STUDY REPORT

TREATMENT OF INSOMNIA WITH ENERGETIC ACUPUNCTURE POINT ACTIVATION

A DOUBLE-BLIND PLACEBO RANDOMIZED TRIAL

Protocol number:	**SN2011-002**
Investigational products:	**LifeWave Silent Nights patches** **Placebo patches**
Form(s):	**Non-transdermal patches**
Application(s):	**Application on acupuncture points**
Location of study site	**Shealy Wellness Center** 5607 S. 222nd Road Fair Grove, MO 65648 United States
Principal Investigator:	**Dr. C. Norman Shealy, M.D., Ph.D.**
Sponsor:	**LifeWave Inc** Dr. Steve Haltiwanger, MD, CCN Health and Science Director 1020 Prospect St. Suite 200 La Jolla, Ca. 92037 United States
Date and report version number:	**Final Version 1.0**

SPONSOR SIGNATURES IN ACCORDANCE WITH THE REPORT

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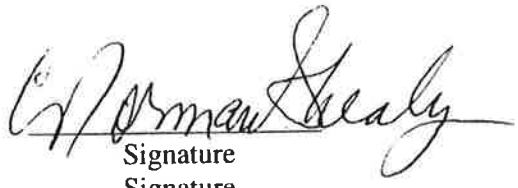
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2 SYNOPSIS

Study number:	**SN2011-002**
Protocol Title:	**Treatment of insomnia with energetic acupuncture point activation. A double-blind placebo randomized trial**
Sponsor:	**LIFEWAVE Inc.**
Objectives:	**Main objective:** To evaluate the effectiveness of LifeWave Silent Nights® patches on quality and depth of sleep. **Secondary objective** To evaluate the LifeWave Silent Nights® patches safety.
Design:	Phase 1: double-blind, controlled-placebo study. During two weeks (D0-D14), subjects were randomly divided in two groups: - One group receiving the active patches - One group receiving the placebo patches. Phase 2: open study After phase 1, all subjects received active patches during 4 weeks.
Sample Size:	50 subjects included. 46 subjects analysed.
Number of centers:	One center
Inclusion criteria:	1. Subjects willing to participate by signing a voluntary informed consent. 2. Subjects with the ability and willingness to follow the instructions of the Principal Investigator (PI) and the research staff. 3. Subjects in reasonably good health and without any major illness, not being on any beta blockers, antidepressants or tranquilizers. 4. Insomnia for a minimum of 3 months with average sleep length less than 6 hours.
Exclusion criteria:	1 Subjects with an implanted electronic device. 2. Subjects with major medical illnesses. 3. Subjects on beta blockers, tranquilizers or antidepressants. 4. Subjects who drank caffeinated beverages after 3 PM 5. Not more than 10 of the 50 potential subjects smokers. 6. Pregnancy.
Investigational product: **Name / code:** **Galenic form:**	**LifeWave Silent Nights patches** Non- transdermal patches system (Class I medical device)
Placebo **Name / code:** **Galenic form:**	**Placebo patches** Non- transdermal patches system (Class I medical device)

Dosage: **Duration:** **Administration route:**	NA One application by day at bedtime. Cutaneous application on acupuncture points (non-transdermal patches)
Safety Parameters:	Analysis of adverse events and adverse reactions.
Efficacy Parameters:	• Sleep Analog Scale (subject's estimate of average length of sleep). • Pittsburgh Sleep Quality Index: the Pittsburgh Sleep Quality Index (PSQI). • Leeds Sleep Evaluation Questionnaire. • Epworth-Sleepiness Scale. • Total Symptom Index.
Statistics:	To assess the change from baseline at each time point, a paired t-test was used. To compare active and placebo groups, a t-test for unpaired data was used. The normality assumption was checked with a Shapiro-Wilk test (α=0.01). In case of deviation, a Wilcoxon signed rank test or Mann-Whitney was applied instead.
Results-Conclusion	After 2 weeks of patches use, the active group improved sleep by 2.22 hours whereas the placebo group improved sleep by 0.98 hours in the same period. So the sleep improvement in the active patch group was 1.24 hours more than the placebo group. The difference between active and placebo groups was statistically significant (p=0.048). At the end of the next 4 weeks, length of sleep in both groups receiving the active patches increased 2.53 hours in average (p<0.001) (66% of sleep increase). No adverse reaction was observed. The patches can then be considered as well tolerated. **Considering the safety and results obtained in this study of LifeWave® Silent Nights Patches, it is reasonable to suggest that they should be one of the preferred potential approaches to insomnia**.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
CRF	Case Report Form
CRA	Clinical Research Associate
GCP	Good Clinical Practice
I.C.H	International Conference on Harmonisation
IRB	Institutional Review Board
MD	Medical Device
SAE	Serious Adverse Event
PSQI	Pittsburgh Sleep Quality Index

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board (IRB)

The protocol and its appendices were reviewed and approved by the Quantum Institutional Review Board (USA) on March 24, 2011.

