Clinical Research Protocol
Effectiveness of nonspecific methods of treatment and Zopiclone for chronic insomnia

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Study Phase:	
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Approval:

PI Signature (Name and Title) *Date*

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential. Furthermore, on behalf of myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 1

Protocol Title: Effectiveness of nonspecific methods of treatment and Zopiclone for chronic insomnia

Protocol Date: 18th March 2015

Investigator Signature *Date*

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LIST OF ABBREVIATIONS

AE	adverse event
CRF	case report form
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PI	Principal Investigator
BDI	Beck Depression Inventory
STAI	State-trait anxiety inventory
PSQI	Pittsburg Sleep Quality Index
DBAS	Dysfunctional beliefs about sleep scale
ISI	Insomnia Severity Index
SHI	Sleep hygiene index
PSG	Polysomnography
CI	Chronic insomnia
CBT-I	Cognitive-behavioral therapy of insomnia
BBT-I	Brief-behavioral therapy of insomnia

PROTOCOL SYNOPSIS

TITLE	Effectiveness of nonspecific methods of treatment and Zopiclone for chronic insomnia
SPONSOR	
FUNDING ORGANIZATION	
NUMBER OF SITES	
RATIONALE	Importance of chronic insomnia (CI) problem is determined by its high prevalence rate, comorbidity and resistance to the treatment. There are pharmacological and cognitive-behavioral approaches to the CI treatment. Even after considering all the specific advantages and drawbacks of both methods of CI treatment a clinician would be still in question, which one would be preferable in a particular case.
STUDY DESIGN	Prospective randomized crossover study
PRIMARY OBJECTIVE	to test the effectiveness of short BBT-I program for chronic insomnia in comparison with zopiclone
SECONDARY OBJECTIVES	to find anthropometric, psychological and polysomnographic predictors of effectiveness of each method
NUMBER OF SUBJECTS	
SUBJECT SELECTION CRITERIA	Inclusion Criteria: meeting the criteria for chronic insomnia according ICSD-3 wilingness to take part in the study and signed informed consent form Exclusion Criteria: (1) unability to stop taking medications that have a proven impact on sleep at least one week before and during the study; (2) history of alcohol or drug abuse; (3) major depressive disorder or other severe mental disorder identified by a clinical assessment and medical history; (4) dementia; (5) pregnancy or lactation; (6) shift or night work; (7) medical problems that would be a direct cause of sleep complaints: moderate/severe sleep apnea, defined as an apnea–hypopnea index of ≥15 events per hour, periodic limb movement disorder defined as a periodic leg movement index ≥15 events per hour or restless legs syndrome; (8) other serious chronic conditions or exacerbation of chronic disorder preventing further participation.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	2-week Brief behavioral therapy program includes a question-and-answer part; a didactic presentation of sleep regulation mechanisms; an examination of patient's sleep log; explanation of sleep restriction method and prescription of individual regimen of sleep; explanation of stimulus control method; sleep hygiene education; discussion of relaxation techniques, providing with relaxation audio recording. BBT-I first group Will receive two-week brief behavioral therapy followed by medication therapy (zopiclone).
CONTROL GROUP OR OTHER STUDY ARMS (if applicable)	Imovan (zopiclone) intake in a dose of 7,5 mg 30 minutes before bedtime for two weeks zopiclone first group will get the medication therapy (zopiclone) for the first two weeks followed by brief behavioral therapy
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 8 weeks **Screening:** every 2 weeks **Treatment:** 2 treatment courses 2 weeks each **Follow-up:** 2-week washout periods after each treatment course The total duration of the study was 24 months
CONCOMMITANT MEDICATIONS	Prohibited: substances affecting sleep (hypnotics, antidepressants, anxiolytics, antihistamine)
EFFICACY EVALUATIONS	*Questionnaires (ISI,* BDI, STAI, PSQI, DBAS, SHI, Big Five Questionnaire, TAS-20), Polysomnography, β-adrenoreactivity test
PRIMARY ENDPOINT	• ISI
SECONDARY ENDPOINTS	• BDI, STAI, PSQI, DBAS, SHI, β-adrenoreactivity test
OTHER EVALUATIONS	Polysomnography, Big Five Questionnaire for evaluation of personal traits
SAFETY EVALUATIONS	All subjects will be asked about well-being and possible adverse effects of treatment, on each biweekly visit. In the case of condition exclusionary for study participation (exacerbation of disease, starting medicines, incompatible with zopiclone etc.) when it is not in the subject's best interest to continue the subject may be discontinued from study
PLANNED INTERIM ANALYSES	When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the investigator. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

