Multicenter Double-Blind Placebo-Controlled Parallel-Group Randomized Clinical Trial of Efficacy and Safety of Rengalin in the Treatment of Cough in Patients with Chronic Obstructive Pulmonary Disease

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-RN-005**
Version date:	**October 17, 2016**
ClinicalTrials.gov Id:	**NCT03159091**

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

Multicenter double-blind placebo-controlled parallel-group randomized clinical trial of efficacy and safety of Rengalin in the treatment of Cough in patients with chronic obstructive pulmonary disease.

Phase: IV
Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia
Protocol No. MMH-RN-005

Objective of the study

- To obtain additional data on the efficacy and safety of Rengalin in the treatment of cough in patients with stable chronic obstructive pulmonary disease (COPD).

Endpoints

Primary endpoint

1. Percentage of patients with a positive response after 4 weeks of the treatment (response criterion is the reducing of the Total Cough Severity Score (TCSS)* by ≥1 compared to baseline).

   ** according to the 12-point of the Cough Severity Scale.*

Secondary endpoints

1. Severity of cough (TCSS according to the Cough Severity Scale) after 4 weeks of the treatment compared to baseline.
2. Percentage of patients with ≥50% lesser cough severity (according to TCSS) after 4 weeks of the treatment.
3. The severity of the clinical symptoms of COPD (according to COPD Assessment Test [CAT]) after 4 weeks of the treatment.
4. Percentage of patients with no exacerbation of COPD[1] within 4 weeks of the treatment.

[1] COPD exacerbation is defined as an acute event characterized by aggravation of the event within 2-3 or more days. Exacerbation manifests in intensification of respiratory disorders beyond their regular daily fluctuations and require administration of products in addition to the previously prescribed basic therapy as well as a rescue drug for symptom relief (salbutamol). Additional products include antibacterial drugs, systemic corticosteroids and/or emergency therapy (ambulance call) or hospitalization for COPD exacerbation.
COPD exacerbation is recorded as an adverse event. If a COPD exacerbation develops within the first week of the subject participation in the study, it will not be considered as a secondary inefficacy criterion.

5. Frequency of cough and other respiratory patterns according to 24-hour daily monitoring (using **WHolter™**) after 4 weeks of the treatment compared to baseline.

Safety assessment

- Adverse events (AEs) during the treatment, AEs severity and relations to the study drug, and AEs outcomes.
- Changes in vital signs.

Study design

Study design: multicenter, double-blind, randomized, parallel group placebo-controlled study.

The study will enroll men and women (aged 40 to 80 years) with cough associated with stable COPD[2]. Subjects with COPD diagnosed more than 12 months earlier obtaining allowed basic therapy[3] and retaining cough ≥2 points (according to Cough Severity Scale [CSS]) despite their therapy should be considered as the study candidates.

After signing patient information sheet (informed consent form) to participate in the clinical trial, medical history and objective examination are performed, cough severity is assessed (using TCSS; at baseline evaluation of diurnal and nocturnal cough the number of episodes and cough severity in the preceding day is taken into account) as well as intensity of COPD effect on the subject (CAT test), concomitant therapy is recorded, computer spirometry with evaluation of baseline FEV_1/FVC and post-bronchodilator FEV_1 (where respiratory function cannot be assessed, the results of the previous examination dating no more than 3 months earlier may be used). Females of childbearing potential will undergo pregnancy test.

If a patient meets the inclusion criteria and does not have any exclusion criteria at Visit 1 (Day 1), he/she is randomized to one of 2 groups: group 1 patients will receive Rengalin at 2 tablets 3 times a day for 4 weeks; group 2 patients will receive placebo using Rengalin dosing regimen for 4 weeks.

The patient will be monitored for 4 weeks (screening, randomization before day 1, treatment for 4 weeks). During follow-up period two visits are scheduled: Visit 1 (Day 1) and Visit 2 (Week 4) at which objective examination, recording cough severity (using TCSS) will be carried out, COPD effect on the subjects (CAT) and concomitant therapy will be evaluated. At Visit 2 (after 4-week treatment period) compliance will be additionally assessed.

---

[2] Condition may be considered stable where no disease progression is observed for ≥6 months [7, 20].