5.2 Ethical conduct of the study

Declaration of HELSINKI[(1)]
The current revision of the Declaration of Helsinki is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol. Independent insurance that subjects are protected can only be provided by an ethics committee/institutional review board and freely obtained informed consent.

Good Clinical Practice[(2)]
Good clinical practice is a standard for clinical studies, which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures the studies are ethically justified and scientifically sound, and that the clinical properties of the diagnostic/therapeutic/prophylactic product under investigation are properly documented.

Ethics Committee or IRB[(3)]
It is the responsibility of the sponsor or its legal representative to submit a copy of the protocol and detailed patient information sheet and consent form to an ethics committee/institutional review board in order to obtain independent approval to conduct the study. Ethics committee/institutional review board approval must be obtained before the study is started. The approval of the ethics committee/institutional review board must be sent in writing, to the sponsor or its legal representative. The Ethics Committee approval letter must mention the Ethics Committee members and their function.

This clinical study was conducted on subjects in accordance with Good Clinical Practice (GCP) (ICH Topic E6 Note for Guidance on GCP CPMP/ICH/135/95, ISO1455 standard).

5.3 Subject information and consent form

It is the responsibility of the investigator(s) to obtain informed consent from each subject participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study.
It should be completely and unambiguously clear to each subject that she/he is free to refuse to participate in the study, or that she/he can withdraw her/his consent at any time and for any reason, without incurring any penalty or withholding of treatment on the part of the investigator.
The consent obtaining should be done under such conditions that permit to the subject to consider in the best way the ratio benefits/ risks associated to his/her participation in the study.
The investigator insures that the content of the information and consent form is appropriate to the study and that the process for obtaining the consent is in conformity with the applicable regulation.

In the frame of this study, the consent has been obtained before any study-specific procedures were performed, and thus in accordance with the Helsinki declaration.
No subject could be included and/or randomized before having signed the consent form, written in an understandable language.

Each subject received oral and written information concerning the studied product(s), its nature, the duration and the conditions of the study. The consent was personally signed and dated by the subject in two exemplars and by the person in charge of the consent obtaining.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was conducted on Shealy Wellness Center (5607 S. 222nd Road, Fair Grove, MO 65648, United States).

The list of the main participants in the study is presented in **Appendix 16.1.4.**

7 INTRODUCTION

Just over 200 years ago, most Americans slept an average of 10 hours, adjusting their wake-sleep hours to daylight. Today a huge number of individuals sleep not more than 5.5 hours per night and they do not consider that a sleep problem. In a number of surveys, 40% of individuals report that they have significant problems with insomnia.[1] There are excellent studies showing that within a month or less, insomnia leads to excessive sleepiness at work, mood disturbances, increase in errors, increase in accidents and family and social problems. Chronic insomniacs have a much higher incidence of cardiovascular disease, diabetes, obesity, gastrointestinal disease, absenteeism, disciplinary problems, separation, divorce and death. The problems and the incidence of illness in general markedly increase in individuals who work anything other than a normal 8 to 5 pattern. Those who work the evening shift, roughly 4 p.m. to midnight, have increased illnesses and those who work the night shift, roughly midnight to 8 a.m. or 11 p.m. to 7 a.m., have an even greater number of illnesses. And finally, those who have swing shifts, working one month one shift and the next month a different shift, have the greatest number of illnesses of all.[2-8]

There are a number of medications that have been used to treat insomnia. None of these is totally satisfactory and all of them carry significant potential, and often “undesirable,” side effects. Benzodiazepines are particularly harmful as they interfere with stage 4 sleep. Antidepressant drugs most often also have many undesirable effects when used only to treat insomnia. Finally, the drugs specifically for sleep often lead to the feeling of a hangover or sleep walking, driving and other activities while asleep, and even modest use of hypnotic sleep prescriptions leads to marked increase in the risk of death.[9] In the current study, our objective is to determine the potential for safe and effective enhancement of sleep with the application of specific acupuncture patches designed to improve sleep.

LifeWave Patches are designed to stimulate acupuncture points by a mechanism that involves both acupressure and energetic principles to stimulate specific acupuncture points.

Initially, under an Institutional Review Board approved protocol, 25 individuals suffering from long-standing insomnia were entered into an open-label study. The LifeWave Patches are comprised of solutions of optically active organic material, which serve as organic molecular antennae (nano-sized molecular structures) using a solution based self-regulation process. All subjects were in reasonably good health with no major illnesses and were not on beta blockers, antidepressants or tranquilizers. None of them had an implanted electronic device. After initial evaluation, which consisted of a history and physical exam, participants completed the following questionnaires: Pittsburgh Sleep Quality Index, Leeds Sleep Evaluation Questionnaire, Epworth-Sleepiness Scale , Sleep Analog Scale. Individuals were instructed to place one of the patches on 1 of 5 specific acupuncture points at bedtime. If individuals did not sleep adequately the first night, they could go through each of these points until they had achieved the best possible sleep and then rotate between the points that had the best effect for the duration of the 30 day study. One individual dropped out of the study and could not be contacted for further evaluation. There were no negative reports. The results showed that **seventy-two percent of the individuals had normal daytime sleeping (ESS Test) after using the Silent Nights patches**. **Eighty percent noted improved quality of sleep (LESQ Test) and 88% had improved length of sleep (PSQ Test). In general, the PSQ Test and the Sleep Analog yielded equal results.**

Following this, a follow-up study was designed as a double blind/placebo controlled randomized study of the Silent Nights patches.