STATISTICS **Primary Analysis Plan**	Analysis of insomnia treatment will be conducted only for patients matching inclusion and exclusion criteria who will complete at least one treatment course (BBT-I or medication) and fill in questionnaires prior and after the treatment. Continuous variables will be presented in means and standard deviation (M±SD). Categorical and rank variables will be presented as percentages. Statistical significance of differences between group for continuous variables will be evaluated with Student's t-test after confirmation of normal variable distribution by Kolmogorov-Smirnov test. For continuous variables with distribution other than normal Mann-Whitney U-test will be used. For comparison of the proportions Pearson chi-squared test will be performed. Criterion of response to the treatment is defined as the reduction of ISI score reduction of >7 points from baseline. Remission criterion is defined as final ISI score of 7 points or less. Nonresponse criterion is defined as ISI score decrease of ≤7 points from baseline. Based on these dichotomic values participants will be divided into two groups: responders and nonresponders for each method of treatment. Comparison of responders and nonresponders baseline quantitative characteristics will be performed using Student's t-test (for normal data distribution) or Mann-Whitney U-test (for abnormal data distribution). Statistical significance will be set at a p-value less 0,05.
Rationale for Number of Subjects	Study design allows to compare two therapeutic approaches with a relatively small sample size and to determine the predictors of effectiveness for each treatment. Thus 40 patients get 2 therapeutic approaches. This is the representative sample size enough to produce normal variable distribution for further parameter statistical analysis.

PURPOSE OF THE INVESTIGATION

Name of investigational method

Brief behavioral therapy program
Imovan (zopiclone)

Intended use of the investigational method

2-week Brief behavioral therapy will be performed in two 1 hour session for treatment of chronic insomnia (CI)

Imovan (zopiclone) in a dose of 7,5 mg has to be taken 30 minutes before bedtime for two weeks

Overview of Clinical Studies

The main treatment approaches for chronic insomnia with proven efficacy are pharmacologic and behavioral treatment. In accordance with the results of multiple clinical trials and meta-analyses both methods have comparable effectiveness in terms of sleep quality ranging between 64% (Buysse et.al., 2011) and 88% (Carson, McDonagh, Thakurta, and Yen P. 2008).

GABA(a) agonists being the most widely used hypnotics could cause residual daytime sedation and safety concerns like the risk of drug addiction, overdose and intoxication along with cognitive toxicity, falls and hip fractures especially in elderly persons (Pagel & Parnes, 2001)

The second approved treatment option for insomnia is cognitive-behavioral treatment of insomnia combining behavioral and psychological techniques. Unlike hypnotics this method has consistent long-term efficacy with few adverse effects (Morin et.al., 2016). On the other hand it requires special training of therapist, compliance of patient and noticeable time expenditures of both. Hence shortened and simplified behavioral approaches have been developed. It includes brief behavioral treatment for insomnia (BBT-I) lasting four weekly sessions instead of 6-8, online sessions, telephone consultations, and self-help approaches. Although there are no enough data for meta-analysis, BBT-I proved its efficacy in a number of clinical comparative studies (Bootzin, 2004).

STUDY RATIONALE

Even after considering all the specific advantages and drawbacks of pharmacological and cognitive-behavioral methods of CI treatment a clinician would be still in question, which one would be preferable in a particular case. There are still questions about the reason why CBT or pharmacotherapy or even their combination didn't reach 100% treatment response. So the treatment response predictors identification is required for individualized treatment

Risk / Benefit Assessment

Brief behavioral therapy has no potential adverse effects, risks of addiction or tolerance.

