

ABSTRACT OF FIBRONOL® PHASE I-a CLINICAL TRIAL RESULTS

November 25, 2005

Abstract

Fibronol® , a polyphenol/phlorotannin rich nutraceutical, was used in a preliminary Phase I-a study of established fibromyalgia patients (original recruitment of 36 patients, with completion by 29). This 8-week clinical study was a double-blinded, placebo-controlled study using Fibronol as an adjunct therapy to the FM patients' current standard of physician care. The trial was to establish safety of Fibronol with FM patients, as well as initial indications of efficacy on both a single dose and high dose. Standard FM clinical trial assessment forms typically found in FM clinical trials were used, together with physician visits to monitor for toxicity, adverse events, as well as performance of blood tests and EKGs. The results established the general safety of Fibronol, other than discontinuation of the study by 6 patients who had pre-existing diarrhea form of IBS. Preliminary efficacy measures evidenced statistically significant changes in: a) *sleep*: mean time to sleep (<47 min, $p<.024$), amount of sleep (+1.6 hrs/night, $p<.001$), soundness of sleep (+80%, $p<.01$); *fatigue* (-30%, $p<.001$); *energy* (+71%, $p<.001$); *number of "good days"* (+56 hrs/week, $p<.001$); *number of lost "work" days/week* (-31 hrs/wk, $p<.001$); *pain* (-31%, $p<.001$); and *global assessment of general condition* (+39%, $p<.001$). A strong dose-response relationship was not established at statistically significant levels. Fibronol was concluded to offer reasonable safety and statistically significant improvement in symptoms for most of the study population over the eight-week trial period.

Summary

This double-blinded, randomized, placebo-controlled I-a study was conducted over an 8-week period was designed to evaluate the safety and gain a preliminary assessment of the efficacy of Fibronol as an adjunct treatment for fibromyalgia syndrome ('FMS'). The initial trial was designed as a dual dose study in three cohorts of ten patients, eight patients in each group to be treated with Fibronol, two with placebo. Placebo patients were converted to active product on an open-label basis following two weeks of placebo. Anticipating some patient losses during the trial, 22 patients were recruited in Korea, and 14 patients were recruited in Seattle-Everett. One of the three cohorts was high-dose (i.e., 12 Fibronol capsules/day), while two cohorts were moderate dose (i.e., 6 capsules/day). The study was conducted in ten centers with both arms under the same protocols: a) the first arm, consisting of 14 patients (all female), were located in the Seattle and Everett, WA, area; b) the second arm, consisting of 22 patients (one male, the other 23 female), was located in Seoul, Korea. All Korean patients were on the moderate dose. 8 of the US patients were on high dose, 6 on moderate dose. 19 of 22 Korean patients completed the study, while 10 of 14 US patients completed the study (6 high dose, 4 moderate dose). All patients signed patient consent forms, with copies kept on hand by the investigator, together with a copy of all raw data on patient evaluations and physician lab/EKG tests. Patients went in for physician visits and lab/EKG tests at baseline, 2 weeks (placebo), and 8 weeks termination.

Objectives

Primary objective:

To demonstrate the safety of Fibronol in a single dose.

Secondary objectives:

To determine if there is an acute effect on pain, fatigue, or sleep quantity/quality after a single dose of Fibronol;

To determine whether a high dose offers more efficacy than a moderate dose

Background

Fibronol Description

SEANOL[®], the primary ingredient in Fibronol, is an inert, purified dry powder extract of polyphenols and phlorotannins (13 peaks under HPLC) from Cava Ecklonia brown seaweed. 200mg/tablet potency: 12% polyphenols, balance phlorotannins. Stability a.l. one year demonstrated. Other active Fibronol[®] ingredients include: 40 mg of malic acid, 30 mg of aloe vera gel 200:1, 10 mg of vitamin B-1. Inactive ingredients include magnesium stearate (20mg) and microcrystalline cellulose (7mg). Standard dosing = 2 tablets 3X daily, high dosing is twice this level (i.e., 4 tablets 3X daily).

Fibronol Pharmacokinetics

Absorption, distribution and biotransformation of SEANOL occur within 30 minutes from ingestion with elimination 6-7 hours following consumption. Since radioactive tagging for PK not feasible, FRAP assays in circulating blood, muscle and vital organs used as a surrogate for ADME.

