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A PLACEBO CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY & SAFETY OF INSTAVIT® SWEET DREAMS ORAL SPRAY IN THE TREATMENT OF OCCASIONAL SLEEPLESSNESS."

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ABSTRACT

Background: NEW Instavit® Sweet Dreams is a Melatonin based oral spray supplement that has been physician formulated. It is designed to promote a natural sleep cycle and a soothing night's sleep with just 2 sprays. Melatonin is a natural hormone made by the pineal gland, a small gland in the brain. Melatonin helps control your sleep and wake cycles. Melatonin is sometimes called the "Dracula of hormones" - it only comes out in the dark. **Objectives:** The aim of the study is to evaluate the safety and efficacy of Instavit sweet Dreams oral spray in the treatment of occasional sleeplessness. **Conclusion:** Considering all data evaluations for Primary and secondary end-points it has been clearly determined that Instavit sweet Dreams oral spray is more efficacious than Placebo in the treatment of occasional sleeplessness. All the scales used i.e., Insomnia Severity Index, Pittsburgh Insomnia scale and Epworth sleepiness scale showed improvement in the sleeping disorders of the patients for Instavit sweet Dreams oral spray arm up to major extent in comparison to Placebo arm. No serious adverse events were observed during the clinical trial, though 6 adverse events were reported in Visit II and 7 adverse events were reported in Visit III but none of them is related with the study drug and this concludes that investigational product is safe enough to use.

KEYWORDS: Melatonin, End of Treatment (EOT) seasonal affective disorder (SAD).

INTRODUCTION

What is Melatonin?

Melatonin is a natural hormone made by your body's pineal (pih-knee-uhl) gland. This is a pea-sized gland located just above the middle of the brain. During the day the pineal is inactive. When the sun goes down and darkness occurs, the pineal is "turned on" by the SCN and begins to actively produce Melatonin, which is released into the blood. Usually, this occurs around 9 pm. As a result, Melatonin levels in the blood rise sharply and you begin to feel less alert. Sleep becomes more inviting. Melatonin levels in the blood stay elevated for about 12 hours - all through the night - before the light of a new day when they fall back to low daytime levels by about 9 am. Daytime levels of Melatonin are barely detectable.

Besides adjusting the timing of the clock, bright light has another effect. It directly inhibits the release of Melatonin. That is why Melatonin is sometimes called the "Dracula of hormones" - it only comes out in the dark. Even if the pineal gland is switched "on" by the clock, it will not produce Melatonin unless the person is in a dimly lit environment. In addition to sunlight, artificial indoor lighting can be bright enough to prevent the release of Melatonin.

Melatonin is a hormone made by the pineal gland, a small gland in the brain. Melatonin helps control your sleep and wake cycles. Very small amounts of it are found in foods such as meats, grains, fruits, and vegetables.

What does natural Melatonin do in the body?

Your body has its own internal clock that controls your natural cycle of sleeping and waking hours. In part, your body clock controls how much Melatonin your body makes. Normally, Melatonin levels begin to rise in the mid- to late evening, remain high for most of the night, and then drop in the early morning hours.

Light affects how much Melatonin your body produces. During the shorter days of the winter months, your body may produce Melatonin either earlier or later in the day than usual. This change can lead to symptoms of seasonal affective disorder (SAD), or winter depression.

Natural Melatonin levels slowly drop with age. Some older adults make very small amounts of it or none at all.

Why is Melatonin used as a dietary supplement?
Melatonin supplements are sometimes used to treat jet lag or sleep problems (insomnia). Scientists are also looking at other good uses for Melatonin, such as:

- Treating seasonal affective disorder (SAD).
- Helping to control sleep patterns for people who work night shifts.
- Preventing or reducing problems with sleeping and confusion after surgery.
- Reducing chronic cluster headaches.

Is taking a Melatonin dietary supplement safe?
In most cases, Melatonin supplements are safe in low doses for short-term and long-term use. But be sure to talk with your doctor about taking them.

Children and pregnant or nursing women should not take Melatonin without talking to a doctor first.

Melatonin does have side effects. But they will go away when you stop taking the supplement. Side effects may include:

- Sleepiness.
- Lower body temperature.
- Vivid dreams.
- Morning grogginess.
- Small changes in blood pressure.

In adults, Melatonin is taken in doses from 0.2 mg to 20.0 mg, based on the reason for its use. The right dose varies widely from one person to another. Talk to your doctor to learn the right dosage and to find out if Melatonin is right for you.

Description
NEW Instavit® Sweet Dreams is a doctor formulated natural sleep supplement which utilizes calming chamomile and Melatonin to help improve your natural sleep cycle. Whether you are jet lagged or struggling with occasional sleeplessness, this great-tasting, pill-free and pocket-sized spray makes falling asleep a dream come true with just 2 sprays.*

- May help remedy jet-lag and occasional sleeplessness.*
- Zero sugar, zero calorie oral spray supplement.
- Great taste; contains xylitol.
- Pure. Potent. Portable.
- 28 restful nights per bottle.*

OBJECTIVES

Primary Objective

- To assess the efficacy of Instavit® sweet Dreams spray in the treatment of occasional sleeplessness.

Secondary Objective

- To evaluate the safety of Instavit® sweet Dreams in the treatment of occasional sleeplessness.

METHODS

Inclusion Criteria
Healthy male and female between age 18-65 years, have the willingness to undergo treatment of occasional sleeplessness. and able to comply with all trial requirements were included in the study. Subjects who works in shifts and who travels regularly facing problems of jetlag and occasional sleeplessness and meet the Criteria for Insomnia Disorder as per Epworth sleepiness scale. Subjects who scores ≤ 21 of Insomnia Severity Index and willing to provide written informed consent for participation in the study and adhere to the protocol requirements.

Exclusion Criteria
Subjects having a medical history of significant hypersensitivity or allergic reaction to any of the active or inactive ingredients. Subjects with high severity of Insomnia scoring > 21 of Insomnia Severity Index will be excluded. Subject having diagnosed or occult sleep disorders (evident on screening polysomnography) other than Primary Insomnia. Subjects having history of drug or alcohol abuse. Subjects having a medical history HIV, HAV, HBs Ag or psychiatric illness and Hearing or memory impairments. Pregnant or lactating women and Volunteers who have participated in any drug research study within past 3 months will be excluded from the study.

Study was conducted by randomized, Double Blind, parallel group, placebo controlled clinical study by ICBio Clinical Research Pvt. Ltd. It involved in the clinical attendance of the subjects on recruitment and on follow –up. Subjects enrolled in the study received Study drug (from Baseline visit to EOT-28 days – Instavit® Sweet Dreams 7ml/0.24 Fl OZ spray.

The safety and efficacy parameters were compared with baseline and follow-up data with laboratory investigations, demographics were analyzed in the study. Adverse events / side effects were noted for each follow-up visits.

Ethics Committee Approval
All study related documents Protocol, Case Report Form, Dairy card, Investigator Brochure and Informed Consent Documents (English and Kannada Versions). Written Informed Consent was obtained from the subjects before the start of the trial and after due approval from IEC/IRB. Ethics Committee notifications as per the GCP guidelines issued by Central Drugs Standard Control Organization and Ethical guidelines for biomedical research on human subjects issued by Indian council of Medical Research has been followed during the Conduct of the Study (Sapthagiri Institute of Medical Science & Research Centre and Approved on 30 Aug 2017).