8 RESEARCH OBJECTIVES

8.1 Primary objective

The main objective of the study was to evaluate the effectiveness of LifeWave Silent Nights® patches on quality and depth of sleep.

8.2 Secondary objective(s)

The secondary objective of the study was to evaluate the LifeWave Silent Nights® patches safety.

9 CONCEPTION OF THE RESEARCH

9.1 Methodology of the research

There was two phases in the study

Phase 1: double-blind, controlled-placebo study.

During two weeks (D0-D14), subjects were randomly divided in two groups:
- One group receiving the active patches
- One group receiving the placebo patches.

Phase 2: open study
After phase 1, all subjects received active patches during 4 weeks.

9.2 Research Flow chart

Figure 1 - Study flow chart

Schedule	Visit 1 Screening/Inclusion	Visit 2 Evaluation	Visit 3 Evaluation
Days	**D0**	**D14 ± 1**	**D42 ± 2**
Informed consent form signature	■		
Medical examination	■		
Medical history	■		
Checking of the inclusion and exclusion criteria	■		
Inclusion	■		
Patch distribution (active or placebo) for the first part of the study	■		
Patch distribution (active) for the second part of the study		■	
Sleep scales completion by the subjects	■	■	■
AE collection		■	■
Study end			■

9.3 Description of the research schedule

Screening/inclusion visit:

- Subjects were recruited on a weekly radio program, which the lead author has done for 22 years. They were informed over the phone about the details of the study and an appointment was made.
- Subjects came to the study site. They were orally informed about study aims, restrictions and risks, and then, in writing by the informed consent form. If they agreed to participate to this study, they signed the informed consent form in duplicate.
- They underwent a general medical evaluation and physical examination, which included a medical history, general physical and neurological exam. Inclusion and exclusion criteria were checked.
- Eligible subjects were then assigned a Subject ID and randomized to a treatment group for the two week, placebo-controlled portion of the study.
- Subjects completed the different sleep scales.
- Active or Placebo patches were given to the subjects according to a randomization list. Neither the subject nor the investigators knew which patch was attributed to each subject (double-blind study).
- Subjects were instructed to use one of the five placements as in the previous pilot study and to proceed with all variations until they found the best personal preferred location.

After 2 weeks (D14):
- Subjects returned to the study site.
- Possible adverse events were collected.
- They completed the different sleep scales.
- All subjects were provided with active patches to be used for the next 4 weeks, as part of the open-label portion of the study.

After 4 additional weeks (D42):
- Subjects returned to the study site.
- Possible adverse events were collected.
- They completed the different sleep scales.

Remark: when considered appropriate for the study, subjects were shown how to use the patches and given an initial 15-day supply. Each individual was then given instructions to phone us if any concerns or side-effects developed, and were scheduled to return for repeat tests at the end of 14 or 15 days. They returned after two weeks and were given the other set of active patches and returned at the end of another 28 to 30 days for final testing.

9.4 Discussion of research design, including the choice of control group

The placebo controlled phase (phase 1) enables to experiment the placebo effect and to compare it to the active patches effect. The open phase (phase 2) enables to increase the number of subjects receiving the active patches.

9.5 Selection of the studied population

9.5.1 Inclusion criteria

1. Subjects willing to participate by signing a voluntary informed consent.
2. Subjects with the ability and willingness to follow the instructions of the Principal Investigator (PI) and the research staff.
3. Subjects in reasonably good health and without any major illness, not being on any beta blockers, antidepressants or tranquilizers.
4. Insomnia for a minimum of 3 months with average sleep length less than 6 hours.

9.5.2 Exclusion criteria

1. Subjects with an implanted electronic device.
2. Subjects with major medical illnesses.
3. Subjects on beta blockers, tranquilizers or antidepressants.
4. Subjects who drank caffeinated beverages after 3 PM
5. Not more than 10 of the 50 potential subjects smokers.
6. Pregnancy.

9.5.3 Premature study exit

9.5.3.1 Criteria and modalities of premature end of treatment or subject exclusion from the study

Subjects were free to withdraw from the study at any time if they wish so and for any reason, without having to provide any justification to the investigator.
The investigator had the right to withdraw a subject for any reason, for subject's best interests, including illness or adverse events.
The sponsor may decide to withdraw subjects for major deviation to the protocol, for administrative reasons or for any other valuable reason ethically justified.