3 Allowed basic therapy for stable COPD: anticholinergics, long- and short-term β2-agonists, inhalation glucocorticosteroids (ICS), methylxanthines and their combinations.

At one of the clinical sites (Research Institute of Pulmonology, Russian FMBA), patients will be monitored for cough on a daily basis (using the WHolter™ monitor), with the data used as an additional measure to evaluate efficacy.

Patients are allowed to take basic COPD therapy and medications for their comorbidities in the course of the study, except for the medicines listed in "Prohibited concomitant treatment".

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of either gender aged from 40 to 80 years.
2. COPD (in accordance with the GOLD-2014 guidelines) diagnosed ≥12 months before inclusion.
3. Stable COPD (≥ 6 weeks free of disease progression).
4. Mild, moderate or severe degree of airflow limitation ($FEV_1/FVC < 0.7$; post-bronchodilator FEV_1 ≥30% of predicted value).
5. TCSS score ≥2.
6. Stable dose of standard therapy within the previous 4 weeks.
7. Use of and adherence of contraceptive methods by patients of reproductive age of both genders during the study.
8. Availability of signed patient information sheet (Informed Consent form) for participation in the clinical trial.

Exclusion criteria

1. Earlier diagnosis of intra- or extrathoracic causes of cough (e.g., asthma, malignant neoplasm of lung, tuberculosis, sarcoidosis, α1-antitrypsin deficiency, bronchiectasis, cystic fibrosis, interstitial lung diseases, perennial allergic rhinitis, gastro-esophageal reflux disease, use of ACE inhibitors, disease of upper respiratory tract, etc.).
2. Cough associated with eating.
3. An exacerbation of COPD, acute upper and/or lower respiratory infection at inclusion or in the previous 4 weeks.
4. Modifications to standard drug therapy (dose escalation, replacement of medicines prescribed or addition of new medications) in the previous 4 weeks.
5. Very severe degree of airflow limitation (post-bronchodilator FEV1 <30% predicted or < 50% and chronic respiratory failure).
6. Haemoptysis.

7. Stroke in the preceding 3 months or stroke with long-term residual neurological deficit within 6 months before study entry.
8. Acute coronary syndrome, myocardial infarction within 6 months before study enrollment.
9. Unstable or life-threatening arrhythmia in the previous 3 months.
10. Acute or chronic heart failure (NYHA, 1964: Class III or IV).
11. Presence or suspicion of oncological disease.
12. Body Mass Index (BMI) $\leq$18 kg/m^2 or $\geq$40 kg/m^2.
13. Chronic kidney disease (categories C3-5 A3).
14. Hepatic failure (Child-Pugh class C).
15. Exacerbation or decompensation of a chronic disease that would affect the patient's ability to participate in the clinical trial.
16. Intention to quit smoking in the next 4 weeks (for smokers).
17. Allergy/ intolerance to any of the components of study drugs.
18. Course administration of any medicines listed in the section "Prohibited concomitant treatment" for 4 weeks prior to the enrollment in the trial.
19. Participation in other clinical trials within 3 months prior to the enrollment in this study.
20. Patients who, from investigator's point of view, will fail to comply with the observation requirements of the trial or with the dosing regimen of the study drugs.
21. Other conditions preventing the patient from normal participation (e.g., planned business or other trips).
22. Drug addiction, alcohol use in the amount over 2 units of alcohol a day, mental diseases.
23. Pregnancy, breast-feeding, unwillingness to use contraception during the study.
24. Patient is a study specialist of the centre and directly involved in the study, or is an immediate family member of the Investigator. Spouses, parents, children, or siblings, regardless of whether they are siblings or adopted are considered immediate family members.
25. The patients work for OOO "NPF "Materia Medica Holding", i.e. they are employees of the Company, temporary employees on a contract basis or appointed officials responsible for conduction of the study or their immediate family members.

Criteria for Withdrawal or Termination

1. COPD exacerbation.
2. The patient`s inability or refusal to follow the protocol requirements.
3. The necessity to use medications prohibited within this trial.

4. Change in the stereotype of smoking (ceasing smoking for smokers, starting smoking for non-smokers).
5. An adverse event requiring discontinuation of the study drug.
6. Patients wish to complete the study ahead of schedule due to lack of treatment efficacy or for any other reason.
7. Cases not specified by the protocol when, according to the investigator's opinion, further participation in the study harms the patient.
8. Incorrect inclusion of ineligible patient.
9. Patient failed screening procedure.

