Observational multicenter study	
Number/code	
Version	3.0
Date	March 2018

Registry of COPD patients who undergo outpatient treatment or are under surveillance at outpatient polyclinic healthcare institutions of the Russian Federation in Moscow

PROTOCOL SYNOPSIS

Registry of COPD patients who undergo outpatient treatment or are under surveillance at outpatient polyclinic healthcare institutions of the Russian Federation in Moscow

Principal investigator:

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Sites, number of participants

At least (2000) patients at approximately 15 polyclinic sites in Moscow.

Investigators: pulmonologists of outpatient polyclinic care in Moscow

It is planned to enrol approximately 120 patients with diagnosed COPD **at each of approximately 15 polyclinic institutions of Moscow** (in total at least 2000 patients)

Study period	
Planned study timeframes	
Planned timeline for enrolment of first patient	Fourth quarter 2016
Planned timeline for enrolment of last patient	Second quarter 2018
Planned timeline for last patient out	Third quarter 2018
Planned timeline for database lock	Fourth quarter 2018
Planned timeline for final report preparation	First quarter 2019
Planned timeline for publication of results	Third quarter 2019

Medicinal product (name, dose, administration route) and concomitant therapy

Not applicable.

Background

Experts of the World Health Organization (WHO) estimated that approximately 210 mln. people worldwide suffer from COPD. In our modern age, COPD represents one of the leading

chronic diseases alongside with arterial hypertension, coronary heart disease and diabetes mellitus. They account for more than 30% among other human pathologies. COPD ranks fourth among causes of death worldwide, and is assumed to ascend to the third place by2020. According to estimations using epidemiological markers, in the Russian Federation there are approximately 11 mln. people suffering from COPD. Whereas according to official statistics their total number in the Russian Federation amounts to only 2.4 mln. This is due to underdiagnosis and patients seeking medical attention too late, which result in detection of the disease at advanced stages when even the most modern treatment methods cannot delay steady progression of the disease. [1]

In the Russian Federation, diagnosis and treatment of COPD patients is performed primarily at community-based primary care outpatient polyclinic institutions. Every year in the Russian Federation there are approximately 100 thousands new cases of the disease diagnosed (statistics digest "Morbidity rates in adult population of Russia in 2012"). However, as a rule, COPD is diagnosed at advanced stages when complaints become a major problem for the patient. In many regions of the country, spirometric testing have still not been introduced into routine practice of primary care physicians, although on the positive side, in the recent years facilities of primary care outpatient polyclinic institutions have improved substantially.

In 2012 there were 2.7 mln. of COPD patients under surveillance at outpatient polyclinic institutions in the Russian Federation. However, we do not have at our disposal updated information regarding the prevalence of the disease in specific cities, distribution of these COPD patients by extent of airway obstruction. Data on pharmacotherapy are only approximate.

In developed countries, total economy expenses associated with COPD take 2nd place in the structure of pulmonary diseases after lung cancer, and if we consider direct expenses COPD takes the 1st place exceeding direct expenses for bronchial asthma 1.9-fold. Economy expenses per patient associated with COPD 3 times exceed those for an asthma patient. Scarce reports of direct medical expenses in COPD show that more than 80% of resources are spent on inpatient care and less than 20% – on outpatient care. It has been established that 73% of costs are associated with 10% of patients with severe disease. The highest economic losses are brought about by treatment of COPD exacerbations. In Russia, the economic burden of COPD taking into account indirect expenses, including absenteeism (absence from work) and presenteeism (less effective work caused by illness), amounts to 24.1 bln. roubles. [2]

Study conduction rationale

The majority of COPD patients in the Russian Federation seek medical attention from primary care physicians at outpatient polyclinic institutions. Physicians of these institutions can refer a patient for spirometric testing or to a pulmonologist (in this case, as a general rule, spirometry is also performed).

In the recent years in Europe registries of COPD patients have been created: Registry of COPD phenotypes in patients in Central and Eastern Europe (POPE Study- Phenotypes of COPD in Central and Eastern Europe) 2014-2015, Czech multicentre registry of COPD patients, started in 2014 (Czech Multicentre Research Database of COPD, Novotná et al. Czech multicenter research database of severe COPD. International Journal of Chronic Obstructive Pulmonary Disease 2014, 9: 1265-1274".)

Registry of COPD patients includes monitoring of the possible causes of the disease, prevalence of different phenotypes, assessment of disease progression, therapeutic approaches to disease treatment in real-life clinical practice, analysis of social and economical disease burden.

It is an important clinical and economical goal to arrange a registry of COPD patients who undergo outpatient surveillance at polyclinic institutions of Moscow, including description of patient clinical profile, diagnosis flow chart, therapeutic treatment tactics using different groups of medicinal products, compliance of used diagnostic and therapeutic approaches with current Federal clinical guidelines for COPD diagnosis and treatment, evolution of COPD prevalence parameters, monitoring of course of the disease.

In the absence of this information it is impossible to evaluate the quality of medical care provided to COPD patients in the Russian Federation or to plan any actions for treatment refinement.