Study Outcomes

Primary Outcomes

- Improvement in overall condition by assessing the changes in sleep quality using sleep logs and sleep dairy from baseline to EOT.

Secondary Outcomes

- Incidence and Rate of adverse events
- Changes in insomnia severity from baseline to EOT by using insomnia severity index
- Assessment of sleep quality by using Pittsburgh insomnia rating scale

Disposition of Subjects

Total of 50 subjects

Drug A: Instavit® Sweet Dreams 7ml/0.24 Fl OZ Sleep Aid Supplement with Melatonin & Chamomile (25 subjects)

Drug B: Placebo (25 subjects).

Visit Details

The patients were screened and enrolled. The enrollment day was considered as the baseline Day and the patient were follow up till end of treatment visit on Day 37.

Statistical Analysis

Data Analysis was carried out using 5% significance level and 80% power for study using SAS. The difference within the group will be assessed using paired t-test.

RESULTS

In the study 50 patients were screened and enrolled after meeting the inclusion Criteria and they are Randomized randomly into Drug A and Drug B. The enrolled subjects consisted of Healthy male and Female.

Data Sets Analyzed

Table 1: Data sets analyzed for the test and placebo treatments.

Treatments	Placebo	Investigational Product
Enrolled	25	25
Randomized	25	25
No. of patients completed visit	25	25
Withdrawn	0	0

Efficacy Evaluation

Primary Endpoints

Primary endpoints consideration were Improvement in overall condition by assessing the changes in sleep quality using sleep logs and sleep dairy from baseline to EOT. Efficacy evaluation was done based on both Primary and secondary end-points considered in the trial. All the information regarding the sleep quality was captured in the Pittsburg insomnia rating scale from the patient's sleep log and sleep dairy, respectively. It was done in-order to get the exact estimate of the improvement in sleeping pattern of the patients from baseline to EOT. A descriptive demonstration on the efficacy evaluation for all the above mentioned are presented below.

Table 2: Mean Demographic data of the study subjects by Gender.

Drug Groups	Female N (%)	Male N (%)	Total subject in each drug group N (%)
Drug -A	12 (48%)	13 (52%)	25 (50%)
Drug -B	13 (52%)	12 (48%)	25 (50%)
Total	25 (50%)	25 (50%)	50 (100%)

Table 2: Descriptive statistics of Demographic data.

Drug Code	STATISTIC	Age (in Years)	Weight (in Kg)	Height (in M)	BMI
A	N	25	25	25	25
	MIN	21	49.03	151.01	18.6
	MAX	60	79	177.08	32
	MEAN	35.96	64.41	164.05	23.87
	STD	12.7164	8.8785	8.4030	3.0606
B	N	25	25	25	24
	MIN	21	48	149.04	19.5
	MAX	57	80.05	178.24	28.01
	MEAN	33.16	63.67	164.47	23.55
	STD	10.4709	8.8856	7.9740	2.3590

Primary Parameters

Table 3				
How long did it take to fall asleep on the worst night? (At baseline)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	13	3	0	9
Test-B	8	1	1	15
Total	21	4	1	24

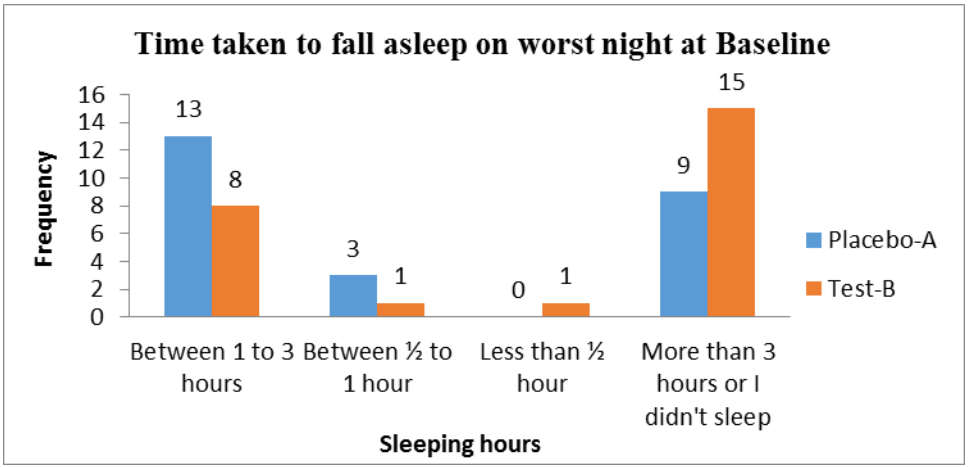

Fig. 01

Table 4				
How long did it take to fall asleep on the worst night? (At EOT)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	11	6	2	6
Test-B	5	13	7	0
Total	16	19	9	6

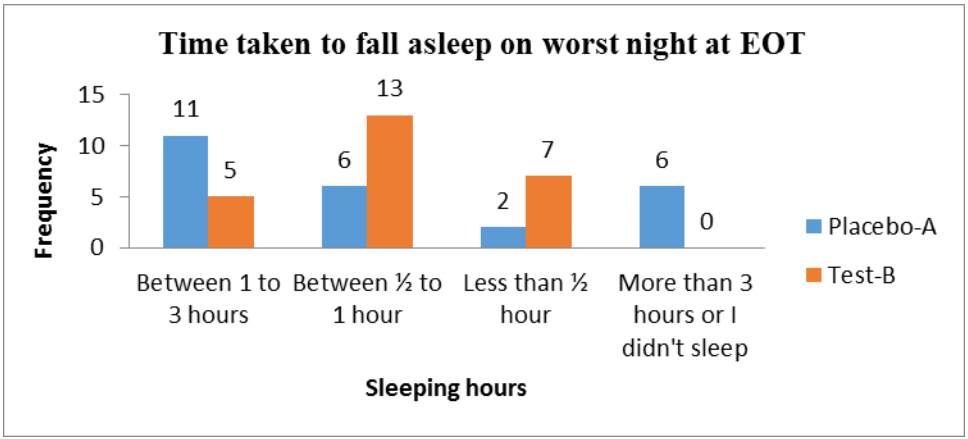

Fig. 02

Table 5				
How long did it take to fall asleep on most nights? (At baseline)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	11	13	1	0
Test-B	15	8	1	1
Total	26	21	2	1