Zopiclone has possible hypersensitivity adverse effects as well as possible effects on central nervous system: taste disturbance; less commonly nausea, vomiting, dizziness, drowsiness, dry mouth, headache; rarely amnesia, confusion, depression, hallucinations, nightmares; very rarely light headedness, incoordination, paradoxical effects. Nevertheless it remains medication recommended for insomnia treatment in accordance with international guidelines

STUDY OBJECTIVES

Primary Objective

To test the effectiveness of short BBT-I program for chronic insomnia in comparison with zopiclone in Russian population.

Secondary Objectives

Identification of anthropometric, psychological and polysomnographic predictors of effectiveness of each method.

STUDY DESIGN

Study Overview

Prospective randomized crossover study. In accordance with this design every patient will receive two different treatment courses in random sequence: zopiclone or structured educational program (BBT-I) delivered in two sessions. Patients of the zopiclone-first group will receive the medication therapy for the first two weeks followed by educational program. Patients of the BBT-I-first group will receive two-week educational program followed by medication therapy.

Each treatment course will be separated by 2-weeks washout period that will provide the opportunity to evaluate the sustainability of treatment effect.

The total duration of the study will be 8 weeks with 6 visits including 1 night polysomnography (PSG), 2 face-to-face structured educational program sessions and 5 diagnostic interviews. Total duration of the study will be 2 years.

Criteria for evaluation

Primary Efficacy Endpoint

Proposed primary efficacy endpoint is change of insomnia severity index (ISI) after treatment. Criterion of response to the treatment will be defined as the reduction of ISI score reduction of >7 points from baseline. This criterion is indicative of moderate improvement and validated as clinically significant (Morin, Belleville & Belanger, 2011). Remission criterion will be defined as final

ISI score of 7 points or less. Nonresponse criterion will be defined as ISI score decrease of ≤7 points from baseline.

Secondary Efficacy Endpoints

1. Insomnia severity index self reported insomnia symptoms severity . Each item is scored 0 (no problem) - 4 (very big problem) with total between 0-28 (absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).
2. Beck Depression Inventory. 21-item questionnaire assessing (on 4-point Likert scales) the intensity of depressive symptoms in the past week
3. State-trait anxiety inventory. 2-part questionnaire assessing state (situational) and trait anxiety. Both situational and trait parts comprise 20 items rated on a 4-point Likert scale.
4. Dysfunctional beliefs about sleep scale. questionnaire assessing sleep related cognitions in 16 item rated on a 10-point Likert scale.
5. Sleep hygiene index. questionnaire assessing sleep related behavior in 13 item rated on a 5-point Likert scale.
6. Pittsburg Sleep Quality Index. 19-item questionnaire evaluating sleep quality over the past month. The first 4 items are open questions, items 5 to 19 are rated on a 4-point Likert scale. A total score range from 0 to 21. A score > 5 suggests poor sleep quality.
7. Big Five Questionnaire. questionnaire assessing personal traits in 134 item rated on a 5-point Likert scale.
8. Toronto alexythymia scale, short version (TAS-20) - questionnaire assessing alexythymia in 20 item rated on a 5-point Likert scale.
9. β-adrenoreactivity test - laboratory peripheral blood sample analysis for evaluation of sympathetic activity
10. Polysomnography. the main variables used were sleep latency, total sleep time, sleep efficiency, wake after sleep onset, number of awakenings, sleep stages proportion

Safety Evaluations

All subjects will be asked about well-being and possible adverse effects of treatment, on each biweekly visit. In the case of condition exclusionary for study participation (exacerbation of disease, starting medicines, incompatible with zopiclone etc.) when it is not in the subject's best interest to continue the subject may be discontinued from study

SUBJECT SELECTION

Study Population

40 subjects with a diagnosis of chronic insomnia who meet the inclusion and exclusion criteria will participate in this study.