Therefore, the purposes of the present study result from the necessity to perform the following:

a) define clinical profile of COPD patients seeking attention and/or present in outpatient polyclinic medical care of healthcare system of Moscow (including diagnosis and therapeutic treatment tactics using different therapy regimens).

b) determine the extent of the therapy conducted and its compliance with diagnosis, disease severity and phenotype

c) define the disease burden (number of outpatient visits, hospitalizations, duration of days of disability, disability)

Investigation of the management of COPD patients in real-life clinical practice will enable us to obtain demographic and social data of the patients, study the natural history of COPD, perform monitoring of disease activity, evaluate the efficacy of therapy, demand for specialized treatment, perform pharmacoeconomic analysis, and develop standard statistical forms.

It is expected that it will be possible to use the results of the present study to assess % of different phenotypes of the COPD patients and treatment of people suffering from COPD not only in Moscow, but in other regions of the Russian Federation as well.

Study objectives

Primary objectives:

1. To describe the clinical profile of COPD patient who is under outpatient surveillance at polyclinic institutions of Moscow (including demographic data (age, gender, ethnicity, occupation), smoking status, disease duration, disease severity grade, distribution by disease phenotype, disease exacerbation rate in the setting of real-life clinical practice).

Secondary objectives:

1. Characterize distribution (percentage (%)) of COPD patients who seek attention from primary medical care physicians by severity of airway obstruction, by reversibility of

airway obstruction according to criteria described in Federal clinical guidelines for COPD diagnosis and treatment 2014.

2. To determine prevalence of the different disease phenotypes among outpatients: chronic bronchitis phenotype, emphysema phenotype, mixed phenotype, frequent exacerbator phenotype, Asthma+COPD phenotype (according to criteria described in Federal clinical guidelines for COPD diagnosis and treatment 2014.

3. To determine the percentage of patients with eosinophilic inflammation according to haematology results.

4. To describe treatment regimens prescribed to COPD patients depending on disease severity grade in the setting of real-life clinical practice.

5. To establish the percentage of medical prescriptions for treatment of COPD patients which comply with current Federal clinical guidelines for diagnosis and treatment of chronic obstructive pulmonary disease.

6. To establish prevalence and pattern of comorbidities in COPD patients.

7. To evaluate the disease burden based on the collected data concerning the duration of temporary disability, number of hospitalizations due to COPD exacerbations, number of outpatient visits concerning COPD patients under outpatient surveillance at polyclinic institutions of Moscow for three years.

Study design

The registry of COPD patients in fact represents non-interventional multicenter retrospective study including all COPD patients included into the registry retrospectively from patients medical records and newly diagnosed under outpatient surveillance at the selected polyclinic institutions of Moscow.

The registry will include all patients with registered diagnoses J40 - J44 according to ICD-10 with spirometry results confirming COPD diagnosis, who are at the study start under outpatient surveillance, and also newly registered patients diagnosed with COPD (ICD-10 J40 - J44, as confirmed by spirometry results) during the conduction of the registry program at the selected polyclinic institutions of Moscow (according to ICD: J40 - Bronchitis, not specified as acute or chronic, J41 - Simple and mucopurulent chronic bronchitis, J41.0 - Simple chronic bronchitis, J41.8 - Mixed simple and mucopurulent chronic bronchitis, J 42 - Unspecified chronic bronchitis, J 43 - Emphysema, J 44 - Other chronic obstructive pulmonary disease) based on regular (yearly) retrospective analysis of patient records with data entry into a consolidated database.

It is planned to enrol into the study approximately **2000** male and female patients over 40 years of age with diagnosed COPD (as confirmed by spirometry results).

The present observational multicenter descriptive study will be conducted in the setting of routine clinical practice of outpatient polyclinic institutions. There is no hypothesis to be tested in this study.

The study will be conducted in outpatient polyclinic institutions of the primary medical care system of Moscow. Pulmonologists of the primary medical care system will be engaged as investigators. These are the physicians, whom the patients with tentative COPD diagnosis are referred to in the Russian Federation and who within the scope of their responsibilities have access to source medical records and who evaluate the quality of diagnosis and extent of treatment prescribed to COPD patients.

The present study is observational therefore it does not require a treatment regimen or directions for patient management. The patients receive medical care in line with routine practice for treatment of this disease in the Russian Federation. Patient participation in the study should not in any way affect the principles and extent of treatment received by the patient according to routine clinical practice.

Physicians-investigators will enter into the study the information (data) concerning COPD patients, both those already registered at the selected medical treatment and preventive care institution, and newly registered patients as they seek attention at the outpatient polyclinic institutions.

The main purpose of the present study consists in collection of data concerning COPD patients who under surveillance at outpatient polyclinic institutions of Moscow using patient medical records and their medical history. This protocol does not specify any obligatory visits or examinations.

Patient data will be entered into the registry de-identified. The patients will be identified by their screening number and initials. Then the Physician-investigator will evaluate patient compliance with inclusion criteria. The study will enrol patients meeting all the inclusion criteria and not having any of the exclusion criteria.

Only the physician who enters patient data into the regional COPD registry possesses patient contact information, and henceforth only this physician will enter de-identified patient data according to study design. This physician does not influence the choice of examination extent, treatment strategy and medication.

