An international multicenter, randomised, double-blind, placebo-controlled parallel-group clinical study of efficacy and safety of various schemes of Tenoten® in the treatment of anxiety in subjects with somatoform, stress-related disorders and other neurotic disorders

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-TN-001**
Version date:	**April 19, 2016**
ClinicalTrials.gov Id:	**NCT03036293**

Protocol Summary

This document represents the protocol summary for the study on human subjects. The study will be carried out in accordance with ICH GCP, National Standard of the Russian Federation GOST 52379-2005 "Good Clinical Practice", Helsinki Declaration of World Medical Association, relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

An international multicenter randomized double-blind placebo-controlled parallel-group clinical study of efficacy and safety of various schemes of Tenoten in the treatment of anxiety in subjects with somatoform, stress-related disorders and other neurotic disorders

Phase: IV

Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia

Protocol No. MMH-TN-001

Objective of the study

- To obtain additional efficacy and safety data for various schemes of Tenoten® dosing in the treatment of anxiety in subjects with somatoform, stress-related or other neurotic disorders.
- To compare efficacy of the two schemes of Tenoten® dosing (daily dose of 4 and 8 tablets for 12 weeks) in the treatment of anxiety in subjects with somatoform, stress-related or other neurotic disorders.

Endpoints

Primary endpoint

1. Change from baseline in mean HAM-A score after 12 weeks of treatment.
    1. group 1 (Tenoten® 4 tablets a day)
    2. group 3 (Tenoten® 8 tablets a day).

Secondary endpoints

1. Change from baseline in mean HAM-A score after 4 weeks of treatment:
    1.1. group 1 (Tenoten® 4 tablets a day)
    1.2. group 3 (Tenoten® 8 tablets a day).
2. Change from baseline in mean HAM-A score after 8 weeks of treatment.
    2.1. group 1 (Tenoten® 4 tablets a day)
    2.2. group 3 (Tenoten® 8 tablets a day).

3. Proportion of the subjects with reduced anxiety by ≥ 50% according to HAM-A scale vs. baseline:
    3.1. group 1 (Tenoten® 4 tablets a day)
        3.1.1. after 4 weeks of therapy
        3.1.2. after 8 weeks of therapy
        3.1.3. after 12 weeks of therapy
    3.2. group 3 (Tenoten® 8 tablets a day)
        3.2.1. after 4 weeks of therapy
        3.2.2. after 8 weeks of therapy
        3.2.3. after 12 weeks of therapy.
4. Proportion of subjects with lack of anxiety (<14 points according to HAM-A scale):
    4.1. group 1 (Tenoten® 4 tablets a day)
        4.1.1. after 4 weeks of therapy
        4.1.2. after 8 weeks of therapy
        4.1.3. after 12 weeks of therapy
    4.2. group 3 (Tenoten® 8 tablets a day)
        4.2.1. after 4 weeks of therapy
        4.2.2. after 8 weeks of therapy
        4.2.3. after 12 weeks of therapy.
5. Change from baseline in total EQ-5D-3L score after 12 weeks of treatment.
    5.1. group 1 (Tenoten® 4 tablets a day)
    5.2. group 3 (Tenoten® 8 tablets a day).
6. Total CGI score:
    6.1. group 1 (Tenoten® 4 tablets a day)
    6.2. group 3 (Tenoten® 8 tablets a day).

Safety assessment

- Occurrence and nature of adverse events, their intensity (severity), causal relationship to the study drug, and outcome.
- Changes in vital signs during the treatment.

Study design

Design – an international multicenter, randomized, double-blind, placebo-controlled parallel-group clinical trial to evaluate efficacy and safety of various schemes of Tenoten® in the treatment of anxiety.

The study will enroll outpatient subjects of both genders aged 18-45 years with verified diagnoses of somatoform, stress-related and other neurotic disorders (F43, F45, F48) and signs of clinically relevant anxiety according to The Hospital Anxiety and Depression scale (HADS).