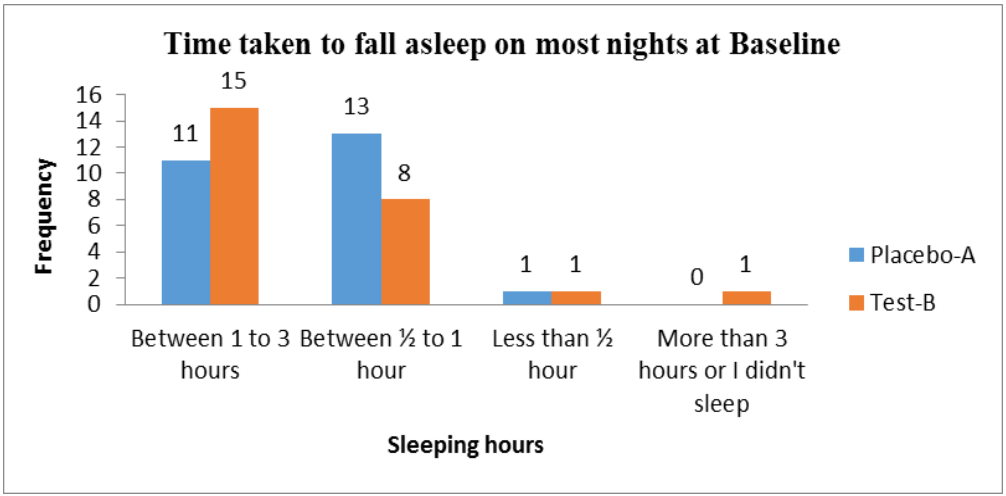

Fig. 03

Table 6				
How long did it take to fall asleep on most nights? (At EOT)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	8	10	7	0
Test-B	1	1	23	0
Total	9	11	30	0

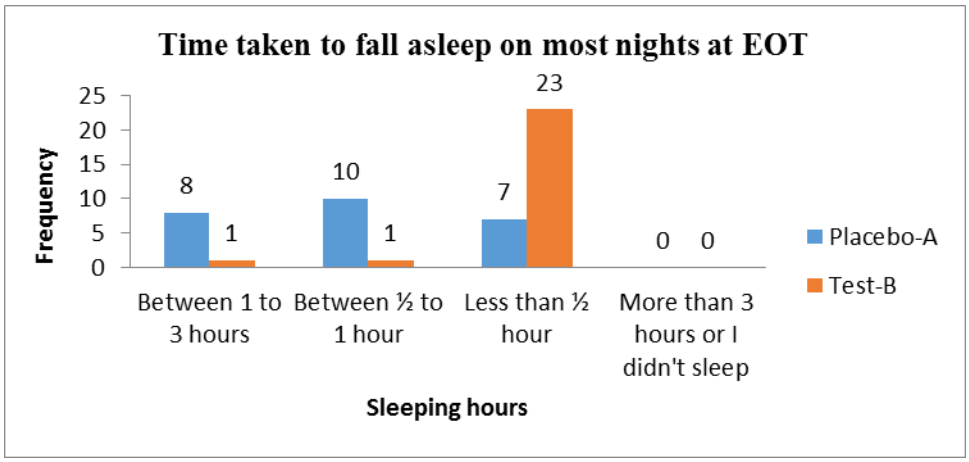

Fig. 04

Table 7				
How long did it take to fall back to sleep on the worst night? (At Baseline)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	10	11	0	4
Test-B	14	5	1	5
Total	24	16	1	9

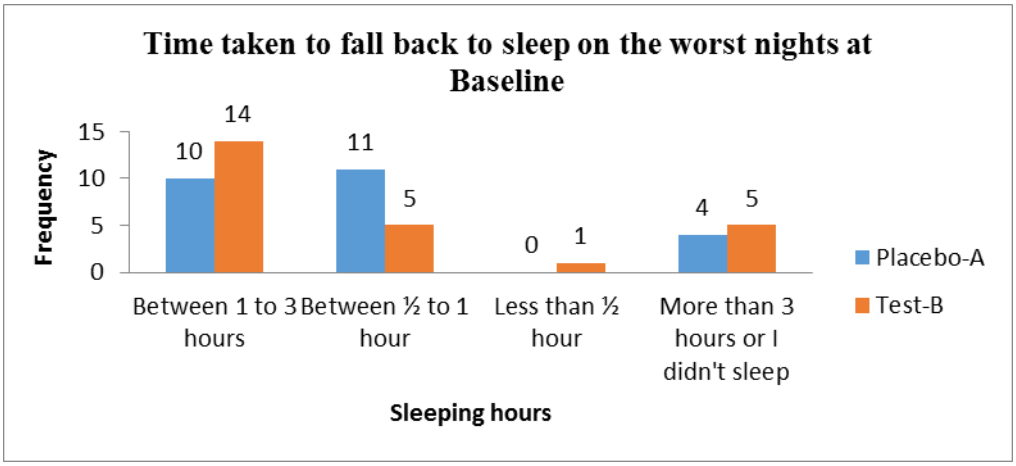

Fig. 05

Table 8

How long did it take to fall back to sleep on the worst night? (At EOT)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	6	14	4	1
Test-B	2	16	6	1
Total	8	30	10	2

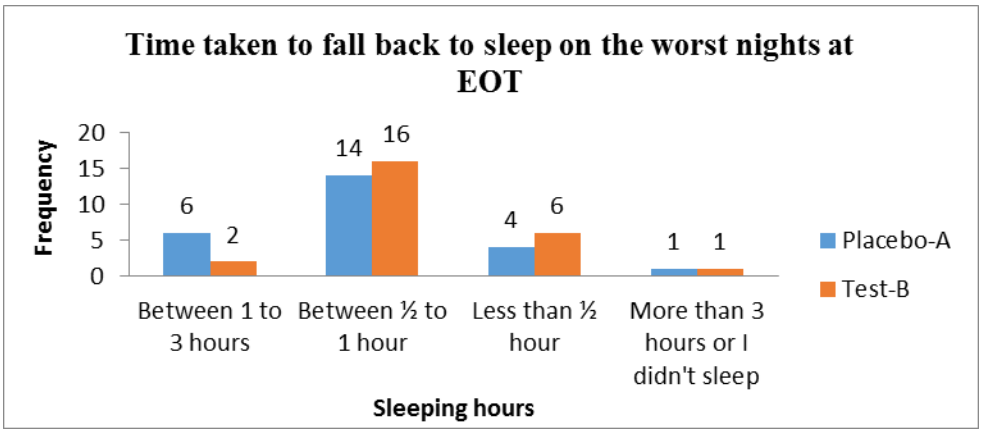

Fig. 06

Table 9

How long did it take to fall back to sleep on the most night? (At Baseline)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	7	16	2	0
Test-B	7	14	4	0
Total	14	30	6	0

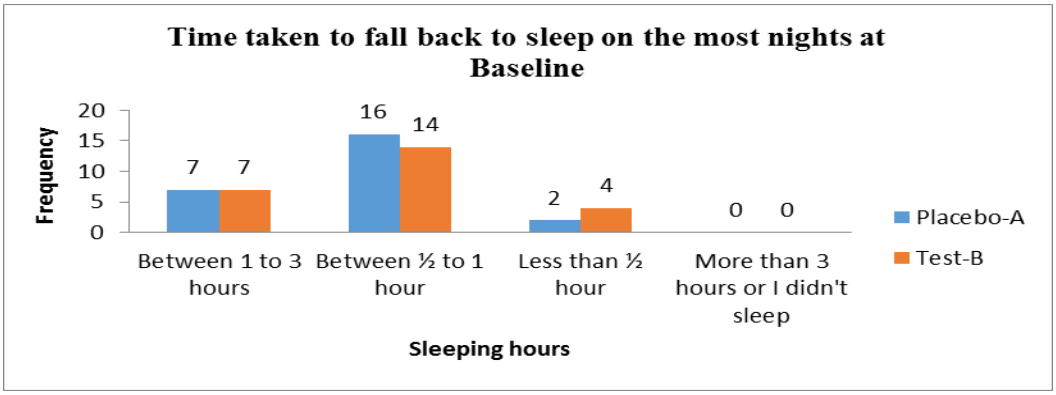

Fig. 07

Table 10				
How long did it take to fall back to sleep on the most night? (At EOT)				
Drug Code	**Between 1 to 3 hours**	**Between ½ to 1 hour**	**Less than ½ hour**	**More than 3 hours or I didn't sleep**
Placebo-A	4	11	10	0
Test-B	0	4	21	0
Total	4	15	31	0