Study variables

Primary variables

1. Description of the clinical profile of COPD patient under outpatient surveillance at polyclinic institutions of Moscow (including demographic data (age, gender, ethnicity, occupation), smoking status, disease duration, disease severity grade, distribution by disease phenotype, disease exacerbation rate in the setting of real-life clinical practice)

Secondary variables:

1. Percentage of patients with different disease phenotypes among outpatients
2. Percentage of prescriptions of medicinal products to COPD patients depending on disease severity grade in the setting of real-life clinical practice

3. Distribution (%) of COPD patients who seek attention from primary medical care physicians by severity of airway obstruction (according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014)
4. Mean number of exacerbations requiring medical attention (outpatient prescription of oral corticosteroids and/or antibiotics) in the last year in COPD patients
5. Mean number of hospitalizations in the last year in COPD patients
6. Percentage of patients with eosinophilic inflammation
7. Description of treatment regimens prescribed to COPD patients depending on disease severity grade in the setting of real-life clinical practice
8. Percentage of prescriptions for treatment of COPD patients in line with the current Federal clinical guidelines for diagnosis and treatment of chronic obstructive pulmonary disease
9. Disease burden based on the collected data concerning the duration of temporary disability, number of hospitalizations due to COPD exacerbations, outpatient visits concerning COPD during follow-up

Statistics

Descriptive analysis approach will be applied for analysis of the study objectives. Descriptive statistics will be used for analysis of the study population, baseline and clinical data.

Descriptive statistics will include frequency tables (n, mean, median, standard deviation, minimum and maximum for continuous variables; n, frequency and percentage for categorical variables). Percentages will be evaluated together with 95% confidence intervals (in appropriate cases).

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APPENDIX 2. FEDERAL CLINICAL GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2014 LIST OF ABBREVIATIONS

List of abbreviations	Definition of the terms
AE	Adverse event
ADR	Adverse drug reaction
CRF	Case report form (paper)
EC	Ethics Committee
GCP	Good clinical practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
NIS	Non-interventional study
PI	Principal investigator
Variables	Parameters, patient examination results which can change in the course of time

1. INTRODUCTION

1.1 Background

Definition of COPD

COPD is a preventable and treatable disease characterized by persisting airflow limitation which typically progresses and associated with marked chronic inflammatory response in the lungs to pathogen particles or gases. In a number of patients, exacerbations and comorbidities can affect the general severity of COPD (GOLD 2015).

COPD diagnosis should be suspected in all patients with dyspnoea, chronic cough or expectoration and/or history of risk factors characteristic of this disease.

Experts of the World Health Organization (WHO) estimated that approximately 210 mln. people worldwide suffer from COPD. In our modern age, COPD represents one of the leading chronic diseases alongside with arterial hypertension, coronary heart disease and diabetes mellitus. They account for more than 30% among other human pathologies. COPD ranks fourth among causes of death worldwide, and is assumed to ascend to the third place by2020. According to estimations using epidemiological markers, in the Russian Federation there are approximately 11 mln. people suffering from COPD. Whereas according to official statistics their total number in the Russian Federation amounts to only 2.4 mln. This is due to underdiagnosis and patients seeking medical attention too late, which result in detection of the disease at advanced stages when even the most modern treatment methods cannot delay steady progression of the disease. [1]

In the Russian Federation, diagnosis and treatment of COPD patients is performed primarily at community-based primary care outpatient polyclinic institutions. Every year in the Russian Federation there are approximately 100 thousands new cases of the disease diagnosed (statistics digest "Morbidity rates in adult population of Russia in 2012"). However, as a rule, COPD is diagnosed at advanced stages when complaints become a major problem for the patient. In many regions of the country, spirometric testing have still not been introduced into routine practice of primary care physicians, although on the positive side, in the recent years facilities of primary care outpatient polyclinic institutions have improved substantially.

In the recent years, several studies with an objective to ascertain the real prevalence of COPD have been conducted in Russia. These studies demonstrated that COPD was observed approximately in 8% of the population over 18 years of age (Postnikova L.B., et al. Pulmonology, 2011) [3], and among those over 18 years of age the prevalence of this disease touches on 14.5% [4], (Zhestkov A.V., et al. Pulmonology, 2009).

In 2012 there were 2.7 mln. of COPD patients under surveillance at outpatient polyclinic institutions in the Russian Federation. However, we do not have at our disposal updated information regarding the prevalence of the disease in specific cities, distribution of these COPD patients by extent of airway obstruction. Data on pharmacotherapy are only approximate.

In developed countries, total economy expenses associated with COPD take 2nd place in the structure of pulmonary diseases after lung cancer, and if we consider direct expenses COPD takes the 1st place exceeding direct expenses for bronchial asthma 1.9-fold. Economy expenses per patient associated with COPD 3 times exceed those for an asthma patient. Scarce reports of direct medical expenses in COPD show that more than 80% of resources are spent on inpatient care and less than 20% – on outpatient care. It has been established that 73% of costs are associated with 10% of patients with severe disease. The highest economic losses are brought about by treatment of COPD exacerbations. In Russia, the economic burden of COPD taking into account indirect expenses, including absenteeism (absence from work) and presenteeism (less effective work caused by illness), amounts to 24.1 bln. roubles. [2]

1.2 Study rationale

The majority of COPD patients in the Russian Federation seek medical attention from primary care physicians at outpatient polyclinic institutions. Physicians of these institutions can refer a patient for spirometric testing or to a pulmonologist (in this case, as a general rule, spirometry is also performed).