After signing information sheet (informed consent form) to participate in the clinical study the subject will be interviewed (complaints, medical history, concomitant therapy) and physical examination will be performed; the subject will fill HADS scale. Degree of anxiety at screening should be ≥ 11 according to HADS. Where the subject meets inclusion criteria and has no exclusion criteria he/she will be enrolled into the study. The investigator will determine degree of anxiety using HAM-A scale; the subject will fill EQ-5D-3L questionnaire. At Visit 1 (Day 1) the subject will be randomized into one of the follow treatment groups:

- Group 1: Tenoten® at 2 tablets twice daily (4 tablets/day);
- Group 2: Placebo at 2 tablets twice daily (4 tablets/day);
- Group 3: Tenoten® at 2 tablets 4 daily (8 tablets/day).
- Group 4: Placebo at 2 tablets 4 daily (8 tablets/day).

The first dose of the study drug should be administered at Visit 1 after the visit procedures are completed. Further administration of the study product will be made according to the dosing scheme. The subject will administer the study drug and will be followed for 12 weeks during which additional three visits will be made. At Visit 2 (Week 4), Visit 3 (Week 8) and Visit 4 (Week 12) the physician will record patients' complaints and physical examination data, fill HAM-A scale, check the study and concomitant therapy, assess treatment safety and patient compliance with the study treatment. At the final Visit 4 the subject will fill EQ-5D-3L questionnaire and the investigator will determine Clinical Global Impression Scale Efficacy Index (CGI-EI) score.

The patients will be allowed to take symptomatic therapy and medications for their co-morbidities during the study, except for the medicines listed in "Forbidden concomitant therapy".

Inclusion and exclusion criteria

Inclusion criteria

1. Age between 18 and 45 years old inclusively.
2. Diagnosis of somatoform, stress-related and other neurotic disorders (F43, F45, F48)[1] established according to ICD-10 study diagnostic criteria.
3. Clinically relevant anxiety at screening (≥11 points according to HADS scale).

[1] Diagnosis of diseases and diagnostic procedures to verify somatoform, stress-related and other neurotic disorders in the subjects will not be the study objective; the diagnostics algorithm will be defined by the investigator.

4. Availability of signed patient information sheet (Informed Consent form) for participation in the clinical trial.
5. Usage of contraceptive methods[2] by both gender patients of reproductive age during the trial and within 30 days of ending the participation in the trial.

Exclusion criteria

1. Expressed depression symptoms at screening (≥ 11 points according to HADS scale).
2. Organic including symptomatic, mental disorders (F00-09).
3. Mental disorders or behavioural disorders associated with psychoactive substances (F10-19).
4. Schizophrenia, schizotic conditions and delusional disorders (F20-29).
5. Mood disorders [affective disorders] (F30-39).
6. Phobic (F40) and other anxiety disorders (F41), obsessive-compulsive disorder (F42), dissociative [conversion] disorders (F44), depersonalization syndrome (F48.1).
7. Behavioural syndromes associated with physiological disorders and physical factors (F50-59).
8. Personality and behavioural disorders at mature age (F60-69).
9. Mental deficiency (F70-79).
10. Inflammatory and traumatic injuries of brain with persistent neurological deficit.
11. Prior diagnosis of heart failure defined by the New York Heart Association classification (1964) as III or IV FC.
12. Malignant neoplasm/suspected malignant neoplasm
13. Patients allergic to/intolerant of any constituent of the medications used in the treatment.
14. Malabsorption syndrome, including congenital or acquired lactase deficiency (or any other disaccharidase deficiency) and galactosemia.
15. Any conditions which, according to the investigator, may interfere with the subject's participation in the study.
16. Scheduled hospiralizations, surgeries during the study.
17. Patients who, from the investigator's point of view, will not comply with the observation requirements of the study or adhere to study drug dosing regimens.
18. Use of any medicine listed in the section "Prohibited concomitant treatment" within 30 days preceding the inclusion in this study.
19. Drug addiction, alcohol usage in the amount exceeding 2 units of alcohol per day[3].
20. Pregnancy, breast-feeding.

[2] Acceptable contraception includes intrauterine device; barrier method (condom, contraceptive cap, cervical cap or spermicide), previous surgical sterilization or vasectomy (for male subjects or partners). Throughout the study systemic hormonal contraceptives including oral contraceptives will not be allowed.
[3] 1 unit of alcohol is equivalent to 0.33 L of lager/150 mL of unfortified wine, or 40 mL of a spirit

21. Participation in other clinical trials in the previous 3 months.
22. Patients who are related to any of the on-site research personnel directly involved in the conduct of the trial or are an immediate relative of the study investigator. 'Immediate relative' means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
23. Patients who work for OOO "NPF "Materia Medica Holding" (i.e. the company's employees, temporary contract workers, appointed officials responsible for carrying out the research or immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Participant's failure or decline to comply with the protocol requirements.
2. Necessity for prescribing medications not permitted during the study.
3. An adverse event requiring discontinuation of the study product;
4. Pregnancy.
5. Patient's decision to withdraw early for lack of efficacy or other reasons.
6. Eligibility error.
7. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.