Number of subjects

At least 238 patients will be enrolled, which is expected to yield at least 190 patients (95 x 2 groups (Rengalin and Placebo) completing all protocol procedures.

Interim analysis

An interim statistical analysis is not scheduled within the study.

Treatment

Group 1

Name of the medicinal product: Rengalin

Active ingredient: affinity purified antibodies to bradykinin – 0.006 g*, affinity purified antibodies to histamine – 0.066 g*, affinity purified antibodies to morphine - 0.066 g*

** Mixture of water-ethanol dilutions 100^{12}, 100^{30}, 100^{50} of active substance used for saturation of isomalt.*

Excipients: isomalt 0.506 g, microcrystalline cellulose 0,0275 g, magnesium stearate 0.0055 g, anhydrous citric acid 0.005225 g, colloidal anhydrous silica 0.00275 g, sodium cyclamate 0.00275 g, sodium saccharin 0.000275 g.

Method of administration: Tablet for oral use. Two tablets per intake. The tablet should be held in the mouth until complete dissolution. 2 tablets 3 times a day without food (i.e. 15-30 min prior to meal or 15-30 min after meal).

Dosage form: Tablets.

Description: White to off-white, round, flat, cylinder-shaped, beveled edge tablets scored on one side, with integral edges.

Storage conditions: Store in a place protected from light, at the temperature not exceeding 25^{o}C. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: NA

Excipients: isomalt 0.506 g, microcrystalline cellulose 0,0275 g, magnesium stearate 0.0055 g, anhydrous citric acid 0.005225 g, colloidal anhydrous silica 0.00275 g, sodium cyclamate 0.00275 g, sodium saccharin 0.000275 g.

Method of administration: Placebo using Rengalin scheme.

Dosage form: Tablets.

Description: White to off-white, round, flat, cylinder-shaped, beveled edge tablets scored on one side, with integral edges.

Storage conditions: Store in a place protected from light, at the temperature not exceeding 25^{o}C. Keep out of the reach of children.

Treatment duration

Rengalin/Placebo treatment duration is 4 weeks.

Observation period

In total, the patient is observed up for 4 weeks (screening + randomization up to 1 days, study therapy for 4 weeks).

Symptomatic (Standard) treatment

During the study the subjects may receive basic COPD therapy (anticholinergic drugs, β2-agonists, IGCS, methylxanthines and their combinations) and therapy of co-morbidities not referred to exclusion criteria.