In the recent years in Europe registries of COPD patients have been created: Registry of COPD phenotypes in patients in Central and Eastern Europe (POPE Study- Phenotypes of COPD in Central and Eastern Europe) 2014-2015, Czech multicentre registry of COPD patients, started in 2014 (Czech Multicentre Research Database of COPD, Novotná et al. Czech multicenter research database of severe COPD. International Journal of Chronic Obstructive Pulmonary Disease 2014, 9: 1265-1274".)

Registry of COPD patients includes monitoring of the possible causes of the disease, prevalence of different phenotypes, assessment of disease progression, therapeutic approaches to disease treatment in real-life clinical practice, analysis of social and economical disease burden.

It is an important clinical and economical goal to arrange a registry of COPD patients who undergo outpatient surveillance at polyclinic institutions of Moscow, including description of patient clinical profile, diagnosis flow chart, therapeutic treatment tactics using different groups of medicinal products, compliance of used diagnostic and therapeutic approaches with current Federal clinical guidelines for COPD diagnosis and treatment, evolution of COPD prevalence parameters, monitoring of course of the disease.

In the absence of this information it is impossible to evaluate the quality of medical care provided to COPD patients in the Russian Federation or to plan any actions for treatment refinement.

Therefore, the purposes of the present study result from the necessity to perform the following:

a) evaluate therapeutic trends in an outpatient polyclinic setting for patients with diagnosed COPD,

b) define clinical profile of COPD patients seeking attention and/or present in outpatient polyclinic medical care of healthcare system of Moscow (including diagnosis and therapeutic treatment tactics using different therapy regimens).

c) determine the extent of the therapy conducted and its compliance with diagnosis, disease severity and phenotype

d) define the disease burden (number of outpatient visits, hospitalizations, disability)

Investigation of the management of COPD patients in real-life clinical practice will enable us to obtain demographic and social data of the patients, study the natural history of COPD, evaluate the efficacy of therapy, demand for specialized treatment, perform pharmacoeconomic analysis, and develop standard statistical forms.

2. STUDY OBJECTIVES

2.1. Primary study objective

1. To describe the clinical profile of COPD patient who is under outpatient surveillance at polyclinic institutions of Moscow (including demographic data (age, gender, ethnicity, occupation), smoking status, disease duration, disease severity grade, distribution by disease phenotype, disease exacerbation rate in the setting of real-life clinical practice)

2.2. Secondary objectives

1. Characterize distribution (percentage (%)) of COPD patients who seek attention from primary medical care physicians by severity of airway obstruction, by reversibility of airway obstruction according to criteria described in Federal clinical guidelines for COPD diagnosis and treatment 2014

2. To determine prevalence of the different disease phenotypes among outpatients: chronic bronchitis phenotype, emphysema phenotype, mixed phenotype, frequent exacerbator phenotype, Asthma+COPD phenotype (according to criteria described in Federal clinical guidelines for COPD diagnosis and treatment 2013)

3. To determine the percentage of patients with eosinophilic inflammation according to haematology results

4. To describe treatment regimens prescribed to COPD patients depending on disease severity grade in the setting of real-life clinical practice

5. To establish the percentage of medical prescriptions for treatment of COPD patients which comply with current Federal clinical guidelines for diagnosis and treatment of chronic obstructive pulmonary disease

6. To establish prevalence and pattern of comorbidities in COPD patients

7. To evaluate the disease burden based on the collected data concerning the duration of temporary disability, number of hospitalizations due to COPD exacerbations, number of outpatient visits concerning COPD patients under outpatient surveillance at polyclinic institutions of Moscow for three years

3. STUDY PLAN AND PROCEDURES

The registry of COPD patients represents a non-interventional multicenter descriptive retrospective study of all COPD patients, which medical records will be retrospectively added to the registry database and newly diagnosed under outpatient surveillance at the selected polyclinic institutions of Moscow with retrospective entry of data.

it will include all patients with registered diagnoses J40 - J44 according to ICD-10 with spirometry results confirming COPD diagnosis, who are at the study start under outpatient surveillance, and also newly registered patients diagnosed with COPD (ICD-10 J40 - J44, as confirmed by spirometry results) during the conduction of the registry program at the selected polyclinic institutions of Moscow (according to ICD: J40 - Bronchitis, not specified as acute or chronic, J41 - Simple and mucopurulent chronic bronchitis, J41.0 - Simple chronic bronchitis, J41.8 - Mixed simple and mucopurulent chronic bronchitis, J 42 - Unspecified chronic bronchitis, J 43 - Emphysema, J 44 - Other chronic obstructive pulmonary disease) based on regular (yearly) retrospective analysis of patient records with data entry into a consolidated database.

It is planned to enrol into the study approximately **2000** male and female patients over 40 years of age with diagnosed COPD (as confirmed by spirometry results).

The present observational multicenter descriptive study will be conducted in the setting of routine clinical practice of outpatient polyclinic institutions. There is no hypothesis to be tested in this study.

The study will be conducted in outpatient polyclinic institutions of the primary medical care system of Moscow. Pulmonologists of the primary medical care system will be engaged as investigators. These are the physicians, whom the patients with tentative COPD diagnosis are referred to in the Russian Federation and who within the scope of their responsibilities have access to source medical records and who evaluate the quality of diagnosis and extent of treatment prescribed to COPD patients.

The present study is observational therefore it does not require a treatment regimen or directions for patient management. The patients receive medical care in line with routine practice for treatment of this disease in the Russian Federation. Patient participation in the

study should not in any way affect the principles and extent of treatment received by the patient according to routine clinical practice.