SEANOL is available as a “nutraceutical” and is used for a wide variety of conditions, especially in Asia. Small placebo-controlled trials in knee osteoarthritis and neuralgia were suggestive of analgesic benefit. Animal and preliminary human studies have not shown significant adverse effects.

Methods

Patient Eligibility

A. Inclusion Criteria

- i. Patients diagnosed with FMS as defined by the 1990 ACR Criteria for the Classification of Fibromyalgia
- ii. Male or female patients between the ages of 18 and 70.
- iii. Females must be either postmenopausal or, if of childbearing potential, must have a negative urine pregnancy test prior to entry into the study and be using a medically acceptable form of contraception.
- iv. Patients must have the ability to give informed consent.

B. Exclusion Criteria

- i. Patients with any significant history of cardiac, pulmonary, gastrointestinal, or neurological disease.
- ii. Patients with documented autoimmune disease
- iii. Patients with active cancer, except basal cell carcinomas, within 5 years of study initiation
- iv. Patients with uncontrolled diabetes or thyroid disease
- v. Pregnant or breastfeeding patients

Study Assessments

- A. Safety assessments at screening, physician visits at baseline, week 2 (placebo), and week 8.
 - i. CBC, serum chemistries, urinalysis, ECG
 - ii. Vital sign assessments
 - iii. Physical exam, including patient weight
 - iv. Adverse event records
- B. Efficacy assessments
 - i. Pain
 - 1. Pain diary – VAS pain scale
 - 2. Brief Pain Inventory (BPI)
 - ii. Patient global status - PGIC
 - iii. Sleep assessment – MOS sleep scale
 - iv. Fatigue – Multidimensional Fatigue Inventory (MFI)
 - v. Global Impact – Global Impact scale (GI)

Conclusions

Safety

Four US patients and three Korean patients dropped from the study, with six of seven dropping due to increased diarrhea, while one drop was due to familial stress. Blood test and ECG parameters for all patients were normal. Study participants reported no significant adverse events. Other than caution regarding dosing for FMS patients with a pre-existing condition of diarrhea, Fibronol evidenced suitable safety.

Efficacy

Fibronol evidenced a statistically significant impact on 24 FMS patients in terms of symptom management in a diverse set of measurements, at significant to very significant levels of statistical significance, compared to placebo, and met the primary study objectives. Principal results can be summarized as follows:

- a. ***Sleep.*** Sleep means changed by an average of +1.6 hours/night ($p < .001$), a gain of 31%, with mean time to get to sleep reduced by .78hr/night (i.e., 47 minutes less, $p < .024$). “Soundness” of sleep mean almost doubled (+80%, $p < .001$). Overall sleep improved in terms of amount of sleep, ease of sleep, and quality of sleep.
- b. ***Fatigue/Energy.*** Mean fatigue was reduced by an average of 30% ($p < .001$), while energy increased by an average of 71% ($p < .001$). Fibronol dosing evidenced a significant impact on fatigue, with a proportionately greater impact on perceived energy.
- c. ***Pain/Comfort.*** Mean pain decreased by an average of 31% ($p < .001$).
- d. ***FM Impact.*** Overall, Fibronol evidenced a mean +15% ($p < .001$) increase on the FM inventory in terms of patient ability to perform daily life functions.
- e. ***Global Impact.*** Overall, Fibronol provided a mean +39% ($p < .001$) improvement in patient assessment as to the overall-improvement in general condition from baseline.

No statistically significant improvement in symptoms was evidenced in placebo patients during their two-week placebo dosing, prior to assumption of open-label dosing of active product.

No statistically significant difference in response was evidenced overall on a dose response level, although in the US patient cohort population a moderately improved response was found with high-dose patients (n=6), as compared to moderate dose patients (n=4). However, the total numbers of each group were too small to confer a significant degree of statistical validity to this observation.

Overall, Fibronol appears to improve FMS patients' sleep (quantity and quality) and energy at statistically very significant levels, with statistically significant reduction in pain. Overall change in general condition was assessed at a statistically very significant +39% level of change over the 8-week clinical trial period. Further, Fibronol appears to have a high degree of safety, as long as an FMS patient does not suffer from a pre-existing condition of diarrhea.