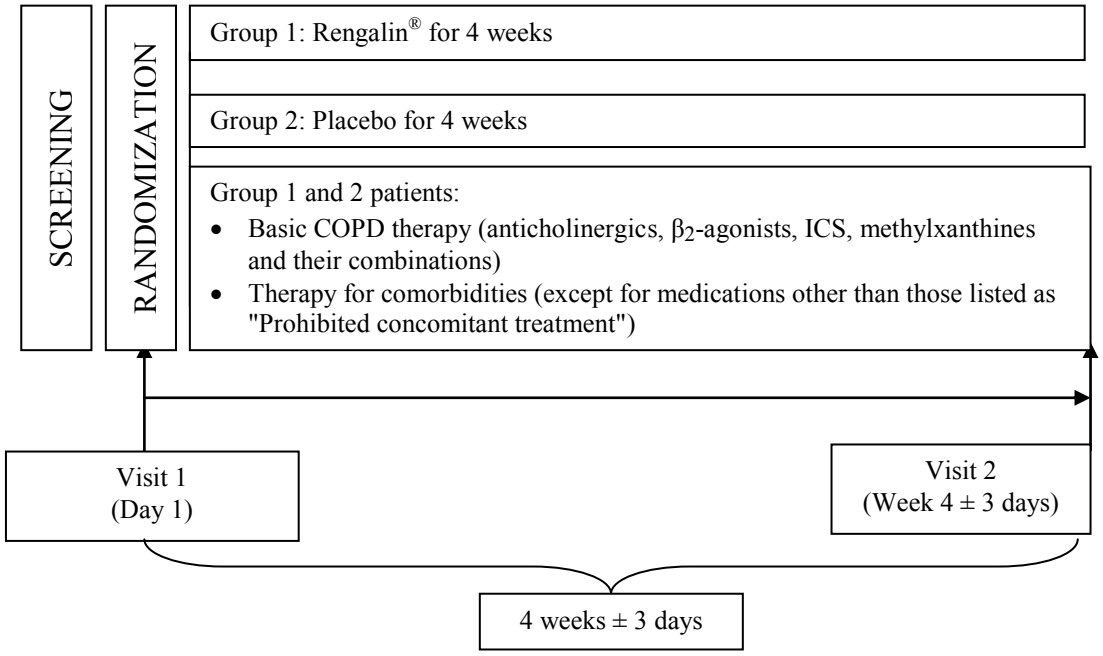
Prohibited concomitant therapy

For 4 weeks prior to inclusion and during the study (from the time of signing the information sheet (Informed Consent Form) and screening initiation), it is prohibited to use the following medications:

1. Expectorant (R05CA), mucolytic (R05CB), antitussive (R05D) medicines and their combinations (R05F).
2. Fenspiride (erespal) (R03DX).
3. Icatibant (firazyr) (C01EB19).
4. Systemic antihistamines (R06).
5. Cold medicines (R05X).
6. ACE inhibitors (C09A) and their combinations (C09B).
7. Systemic glucocorticosteroids (H02AB).

8. Drug products that irritate or suppress the cough centre in the CNS or produce such side effects, as described in the instruction.
9. Centrally acting muscle relaxants (M03B).
10. Antibacterial medicines for systemic use (J01).
11. The products of the company Materia Medica Holding.
12. Homeopathic remedies.
13. Drugs known to previously cause allergic reactions in the patient.

Study design scheme



Schedule of study procedures

Procedure/day	Visit 1 (Day 1)	Visit 2 (Week 4±3 days)
Informed consent	+	
Collection of complaints	+	+
Medical history	+	
Physical examination and vital signs (heart rate, respiratory rate, blood pressure, body temperature)	+	+
Body weight measurement	+	
Measurement of body length/height	+	

Procedure/day	Visit 1 (Day 1)	Visit 2 (Week 4±3 days)
Body mass index calculation	+	
Evaluation of cough severity (according to Cough Severity Scale)	+	+
Evaluation of COPD impact on the subject's life (CAT)	+	+
Pregnancy test	+	
Concomitant therapy	+	+
Computer spirometry* (evaluation of FEV1/FVC and post-bronchodilator FEV1)	+	
Eligibility assessment	+	
Randomization and prescription of study drug	+	
Study drug supply	+	
Study drug accountability, compliance assessment		+
Evaluation of treatment safety	+	+
24-hour cough monitoring**	+ **	+ **

** Where spirometry cannot be performed, spirometry parameters dating no more than 3 months will be recorded in CRF results.*
*** Performed in Institute of Pulmonology, FMBA of Russia.*

Statistical Analyses.

Samples

Total set: all patients included in the study who have signed Informed Consent Form for participation in the study. All AEs including those occurred prior to the study therapy will be considered throughout the study for this sample.

Safety population: all patients who received at least one dose of the study drug. This sample will be used to ***analyze the study treatment safety and tolerability***, since all the AEs identified after the study drug administration will be recorded.

Full Analysis Set. This sample includes all enrolled and randomized patients, except for those who met at least one of the following criteria:

1) non-compliance with inclusion / exclusion criteria ;
2) the patient has not taken as minimum a single dose of the study drug;
3) lack of any data of the patient following randomization;

This sample is the most consistent with the "Intention-to-treat" principle**,** will be used for the ***Intention-to-treat analysis (ITT analysis) of the the study therapy efficacy***.

Per protocol set. This sample includes all patients who completed the therapy as per the study protocol without any missing visits or significant protocol deviations. This sample will be used for the ***Per Protocol analysis (PP- analysis) of the the study therapy efficacy***.

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[4].