Inclusion Criteria

1. 14 males, 28 females from 18 to 80 years of age.
2. Chronic insomnia diagnosis consistent with the criteria of International Classification of Sleep Disorder, third version (ICSD-3):

- any sleep complaints i.e. difficulties falling or staying asleep, nonrestorative sleep;
- waking symptoms such as fatigue, impaired concentration, and mood disturbance etc.;
- adequate opportunity and circumstances for sleep.
- relapse of the mentioned symptoms at least 3 nights per week for at least 3 months:

3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

Exclusion Criteria

1. unability to stop taking medications that have a proven impact on sleep at least one week before and during the study;
2. history of alcohol or drug abuse;
3. major depressive disorder or other severe mental disorder identified by a clinical assessment and medical history;
4. dementia;
5. pregnancy or lactation;
6. shift or night work;
7. medical problems that would be a direct cause of sleep complaints: moderate/severe sleep apnea, defined as an apnea-hypopnea index of ≥15 events per hour, periodic limb movement disorder defined as a periodic leg movement index ≥15 events per hour or restless legs syndrome;
8. other serious chronic conditions or exacerbation of chronic disorder preventing further participation.

Allowed Medications and Treatments

Regular therapy for cardiovascular diseases (beta-blockers, ACE-inhibitors, antiplatelets, antiarrhythmics).

Prohibited Medications and Treatments

The following medications are prohibited during the study and their administration will be considered a protocol violation:

substances affecting sleep (hypnotics, antidepressants, anxiolytics, antihistamine)

STUDY TREATMENTS

Method of Assigning Subjects to Treatment Groups

40 subjects meeting inclusion and exclusion criteria will be randomly assigned to one of treatment sequences (zopiclone-first group or BBT-I-first group) by card sorting method.

Blinding

The study will be open-label

Formulation of Test and Control Products

Formulation of Test Product 1

Brief behavioral therapy program will include a question-and-answer part; a didactic presentation of sleep regulation mechanisms; the review of causes of onset and chronification of illness; an examination of patient's sleep log; explanation of sleep restriction method and prescription of individual regimen of sleep; explanation of stimulus control method; sleep hygiene education; discussion of relaxation techniques. Participants will be supplied with 32 minute audio recording "Relaxation and refreshment session for insomnia" created for this study by Dr. A.Tabidze with verbal relaxing instructions with quiet musical composition behind it. Participants will be instructed to listen to this recording in headphones each day for 2-week BBT-I period after laying into bed and turning the light off.

Formulation of Test Product 2

Imovan is a trade name of ABC, developed by Sanofi winthrop industrie , for oral administration in the management of CI patients. Imovan is a white-colored tablet

Table 2: Formulation and Measured pH of Imovan

	Imovan
Active Ingredient, mg	Zopiclone, 7,5
Other ingredient, mg	Wheat amylum, 60; natrii hydrophosphate dehydrate, 60; lactose monohydrate 31,575; sodium carboxymethyl starch, 4,95; magnesia stearate 0,975

Packaging and Labeling

For BBT-I program doctor will use supporting data with illustrations of process S and process C of sleep regulation, insomnia pathogenesis, sleep hygiene and behavioral treatment techniques for didactic presentation. At the end of the first session patients will be given reminder card containing sleep hygiene rules and condensed information about normal regulation of sleep and insomnia pathogenesis. For the relaxation audio record

listening all patients will be provided with mp3 players (with audio recorded) and individual earphones.

Imovan is produced in 2 blisters containing 10 tablets each. The blisters are contained in carton (1 extra pouch containing 4 ampoules in the event of breakage).

Supply of Study Drug at the Site

Supporting illustrations, mp3 players with audio records and other hand-outs will be provided by the investigator

On the zopiclone treatment stage patients will be given Imovan prescription and buy it in a pharmacy

Dosage/Dosage Regimen

Imovan (zopiclone) in a dose of 7,5 mg will be taken 30 minutes before bedtime for two weeks

Dispensing

Investigator will have the responsibility for dispensing of drug prescriptions and BBT-I handouts

Administration Instructions

BBT-I will be delivered in two weekly 1-hour sessions.
Imovan (zopiclone) will be prescribed in a dose of 7,5 mg to be taken 30 minutes before bedtime for two weeks

Storage

Imovan (zopiclone) should be kept dry at controlled room temperature, to 30ºC.

Study Drug Accountability

There will be no special accounting of the dispensing and return of study drug for subjects.