Fibronol Clinical Study Group:

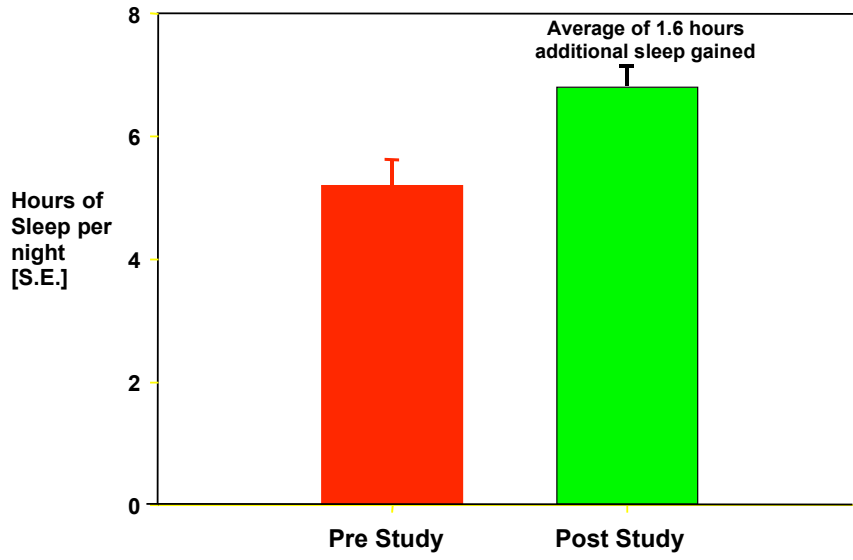
Dr. Craig Palmer, PhD – Study Manager

Dr. James Clagett, PhD – Statistics Manager

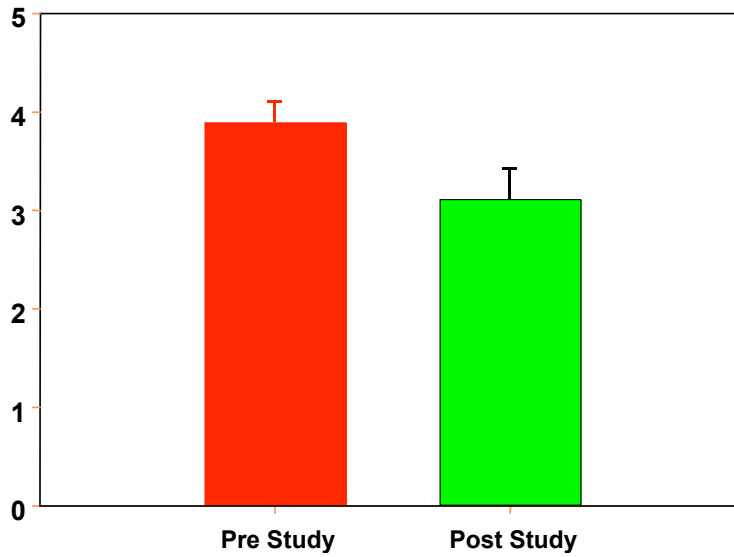
Dr. Kim, M.D. – Rheumatologist, Mirae Medical Foundation, Korea

Dr. Lee, M.D. – Rheumatologist, Mirae Medical Foundation, Korea

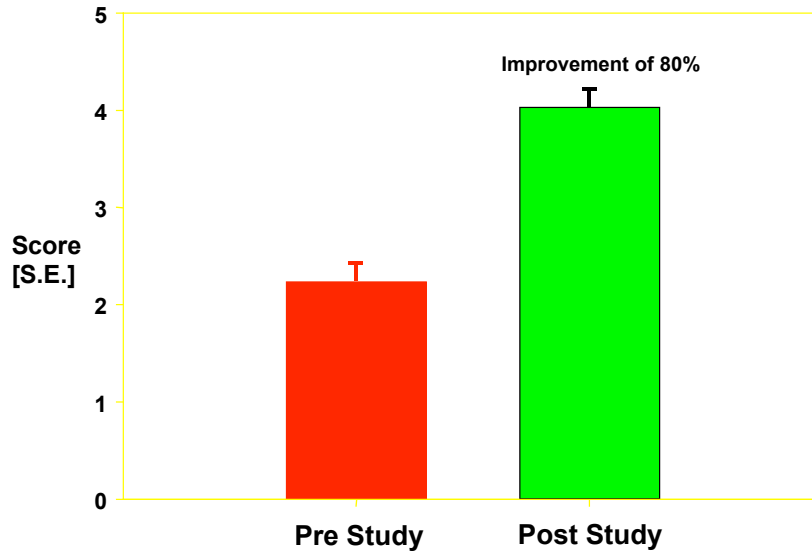
**Affects of Hours Slept Each Night Before
and After Fibronol Therapy**
P<0.001



