Name of Sponsor Company Zambon	***Individual Study Table referring to the dossier***	*(For National Authorities Use only)*
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Name of active ingredient genistin+genistein, daidzin+daidzein, glycitin+glycitein	VOLUME:	
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Title of study.

A MULTICENTER, MULTINATIONAL, RANDOMISED, PARALLEL-GROUP, PLACEBO CONTROLLED DOUBLE BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF A FOOD SUPPLEMENT CONTAINING 80 MG SOY ISOFLAVONES (ZAVITAL™) IN THE CONTROL OF CLIMACTERIC SYNDROME IN POST MENOPAUSAL WOMEN

Principal Investigators and study sites

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Publication (reference) None

Study period:	***Phase of Development***
10 October 2006 (First Subject In) / 28 May 2008 (Last Subject Out)	Equivalent to Phase III

Objectives:

Primary Objective:

1. To show superiority of a 12-week treatment with Zavital™ over placebo in reduction of frequency of hot flushes in postmenopausal women.

Secondary Objective:

1. To evaluate the efficacy of a 12-week treatment with Zavital™ in reduction of intensity of vasomotor symptoms;
2. To evaluate the efficacy of a 12 week treatment with Zavital™ in reduction of all climacteric symptoms (Greene Climacteric Scale);
3. To evaluate the safety of a 12-week treatment with Zavital™ in terms of incidence of adverse events, vital signs and laboratory evaluations;
4. To evaluate the global efficacy and tolerability of a 12-week treatment with Zavital™.

Study Design and Methodology

Multicenter, multinational, randomised, parallel-group, placebo-controlled double-blind study in subjects with climacteric syndrome. Eighteen centres were activated in Italy and 9 in Romania. The overall duration of the study for each subject was 14 weeks: 2 weeks for inclusion, and 12 weeks treatment. Four visits were scheduled for each subject. At each visit (except the final visit), subject received a patient's diary to be completed with daily experienced hot flushes. After the visit 1 (screening visit) subjects started a two-week run-in period. After these two weeks, at visit 2, (randomization visit) subjects compliant with protocol inclusion and exclusion criteria were randomized and were requested to take a tablet once a day for 12 weeks. The subjects were evaluated after 6 weeks (visit 3 – mid-treatment) and 12 weeks (visit 4 – final) since the start of treatment.

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Subject population:
Number of Subjects Planned: 360

Number of Subjects Randomized:	307 Females (152 in group Zavital and 155 in placebo group)
Number of Subjects Analyzed for Safety:	307 (152 in group Zavital and 155 in placebo group)
Number of Subjects Analyzed for Efficacy (Full Analysis set):	287 (143 in group Zavital and 144 in placebo group)
Per Protocol Set 1):	259 (129 in group Zavital and 130 in placebo group)
(Per Protocol Set 2):	238 (121 in group Zavital and 117 in placebo group)

***Diagnosis and main criteria for inclusion*:**

Inclusion criteria:

1. Patients must be female aged 40-65 years;
2. Patients must have a history of menopause with at least 6 months since the last menstrual period or 6 weeks from bilateral oophorectomy;
3. Patients with a minimum average of 5 moderate and severe hot flushes (including night sweats) in 24h during the last 7 days on patient's diary before randomization.
4. Patients with the baseline serum levels of FSH $\geq$ 30 IU/L and estradiol $\leq$ 40 pg/ml.
5. Patient must be willing to give written informed consent and be able to adhere to visit schedules to meet study requirements.

Exclusion criteria:

1. Patients on Hormone Replacement Therapy (HRT) and any other hormone therapies (estrogens, progesterone, androgens) in the last 3 months before the screening visit;
2. Patients taking other agents for the treatment of hot flushes such as megestrol acetate, clonidine, vitamin E, phenobarbital, ergotamine tartrate, antidepressant agents and habitually taking (>4 days a week) products containing isoflavones in the last month before screening visit;
3. Patients who have participated in any other clinical study in which investigational or marketed drugs were employed in the last three months;
4. Patients with severe hepatic failure (AST and ALT>twice the upper limit), renal failure (creatinine>1.5 mg/dl), diabetes mellitus (type I or uncontrolled type II), uncontrolled dysthyroidism, manifest heart failure condition (NYHA Class II-IV), or severe neurologic diseases.
5. Patients with a history of alcohol or drug abuse;
6. Patients with known hypersensitivity to soy products.
7. Patients with previous breast cancer in the last 5 years or suspected breast nodules at physical examination

Test product, dose and mode of administration, batch number

	Test Product	Placebo
Dosage	1 tablet/day	1 tablet/day
Duration of the therapy	12 weeks (± 1 week)	12 weeks (± 1 week)
Mode of administration	oral	oral
Batch number	JC531/NC380	JC380
Expiry date:	May 2008/November 2008	May 2008

Criteria for evaluation

Efficacy

Primary Efficacy Endpoint: The primary efficacy endpoint was the change from baseline in the mean daily frequency of moderate and severe hot flushes during the last 7 days on patient's diary prior to visit of mid-treatment (6th week), first of all, and secondly at the end-of treatment (12th week).

Secondary Efficacy Endpoints were:

- the change from baseline in the mean daily number of total hot flushes at week 6 and 12,
- the change from baseline of vasomotor symptoms intensity at week 6 and 12
- the change from baseline of all climacteric symptoms (Greene Climacteric Scale) at week 6 and 12.
- the global efficacy assessed by the investigator

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Safety

Secondary safety endpoint was the incidence of adverse event.
Safety was assessed by monitoring all adverse events during the study from signing the informed consent up to the end of treatment.