Subjects may discontinue the study for the following reasons:

1. *Subject consent withdrawal:* subjects had the right to exit from the study at any time and for any motive, without their right to treatment being affected.
2. *Medical reasons or adverse events:* the investigator had the right to withdraw a subject in case of intercurrent illness or adverse events or if in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
3. *Appearance of an exclusion criterion.*
4. *Failure to follow-up:* if a subject did not come to the scheduled visits, several attempts had to be done to try to contact him/her; to obtain the reasons for non-attendance.
5. *Violations and deviations from the protocol.*
6. *Administrative reasons.*

9.5.3.2 Modalities for the follow-up of these subjects

All records were maintained for subjects who drop out of the study and for subjects who were screened and failed to meet the study requirements. If a subject drops out within the first 2 weeks of the study, a replacement subject may be chosen and enrolled.

9.6 Investigational products

9.6.1 Description of the investigational product(s)

LifeWave technology creates a variety of patches using proprietary solutions of organic molecules as building blocks. LifeWave Patches are comprised of solutions of optically active organic materials. These special solutions are placed in a reservoir between two pieces of plastic, which create a sealed chamber. Within the sealed reservoir is a piece of **fabric that serves as a template** for the **self assembly** of organic **molecular antennas** (nano-sized molecular structures) using **solution-based self-assembly processes), molecules that are nanometers in size**. **The production of small molecular antennas of nanoscale size is the nanotechnology aspect of this technology**. The fact that the production of LifeWave patches involves making a solution, using proprietary processing techniques and using a special piece of fabric to cause a precipitation out of solution of **nano-sized molecular crystals,** does not in anyway detract from the fact that this is a nanotechnology manufacturing technique.

LifeWave patches are constructed of organic materials. These organic materials have been chosen because they have optical (chiral), liquid crystal and semiconductor properties. By using a nanotechnology production process called **solution-based self-assembly,** these optically active and electrically conductive materials, when placed in LifeWave patches, form small nanosize molecular structures that function as **molecular antennas**. Placing a conducting material in an oscillating magnetic field creates an electrical signal/frequency in the conducting material.

The "very small" molecules in the patches contain electromagnetic properties. These small nanoscale structures serve as passive molecular antennas that are activated by the oscillating electromagnetic field of the body to generate electromagnetic signals that are resonant frequencies for certain structures contained within molecules. THE BASIC ISSUE IS THAT YOU CAN ACTIVATE METABOLIC REACTIONS WITH FREQUENCY SIGNALS AS WELL AS CHEMICAL SIGNALS, IF YOU HAVE THE PROPER FREQUENCY CODE AND WAVEFORM. LifeWave patches basic function is to generate a set of biologically active signals when the patches interact with the human body's mammalian cells. These frequencies are generated by the physics principle of INDUCTION. The patches chosen for this study will be those designed to enhance sleep.

9.6.2 Dosage

Patches were used daily during the whole study.

9.6.3 Instruction(s) of use

9.6.3.1 Administration route and recommendation(s)

Subjects were instructed to place one of the patches on 1 of 5 specific acupuncture points at bedtime.

The points used were:

- Right Liver
- Right Triple Heater
- Right Triple Heater
- Governing Vessel
- Right Stomach

If individuals did not sleep adequately the first night, they could go through each of these points until they had achieved the best possible sleep and then rotate between the points that had the best effect for the duration of the study.

9.6.3.2 Storage conditions

The study products were stored under the supervision of a physician approved for the study under suitable safety conditions ensuring proper storage. **The active and inactive patches were kept in separate Faraday cages to avoid any possible energetic interchange between them.**

The products were used only under conditions defined in this protocol and only for included subjects.

9.6.3.3 Dispensing and accountability of investigational product(s)

The tested products should only be dispensed under the supervision of a physician approved for the study. The investigator (or delegate) was responsible for dispensing the study products to the subjects who were included in the study. The study products should not be administered to subjects who were not included in the study.

9.6.4 Treatments allocation – Randomisation - Blinding

An assistant, not involved in patient care, received the prepared study articles from the Sponsor and placed the placebo and active patches for the first two weeks in Faraday cages in separate rooms. The study articles were coded upon arrival to indicate difference between the two treatments; however which treatment the code indicated was not known. The assistant used a randomized system to determine which initial patch was to be given a patient. The investigator had no contact with or knowledge about the selection of the patches.

9.7 Evaluation variables

9.7.1 Evaluation criteria

9.7.1.1 Main evaluation criterion

- Sleep Analog Scale is subject's estimate of average length of sleep.

9.7.1.2 Secondary evaluation criteria

- Pittsburgh Sleep Quality Index: the Pittsburgh Sleep Quality Index (PSQI).
- Leeds Sleep Evaluation Questionnaire.
- Epworth-Sleepiness Scale.
- Total Symptom Index.

9.7.2 Efficacy Evaluation

9.7.2.1 Description of the efficacy parameters

9.7.2.1.1 Sleep Analog Scale

Sleep Analog is defined as the estimation by the subject of his/her average length of sleep.

9.7.2.1.2 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)[14] was developed to measure sleep quality during the previous month and to discriminate between good and poor sleepers.
The questionnaire used for the PSQI evaluation is presented in appendix 16.1.13.1.