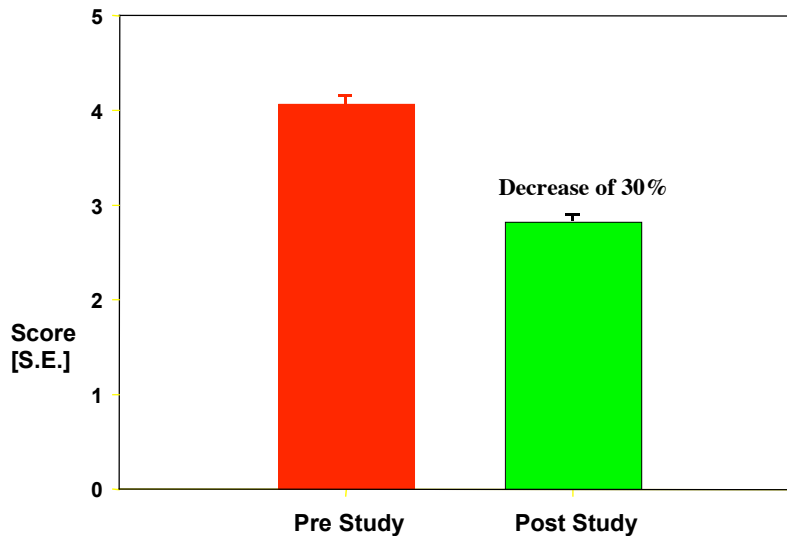
Effects of Fibronol on Time to Fall Asleep
P=0.024



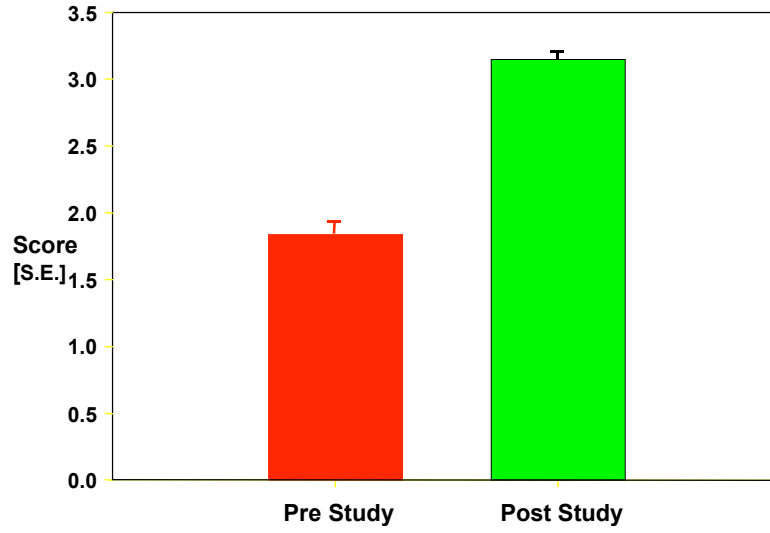
Fibronol Treatment Improved the Quality of Sleep and the Ease of Falling Asleep
 $p < 0.001$