Number of subjects

It is planned to include 390 subjects, which is expected to yield at least 310 patients completing all protocol procedures.

Interim analysis

An interim statistical analysis is not scheduled within the study.

Treatment

Group 1

Name of the medicinal product: Tenoten

Active ingredient: Affinity purified antibodies to brain-specific S-100 protein - 0.003 g*

** applied onto lactose as a water-alcohol mixture containing no more than 10^{-15} ng/g active form of the API.*

Excipients: Lactose monohydrate (lactose) - 0.267g (Eur. Ph.[4], USP[5] NF, BP[6])

Microcrystalline cellulose - 0.03 g (Eur. Ph., USP NF, BP)

Magnesium stearate - 0.003 g (Eur. Ph., USP NF, BP)

[4] Eur. Ph. European Pharmacopoeia (current edition)
[5] USP – current US Pharmacopeia
[6] EP – current European Pharmacopoeia

Method of administration: Tablet for oral use. Dose per administration: 2 tablets. 2 tablets twice daily (4 tablets/day). The tablets should be held in the mouth until dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a place protected from light at a temperature below 25 C. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: Lactose monohydrate (lactose) - 0.267 g (Eur. Ph[4]., USP[5] NF, BP[6])
Microcrystalline cellulose - 0.03 g (Eur. Ph., USP NF, BP)
Magnesium stearate - 0.003 g (Eur. Ph., USP NF, BP)

Method of administration: Tablet for oral use. Dose per administration: 2 tablets. 2 tablets twice daily (4 tablets/day). The tablets should be held in the mouth until dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a place protected from light at a temperature below 25 C. Keep out of the reach of children.

Group 3

Active ingredient: Affinity purified antibodies to brain-specific S-100 protein - 0.003 g*

** applied onto lactose as a water-alcohol mixture containing no more than 10^{-15} ng/g active form of the API.*

Excipients: Lactose monohydrate (lactose) - 0.267g (Eur. Ph.[7], USP[8] NF, BP[9])
Microcrystalline cellulose - 0.03 g (Eur. Ph., USP NF, BP)
Magnesium stearate - 0.003 g (Eur. Ph., USP NF, BP)

Method of administration: Tablet for oral use. Dose per administration: 2 tablets. 2 tablets 4 times daily (8 tablets/days). The tablets should be held in the mouth until dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

[7] Eur. Ph. European Pharmacopoeia (current edition)
[8] USP – current US Pharmacopeia
[9] EP – current European Pharmacopoeia

Storage conditions: Store in a place protected from light at a temperature below 25 C. Keep out of the reach of children.

Group 4

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: Lactose monohydrate (lactose) - 0.267 g (Eur. Ph[4]., USP[5] NF, BP[6])
Microcrystalline cellulose - 0.03 g (Eur. Ph., USP NF, BP)
Magnesium stearate - 0.003 g (Eur. Ph., USP NF, BP)

Method of administration: Tablet for oral use. Dose per administration: 2 tablets. 2 tablets 4 times daily (8 tablets/days). The tablets should be held in the mouth until dissolution, without meal.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a place protected from light at a temperature below 25 C. Keep out of the reach of children.

Treatment duration

Tenoten/Placebo treatment duration is 12 weeks.

Observation period

In total the patients will be monitored for 12 weeks.

Symptomatic (Standard) treatment

Subjects are allowed to receive medications used to treat coexisting diseases other than those representing exclusion criteria, except drugs listed in section "Forbidden concomitant therapy".