Physicians-investigators will enter into the study the information (data) concerning COPD patients, both those already registered at the selected medical treatment and preventive care institution, and newly registered patients as they seek attention at the outpatient polyclinic institutions during the registry conduction period.

The main purpose of the present study consists in collection of data concerning COPD patients under surveillance at outpatient polyclinic institutions of Moscow using patient medical records and their medical history. This protocol does not specify any obligatory visits or examinations.

Patient data will be entered into the registry de-identified. The patients will be identified by their screening number and initials. Then the Physician-investigator will evaluate patient compliance with inclusion criteria. The study will enrol patients meeting all the inclusion criteria and not having any of the exclusion criteria.

Only the physician who enters patient data into the regional COPD registry possesses patient contact information, and henceforth only this physician will enter de-identified patient data according to study design. This physician does not influence the choice of examination extent, treatment strategy and medication.

Visit "Enrolment". At this visit de-identified data of the patients will be included into the study. De-identified data are entered retrospectively based on analysis of the outpatient medical records.

At this visit the Physician-investigator will complete the following information (collected retrospectively):

1. Verify inclusion/ exclusion criteria
2. Establish the date of COPD diagnosis
3. Collect medical history concerning significant comorbidities and clinical characteristics, rate of exacerbations, pneumonia cases, hospitalizations, number of outpatient visits concerning COPD, number of days of disability in the year prior to enrolment
4. Evaluate smoking status. Wherever possible, smoking in pack-years
5. Collect medical history concerning treatment regimens, including different regimens of CS use, which the patient took/was prescribed in the year prior to enrolment into the registry (trade name of the medicinal product and INN, doses, dosing regimen, duration of use)
6. Collect demographic data and information concerning the patient's socioeconomic status

7. Collect data concerning the results of laboratory tests and instrumental examination methods confirming COPD diagnosis, present in the outpatient medical records (spirometry, specific complaints, haematology, instrumental examination methods)
8. Determine the patient's phenotype according to current classification
9. Collect data concerning adverse drug reactions
10. Complete the CRF.

Table 1. Visit schedule

Procedures	**Visit "Enrolment"**
Timelines	**At the moment of enrolment into the registry**
Inclusion / exclusion criteria	X
COPD. Severity grade, reversibility of airway obstruction (according to spirometry results*)	X
Demographics (year of birth, ethnicity, gender),	X
Socioeconomic status (education, occupation)	X
Smoking status	X
Occupational status, including information regarding the number of days of disability in the past 1 year.	X
Height, Weight, BMI (if applicable)	X
Comorbidities and clinical characteristics	X
Number of exacerbations COPD	X
Number of outpatient visits concerning COPD per year	X
Mean number of hospitalizations due to COPD	X
Determination of patient's phenotype according to current classification	X
Medical history concerning prior treatment of COPD	X
Medical history concerning treatment of COPD in the year prior to enrolment	X
Collection of data regarding changes if regimens of COPD treatment in the year prior to enrolment	X
Information concerning new complaints	
Spirometry. Results evolution (if applicable*)	X
Chest X-ray examination (if applicable*)	X*
Eosinophilia (eosinophil blood count based on haematology (Data of Le, EOS in % and incells per µl (haematology)	X
Pulse oximetry (if applicable*)	X*
Adverse drug reactions	X
CRF completion	

4. PATIENT POPULATION

4.1 Physicians-investigators

The present study is non-interventional (an observational, multicenter, descriptive study). Randomly selected polyclinic institutions of Moscow will take part in the study and enrol into the registry 2000 COPD patients.

The patient population includes male and female patients over 40 years of age, smokers or ex-smokers, under outpatient surveillance at polyclinic institutions of Moscow with diagnosis codes according to ICD J40 - J44 and diagnosed COPD, as confirmed by spirometry results.

4.2 Selection criteria for COPD patients

4.2.1 Inclusion criteria for patients with diagnosed COPD

1. Male and female patients ≥ 40 years, smokers or ex-smokers, with previously diagnosed COPD
2. COPD diagnosis corresponding to ICD codes J40 - J44 (J40 - Bronchitis, not specified as acute or chronic, J41 - Simple and mucopurulent chronic bronchitis, J41.0 - Simple chronic bronchitis, J41.8 - Mixed simple and mucopurulent chronic bronchitis, J 42 - Unspecified chronic bronchitis, J 43 - Emphysema, J 44 - Other chronic obstructive pulmonary disease
3. COPD diagnosis confirmed by spirometry results (spirometry is performed as normal with bronchodilator testing using salbutamol 400 μg, post-BD FEV_1\ FVC < 0.7)

   Spirometric diagnosis of disease severity should be made in line with COPD assessment according to GOLD criteria.

4.2.2 Exclusion criteria for patients with COPD risk factors and for patients with previously diagnosed COPD

A patient with diagnosed COPD should not meet any of the exclusion criteria. If a patient with previously diagnosed COPD meets at least one of the exclusion criteria such patient cannot be enrolled into the study.

1. Pulmonary comorbidities, such as tuberculosis, sarcoidosis

5. PATIENT WITHDRAWAL FROM THE STUDY

5.1 Withdrawal criteria

A patient can be withdrawn from the study due to the following reasons:

1. A patient can be withdrawn from the study if he/she was enrolled in breach of inclusion/exclusion criteria.

5.2 Procedures for patient withdrawal from the study

In case if a patient is withdrawn from the study, he/she will continue receiving the necessary treatment in line with routine practice.