The PSQI score calculation is presented below:

PSQIDURAT **DURATION OF SLEEP**
IF Q4 ≥ 7, THEN set value to 0
IF Q4 < 7 and ≥ 6, THEN set value to 1
IF Q4 < 6 and ≥ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB **SLEEP DISTURBANCE**
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) ≥ 1 and ≤ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and ≤ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN **SLEEP LATENCY**
First, recode Q2 into Q2new thusly:
IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0
IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1
IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1
IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2
IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS **DAY DYSFUNCTION DUE TO SLEEPINESS**
IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1
IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2
IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE **SLEEP EFFICIENCY**

Diffsec = Difference in seconds between day and time of day Q1 and day Q3
Diffhour = Absolute value of diffsec / 3600
newtib =IF diffhour > 24, then newtib = diffhour – 24
IF diffhour ≤ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0
IF tmphse < 85 and ≥ 75, THEN set value to 1
IF tmphse < 75 and ≥ 65, THEN set value to 2
IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL **OVERALL SLEEP QUALITY**
Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS **NEED MEDS TO SLEEP**
Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI **TOTAL**
DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL ≤ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality

9.7.2.1.3 Leeds Sleep Evaluation Questionnaire

The Leeds Sleep Evaluation Questionnaire comprises ten self-rating 100-mm-line analogue questions concerned with aspects of sleep and early morning behaviour. The Leeds Sleep Evaluation Questionnaire is presented in Appendix 16.1.13.2.

9.7.2.1.4 Epworth-Sleepiness Scale

The Epworth Sleepiness Scale (ESS)[15] is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. This questionnaire is presented in Appendix 16.1.13.2.

9.7.2.1.5 Total Symptom Index [11]

Although this has not been evaluated in relation to sleep, it has been shown to correlate with total stress.

9.7.2.2 Method and calendar for measure, collect and analyze the efficacy parameters

All the sleep scales were completed by the subjects at baseline, after two weeks of placebo or active patches use, and after 4 additional weeks of active patches use.

9.7.3 Safety Evaluation

9.7.3.1 Description of the safety parameters

Safety of the patches was evaluated by collection of possible adverse reactions.

9.7.3.2 Method and calendar for measure, collect and analyze the safety parameters

Adverse events were collected at each visit after the baseline.

9.8 Data Quality Assurance – Monitoring

9.8.1 Collection and data control

At each visit of the subject, the investigator reported in the CRF the data related to the subject's health state, safety of the products applied and scores of each sleep scale, according to the protocol within the study.
The case report forms were designed to identify each subject by a subject number and, where appropriate, subject's initials. One Case Report Form existed for each subject participating in the study. The case report form was completed legibly, using a black ballpoint pen. Erroneous values and/or text were not erased. Instead, the error was crossed out with a single line, the correct value/text added, and the correction signed, initialled and dated by the investigator(s).

9.8.2 Access right to source data

In accordance with good clinical practices and the standards of the data protection law, data obtained in the course of a biomedical research has to be treated confidentially to guarantee the subjects' privacy.

The investigator agreed that, subject to local regulations and ethical considerations, the sponsor representatives designee and/or any regulatory agency may have direct access to all study records, CRFs, corresponding subject medical records, study drug dispensing records and study drug storage area, and any other documents considered source documentation. The investigator also agreed to assist the representative, if required.
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9.9 Statistics

To assess the change from baseline at each time point, a paired t-test was used. To compare active and placebo groups, a t-test for unpaired data was used. The normality assumption was checked with a Shapiro-Wilk test (α=0.01). In case of deviation, a Wilcoxon signed rank test or Mann-Whitney was applied instead.

9.10 Administrative Procedures

9.10.1 Archiving of study data and documents

Study data will be kept by the researcher in locked files for 5 years.

9.10.2 Audit and inspection

The study was conducted under the responsibility of the sponsor in compliance with the applicable international and local regulatory requirements and in respect of the sponsor and/or CRO SOPs for study conduct and monitoring.

Inspection may be performed by regulatory authorities' inspectorate before, during, or after the study.

9.10.3 Publication

The sponsor reserves the right to review all the manuscript(s) and abstract(s) before their submission for publication or presentation. Publication of data will be at the discretion of the sponsor

This is not intended to restrict or hinder publication or presentation, but to allow the sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator(s).

10 STUDY SUBJECTS

10.1 Disposition of subjects

There were 50 subjects included: 31 women and 19 men, ranging in age from 18 to 80.
Four subjects (17, 24, 25 and 29) dropped out during the study.

Phase 1 (double-blind study versus placebo):

	Active	Placebo
Number of subject initially included	25	25
Number of subjects who ended the study after 2 weeks	23	23

Phase 2 (open study):

	Active
Number of subject at the beginning of phase 2	46
Number of subjects who ended the study after 4 weeks	46

10.2 Protocol deviations

No deviation occured.

11 EFFICACY EVALUATION

There were no significant differences in the Sleep Inventories, perhaps because of the wide variation in the initial testing. **Only the Sleep Analog (number of hours of sleep)**, which had been shown to be as accurate as the length of sleep in the Pittsburg Sleep Quality Index in the open label study, showed significant increases in length of sleep, and **is presented in this report.**

The individual data of Sleep Analog are presented in Appendix 16.2.