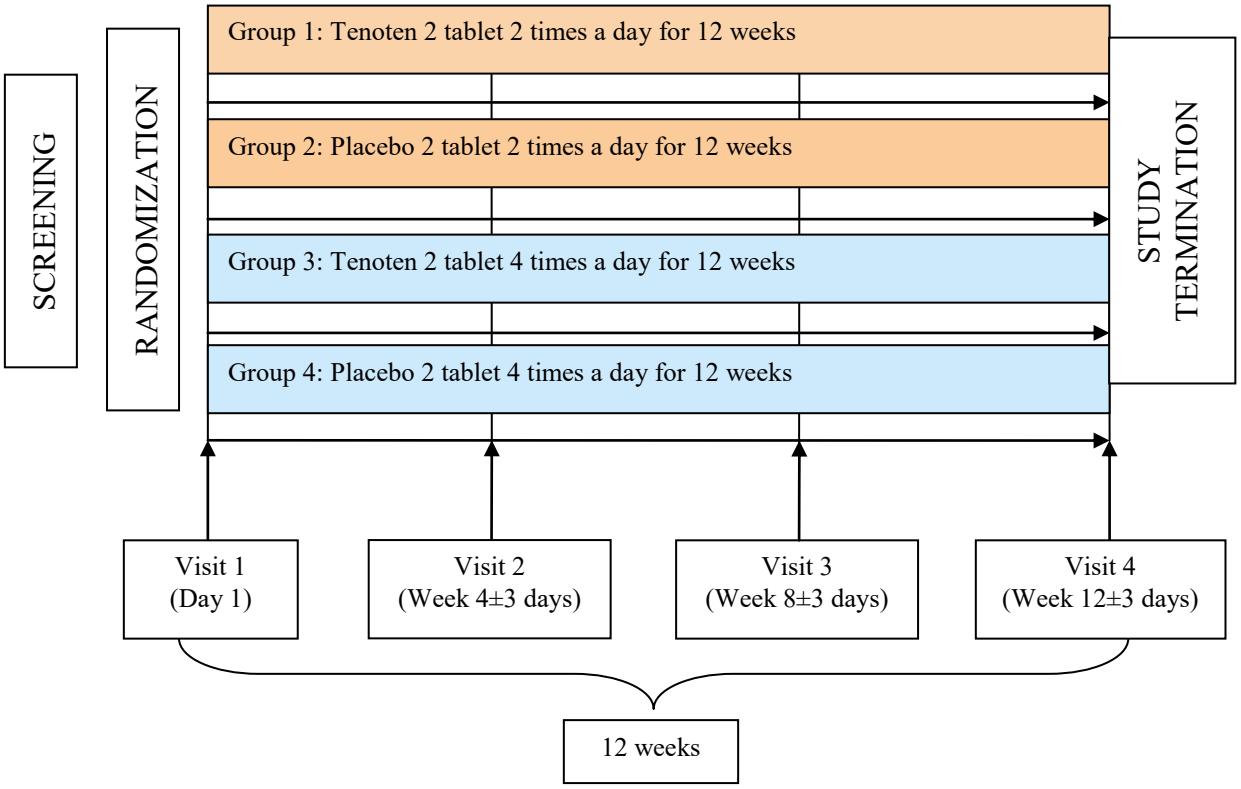
Prohibited concomitant therapy

Within 4 weeks prior to enrollment and during the study (beginning from signing informed consent form and initiation of screening) subjects are not allowed to receive any medications that may affect mental and emotional status (parenthesized is the ATC group):

1. Psycholeptics (ATC group - N05), including antipsychotics, anxiolytics (tranquilizers), hypnotics and sedatives.
2. Psychoanaleptics (ATC group – N06) including antidepressants, psychostimulants, nootropic drugs and their combinations.
3. Antiepileptic drugs (ATC group – N03A).
4. Anticholinergic drugs (ATC group − N04A).
5. Dopaminergic drugs (ATC group − N04B).

6. Antiaddictive drugs (ATC group − N07B).
7. Antihypoxic and antioxidant drugs (ethylmethylhydroxypyridine succinate, citicoline, etc.).
8. Agents improving metabolism and energy supply to tissues, reducing tissue hypoxia (cytoflavin, corylip, eltacin, inosie, etc.).
9. Sex hormones and reproductive function modulators (ATC group - G03).
10. Vitamins B including combinations with other products (ATC group – A11E).
11. Materia Medica Holding products except for the ones assigned in this study.
12. Homeopathic remedies.
13. Herbal psychotropic agents (medicinal products and biologically active additives).
14. Drugs known to have caused allergic reactions.
15. Psychotherapeutic methods.
16. Physiotherapeutic treatments for psychoemotional state.