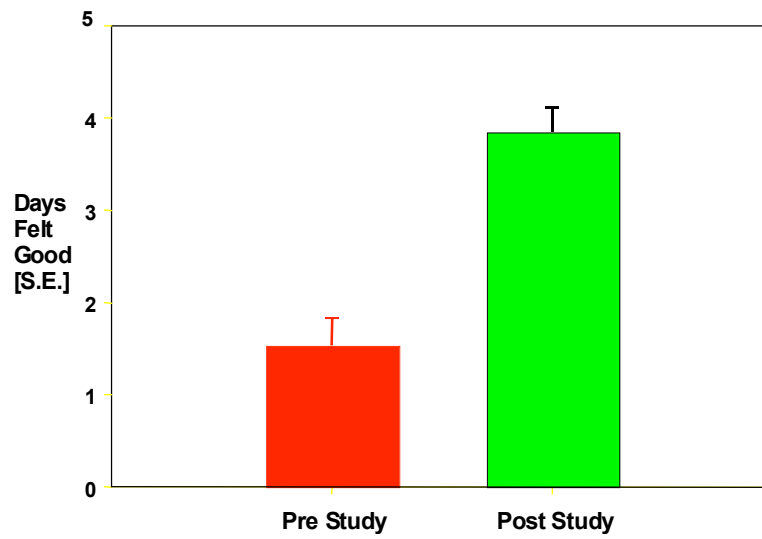
Overall Fatigue Levels Declined 30% after Fibronol Therapy - $p < 0.001$



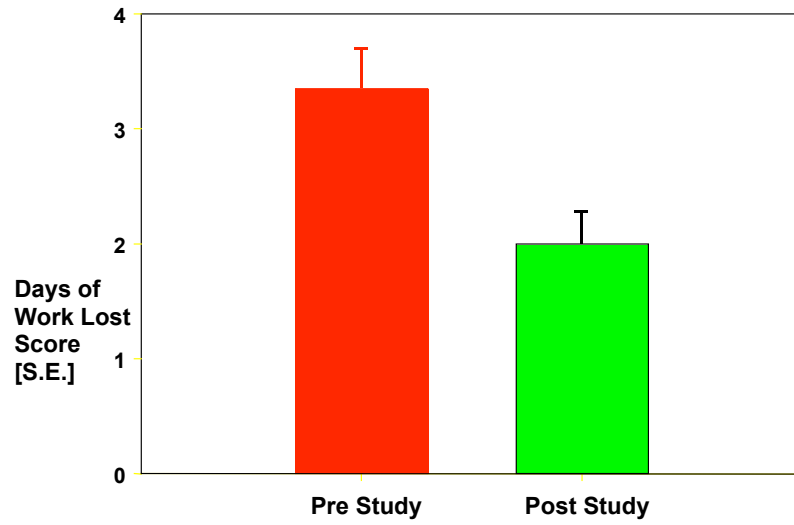
Fibronol Increased Energy by 71% after 8 Weeks of Therapy - $p < 0.001$



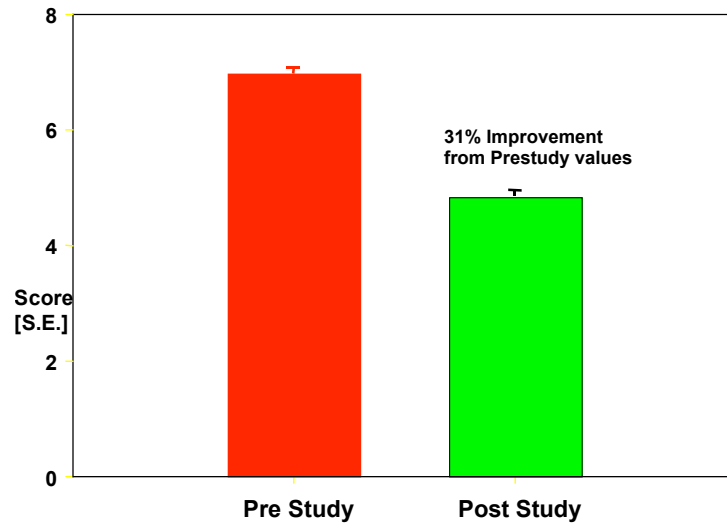
Fibronol Therapy Improves the Number of Days per Week Felt Good by 56 hours – $p < 0.001$



Fibronol Therapy Reduced the Lost Time at Work by 40%
p<0.001



Summary Data for Pain Inventory
p<0.001



**Fibronol Therapy Improved Global
Assessment of General Condition by 40%
p<0.001**

