). The numbers to the right display the significance levels for the differences between treatment groups (columns 4-6). All of the significant levels are much less than 0.05, which means the differences between groups are considered statistically valid. For all four primary outcome variables (treatment response, physician assessment, patient assessment and joint swelling score), *cis-9-cetyl myristoleate* & GS, SC, and HC did significantly better than the *cis-9-cetyl myristoleate* group, and the *cis-9-cetyl myristoleate* group did significantly better than placebo.

The chart also displays the results for the secondary outcome variables. The averages (mean average as opposed to median or mode) are presented in columns 1-3 along with their standard deviations (statistical measurement of data variations). Again, the numbers to the right display the significance levels for the differences between treatment groups (columns 4-6). "NS", means that there was no significant difference between any measured groups labeled as such. When the groups are significantly different from each other, the significance is displayed. None of the secondary outcome variables were significantly different between the *cis-9-cetyl myristoleate* group and placebo. The *cis-9-cetyl myristoleate* & GS, SC, HC, group did significantly better than placebo for duration of starting involvement, joint pain/tenderness score, joint swelling score, Enthesopathy index, spondylitis articular index and the modified Schober's test. The *cis-9-cetyl myristoleate* & GS, SC, HC, group did better than *cis-9-cetyl myristoleate* alone for the joint pain/tenderness score and the modified Schober's test.

#### DISCUSSION

The results of this trial suggest that cetyl myristoleate and cetyl myristoleate supporting formulas may be beneficial in the treatment of many forms of arthritic based diseases, including psoriatic arthritis. The definition of response was determined *a priori* and included assessment of joint pain/tenderness and swelling as well as patient and physician overall assessments. Cetyl myristoleate & supporting formulas produced the best treatment response by a factor of 72.8% more patients than did placebo. Considering the components of response individually, cetyl myristoleate & supporting formulas resulted in 70.3% more patients having improved as assessed by physician, and 56.1% more having improved joint swelling. Therefore, while the amount of treatment response using cetyl myristoleate and cetyl myristoleate & supporting formulas seems to be consistent with the treatment affects on joint counts, it is obvious that there is a statistically significant improvement in the use of the CMO with supporting formulas.

The time-line based response rate of cetyl myristoleate and cetyl myristoleate supporting formulas, not adequately reflected in data, by patient, showed the majority of patients responding to cetyl myristoleate and cetyl myristoleate supporting formulas did so within the first three weeks. Also, not reflected in the data, was the continued use of cetyl myristoleate and cetyl myristoleate supporting formulas beyond the study time limits and dispensed on request to 21 patients. These 21 patients were determined to have received only marginal benefits from cetyl myristoleate and cetyl myristoleate supporting formulas but one more course of treatment showed responses approximately equal to the first patient response results.

Cetyl myristoleate and cetyl myristoleate supporting formulas were well tolerated in this trial. This finding was not unexpected as cetyl myristoleate and the cetyl myristoleate supporting formula components are naturally occurring and have been used as diet supplementation for many years and are widely available singularly and in various combinations.

In summary, cetyl myristoleate and cetyl myristoleate supporting formulas appear to be beneficial in the treatment of a wide range of arthritic conditions including long standing and refractive cases.

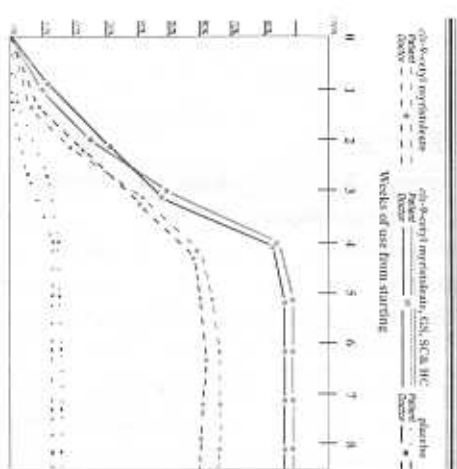
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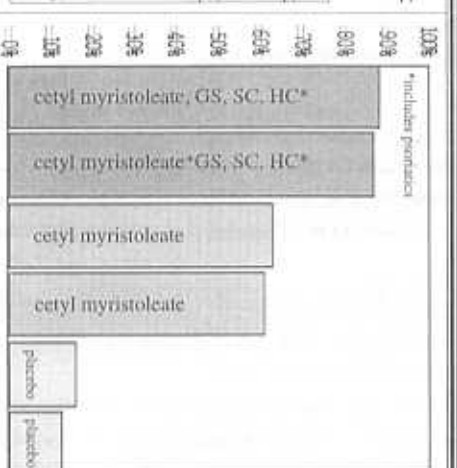
## STATISTICAL DATA