Study design scheme



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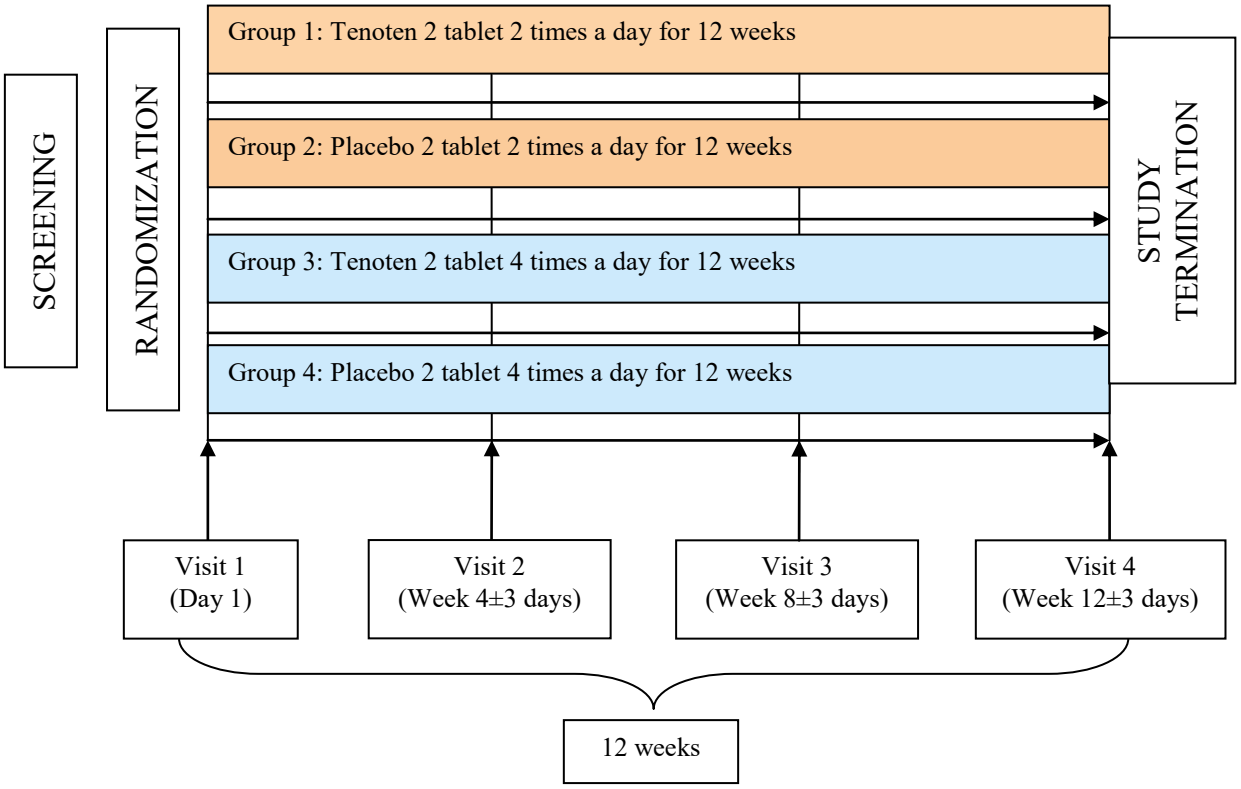