In addition, the following safety variables were measured during all visits: physical examination, vital signs (blood pressure and heart rate). Baseline value is at visit 2 (randomization).
Laboratory evaluations (blood and urine) were measured at inclusion (visit 1) and at the end of the treatment (visit 4).The global tolerability was evaluated as reported by the Investigator and by the patient.

Statistical methods

Primary analysis: Efficacy data are presented in listings and summary tables. A Covariance analysis was planned to be carried out to compare treatment groups for the change from baseline to post-dose in average hot flushes. Differences in LSmeans and 95% confidence interval are presented. Confirmatory analysis are conducted on the Full Analysis Set (FAS); the same analysis was performed on the per protocol set. To correct for a possible imbalance between centres, small centres were combined to be included in the model: the method used to pool centres is described in the statistical analysis plan.

Safety data were to be analysed descriptively.

Secondary analysis: The secondary efficacy evaluations were conducted only in the FAS population. Inferential statistics on secondary variables were used to compare treatment groups only for exploratory purpose and to support the main variable.: methods include covariance model and non parametric tests.

Summary

Efficacy Results

Primary End-point: Baseline values of daily frequency of moderate/severe hot flushes, were comparable [8.53 (SD 2.82) in the Zavital group and 8.60 (SD 3.72) in the placebo group]. They significantly decreased both in the Zavital group (-4.56 [-53.5%] and -4.99 [-58.5%], at 6 and 12 weeks respectively) and in placebo group (-3.94 [-45.8%] and -4.65 [-54.1%], at 6 and 12 weeks respectively) but the difference between the two treatment groups was not statistically significant (-0.68 95% CI[-1.58;0.28] p=0.17 week 6 and -0.36 95% CI[-1.23;0.51] p=0.41 week 12). However, in a separate analysis considering only Romanian subjects, significant difference between treatments (p= 0.026), was reached after six weeks of treatment.

Secondary End-points:
The total number of hot flushes at baseline was 10.31 in the Zavital group and 10.38 in the placebo group and decreased to 5.42 and to 6.31 in the two groups respectively after 6 weeks and to 4.83 and 5.56 after 12 weeks. The differences between the two groups are not significant (p=0.13 and 0.120). Also intensity of hot flushes in the population decreased from baseline for both groups but did not present any statistical difference
The intensity of all symptoms included in the Greene Climacteric Scale decrease from a baseline value of 27.9 for both groups to 16.2 and 18.0 for Zavital and placebo groups, respectively, at the end of treatment. The difference between groups was in favour of Zavital with a trend towards significance (p=0.079 and 0.099 at 6 and 12 weeks respectively). Only in the case of the psychological sub-score of the Greene Climacteric scale, after 6 weeks of treatment a statistically significant difference between treatments (p=0.030) was observed and confirmed also in the Romanian subpopulation (p=0.042).
Per-protocol population did confirm the same results of the full analysis set.
The same type of result was observed for other secondary variables (global evaluation of efficacy by investigator and patient's satisfaction) with no statistically significant differences between treatments.
Analyses of two subgroups (time from last menstrual period and BMI at baseline) did not show any statistically significant difference between treatments, whilst a third analysis by previously or not taken HRT did. Women with no previous HRT (79%, 160 Romanian and 83 Italian women) showed statistically significant difference between treatment groups in moderate/severe hot flushes frequency, in total hot flushes, and in Greene Climacteric Scale (total score, hot flushes intensity, vasomotor symptoms, psychological score). This result was also confirmed by the global opinion of the investigator on efficacy.

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Safety results

Out of all 268 AEs observed during the study, only 15 (8 in the Zavital group and 7 in the placebo group) were considered as related to the product administration (ADR). There were 4 SAEs but none related to treatment. The most frequent AEs in both groups were changes in laboratory examinations results, occurred in 17.8% and 13.5% patients in the Zavital and placebo groups respectively . In particular, it is interesting to see that at the end of treatment triglycerides decreased in the Zavital group, but not in the placebo group, and total cholesterol and LDL decreased more in the Zavital group than in placebo group. So it seems that Zavital improved lipidic plasma levels. Related AE were reported only in 3.3% in Zavital and 2.6% in placebo groups respectively: gastrointestinal events (abdominal pain, epigastric discomfort, gastritis with Zavital and dyspepsia with placebo) were the most frequent. Overall, the safety results showed that a 12-week treatment with Zavital in women suffering from climacteric syndrome is safe and well tolerated: considering both the frequency and the category of adverse events, there is no difference compared to placebo.

Conclusions

As far as the safety and tolerability of soy isoflavones in the climacteric syndrome are concerned, the results of this study are positive, being the safety profile of a 12-week treatment with soy isoflavones comparable to placebo. However, in term of efficacy, the study failed to show a significant difference between the two treatment groups in decreasing hot flushes, probably due to the great placebo effect that showed a great improvement in the reference group. Statistically significant difference ($p<0.030$) favourable to Zavital, was noted only in psychological score of the Greene Climacteric Scale. Moreover, additional analyses including only Romanian women showed statistically significant difference between groups, with a decrease in daily frequency of moderate and severe hot flushes. One interesting finding to underline is that Zavital was more effective in the population who did not take any HRT in the past (the majority in Romania) with superiority from placebo in frequency and intensity of hot flushes and other symptoms. In this subgroup of naives patients the isoflavones treatment was beneficial and this could explain why efficacy parameters in Romanian population showed a greater effect.

Date of the report: 01/09/2009