6. PATIENT TREATMENT

6.1 Treatment strategy in observational studies

This study is observational therefore it does not require a specific treatment regimen or instructions for patient management. The question of patient "assignment" to a specific treatment strategy is not predetermined by the study protocol. The patients receive medical care in line with routine practice for treatment of this disease in the Russian Federation. Patient participation in the study should not in any way affect the principles and extent of treatment received by him/her according to routine clinical practice.

7. STUDY CONDUCTION

7.1 Description of the visits

Visit "Enrolment". At this visit the patients will be enrolled into the study. De-identified data are entered retrospectively based on analysis of the outpatient medical records.

At this visit the Physician-investigator will complete the following information (collected retrospectively):

1. Verify inclusion/exclusion criteria
2. Establish the date of COPD diagnosis
3. Collect medical history concerning significant comorbidities and clinical characteristics, rate of exacerbations, pneumonia cases, hospitalizations, number of emergency calls, number of outpatient visits concerning COPD, number of days of disability in the year prior to enrolment
4. Evaluate smoking status. Wherever possible, smoking in pack-years
5. Collect medical history concerning treatment regimens, including different regimens of CS use, which the patient took/was prescribed in the year prior to enrolment into the registry (trade name of the medicinal product and INN, doses, dosing regimen, duration of use)
6. Collect demographic data and information concerning the patient's socioeconomic status
7. Collect data concerning the results of laboratory tests and instrumental examination methods confirming COPD diagnosis, present in the outpatient medical records (spirometry, specific complaints, haematology, instrumental examination methods)
8. Determine the patient's phenotype according to current classification
9. Collect data concerning adverse drug reactions
10. Complete the CRF.

8. PARAMETERS COLLECTED FOR STUDY, ASSESSMENT AND REGISTRATION METHODS

Spirometric classification of airflow limitation in COPD (refer to Appendix 2)

Spirometric classification of airflow limitation is divided into 4 stages (GOLD 1 –mild; GOLD 2 – moderate; GOLD 3 – severe; GOLD 4 – very severe), as seen in patients with $FEV_1/FVC < 0.70$, based on post-bronchodilator FEV_1 (reference to GOLD).

Assessment of exacerbations

A COPD exacerbation is defined as an acute event characterized by deterioration of respiratory symptoms outside the range of their day-to-day variations and requiring change of treatment. The rate of exacerbations substantially varies in different patients.

In the group people suffering from COPD, the number of disease exacerbations in the last year is of outstanding interest to us. A COPD exacerbation represents any deterioration in the patient's health which manifests as intensification of symptoms: worsened dyspnoea, cough, more sputum or altered sputum characteristics –purulent sputum. During exacerbations, either all of these symptoms or only some may intensify. Very often (approximately in 50% of cases) an exacerbation is associated with a viral or bacterial infection and accompanied with fever and/or respiratory infection symptoms.

8.1 Primary endpoint

1. Description of the clinical profile of COPD patient under outpatient treatment/ surveillance at outpatient polyclinic healthcare institutions of the Russian Federation in Moscow.

8.2 Secondary endpoints

1. Percentage (%) of patients with different disease phenotypes among outpatients
2. Percentage (%)of prescriptions of medicinal products to COPD patients which are in line with their disease severity according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014
3. Distribution (%) of COPD patients who seek attention from primary medical care physicians by severity of airway obstruction (according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014)
4. Mean number of exacerbations requiring medical attention (outpatient prescription of oral corticosteroids CS and/or antibiotics) in the last year in COPD patients
5. Mean number of hospitalizations in the last year in COPD patients
6. Mean duration (seriousness) of a temporary disability case. Number of days of temporary disability /Number of cases of temporary disability (reference form 16-BH)
7. Percentage (%) of COPD patients who received different regimens for treatment of COPD, including short-acting muscarinic antagonist (SAMA), short-acting β_2-agonists (SABA), long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA),

oral corticosteroids (oral CS), fixed dose combination (FDC), phosphodeisterase-4 inhibitor, theophylline for the past year

8. Percentage (%) prescriptions to COPD patients which are in line with their disease severity according to GOLD classification and Federal clinical guidelines for treatment choice

9. Percentage (%) of patients with eosinophilic inflammation (eosinophil count according to haematology >2%,> 3%, >4% or equivalent to absolute counts of >200, > 300, >400 cells per µl)

10. Percentage of patients receiving sufficient extent of treatment in line with disease severity according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014

11. Disease burden based on the collected data concerning the duration of temporary disability, number of hospitalizations due to COPD exacerbations, outpatient visits concerning COPD during follow-up

8.3 Economic health assessment

An assessment of the duration of health-related temporary disability will be made based on the collected data (number of hospitalizations due to COPD exacerbations, outpatient visits concerning COPD) in the observational study.

8.3.1 Disease burden assessment

An assessment of the duration of health-related temporary disability will be made based on the collected data (number of hospitalizations due to COPD exacerbations, outpatient visits concerning COPD) in the observational study.

8.3.2 Other parameters for disease burden assessment

No other parameters will be evaluated as part of this Protocol.