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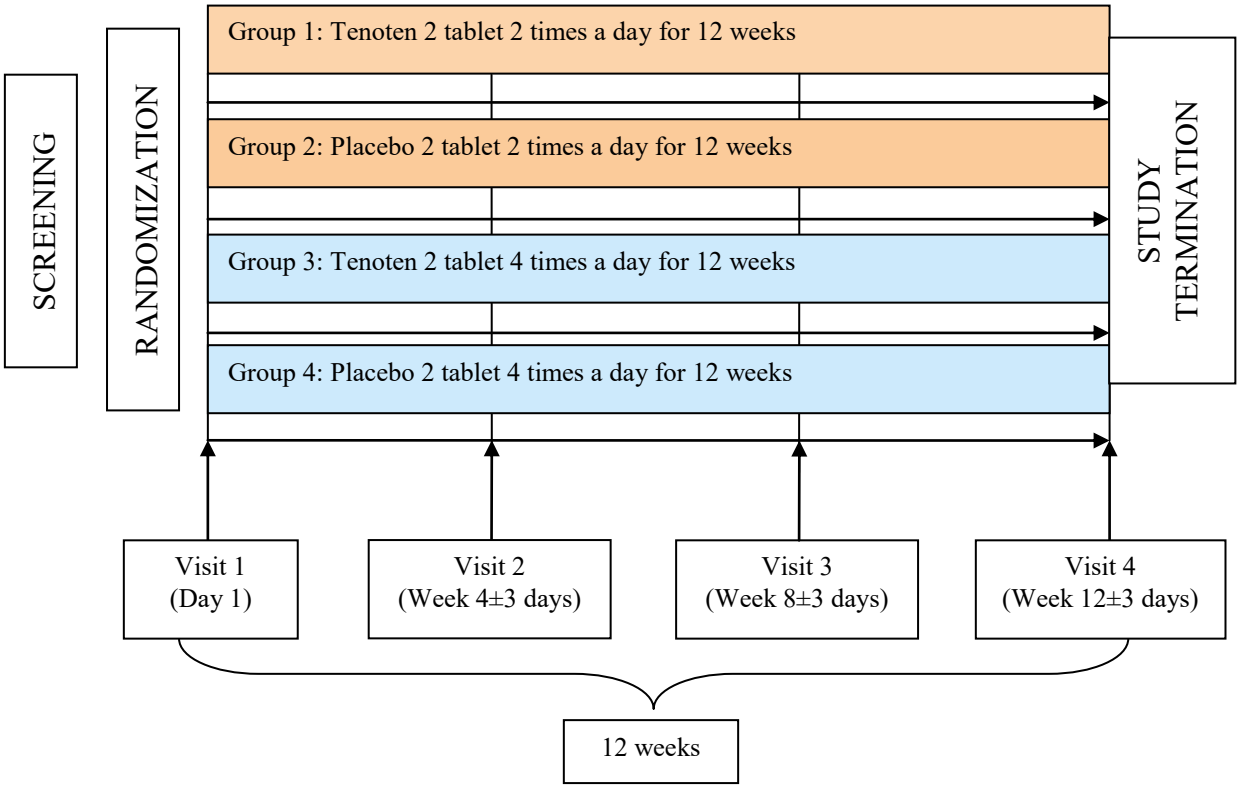

Schedule of study procedures

Procedure/visit	Visit 1 (Day 1)	Visit 2 (Week 4±3 days)	Visit 3 (Week 8±3 days)	Visit 4 (Week 12±3 days)
Informed consent	+			
Collection of complaints	+	+	+	+
Medical history	+			
Physical examination	+	+	+	+
HADS scale filling	+			
HAM-A scale filling	+	+	+	+
EQ-5D-3L questionnaire filling	+			+
Pregnancy test	+			
Concomitant therapy	+	+	+	+
Inclusion/exclusion criteria	+			
Randomization and prescription of study therapy	+			
Study drug supply	+	+	+	
Study drug accountability, compliance assessment		+	+	+
CGI scale filling				+
Evaluation of treatment safety		+	+	+

Statistical Analyses

Samples

Total set includes all the subjects who have signed ICF. This sample will consider all adverse events throughout the study, including those occurred prior to the study therapy.

The sample including all subjects who received at least one dose of the study product to be used for ***analysis of the study treatment safety and tolerability*** (*Safety population*), as all adverse events identified after the study product administration will be recorded.

Full Analysis Set This sample will consist of all enrolled subjects, except for those who met at least one of the following criteria:

1) failure to meet inclusion/non-inclusion criteria;
2) subject failing to take any dose of the study drug;
3) absence of any data on the subject after the study drug administration.

This was the best set for the Intention-to-treat method, so it will be used in the ***Intention-to-treat efficacy analysis of the test therapy.***

Per Protocol set. This sample includes all subjects who completed the therapy as per the study protocol, without any missing visits or major protocol deviations. This set will be used in the ***Per Protocol efficacy analysis of the test therapy.***

Mean value of the total set for the relevant day will be used to fill lacking/missing data.