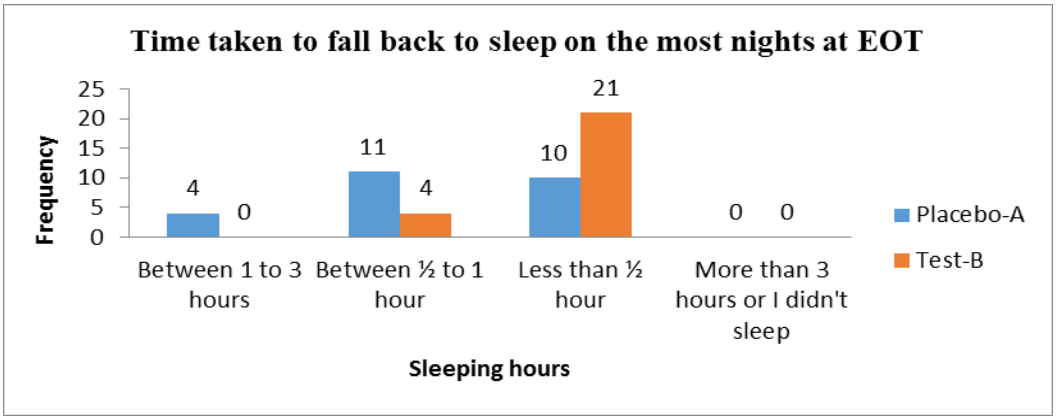

Fig. 08

Table 11				
How many hours of Actual sleep did you get during the worst night?				
Drug Code	**Between 2 to 4 hours**	**Between 4 to 7 hours**	**Less than 2 hours or I didn't sleep**	**Less than ½ hour**
Placebo-A	13	6	5	1
Test-B	9	4	12	0
Total	22	10	17	1

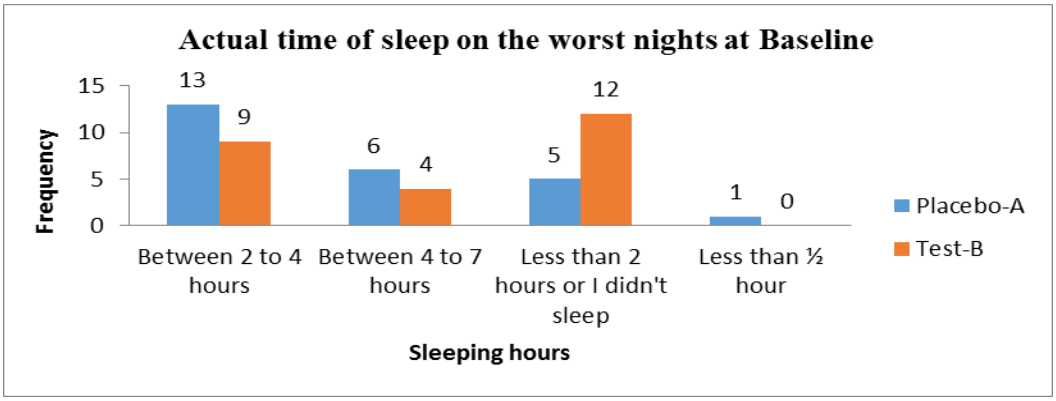

Fig. 09

Table 12				
How many hours of Actual sleep did you get during the worst night? (At EOT)				
Drug Code	**Between 2 to 4 hours**	**Between 4 to 7 hours**	**Less than 2 hours or I didn't sleep**	**More than 7 hours**
Placebo-A	10	10	4	1
Test-B	7	15	0	3
Total	17	25	4	4

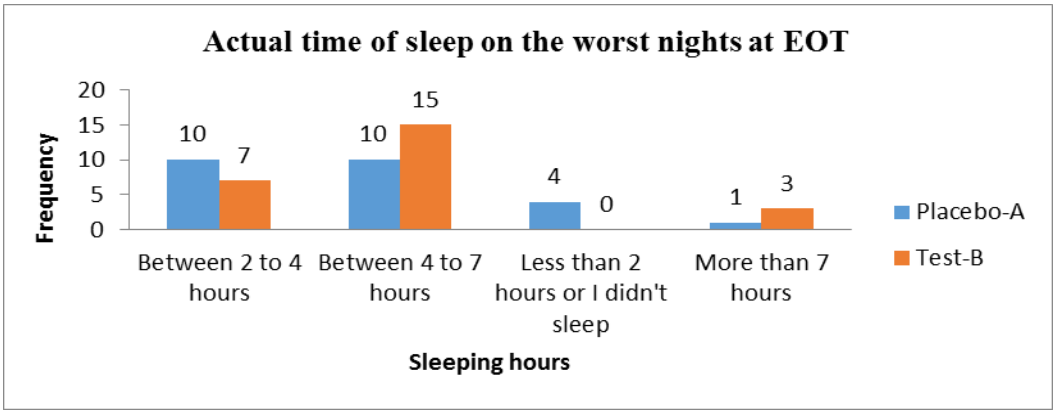

Fig. 10

Table 13				
How many hours of Actual sleep did you get during the most night? (At Baseline)				
Drug Code	**Between 2 to 4 hours**	**Between 4 to 7 hours**	**More than 7 hours**	**Less than 2 hours or I didn't sleep**
Placebo-A	6	17	2	0
Test-B	6	15	4	0
Total	12	32	6	0

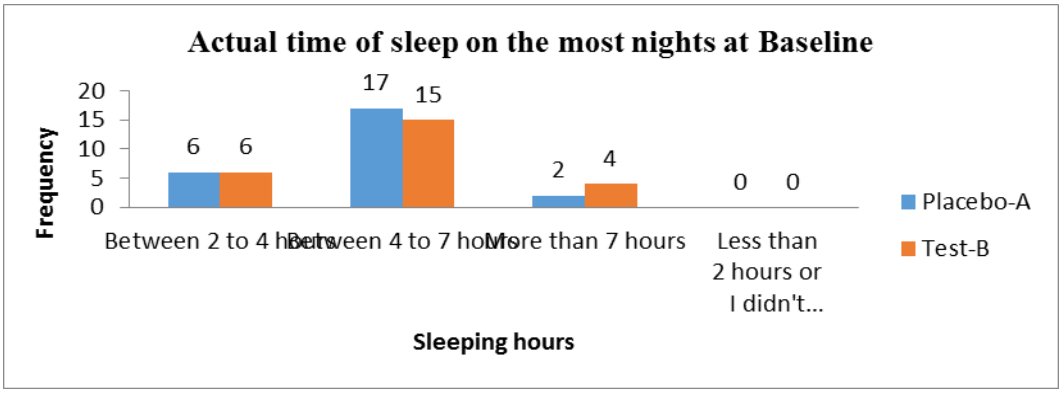

Fig. 11

Table 14				
How many hours of Actual sleep did you get during the most night? (At EOT)				
Drug Code	**Between 2 to 4 hours**	**Between 4 to 7 hours**	**More than 7 hours**	**Less than 2 hours or I didn't sleep**
Placebo-A	4	13	8	0
Test-B	0	1	24	0
Total	4	14	32	0