Measures of Treatment Compliance

Subjects will be asked to keep a sleep diary noting their bedtime, wake up time, sleep latency time, arising time, possible causes of bed sleep, drug intake and any adverse events. They will be asked to bring their diary to each biweekly study visit along with questionnaires evaluating quality of sleep for that period

STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures supposed to be performed for the duration of the study is in Appendix 1.

Prior to conducting any study-related activities, written informed consent will be signed and dated by the subject.

Clinical Assessments

Concomitant Medications

All concomitant medication and concurrent therapies will be documented at baseline examination and at visit days. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Demographics

Demographic information (date of birth, gender) will be recorded at baseline examination.

Medical History

Relevant medical history, including history of current disease, other insomnia history, and information regarding underlying diseases will be recorded at baseline examination.

Physical Examination

A complete physical and neurological examination will be performed by the investigator who is a neurologist at baseline examination.

Vital Signs

Body temperature, blood pressure, pulse will be measured after resting for 5 minutes at baseline examination.

Polysomnography

1-night in-lab PSG (without adaptation night) will be performed at baseline examination. Standard polysomnography montage includes 6 monopolar electroencephalography (EEG) channels Fp_1A_2, Fp_2A_1, C_3A_2, C_4A_1, O_1A_2, O_2A_1; 1 submental electromyogram (EMG) channel; 2 electrooculogram (EOG) channels; 2 EMG channels of the right and left tibialis anterior muscles; 1 electrocardiogram channel; oronasal airflow pressure; thoracic and abdominal efforts; respiratory sound; oxygen saturation; body position with videomonitoring

Questionnaire

Subjects will be asked to fill in self-report questionnaires: Beck Depression Inventory (BDI), State-trait anxiety inventory (STAI), Toronto Alexithymia Scale – short version TAS-20, Big Five Questionnaire (BFQ-2R), Pittsburg Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Dysfunctional beliefs about sleep scale (DBAS), Sleep hygiene index (SHI) at baseline examination.

During the next 4 visits participants will repeatedly undergo diagnostic tests including BDI, STAI, PSQI, ISI, DBAS, SHI.

Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

Clinical Laboratory Measurements

β-adrenoreactivity test

Peripheral blood sample will be collected in a sterile tube and tested in lab for erytrosyte membranes β-adrenoreactivity by a method based on detection of adrenoreceptor sensitivity to-endogenous catecholamines

EVALUATIONS BY VISIT

Visit 1 (Day 1/Week 1/ Month 1)

1. Review the study with the subject and obtain written informed consent.
2. Record demographics data.
3. Record medical history, including a history of insomnia, diagnosis date, and prior treatments.
4. Record concomitant medications.
5. Perform a complete physical and neurological examination.
6. Perform and record vital signs.
7. Perform and record Polysomnography
8. Perform questionnaire completion
9. Perform and record results of β-adrenoreactivity testing.
10. Randomize subject for zopiclone-first or BBT-I-first group.
11. Writing Imovan prescription for zopiclone-first group subjects
12. First BBT-I session BBT-I-first group subjects
13. Initiate subject diary.

Visit 1.2 (for subjects of BBT-I-first group) (Day 8/Week 2/ Month 1)

1. Second BBT-I session

Visit 2 (Day 14/Week 2/Month 1)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Perform questionnaire completion
3. Perform and record results of β-adrenoreactivity testing.

Visit 3 (Day 28/Week 4/Month 1)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Perform questionnaire completion
3. Perform and record results of β-adrenoreactivity testing.
4. Writing Imovan prescription for BBT-I-first group subjects
5. First BBT-I session for zopiclone-first group subjects

Visit 3.2 (for subjects of zopiclone-first group) (Day 35/Week 5/ Month 2)

1. Second BBT-I session

Visit 4 (Day 42/Week 6/Month 2)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Perform questionnaire completion
3. Perform and record results of β-adrenoreactivity testing.