Evaluation of sample size

The sample size has been assessed on the basis of the following rules and assumptions:

1. Statistical provisions.
   - 1.1 the power of the statistical tests "P = (1 - β)" is assumed to be 80% (the probability of correct rejection of the null hypothesis is 0.8);
   - 1.2 the probability of a type I error "α" is allowed to be less than 5% (the probability of the erroneous acceptance of an alternative hypothesis is less than 0.05);
   - 1.3 the statistical tests are 2-sided;
   - 1.4 the calculation of the sample size is based on the assumptions about the expected effects, declared in the primary efficacy endpoint of the Protocol;
   - 1.5 the ratio between the sample sizes of Rengalin and Placebo groups is 1:1 (1 Rengalin patient - 1 Placebo patient);
   - 1.6 statistical null and alternative hypotheses using the applied dosing regimen are formulated as follows:

$$\mathbf{H_0: p_1=p_2}$$

$$\mathbf{H_a: p_1>p_2},$$

where $\mathbf{p_1}$ – proportion of subjects in Product group with improvement ≥ 1;

$\mathbf{p_2}$ – proportion of subjects in Placebo group with improvement ≥ 1;

1.7 the calculation of sample size for statistical criteria will be made using the formula:

2. $\mathbf{n_1 = kn_2}$

$$\mathbf{n_2} = \frac{\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2}{\epsilon^2}\left[\frac{p_1(1-p_1)}{\mathbf{k}} + p_2(1-p_2)\right]$$

where $\mathbf{n_1}$, $\mathbf{n_2}$ – sample size in Rengalin and Placebo groups;

ϵ – expected difference between proportions of subjects with improvement in Rengalin and Placebo groups;

k – sample size ratio (in this study equal to 1);

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

$z_{\alpha/2}$ – tabular value of two-sided z-test for **α**;

z_{β} – tabular value for one-sided z-test for **β**;

1.8 the 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: difference between proportion of the subjects with improvement (relative to visit 1) in product group and proportion of the subjects with improvement (relative to visit 1) in placebo group will be at least 0.2; conservative approach to evaluation of sample size will be applied[5].

Therefore, sample size will be **95** patients in each group (Rengalin and Placebo) to estimate superiority of the study drug over placebo.

Given potential withdrawal of at least 20% subjects during the study for various reasons, at least 238 subjects will be required to sign informed consent (119 per group).

Statistical criteria

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

- parametric – to evaluate continuous and interval random variables;
- non-parametric – for:
  - assessments of equality / inequality in the proportion of patients when compared for different visits,
  - analysis of frequencies of the compared variables,
  - assessment of continuous and interval random variables in case of violation of the normality assumption.

Parametric criteria

The application of parametric criteria will be accompanied by a check for normality of the compared samples (Kolmogorov-Smirnov test).

The following parametric methods and approaches are to be used:

- To assess the differences of continuous variables obtained in two different (independent) groups – Student t-test for independent samples.

[5] The highest potential sample size at this effect size.

- To assess the dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
- In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity Dunnett, Tukey, Scheffe, Holm adaptive test, etc.
- In case of abnormal data distribution, approaches with the Generalized Linear Models and / or Mixed Linear Models will be used.
- Selection of the type of distribution, clarification of the factor and covariance structures of the model is carried out with fit statistics such as AIC (Akaike information criterion).

To perform the above-mentioned statistical tests and techniques, it is assumed that the following SAS procedures are used:

- UNIVARIATE – check for normality of the compared distributions;
- CORR, MEANS – calculation of descriptive statistics;
- TTEST – Student t-test with all the modifications;
- GLM – analysis of Generalized Linear Models for studying temporal dynamics (ANOVA, ANCOVA);
- GENMOD – analysis of Generalized Linear Models.
- MIXED – analysis of Generalized Linear Models.

Non-parametric criteria

Below, there are the main types of possible comparisons with the respective criteria:

1. To assess the dynamics of the compared indicators – Friedman test, non-parametric analogue of analysis of variance with repeated measures.
2. For the frequency analysis of 2×2 cross tables – χ^2-test (if the compared frequencies are greater than 5) or Fisher exact test (if one of the compared frequencies is less than 5).
3. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test.
4. For the frequency analysis of data on the presence / absence of an event or outcome during repeated measures (cross tables with dependent strata) – survival analysis.

To perform the above-mentioned non-parametric statistical analysis options, it is assumed that the following SAS procedures are used:

- FREQ – Friedman test, χ^2-test and / or Fisher exact test; Cochran–Mantel–Haenszel test
- LIFETEST – survival analysis
- NPAR1WAY – Mann-Whitney U-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. Statistic 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.