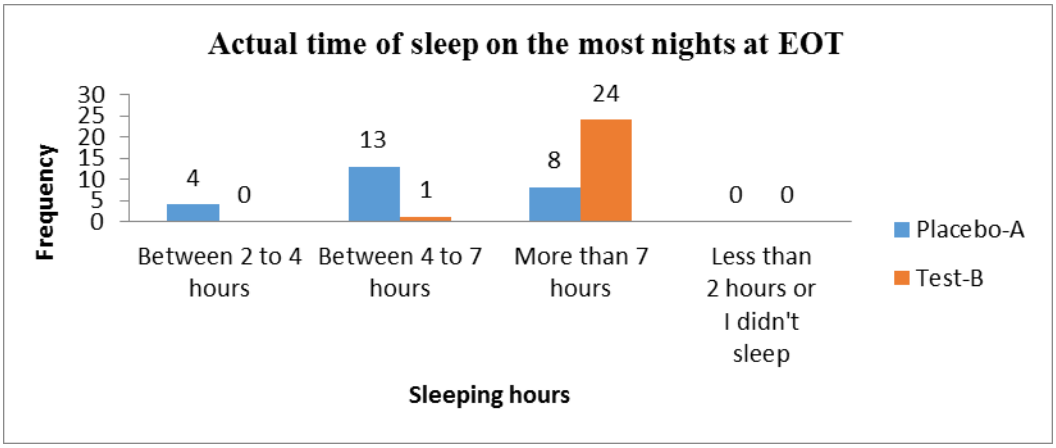

Fig. 12

Table 15				
Your sleep quality compared to others (At Baseline)				
Drug Code	**Excellent**	**Fair**	**Good**	**Poor**
Placebo-A	0	13	5	7
Test-B	0	8	4	13
Total	0	21	9	20

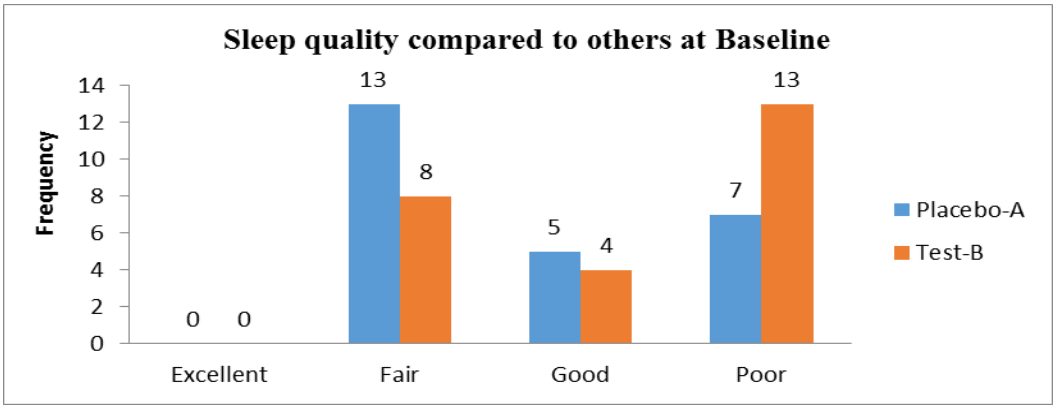

Fig. 13

Table 16				
Your sleep quality compared to others (At EOT)				
Drug Code	**Excellent**	**Fair**	**Good**	**Poor**
Placebo-A	1	12	5	7
Test-B	6	2	17	0
Total	7	14	22	7

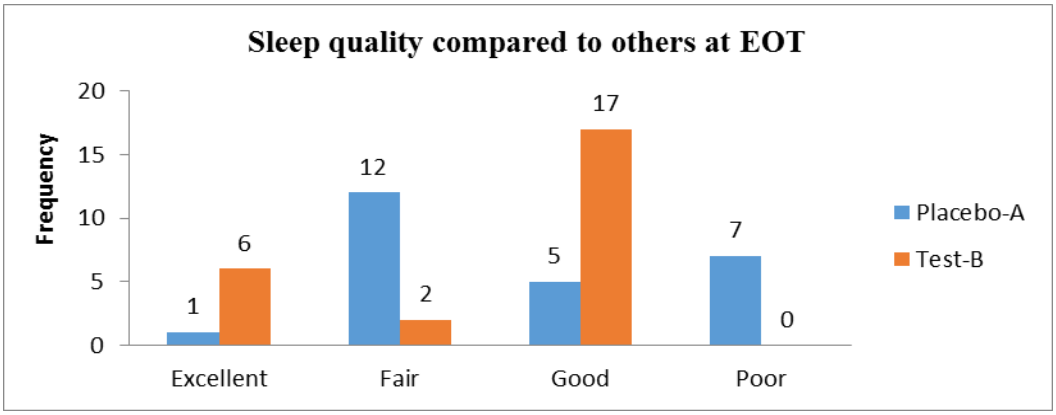

Fig. 14

Table 17				
Your satisfaction with your sleep (At Baseline)				
Drug Code	**Excellent**	**Fair**	**Good**	**Poor**
Placebo-A	0	10	6	9
Test-B	0	10	2	13
Total	0	20	8	22

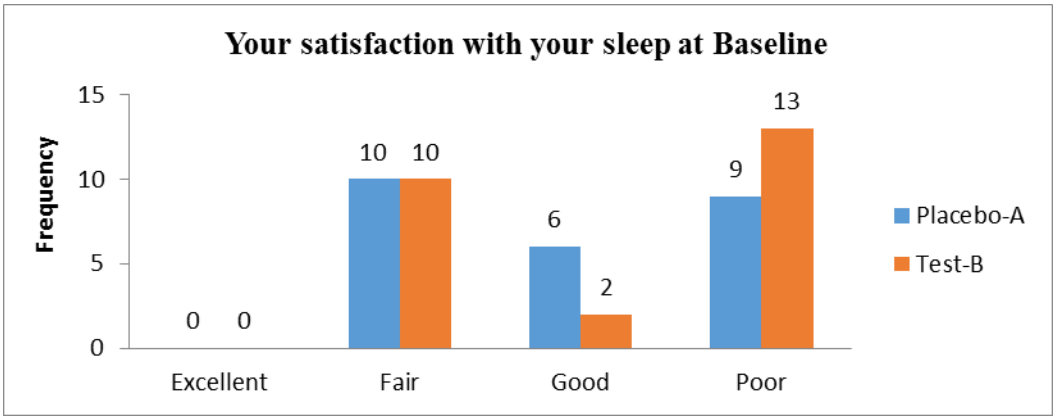

Fig. 15

Table 18				
Your satisfaction with your sleep (At EOT)				
Drug Code	**Excellent**	**Fair**	**Good**	**Poor**
Placebo-A	1	12	7	5
Test-B	10	1	14	0
Total	11	13	21	5