Visit 5 (Day 56/Week 8/Month 2)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Perform questionnaire completion
3. Perform and record results of β-adrenoreactivity testing.
4. Medical consultation for treatment and health maintenance

Early Withdrawal Visit

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Perform questionnaire completion
3. Perform and record results of β-adrenoreactivity testing.
4. Medical consultation for treatment and health maintenance

ADVERSE Experience REPORTING AND DOCUMENTATION

Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. The Investigator will discuss with the subject, possible AEs during each subject visit and record the information in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

All reported adverse effects will be graded as mild in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Medical Monitoring

Pchelina Polina should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: +79036701725

DISCONTINUATION AND REPLACEMENT OF SUBJECTS

Early Discontinuation of Study

A subject may be discontinued from study treatment at any time if the subject or the investigator, feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject had a condition exclusionary for study participation
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment will be recommended to come in for an early discontinuation visit as soon as possible and then will be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's CRF. Subjects withdrawn after Visit 5 but prior to Visit 6 will be encouraged to come in for a final visit (pass the procedures supposed for their next scheduled visit).

Replacement of Subjects

Subjects withdrawn from the study treatment will be replaced. Subjects withdrawn from the study after Visit 5 but prior to Visit 6 won't be replaced.

Protocol Violations

Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria

- Use of a prohibited concomitant medication
- Non-compliance with study drug regimen, and questionnaires completion

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. If a protocol violation occurs, a Protocol Violation Form detailing the violation will be generated.

DATA SAFETY MONITORING

There will be no data monitoring committee

STATISTICAL METHODS AND CONSIDERATIONS

A Statistical Analysis Plan (SAP) is written describing all analyses that will be performed.

Data Sets Analyzed

All subjects matching inclusion and exclusion criteria who will complete at least one treatment course (BBT-I or medication) and fill in questionnaires prior and after the treatment will be included in the safety analysis.

Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by dose level: gender, age, height and weight. Continuous variables will be presented in means and standard deviation (M±SD).

Analysis of Primary Endpoint

Statistical significance of differences between ISI level before and after treatment for both treatment methods will be evaluated with Student's t-test after confirmation of normal variable distribution by Kolmogorov-Smirnov test. For continuous variables with distribution other than normal Mann-Whitney U-test will be used. For comparison of the proportions Pearson chi-squared test will be performed.

Criterion of response to the treatment is defined as the reduction of ISI score reduction of >7 points from baseline. This criterion is indicative of moderate improvement and validated as clinically significant (Morin, Belleville & Belanger, 2011). As well the criterion corresponds to approximately 1 standard deviation of the pretreatment values (Cohen effect size of approximately 1.0). Remission criterion is defined as final ISI score of 7 points or less. Nonresponse criterion is defined as ISI score decrease of ≤7 points from baseline.

Analysis of Secondary Endpoints

Statistical significance of differences between BDI, STAI, PSQI, DBAS, SHI, β-adrenoreactivity level, sleep diary data before and after treatment for both treatment methods will be evaluated with Student's t-test after confirmation of normal variable distribution by Kolmogorov-Smirnov test. For continuous variables with distribution

other than normal Mann-Whitney U-test will be used. For comparison of the proportions Pearson chi-squared test will be performed.

Based on the response criterion participants will be divided into two groups: responders and nonresponders for each method of treatment. Comparison of responders and nonresponders baseline quantitative characteristics (polysomnographic, antropometric, psychometric) will be performed using Student's t-test (for normal data distribution) or Mann-Whitney U-test (for abnormal data distribution). Statistical significance will be set at a p-value less 0,05.

Safety and tolerability data will be summarized by treatment group. Adverse events will be tabulated by treatment group and include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

Interim Analysis

Interim statistical analysis will be performed after 20 patients complete the study protocol.

Sample Size and Randomization

The number of subjects planned to be enrolled is 40. This is a representative sample for study of treatment effects. The crossover design of the study will allow us to compare two therapeutic approaches with a relatively small sample size and to determine the predictors of effectiveness for each treatment.

DATA COLLECTION, RETENTION AND MONITORING

Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each study subject. The information corresponding to each visit will be entered to the study database and to paper CRF.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study will be reviewed and verified for completeness and accuracy by the Investigator.

Data Management Procedures

The data will be entered into a validated database. The Investigator is responsible for data processing, in accordance with procedural documentation.

All procedures for the handling and analysis of data will be conducted using Microsoft Office Excel 2007 and STATISTICA 7

Data Quality Control and Reporting

The Investigator is responsible for data collection, validation, processing and reporting in accordance with procedural documentation.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases will be backed up by the Investigator in conjunction with any updates or changes to the database.