Phase 1: double-blind study versus placebo

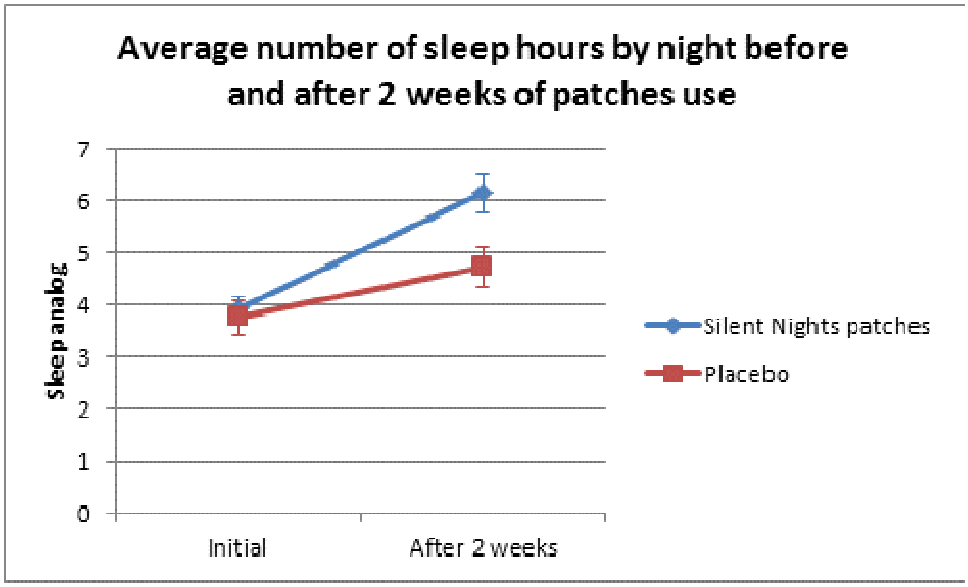
The results are summarized in the table below:

Average number of sleep by night (mean ± SEM)

	Initial	After 2 weeks	Difference	Student t-test
Silent Nights patches (n=23)	3.93 ± 0.21	6.15 ± 0.39	2.22 ± 0.41	p<0.001
Placebo (n=23)	3.76 ± 0.32	4.74 ± 0.38	0.98 ± 0.45	p=0.039

The active group improved sleep by 2.22 hours after the 2nd week compared to baseline whereas the placebo group improved sleep by 0.98 hours in the same period. So the sleep improvement in the active patch group was 1.24 hours more than the placebo group. The difference between active and placebo groups was statistically significant (p=0.048).

Results are illustrated in the graph below:



Phase 2: open study

At the end of the 2 week period, the placebo group received the active treatment as well

Average number of sleep by night (mean ± SEM)

	Initial	Final	Difference	Student t-test
Silent Nights patches (n=23)	3.93 ± 0.21	6.15 ± 0.32	2.22 ± 0.35	p<0.001
Placebo (n=23)	3.76 ± 0.32	6.61 ± 0.45	2.85 ± 0.45	p<0.001
Total (n=46)	3.85 ± 0.19	6.38 ± 0.28	2.53 ± 0.29	p<0.001

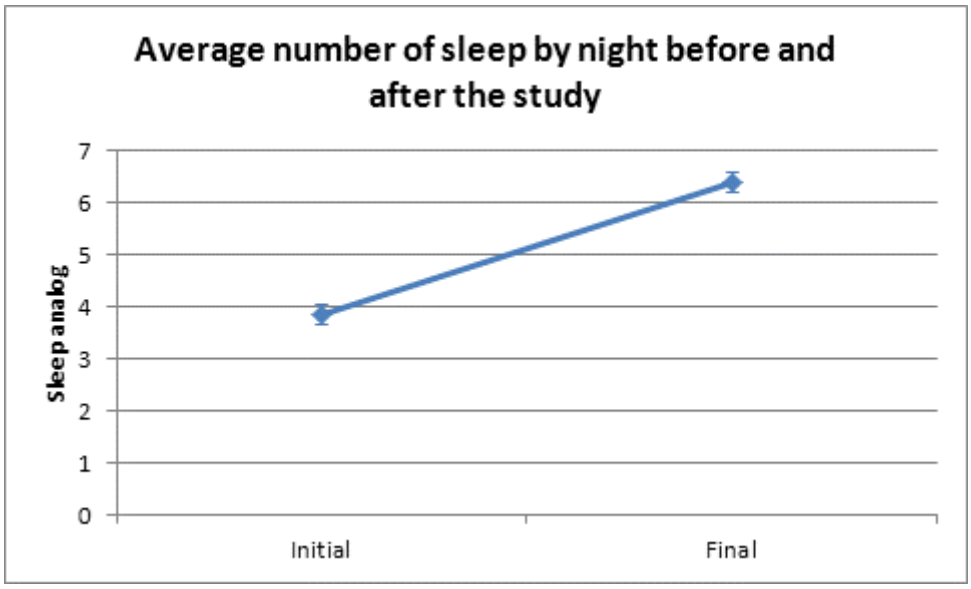
When we examine the placebo group's increase in numbers of hours asleep at final compared to baseline (when they were wearing active patches for the last 4 weeks) we find 2.85 hours longer sleep.