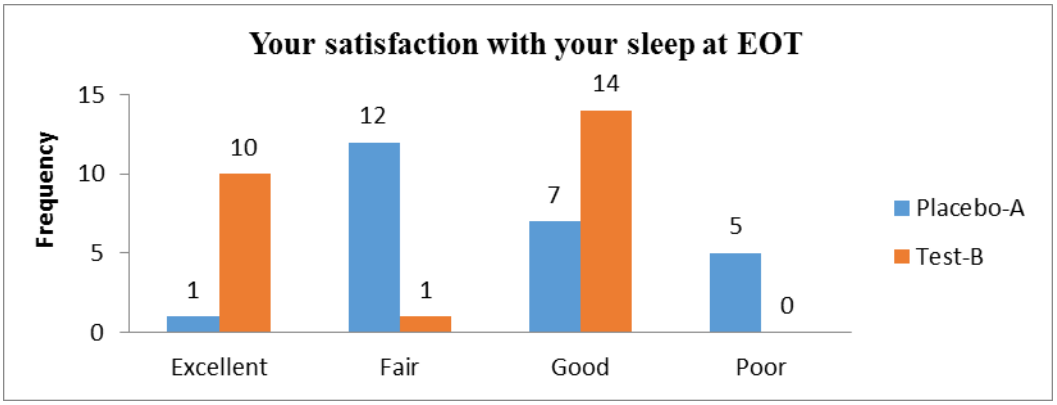

Fig. 16

Secondary parameters

1. **Insomnia Severity Index-** Total scores were calculated in insomnia severity index and the scores were divided into several categories to check the level and extent of sleep of the patients. Comparisons between the scores were done from baseline to EOT using paired t-test for both Test and Placebo arm, respectively.

Table 19		
Mean Change in Insomnia Severity Index Scores from Baseline to EOT		p-value
Drug Code	**Mean Change**	
A	-6.52	<.0001
B	-13.62	<.0001

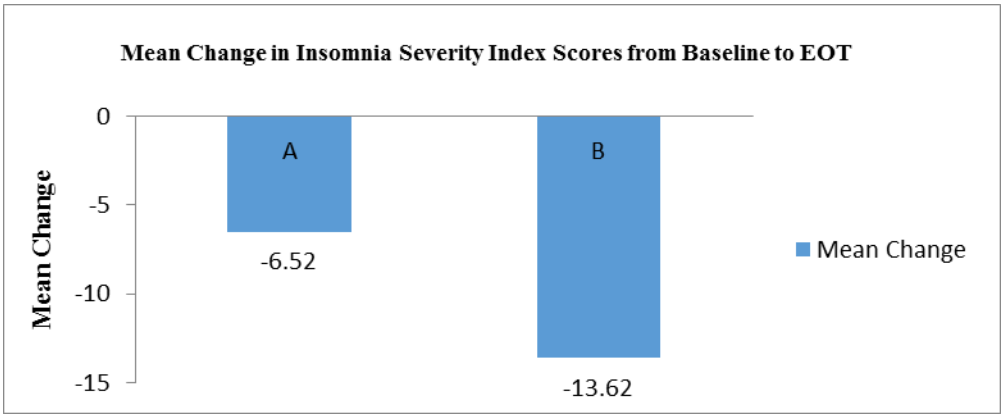

Fig. 17

2. **Pittsburg Insomnia Scale-** This scaling procedure was used to identify the level of sleepiness and the improvement in the sleep and quality of life associated with the sleeping disorders. The main content of this scale contained the sleep timings, comparison of sleep of patients with others and the satisfaction of the patients for their sleep. Sleep timings on this scale were captured from the sleep log and sleep dairy of the respective patients. As the entire data was categorical so the frequency distribution for all the variables were drawn for baseline visit and EOT, respectively for the Test and Placebo product.

Table 20

Table of Drug Code by Overall sleep quality at baseline		
Drug Code	**Overall_sleep_quality**	**Total**
	Horrible	
A	25	25
B	25	25
Total	50	50

Table 21

Table of Drug Code by Overall sleep quality at EOT			
Drug Code	**Overall sleep quality**		**Total**
	Horrible	**Wonderful**	
A	25	0	25
B	0	25	25
Total	25	25	50

Table 22

Table of Drug Code by Your quality of life at baseline				
Drug Code	**Your quality of life**			**Total**
	Fair	**Good**	**Poor**	
A	18	4	3	25
B	12	10	3	25
Total	30	14	6	50

Table 23

Table of Drug Code by Your quality of life at EOT					
Drug Code	**Your quality of life**				**Total**
	Excellent	**Fair**	**Good**	**Poor**	
A	1	10	11	3	25
B	9	0	16	0	25
Total	10	10	27	3	50

3. **Epworth Sleepiness Scale-** This scaling procedure was used to check the chances of dozing of the patients in order to determine the sleepiness of the patients at baseline and EOT. As this was also a fully categorical data so the frequency distribution of the scores were presented and also the base shift changes from baseline to EOT was assessed to check the improvement in sleep pattern of the patients.

Table 24: Base shift changes from Baseline to EOT for Epworth Sleepiness scale.