Availability and Retention of Investigational Records

The Investigator must make study documents (patient files, signed informed consent forms, copies of CRFs, questionnaires, sleep diaries) accessible to the monitor, IRB/IEC, and Regulatory Agency inspectors upon request. A file for each subject will be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF is derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, questionnaires, sleep diaries) must be kept secured for the whole study period and two years after study completion.

Subject Confidentiality

The study is open-label. All subjects will give written consent allowing their personal data to be maintained and used for scientific purposes and published. In order to maintain subject confidentiality, only a subject number will identify all study subjects on data reports.

ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects October 2013; Ethical Issues in Patient Safety Research: Interpreting existing guidance, WHO, 2013; Consolidated Guideline for good clinical practice (ICH), 1996; European Union Council and Parliament guidelines (for instance, Guidelines on the practice of ethics committees in medical research, 2007; The Constitution of the Russian Federation (Article 21); OrderN 323-FZ «About the Fundamentals of Health Protection of the Russian Federation citizens» 21 November 2011; Order N 61-FZ “About the drug use” from 22 December 2014; The Russian Federation National Standard «Good Clinical Practice» (National Standard P 52379-2005); and local regulations

All study records will be kept in a locked file. Only a subject number will identify all study subjects on data reports The Investigator is responsible for confidentiality of subjects personal data.

Protocol Amendments

Any amendment to the protocol will not be implemented without prior written IRB/IEC approval.

Institutional Review Boards and Independent Ethics Committees

The protocol will be reviewed and approved by the IRB/IEC of I.M. Sechenov Moscow State Medical University on 18th March, 2015. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, etc.) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained. The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study.

Informed Consent Form

Informed consent will be designed in accordance with the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects October 2013; Ethical Issues in Patient Safety Research: Interpreting existing guidance, WHO, 2013; Consolidated Guideline for good clinical practice (ICH), 1996; European Union Council and Parliament guidelines (for instance, Guidelines on the practice of ethics committees in medical research, 2007; The Constitution of the Russian Federation (Article 21); OrderN 323-FZ «About the Fundamentals of Health Protection of the Russian Federation citizens» 21 November 2011; Order N 61-FZ "About the drug use" from 22 December 2014; The Russian Federation National Standard «Good Clinical Practice» (National Standard P 52379-2005); and local regulations

The consent form generated by the Investigator will be approved by the IRB/IEC of I.M. Sechenov Moscow State Medical University on 18th March, 2015. The written consent

document embodies the elements of informed consent as described in the International Conference on Harmonisation and comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

Publications

The preparation and submittal for publication of manuscripts containing the study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct the study
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines.
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
5. Maintain adequate and accurate records and to make those records available for inspection of IRB/IEC.
6. Ensure that an IRB will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others.
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in regulatory documents.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	VISIT 1 (Day1/Week1/Month 1)[a]	VISIT 2 (Day14/Week2/Month 1)[a]	VISIT 3 (Day28/Week4/Month 1)[a]	VISIT 4 (Day42/Week6/Month 2)[a]	VISIT 5 (Day56/Week8/Month 2)
Informed Consent	**X**				
Medical History	**X**				
Complete Physical and neurological Exam	**X**				
Abbreviated Physical Exam		**X**	**X**	**X**	**X**
Height	**X**				
Weight	**X**				
Vital Signs	**X**				
Polysomnography	**X**				
β-adrenoreactivity test	**X**	**X**	**X**	**X**	**X**
BDI, STAI, PSQI, DBAS, SHI	**X**	**X**	**X**	**X**	**X**
Big five questionnaire, TAS-20	**X**				
Randomization	**X**				
Administration of Study Drug	**X**		**X**		
BBT-I[b]	**X**		**X**		
Initiate Subject Diary	**X**				
Subject Diary Review		**X**	**X**	**X**	**X**
Adverse Experiences		**X**	**X**	**X**	**X**

[a] ±2 day

[b] BBT-I was delivered in two weekly sessions, so during BBT-I phase each subject had additional (1.2 or 3.2) visit for BBT-I session

Study design