When we examine the active group's increase in numbers of hours asleep at final compared to baseline (when they were wearing active patches for the last 4 weeks), we find 2.22 hours longer sleep.

Taking the whole together, we find that use of active LifeWave patches in all 46 people (who used active patches for the last 4 weeks increased sleep length of 2.53 hours in average (p<0.001) (66% of sleep increase).

This is a significant number to sleep over 2 and one-half hours longer with use of the patches..

Results are illustrated in the graph below:



12 SAFETY EVALUATION

12.1 Extent of Exposure

23 subjects tested the active patches during 6 weeks.
23 subjects tested the placebo patches during 2 weeks and then the active patches during 4 weeks.

No subject stopped the treatments following intolerance reactions.

12.2 Adverse reactions

No adverse reactions occurred during the study.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Not applicable.

12.4 Clinical laboratory results

Not applicable.

12.5 Safety conclusions

Both active and placebo patches can be considered as very well tolerated.

13 DISCUSSION AND OVERALL CONCLUSION

The results in the open label and the randomized double-blind placebo controlled study are remarkably similar, with only 8% less increase in length of sleep in the placebo-controlled study. There were no complications or adverse effects in either study. The subjects in this study started with an average sleep length of 2 to 5.5 hours, with one exception of 7 hours. Those receiving active patches entered with 3.9 hours average length of sleep. At the end of the first 2weeks, they were sleeping an average of 6.2 hours and after another 4 weeks they were still sleeping an average of 6.2 hours. Those receiving placebo patches initially entered with average length of sleep from one to 5 hours. Those who initially received placebo patches entered sleeping an average of 3.8 hours. At the end of the first two weeks, they averaged 4.7 hours and after 4 weeks using the active patches, they averaged 6.6 hours of sleep.

There are several other studies of LifeWave technology including one that showed marked improvement in heart rate variability signals, of LifeWave Energy Patches during rest and exercise in 20 young and healthy volunteers.[12]

Another study called “Nanoscale Wearable Devices Reduce Qualitative and Quantitative Measures of Neuromuscular Pain”, which was published in the International Journal of Medical Implants & Devices, demonstrated a highly significant reduction in quantitative and qualitative measures of pain with an average statistical power of at least 94% and significant at the greater than 0.001 level.[13] Thus, there appears to be increasing evidence that these energetic acupuncture patches have physiological effects.

Considering the safety and results obtained in this study of LifeWave® Silent Nights Patches, it is reasonable to suggest that they should be one of the preferred potential approaches to insomnia.

14 TABLES, FIGURES AND GRAPHS REFFERED TO BUT NOT INCLUDED IN THE TEXT

Not applicable.

15 REFERENCES LIST

15.1 Ethical aspect

1 - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI/ Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates

2 - ICH TOPIC E6/ Note for guidance on Good Clinical Practice- CPMP / ICH / 135 / 95, January 1997

15.2 Insomnia and investigational product

1. Moore-Ede, M. *The 24 Hour Society*. Redding, MA:Addison Wesley Publishing, 1993.

2. Leger D, Guilleminault C, Bader G, et al. Medical and socio-professional impact of insomnia. *Sleep* 2002;25(6):621-25.

3. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6(2):97-111.

4. Goley DJ, Monjan A, Simonsick EM, et al. Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. *Sleep* 1999;22(Sup2):S366-S372.

5. Kripke DF, Garfinkel L, Wingard DL, et al. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry* 2002;59:131-36.

6. Stoller MK. Economic effects of insomnia. *Clin Ther*. 1994;16(5):873-97.

7. Perlis ML, Smith, MT, Andrews PJ, et al. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep* 2001;24:110-17.

8. Chang PP, Ford DE, Mead LA, et al. Insomnia in young men and subsequent depression. *American Journal of Epidemiology* 1997;146(2):105-14.

9. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2(1):e000850.

10.Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations – a review. *Psychopharmacology* 1980;71:173-179.

11.Shealy CN. Total life stress and symptomatology. *Journal of Holistic Medicine* 1984;6(2):112-29.

12.Nazeran H. Heart rate variability signal parameters quantify skin cooling effect of Energy Patches during rest and exercise in young healthy individuals. *Biomedical Engineering Recent Developments* 2007:13-19.

13.Nazeran H, Haltiwanger E. "Nanoscale Wearable Devices Reduce Qualitative and Quantitative Measures of Neuromuscular Pain." International Journal of Medical Implants & Devices. Vol 5. Number 2, 2011.

14. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989

15.Johns, M.W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep, 14, 540-545.