Drug Code	Sitting and reading	Watching TV	Sitting inactive in public place	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 lunch without alcohol	In a car, while stopped for a few minutes in the traffic	Sitting and observing children/ grand children do Homework / pla	Watching TV/ listening to radio / Music	Sitting inactive in public place1	As a passenger in a vehicle for an hour without a break	Lying down to rest in the afternoon when circumstances permit1	Sitting and talking to someone1	Sitting quietly after lunch without alcohol1	During work when taking a Short break
A	No Change	Improved	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Improved	Improved	No Change	No Change	No Change	No Change	No Change
A	No Change	No Change	No Change	Worsened	Worsened	Worsened	No Change	No Change	No Change	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened
A	No Change	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened
A	Worsened	No Change	Worsened	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	Worsened	Worsened
A	Worsened	Worsened	Worsened	No Change	Worsened	No Change	Worsened	Worsened	No Change	No Change	Worsened	No Change	Worsened	No Change	Worsened	No Change
A	No Change	Worsened	No Change	Improved	Worsened	Worsened	Improved	No Change	Worsened	Worsened	Worsened	Improved	Worsened	Worsened	Worsened	Worsened
A	Improved	Worsened	No Change	Improved	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	Improved	Improved	Worsened	Worsened	No Change	Worsened
A	Improved	Worsened	No Change	Improved	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	No Change	Improved	Worsened	Worsened	Worsened	Worsened
A	Improved	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	Improved	Worsened	Worsened	Worsened	Worsened
A	No Change	No Change	No Change	No Change	No Change	Worsened	Worsened	No Change	No Change	No Change	No Change	Worsened	Worsened	Worsened	Worsened	Worsened
A	No Change	Worsened	Worsened	No Change	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened	No Change	Worsened	No Change	No Change	No Change
A	Worsened	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened
A	Worsened	No Change	Worsened	No Change	Improved	No Change	Worsened	Improved	No Change	No Change	Worsened	No Change	Improved	No Change	Improved	Improved
A	Worsened	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	No Change	Worsened	No Change	Worsened	Worsened
A	Worsened	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change
A	No Change	Worsened	No Change	No Change	Worsened	No Change	Worsened	Worsened	No Change	No Change	No Change	No Change	Worsened	No Change	Worsened	Improved
A	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	No Change
A	Worsened	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Worsened	No Change
A	No Change	No Change	Worsened	Worsened	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Improved	No Change	Improved	Worsened
A	No Change	No Change	No Change	Worsened	Worsened	No Change	Improved	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Improved	Worsened
A	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	Worsened	Worsened	Worsened	Worsened	No Change	Worsened	No Change
A	No Change	No Change	No Change	Improved	Worsened	Improved	Worsened	Worsened	Worsened	No Change	Improved	Worsened	Worsened	No Change	Improved	Improved
A	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Improved	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change
A	No Change	No Change	No Change	No Change	Improved	No Change	No Change	No Change	No Change	No Change	No Change	Worsened	Worsened	Improved	No Change	No Change
A	No Change	Worsened	Worsened	Worsened	Worsened	Improved	No Change	Worsened	No Change	Improved	No Change	Worsened	Worsened	Worsened	Worsened	No Change
B	Worsened	Worsened	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	Worsened	No Change	No Change	Worsened	No Change	Worsened	No Change
B	Worsened	Worsened	Worsened	No Change	Worsened	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	Worsened	No Change	No Change	No Change
B	Worsened	Worsened	Worsened	Worsened	No Change	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	No Change
B	Worsened	Worsened	Worsened	No Change	No Change	Improved	Worsened	Worsened	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened
B	Worsened	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened
B	Worsened	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change
B	Worsened	Worsened	Worsened	No Change	Worsened	No Change	No Change	Worsened	No Change	Worsened	Worsened	No Change	Worsened	No Change	No Change	No Change
B	No Change	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change
B	No Change	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	No Change	No Change	Worsened	No Change	Worsened	Worsened	Worsened	Worsened
B	No Change	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	Worsened
B	Worsened	No Change	Worsened	Worsened	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened
B	Worsened	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	Worsened	Worsened	Improved	Improved	Improved
B	Worsened	No Change	Improved	No Change	Worsened	No Change	Worsened	Improved	No Change	No Change	Improved	Worsened	Worsened	No Change	Worsened	No Change
B	Worsened	Worsened	No Change	No Change	Worsened	No Change	Improved	No Change	No Change	Worsened	Worsened	No Change	No Change	No Change	Improved	Worsened
B	Worsened	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened	No Change	Worsened	No Change	Worsened	Worsened	No Change	Worsened	No Change
B	Worsened	No Change	No Change	Worsened	Worsened	No Change	Worsened	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	Worsened	No Change
B	No Change	No Change	Worsened	No Change	Worsened	No Change	Worsened	No Change	No Change	No Change	Worsened	No Change	Worsened	No Change	Worsened	No Change
B	Worsened	Worsened	Worsened	Worsened	Worsened	No Change	Worsened	No Change	Worsened	No Change	Improved	Worsened	Worsened	Worsened	No Change	Worsened
B	No Change	No Change	No Change	No Change	Worsened	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	No Change	Worsened
B	Worsened	No Change	No Change	Worsened	Worsened	No Change	Worsened	No Change	No Change	No Change	No Change	Worsened	Worsened	No Change	Worsened	No Change
B	Worsened	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened	No Change	No Change	No Change	Worsened	Worsened	No Change	Worsened	Worsened
B	Worsened	No Change	Worsened	Worsened	Worsened	No Change	Worsened	Worsened	No Change	Improved	Worsened	Worsened	Worsened	No Change	Worsened	Worsened
B	Worsened	Improved	Worsened	Worsened	No Change	No Change	No Change	Worsened	No Change	No Change	No Change	Worsened	No Change	No Change	No Change	Worsened
B	Worsened	Worsened	No Change	No Change	Improved	Improved	Worsened	Improved	Improved	Worsened	Worsened	No Change	No Change	Worsened	Worsened	No Change
B	Improved	Improved	Improved	Improved	Worsened	No Change	No Change	Improved	Worsened	Improved	Improved	Improved	Improved	Improved	Improved	No Change
B	Improved	Improved	Worsened	Improved	No Change	No Change	No Change	Improved	Improved	Improved	No Change	Improved	No Change	No Change	No Change	No Change

Safety Evaluation

Adverse Events

Adverse Events were observed for the Instavit® Sweet Dreams oral spray and Placebo products in Visit-II & EOT i.e. Visit-III and the same are represented in the below tables:

Table 25	**Number of subjects experienced AE (SAE), related AE (SAE) at Visit II (Day 14).**	
Number of subjects with at least one of the following items		**N (%)**
Any adverse event		6 (100.00)
Any serious adverse event		0 (0.00)
SAE = YES	Relationship	
	Possible	0.00
	Probable/Likely	0.00
	Certain	0.00
	Unlikely	0.00
SAE = No	Relationship	
	Possible	1 (16.67)
	Probable	1 (16.67)
	Certain	0.00
	Unlikely	4 (66.67)
* number of subjects (%)		

Table 26: Frequency of AEs by seriousness, intensity and relationship to study treatment at Visit II (Day 14).			
Adverse events		**Instavit® Sweet Dreams oral spray**	**Placebo**
		N (%)	**N (%)**
Serious adverse event	**Yes**	**0 (0.00)**	**0 (0.00)**
	No	4 (66.67)	2 (33.33)
Intensity	Mild	4 (66.67)	1 (16.67)
	Moderate	0 (0.00)	1 (16.67)
	Severe	**0 (0.00)**	**0 (0.00)**
Relationship to the test product	Certain	0 (0.00)	0 (0.00)
	Probable/Likely	0 (0.00)	1 (16.67)
	Possible	1 (16.67)	0 (0.00)
	Unlikely	**3 (75.00)**	1 (16.67)
	No relationship	0 (0.00)	0 (0.00)
Frequency	Isolated	3 (50.00)	2 (33.33)
	Continuous	1 (16.67)	0 (0.00)
Occurrence of adverse device effect	**Yes**	**NR**	**NR**
	No	NR	NR
Event outcome at the end of the trial	Resolved, no sequelae	4 (66.67)	2 (33.33)
	Resolved with sequelae	0 (0.00)	0 (0.00)
	Present at final visit	0 (0.00)	0 (0.00)
	Death	0 (0.00)	0 (0.00)
	Lost to follow-up	0 (0.00)	0 (0.00)
	Unknown	0 (0.00)	0 (0.00)

Table 27	**Number of subjects experienced AE (SAE), related AE (SAE) at Visit III (Day 28).**	
Number of subjects with at least one of the following items		**N (%)**
Any adverse event		7 (100.00)
Any serious adverse event		0 (0.00)
SAE = YES	Relationship	
	Possible	0.00
	Probable/Likely	0.00
	Certain	0.00
	Unlikely	0.00
SAE = No	Relationship	
	Possible	1 (16.67)
	Probable	0 (0.00)
	Certain	0.00
	Unlikely	6 (85.71)
* number of subjects (%)		