Study group baselines

System	Study group			
	Control (placebo)	Control (placebo + GS, SC, HC)	Placebo	Total
<b>Demographic</b>				
Number of patients	106	99	226	78
Age, mean ± SD, years	58.3 ± 12.0	57.7 ± 10.4	58.0 ± 11.2	100
Percent male	60	59	60	130
Percent female	46	41	40	130
Ethnicity, percent				
Caucasian	72	63	78	24
Black	17	9	12	28
Hispanic	6	7	6	19
Other	7	1	4	11
<b>Clinical</b>				
Duration of involvement, ± SD, years	10.5 ± 10.0	10.2 ± 8.3	10.3 ± 9.1	75
Weight, mean ± SD, lb	175 ± 28	181 ± 38	170 ± 32	17
Serostatus, percent positive	10	13	11	28
HLA-B*27, percent positive	71	70	72	85
Lesion involved, mean ± SD	6.1 ± 5.8	6.4 ± 5.5	6.3 ± 6.1	54
Joint tenderness score, 1, mean SD	32.2 ± 10.0	32.2 ± 10.0	32.1 ± 10.1	90
Joint swelling score, 2, mean SD	10.0 ± 8.0	11.2 ± 10.6	11.1 ± 9.4	90
Early stiffness, hours, 4, mean SD	3.8 ± 3.3	4.3 ± 3.9	3.9 ± 4.5	28
Finger flexion, mean ± SD	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	100
Edema of hands, mean ± SD	43.1 ± 4.1	43.7 ± 3.8	43.7 ± 3.8	26
mean ± SD				
<b>Laboratory</b>				
Hemoglobin, 2, mean SD percent	41.7 ± 1.8	41.7 ± 1.8	43.1 ± 2.1	28
Platelet, mean ± SD mm <sup>3</sup> (10 <sup>9</sup> )	231 ± 101	230 ± 105	213 ± 97	27
White blood cell count, mean ± SD, mm <sup>3</sup>	282 ± 20.4	221 ± 29.4	251 ± 28.4	20
± SD, mm <sup>3</sup> per hour				
C-reactive protein, 2 SD μg/dl (normal < 0.5)	1.7 ± 2.5	1.5 ± 2.4	1.8 ± 2.9	43



Statistical Graph 1. Time rate of early patients taking cetyl myristoleate group and in the cetyl myristoleate plus GS, SC & HC or placebo.



Statistical Graph 2. Response rate of study participants taking cetyl myristoleate group and in the cetyl myristoleate plus GS, SC & HC or placebo.

Statistical Chart 2. Overview statistics of study patients taking cetyl myristoleate group and in the cetyl myristoleate plus GS, SC & HC and placebo.

Primary %	Study group			
	Control (placebo)	Control (placebo + GS, SC, HC)	Placebo	Total
Treatment response	63.3	67.3	74.5	68.4
MDL overall assessment	58.1	64.2	73.9	65.4
Patient overall assessment	59.2	68.2	78.1	68.8
Joint swelling score	47.2	77.2	71.1	61.8
<b>Secondary, mean ± SD</b>				
Duration of activity as assessed (no. of days)	21 ± 5.9	21 ± 7.9	3.9 ± 8.3	0.0
End of study				
Change from baseline				
Spondylitis function index (number)	8.9 ± 6.9	8.9 ± 6.1	10.3 ± 5.7	8.6
End of study				
Change from baseline				
Joint tenderness score (number)	11.9 ± 6.9	8.7 ± 4.2	13.2 ± 4.7	10.0
End of study				
Joint swelling score (number)	6.9 ± 7.9	5.8 ± 4.2	7.4 ± 5.9	6.0
Change from baseline (number)				
Early stiffness (hours score)	0.5 ± 2.3	0.4 ± 2.1	0.9 ± 4.1	0.6
End of study				
Change from baseline				
Edema of hands (number)	4.8 ± 6.2	5.6 ± 6.1	4.2 ± 5.3	4.8
End of study				
Change from baseline				
Spondylitis Ankylosing index (number)	3.3 ± 4.1	2.7 ± 3.1	3.7 ± 4.5	3.0
End of study				
Change from baseline				
Ostei expression (mm)	4.7 ± 2.0	4.9 ± 1.9	4.3 ± 4.7	4.6
End of study				
Change from baseline				
Medical Sickness (mm)	14.1 ± 1.1	14.7 ± 1.4	13.9 ± 1.4	14.0
End of study				
Change from baseline				
Ostei (no. of feet)	2.7 ± 3.1	2.9 ± 3.0	2.3 ± 2.1	2.6
End of study				
Change from baseline				
Finger-to-floor (cm)	15.8 ± 16.8	16.1 ± 17.4	15.7 ± 16.1	15.8
End of study				
Change from baseline				
Laboratory score ± SD				
White blood cell count (mm <sup>3</sup> )	21.9 ± 27.9	22.8 ± 26.3	21.4 ± 27.1	21.9
End of study				
Change from baseline				
C-reactive protein (μg/dl)	1.26 ± 1.87	1.29 ± 1.93	1.18 ± 1.87	1.25
End of study				
Change from baseline				

Statistical Chart 3. Exam from efficacy study.

Statistical Chart 3. Exam from efficacy study.

Reason for discontinuation	Study group	
	Control (placebo)	Control (placebo + GS, SC, HC)
Exiting factors	16	12
Randomized to treatment	166	99
Withdrawn from study	16	12
Voluntary withdrawal	3	5
Worse	3	2
Adverse study material reaction	0	0
Gastrointestinal symptoms	3	2
CNS symptoms	0	0
Decreased platelets	0	0
Increased liver enzymes	0	0
Promoted violation	2	3
Completed study	90	87

Statistical Chart 4. Exam from efficacy study.