16 APPENDICES

16.1 General description of the research

16.1.1 Protocol and amendments
Not included.

16.1.2 Blank Case Report Form
Not included.

16.1.3 List of CPP (or IRB) with the name of the president if required by the competent authority
Not included.

16.1.4 Blank information and consent form
Not included.

16.1.5 List and identification of the investigators and important personal participating in the study

NAME	FUNCTION
C. Norman Shealy, M.D., Ph.D.	Main investigator
Julie A. Penick, FNP, Ph.D	Co-investigator
Robert Mueller	Research Associate

16.1.6 Listing of subjects receiving investigational product(s) from specific batches where more than one batch was used
Not applicable.

16.1.7 Randomisation scheme and codes (subject identification and treatment assigned)

Subject #	Product	Subject #	Product
1	Active	26	Active
2	Placebo	27	Placebo
3	Active	28	Active
4	Placebo	29	Placebo
5	Placebo	30	Active
6	Active	31	Active
7	Active	32	Placebo
8	Placebo	33	Active
9	Active	34	Placebo
10	Placebo	35	Active
11	Placebo	36	Placebo
12	Active	37	Placebo
13	Active	38	Active
14	Placebo	39	Active
15	Active	40	Placebo
16	Placebo	41	Placebo
17	Placebo	42	Placebo
18	Placebo	43	Active
19	Active	44	Active
20	Placebo	45	Placebo
21	Placebo	46	Active
22	Active	47	Active
23	Active	48	Placebo
24	Placebo	49	Placebo
25	Active	50	Active

16.1.8 Audit certificates (if available)
Not applicable.

16.1.9 Documentation of statistical methods
Not applicable

16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used

Not applicable.

16.1.11 Publications based on the research

16.1.11.1 PITTSBURGH SLEEP QUALITY INDEX

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?
BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?
GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

b) Wake up in the middle of the night or early morning
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

c) Have to get up to use the bathroom
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

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d) Cannot breathe comfortably
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

e) Cough or snore loudly
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

f) Feel too cold
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

g) Feel too hot
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

h) Had bad dreams
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

i) Have pain
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

j) Other reason(s), please describe_____
_____
How often during the past month have you had trouble sleeping because of this?
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

6. During the past month, how would you rate your sleep quality overall?
Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or room mate?
No bed partner or room mate _____
Partner/room mate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____
If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .
a) Loud snoring
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____
b) Long pauses between breaths while asleep
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____
c) Legs twitching or jerking while you sleep
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.
d) Episodes of disorientation or confusion during sleep
Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____
e) Other restlessness while you sleep; please describe_____
_____
Not during the Less than Once or twice Three or more

past month_____ once a week_____ a week_____ times a week_____

16.1.11.2 Leeds Sleep Evaluation Questionnaire

How would you describe the way you currently fall asleep in comparison to usual?

1. More difficult than usual _____ Easier than usual
2. Slower than usual _____ More quickly than usual
3. I feel less sleepy than usual _____ More sleepy than usual

How would you describe the quality of your sleep compared to normal sleep?

4. More restless than usual _____ Calmer than usual
5. With more wakeful periods than usual _____ With less wakeful periods than usual

How would you describe your awakening in comparison to usual?

6. More difficult than usual _____ Easier than usual
7. Requires a period of time longer than usual _____ Shorter than usual

How do you feel when you wake up?

8.Tired _____ Alert

How do you feel now?

9.Tired _____ Alert

How would you describe your balance and co-ordination upon awakening?

10. More disrupted than usual _____ Less disrupted than usual

16.1.11.3 Epworth-Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

TOTAL SCORE = _____

Score Results :

1-6 Congratulations, you are getting enough sleep!
7-8 Your score is average
9 and up Very sleepy and should seek medical advice

Johns, M.W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep, 14, 540-545.

16.2 Subject data listings

Sleep Analog data:

	Active		
Subject #	**Initial**	**After 2 weeks**	**Final**
1	5	5.5	7
3	2	3	3
6	3	6	6.5
7	4	7	7
9	5	8	8
12	5	6	7
13	3	8	7
15	5	8	7
19	2	7	8
22	4.5	4	5
23	Dropped	Dropped	Dropped
25	Dropped	Dropped	Dropped
26	4	6	6
28	5	6	7
30	3	4	6
31	3	4	5
33	5	9	8
35	4	6	6
38	4	8	8
39	5	2	2
43	5	5	5
44	4	7	6
46	4	9	7
47	3	7	5
50	3	6	5

	Placebo		
Subject #	**Initial**	**After 2 weeks**	**Final**
2	4	5	7
4	2	3	4
5	4	4	2
8	5.5	5.5	7
10	7	3	10
11	4	5	8
14	1	3	7
16	2	4	5
17	Dropped	Dropped	Dropped
18	5	6	4
20	4	8	8
21	3	8	8
24	2	3	5
27	1	6	8
29	Dropped	Dropped	Dropped
32	4	6	7
34	4	3	10
36	2	2	2
37	5	5.5	6.5
40	3	6	7
41	5	5	7
42	4	1	5
45	5	7	9
48	5	5	7.5
49	5	5	8

16.3 Case report forms

16.3.1 CRFs of deaths, other serious adverse events and withdrawals for AE

Not applicable.

16.3.2 Other CRFs submitted

Not applicable.

16.4 Other Individual subject data listings (US Archival Listings)

Not applicable.