Table 28: Frequency of AEs by seriousness, intensity and relationship to study treatment at Visit III.			
Adverse events		**Instavit® Sweet Dreams oral spray**	**Placebo**
		N (%)	**N (%)**
Serious adverse event	**Yes**	**0 (0.00)**	**0 (0.00)**
	No	4 (57.14)	3 (42.86)
Intensity	Mild	4 (57.14)	2 (28.57)
	Moderate	0 (0.00)	1 (14.29)
Relationship to the test product	**Severe**	**0 (0.00)**	**0 (0.00)**
	Certain	0 (0.00)	0 (0.00)
	Probable/Likely	0 (0.00)	0 (0.00)
	Possible	0 (0.00)	1 (14.29)
	Unlikely	4 (57.14)	2 (28.57)
	No relationship	0 (0.00)	0 (0.00)
Frequency	Isolated	3 (42.86)	3 (42.86)
	Continuous	1 (14.29)	0 (0.00)
Occurrence of adverse device effect	**Yes**	**NR**	**NR**
	No	NR	NR
Event outcome at the end of the trial	Resolved, no sequelae	4 (66.67)	2 (33.33)
	Resolved with sequelae	0 (0.00)	0 (0.00)
	Present at final visit	0 (0.00)	0 (0.00)
	Death	0 (0.00)	0 (0.00)
	Lost to follow-up	0 (0.00)	0 (0.00)
	Unknown	0 (0.00)	0 (0.00)

DISCUSSION AND CONCLUSION

Statistical Analysis of data obtained after the completion of study was analyzed using SAS software for windows, version 9.1, at 5% level of significance ($\alpha = 0.05$).

Efficacy Analysis

A separate set of analyses were performed to check the efficacy of Instavit® Sweet Dreams oral spray in comparison to Placebo. As this study was performed on 50 patients and all 50 patients completed the entire clinical phase of the study so per protocol population considered for this study is equal to ITT population.

The primary parameters considered for the check of efficacy of the Test product in comparison to Placebo from baseline to EOT was "Improvement in overall condition by assessing the changes in sleep quality using sleep logs and sleep dairy from baseline to EOT". The comparison was done for both the treatment groups separately.

As the entire data was made up of scales to measure the level of sleepiness so the entire categorical data was presented in the form of frequency distribution whereas for the continuous data descriptive statistics were reported.

Considering the objectives from the primary parameters the first parameter under consideration is "How long did it take to fall asleep on the worst night?" so we can observe from Table 3 & Table 4 that patients who were taking longer time to fall asleep on the worst night decreased more in the test arm in comparison to the placebo arm at EOT and the same is reflected in the Fig. 01 & Fig. 02, which gives clear indication that Test is more efficacious than Placebo.

Second parameter under consideration is "How long did it take to fall asleep on the most nights?" so we can observe from Table 5and Table 6 that patients out of 25 patients 23 patients are able to fall asleep in a duration of less than ½ hour in the test arm at EOT, whereas for the placebo arm at EOT only 7 patients have reported for falling asleep in a duration of less than ½ hour. The same has been reflected in the Fig. 04, which gives clear indication that Test is more efficacious than Placebo.

Third parameter under consideration is "How long did it take to fall back to sleep on the worst nights?" so we can observe from Table 7 & Table 8 that patients out of 25 patients 16 patients are able to fall back to sleep on worst nights between ½ to 1 hour duration and only 2 patients have reported for falling back to sleep between 1 to 3 hours, so this gives clear indication that Test is more efficacious than Placebo.

Fourth parameter under consideration is "How long did it take to fall back to sleep on the most nights?" so we can observe from Table 9 and Table 10 that patients out of 25 patients 21 patients are able to fall back to sleep on most nights in less than ½ hour duration and only 4 patients have reported for falling back to sleep between ½ to 1 hours. Also for placebo arm the counts are on the lower side and the same is reflected in Fig. 08, so this gives clear indication that Test is more efficacious than Placebo.

Fifth parameter under consideration is "How many hours of Actual sleep did you get during the worst night?" so we can observe from Table 11 and Table 12 that patients out of 25 patients 15 patients are able to sleep for between 4 to 7 hours on the worst nights and 3 patients reported for getting more than 7 hours sleep on worst nights for test arm and the same has been reflected in Fig. 10, so this gives clear indication that Test is more efficacious than Placebo.

Sixth parameter under consideration is "How many hours of Actual sleep did you get during the most nights?" so we can observe from Table 13 and Table 14 that patients out of 25 patients 24 patients are able to sleep for more than 7 hours on the most nights in test arm and the same has been reflected in Fig. 12, so this gives clear indication that Test is more efficacious than Placebo.

Also considering the Sleep quality most of the patients have given an excellent response in the improvement of their sleep in test arm in comparison to the placebo arm.

Also considering the satisfaction with Sleep most of the patients have given an excellent response in the satisfaction level of their sleep in test arm in comparison to the placebo arm. So the above findings proves the efficacy of Instavit® Sweet Dreams oral spray in comparison to the Placebo.

For the secondary parameters total scores were calculated in insomnia severity index for all the patients and the scores were divided into several categories to check the level and extent of sleep of the patients. A check of Normality was performed on the Total scores obtained at baseline and EOT, the Shapiro-Wilk statistic was used to check the normality. The results obtained showed that the p-value is greater than 0.05 for the Total scores at baseline and EOT so this proved that the Total scores are following a normal distribution at 5% level of significance.

Comparisons between the scores were done from baseline to EOT using paired t-test for both Instavit® Sweet Dreams oral spray and Placebo arm, respectively.

For the comparison of scores from baseline to EOT the p-value was found as <.0001 for Instavit® Sweet Dreams oral spray arm which shows that there is significant statistical difference among the scores from baseline to the EOT. But for Placebo arm also the p-value was obtained as <.0001 which again shows that there is significant statistical difference among the scores from baseline to the EOT. Considering Table 19 we can observe that mean change was more for Instavit® Sweet Dreams oral spray arm in comparison to the Placebo-B arm, respectively and the same has been reflected in Fig. 17 and this proves that Instavit® Sweet Dreams oral spray is more efficacious in comparison to Placebo.

From Table nos. 20,21,22 & 23 it is quite evident that from Pittsburg Insomnia scale assessment sleep disorders have been reduced up to a major extent in Instavit® Sweet Dreams oral spray arm and the patients quality of sleep and satisfaction of sleep has also been increased much more in the Instavit® Sweet Dreams oral spray arm.

So considering all above data evaluations it has been clearly determined that Instavit® Sweet Dreams oral spray is more efficacious than Placebo in the treatment of occasional sleeplessness.

16.0 CONCLUSION

Considering all safety and efficacy parameters, it was concluded that the Instavit® Sweet Dreams oral spray product is much efficacious in the treatment of occasional sleepiness. Also, as per the study outcomes no serious adverse events were observed during the clinical trial, though 6 adverse events were reported in Visit II and 7 adverse events were reported in Visit III but none of them is related to the study drug and this concludes that investigational product is safe enough to use.

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