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[10]

Evaluation of sample size

The sample size was assessed in accordance with the following rules and assumptions:

1. Statistical assumptions
   - 1.1 the power of statistical tests 'P = (1 − β)' is 80% (the probability of correct rejection of the null hypothesis is 0.8)
   - 1.2 the probability of type 1 error 'a' is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05);
   - 1.3 statistical criteria of intergroup comparisons will be two-sided, equivalence criterion - one-sided;
   - 1.4 calculation of sample size will be based on the assumptions on the expected effect declared in the primary efficacy criterion of the protocol;
   - 1.5 ratio between sample sizes of Tenoten and Placebo groups receiving similar dosing schemes will be 2:1 (1 Placebo patient - 2 Tenoten patients);
   - 1.6 statistical analysis will utilize pooled Placebo group including Placebo with dosing scheme 2 tablets 2 times and Placebo group with dosing scheme 4 tablets 2 times a day, as the differences between Placebo groups with different dosing schemes are not suggested;
   - 1.7 the study is supposed to use three groups of statistical hypotheses; for this purpose probability of type I error α will be corrected by introducing the relevant correction for three hypotheses (α=0.05/3);
   - 1.8 statistical hypotheses will be as follows:
     - 1.8.1. null and alternative hypotheses on superiority of the study product with dosing scheme 2 tablets 2 times a day:

       $$\mathbf{H_0: \Delta\mu_{т1}=\Delta\mu_{п}}$$

       $$\mathbf{H_a: \Delta\mu_{т1}\neq\Delta\mu_{п}},$$

       where $\mathbf{\Delta\mu_{т1}}$ – mean reduction (initial – final score) of **HAM-A** total score in Tenoten group with dosing scheme 2 tablets 2 times a day, $\mathbf{\Delta\mu_{п}}$ – mean reduction (initial – final score) of **HAM-A** total score in Placebo group;
     - 1.8.2. null and alternative hypotheses on superiority of the study product with dosing scheme 4 tablets 2 times a day:

       $$\mathbf{H_0: \Delta\mu_{т2}=\Delta\mu_{п}}$$

[10] Holder of license: OOO "NPF "Materia Medica Holding", No. 70100045.

$\mathbf{H_a: \Delta\mu_{T2} \neq \Delta\mu_{П}}$,

where $\mathbf{\Delta\mu_{T2}}$ – mean reduction (initial – final score) of **HAM-A** total score in Tenoten group with dosing scheme 4 tablets 2 times a day, $\mathbf{\Delta\mu_{П}}$ – mean reduction (initial – final score) of **HAM-A** total score in Placebo group;

1.8.3. null and alternative hypotheses on equivalence of the study product with dosing scheme 2 tablets 2 times a day with the study product with dosing scheme 4 tablets 2 times a day:

$\mathbf{H_0: |\Delta\mu_{T1} - \Delta\mu_{T2}| \geq \delta}$

$\mathbf{H_a: |\Delta\mu_{T1} - \Delta\mu_{T2}| < \delta}$,

where $\mathbf{\mu_{T1}}$ – mean reduction (initial – final score) of **HAM-A** total score in Tenoten group with dosing scheme 2 tablets 2 times a day, $\mathbf{\mu_{T2}}$ – mean reduction (initial – final score) of **HAM-A** total score in Tenoten group with dosing scheme 4 tablets 2 times a day, **δ** – equivalence margin accepted as **0.15*M** where **M –** mean total population score at baseline;

1.9 calculation of sample size for statistical criteria will be made using the group of formulas:

1.9.1. calculation of sample size to evaluate superiority of the study product over placebo:

$$n_1 = n_2 = \frac{2(z_{\alpha/2} + z_\beta)^2\sigma^2}{\epsilon^2},$$

where $\mathbf{n_1, n_2}$ is sample size for the study product group; **ε** – expected difference in mean reduction of the total score between Placebo and Tenoten groups; **σ** – standard deviation of mean reduction of the total score (calculated as standard deviation of difference between two uncorrelated random variables); $\mathbf{z_{\alpha/2}}$ – tabular value of two-sided z-test for **α** value; $\mathbf{z_\beta}$ – tabular value of one-sided z-test for **β** value;

1.9.2. calculation of sample size for equivalence evaluation:

$$n_1 = n_2 = \frac{2(z_\alpha + z_{\beta/2})^2\sigma^2}{(\delta - |\epsilon|)^2},$$

where $\mathbf{n_1, n_2}$ is sample size for the study product group; **ε** – expected difference in mean reduction of the total score between Tenoten with dosing scheme 2 tablets 2 times a day and Tenoten with dosing scheme 4 tablets 2 times a day; **σ** – standard deviation of mean reduction of the total score (calculated as standard

deviation of the difference between two uncorrelated random variables); z_{α} – tabular value of z-test for **α** value; z_{β} – tabular value of z-test for **β** value, **δ** – equivalence margin accepted as **0.15*M** where **M –** mean total population score at baseline;