9. SAFETY ASSESSMENT

9.1 Definitions

9.1.1 Definition of an adverse event (AE)

Adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical study/trial subject administered a pharmaceutical/investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse event can be any unfavourable symptom (e.g. nausea, chest pain) and unintended sign (e.g. tachycardia, enlarged liver) or an abnormal result of investigation (e.g. abnormal laboratory finding, electrocardiogram)

The AE definition is used both for serious and non-serious adverse events to regulatory authorities of the Russian Federation.
Furthermore the following events are subject to registration and Investigator is responsible for reporting the medicinal product safety related information to the regulatory authorities of the Russian Federation including but not limited: reports regarding administration of the medicinal product during pregnancy and/or lactation, drug interactions, lack of therapeutic effect, overdose, abuse, misuse, off-label use, suicide attempt or suicide death

9.1.2 Definition of a serious adverse event (SAE)

Any untoward medical occurrence that at any dose of the medicinal product:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is any other clinically significant medical occurrence which may threaten the patient or require medical attention.

NOTE.

- The term "life-threatening" refers to any event during which there is a risk of death for the patient; it does not refer to an event which hypothetically could have led to a lethal outcome if it were more severe.

Medical occurrences of special interest, but not resulting in death or life-threatening events or requiring hospitalization, can also be considered serious adverse events in those cases when according to medical and scientific judgement they might jeopardise the patient (or patients) and might require therapeutic or surgical intervention to prevent one of the other outcomes listed above. Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. In such case these events are regarded as serious. Examples of such events are advanced or malignant tumour, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of dependency, or drug abuse.

9.2 Non-interventional studies without specific safety assessment objectives

As the present study is non-interventional, there will be no proactive collection of any safety data. All the reports concerning events associated with safety of medicinal products will be reported in line with pharmacovigilance regulatory requirements in the post-marketing period as spontaneous adverse event reports. It is crucial that all the employees participating in the study are aware of the contents of this section. The Principal Investigator or a designated

authorized representative is responsible for AE reporting to regulatory authorities in according local regulations and timelines, ensure that all the site employees participating in the study aware about the procedures for handling of spontaneous reports (the term spontaneous reports implies reports associated with safety of medicinal products), and also national pharmacovigilance regulatory requirements in Russia.

9.3 Non-interventional studies with specific safety assessment objectives

As the present study is non-interventional, there will be no proactive collection of any safety data.

9.4 Safety data reporting

9.4.1 Adverse event reports

Monitoring of the safety relation information of the investigation medicinal products should be performed according to the local pharmacovigilance requirements to standard medical practice in the territory of the Russian legislation.

9.4.2 Reports of unexpected adverse events during use of medicinal products for human use

As the present study does not stipulate any investigational medicinal product or vaccine, and includes only observation of patients receiving standard treatment with medicinal products approved for use in the territory of the Russian Federation, safety monitoring and reports regarding adverse events (including unexpected events) will be performed according to local pharmacovigilance requirements to standard medical practice in the territory of the Russian Federation.

9.4.3 Registration of spontaneous reports regarding adverse events

The following principles should be applied in case of registration of adverse events in study participants: the investigator should report adverse events per pharmacovigilance procedures according to local regulatory requirements:

1. To the Federal Service for Surveillance in Healthcare: In writing to the following address: Russian Federation, 109074, Moscow, Slavianskaya sq., 4, b. 1. A specific form should be used currently available at: http://www.roszdravnadzor.ru/i/upload/files/1308641445.19876-26263.doc

2. To the corresponding pharmaceutical company, i.e. the marketing authorization holder of the appropriate medicinal product, according to local regulatory requirements.

10. ETHICS

This non-interventional multicenter study will be conducted in compliance with the Protocol, the Declaration of Helsinki, ICH GCP guideline, GEP and all the current local legislative requirements to conduction of non-interventional studies.

Physicians will conduct this non-interventional multicenter study in line with all current regulatory and legislative requirements to routine medical practice in the Russian Federation.

10.1 Committee on ethical review for clinical studies (EC)

Before study start, written favourable conclusion of EC (ethics committee) should be received concerning the study protocol, ICF and CRF. If in the course of the study any amendments to these documents are made, written approval should be received before their implementation.

10.2 Informed consent

The present study is retrospective and thus based on data which will be retrieved from archives kept by the investigators. Therefore, in this non-interventional study the choice of a specific therapeutic strategy for each patient has already been made and there is no need for prospective conduction of any additional diagnostic or monitoring procedures. Collection of patient data will be performed only by the personnel of the clinical institution; as these data will not include any information enabling identification of the patient, in the present study there is no need to obtain patient informed consent (according to the personal data protection law of the Russian Federation).

10.3 Patient data confidentiality

The present study is retrospective and is thus based on data which will be retrieved from archives kept by the investigators. Collection of patient data will be performed by the personnel of the clinical institution; as these data will not include any information enabling identification of the patient, in the present study there is no need to obtain patient informed consent (according to the personal data protection law of the Russian Federation).

Identification number assigned by the investigator to each patient will be used instead of the patient's name in order to protect patient's personal data during reporting of adverse events and/or other study-related data. Identification number will consist of four digits, the first two will stay the same for all the patients from the same investigational site (site code), and the last two digits will be individual for this patient, whose medical records will be analysed at the site (patient code).