1.10 sample size will be determined using the formula:

$$N_{PP}=\max\{ n_i, \text{ all pairs of interest (i)}\},$$

where N_{PP} – Per Protocol sample size; n_i – result of calculation in cl. 1.6, i.e. the result for each of the three study hypotheses;

1.11 final sample size will be determined using the formula:

$$N_T=N_{PP}/(1-C_w),$$

where N_T – final sample size; N_{PP} – result of calculation in cl. 1.7, i.e. the scheduled number of the subjects completing the study per protocol; C_w – withdrawal coefficient.

2. Assumptions on expected clinical study effects:

Mean **HAM-A** total score at 12 weeks of therapy in Tenoten groups with both dosing schemes is expected to reduced by at least **10** units, in Placebo - by no more than **6** units (difference – at least **4** points). Population variance for total score change was $\sigma^2=44$ (based on preliminary analysis).

HAM-A mean score changes after 12 weeks in Tenoten groups for both dosing schemes are expected to differ by less than **3** points. Population variance was accepted as $\sigma^2=44$ (based on preliminary analysis).

According to the statistical criteria and the assumptions above, for evaluation of differences in various dosing schemes, group size will be **103** subjects for Tenoten group (each dosing scheme) and **52** subjects for Placebo group (each dosing scheme). To evaluate superiority of the study product over placebo at different dosing schemes the group size will be 58 subjects for Tenoten group (each dosing scheme) and 26 subjects for Placebo group (each dosing scheme). The final sample size will be **103** subjects for Tenoten groups (each dosing scheme) and **52** subjects for Placebo group (each dosing scheme).

Given potential withdrawal of at least 20% subjects during the study for various reasons, at least **390** subjects will be required to sign informed consent.

Statistical criteria

All statistical calculations will be made using two groups of statistical criteria:

- parametric - to evaluate continuous and interval random values;
- nonparametric – to obtain:
  - evaluations of equality/inequality of proportions of the subjects upon their comparison for various visits,

- analysis of frequencies of the features compared,

and

- evaluation of continuous and interval random values in case of non-compliance with normal random distribution.

Parametric criteria

Prior to analysis using parametric statistics, data samples under comparison will be tested for normality (the Kolmogorov-Smirnov test). Data normalizing transformations (e.g. Box-Cox, Yeo-Johnson etc.) would be applied if necessary.

The following parameters and approaches are to be used:

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
3. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
4. Generalized Linear Models and/or Mixed Linear Models will be used in case of abnormal data distribution.
5. Selection of the type of distribution, specification of factor and covariance structures of the model will be made using fit-statistics such as AIC (Akaike information criterion).

The following SAS software programs are supposed to be applied to the above listed tests and techniques:

- UNIVARIATE: normality verification of the distributions under comparison;
- CORR, MEANS - calculation of descriptive statistics
- TTEST – Student's test with all modifications;
- GLM – generalized linear models for analysis of time changes (ANOVA, ANCOVA);
- GENMOD – generalized linear models.
- MIXED – mixed linear models.

Non-parametric criteria

Below are potential types of comparisons with relevant criteria:

1. To evaluate time changes in the parameters compared – Friedman test, nonparametric analogue of repeated measures analysis of variance.
2. For frequency analysis of contingency tables 2×2 – $\chi 2$ (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).
3. Cochran-Mantel-Haenszel test (modified $\chi 2$ test for multiple comparisons) – to perform frequency analysis based on independent strata.

4. For frequency analysis of data on presence/absence of an event or outcome during repeated measurements (contingency tables with dependent strata) – survival analysis.

To perform the above-mentioned nonparametric statistical analysis the following SAS procedures are to be used:

- FREQ – Friedman test, $\chi 2$ test and/or exact Fisher's test; Cochran-Mantel-Haenszel test.
- LIFETEST – survival analysis.
- NPAR1WAY - Mann-Whitney test.

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug.

Data presentation

Descriptive statistics will be provided for each study continuous / interval variable. Numerical data will be presented by mean, standard deviation, min and max values. Comparisons suggesting statistical conclusion will have the relevant confidence intervals. Outliers will be analyzed individually. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.