10.4 Training for physicians

Physicians should be trained on study conduction. New information regarding the study conduction should be provided to the physicians in a timely manner.

Physicians should be trained on local regulatory requirements to pharmacovigilance procedures. If they become aware of an adverse event occurring in the setting of

administration of either an investigational medicinal product or a vaccine, they should register and report the information to the contacts provided above within the timelines set by the requirements of local pharmacovigilance.

10.5 Study timeframes and completion timelines

Study conduction plan:

- Date of enrolment of first patient: 4 quarter 2016
- Date of enrolment of last patient: 2 quarter 2018
- Date of database lock: 4 quarter 2018

11. DATA MANAGEMENT

11.1 Data collection, monitoring, data processing and archiving procedures

The physician participating in the study collects data according to this study and any rules set by his/her institution.

By signing this protocol, the physician consents to conduct the present non-interventional study with all due efforts in line with the protocol, general provisions of Good clinical practice and all local legislation and regulations applicable to conduction of non-interventional studies.

The physician also provides his/her consent for monitoring, auditing, inspections by the Ethics Committee and inspections of documentation and study procedures by the regulatory authorities and undertakes to provide direct access to all study data and documentation.

The physician undertakes to prepare and maintain accurate study documentation in line with principles of Good clinical practice and local legislation, regulations and restrictions, and to provide comprehensive data concerning each patient in de-identified format.

The investigator is obliged to maintain copies of all study-specific documentation and records in line with all legislative and regulatory requirements. Such documentations includes without limitation the protocol, CRF/source documentation, adverse event reports, communication with regulatory authorities and institutional review board/ Independent Ethics Committee, documentation regarding all monitoring visits, normal ranges. All study documentation should be readily available upon request from the regulatory authorities.

The physician is responsible for accuracy and correctness of patient data records.

11.2 Report and data publishing

- Preparation of a study report within 12 months of its completion.
- The report should be signed by the Principal investigator
- Physicians will receive the study report

According to the Declaration of Helsinki, both authors, and editors, and publishers are ethically responsible for the publication of study results. The authors are obliged to maintain the accuracy of results. Both favourable and negative findings should be published or otherwise made publicly available.

The publication of individual pieces of data collected in individual institutions participating in multicenter studies should not precede publication of the primary manuscript. When individual data are prepared for publication, the first publication of the study data should always be referenced.

12. STATISTICS

12.1 Statistical analysis – general information

Non-interventional study is a study which applies epidemiological methods, including other methods used for analysis of data concerning human health.

12.2 Description of endpoints

Primary endpoints

1. Description of the clinical profile of COPD patient under outpatient treatment/ surveillance at outpatient polyclinic healthcare institutions of the Russian Federation in Moscow

Secondary endpoints

1. Percentage (%) of patients with different disease phenotypes among outpatients
2. Percentage (%)of prescriptions of medicinal products to COPD patients which are in line with their disease severity according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014
3. Distribution (%) of COPD patients who seek attention from primary medical care physicians by severity of airway obstruction (according to Federal clinical guidelines for diagnosis and treatment of COPD patients, 2014)
4. Mean number of exacerbations requiring medical attention (outpatient prescription of oral corticosteroids CS and/or antibiotics) in the last year in COPD patients
5. Mean number of hospitalizations in the last year in COPD patients
6. Mean duration (seriousness) of a temporary disability case. Number of days of temporary disability /Number of cases of temporary disability (reference form 16-BH)
7. Percentage (%) of COPD patients who received different regimens for treatment of COPD, including short-acting muscarinic antagonist (SAMA), short-acting β_2-agonists

(SABA), long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA), oral corticosteroids (oral CS), fixed dose combination (FDC), phosphodeisterase-4 inhibitor, theophylline for the past year

8. Percentage (%) prescriptions to COPD patients which are in line with their disease severity according to GOLD classification and Federal clinical guidelines for treatment choice

9. Percentage (%) of patients with eosinophilic inflammation (eosinophil count according to haematology >2%,> 3%, >4% or equivalent to absolute counts of >200, > 300, >400 cells per μl)

10. Percentage of patients receiving sufficient extent of treatment in line with disease severity according to Federal clinical guidelines

11. Disease burden based on the collected data concerning the duration of temporary disability, number of hospitalizations due to COPD exacerbations, outpatient visits concerning COPD during follow-up

12.3 Description of stages of data analysis

All data will be analysed after database lock.

12.4 Statistical methods

Descriptive statistics methods will be used for data processing.

12.5 Determination of sample size

Sample size in this study was not calculated.

13. REFERENCES

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APPENDIX 1. CLASSIFICATION OF SEVERITY OF AIRFLOW LIMITATION IN COPD (BASED ON POST-BRONCHODILATOR FEV_1)

Classification of severity of airflow limitation in COPD (based on post-bronchodilator FEV_1)

In patients with $FEV_1/FVC < 0.70$:	
GOLD 1:	Mild $FEV_1 \geq 80\%$ of predicted
GOLD 2:	Moderate $50\% \leq FEV_1 < 80\%$ of predicted
GOLD 3:	Severe $30\% \leq FEV_1 < 50\%$ of predicted
GOLD 4:	Very severe $FEV_1 < 30\%$ of predicted

APPENDIX 2. FEDERAL CLINICAL GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2014

REFERENCE HTTP://PULMONOLOGY.RU/PUBLICATIONS/GUIDE.PHP