PROTOCOL SYNOPSIS
of research project
"The program to assess the influence of routing and in-depth consultation of patients with cardiovascular risk factors on the choice of medicine and treatment compliance"

Version 3, March 30, 2018

Organized by:	Russian Society for Prevention of Non-Infectious Diseases League of Clinical Research
Study sponsor	Pfizer Ltd.
Project title	The program to assess the influence of routing and in-depth consultation of patients with cardiovascular risk factors on the choice of medicine and treatment compliance.
Short title of the project	3P (Primary Prevention Program)
Study type	A pharmacoepidemiological study (evaluation of specifics of the use and the effects of drugs in a large patient number in the real world medical settings).
Methodology of the study	A systematic collection of retrospective and prospective data based on non-interventional patient observation, aimed to assess the risks, course and outcomes of a disease or a group of diseases: • the retrospective part: database of patients with cardiovascular risks; • the prospective part: observation of patients in the real world medical practice. The research program will have two parts: • The main part of the program (from the beginning of treatment to month 6): subjects with cardiovascular risk will be followed for 6 month after administration of treatments to reduce the risks. All study sites that have consented to participated in this research project, will take part in this study phase • A 6-month extension of the main program (from month 6 to month 12): subjects with the risk of cardiovascular disease will be followed for additional 6 months after the end of the main part of the program (from month 6 to month 12 after administration of treatments to reduce the risks). All study sites that have consented to participated in the 6-month extension of the research project can take part in this extension.
Background and rationale	It is common that subjects with the risk of cardiovascular disease do not have proper preventive care. Cardiovascular disorders are known to be the leading cause of death

in Europe. About 4,3 million people die annually from these diseases. In November 2010, the results of a large European study were released that showed that an improvement of preventive care can substantially reduce cardiovascular mortality.

The Epidemiological study of European Cardiovascular Risk patients: Disease prevention and management in usual daily practice aimed at evaluation of the influence of cardiovascular risk factors on mortality. In addition, the investigators assessed how successful was the management of these risk factors. The results obtained confirmed an increase of cardiovascular mortality in the presence of one or more risk factors (smoking, arterial hypertension, diabetes mellitus, increased cholesterol levels and obesity). It raises concern that in everyday clinical practice these factors are not adequately managed, that may be a cause of the rise in cardiovascular mortality.

Hyperlipidemia is the second (after arterial hypertension) cause of early mortality in Russia. Hyperlipidemia can be associated with both increased low density lipoprotein cholesterol and triglyceride levels. Hypercholesterolemia is a confirmed risk factor of atherosclerotic cardiovascular disease and its complications.

Objectives of the project

1. To make physicians (internists, cardiologists, medical specialists working in preventive facilities) familiar with current approaches to assessment of cardiovascular risks and their management through timely administration of corresponding treatments, by organization of training activities (web conferences, meetings, round table discussions).
2. To inform physicians, especially those in primary care, on the importance of a thorough assessment of cardiovascular risks and timely administration of therapy.
3. To analyze databases currently effective in medical institutions (those on healthy subjects and patients) in order to identify subjects with cardiovascular risk factors.
4. To assess blood lipids in subjects with suspected high cardiovascular risk.
5. To perform in-depth medical consultations of subjects on the importance of primary cardiovascular prophylaxis, including by means of preventive statin treatment (with the information on original drugs and generics, social programs by manufacturers implemented in pharmacies).
6. To assess efficacy of the combination of preventive activities (in-depth medical consultation of patients on their treatment; sms reminders on the necessity to comply with their doctor's prescriptions) on patients' compliance to treatment.
7. To follow changes in cardiovascular risk factors with associated assessment of patients' compliance to medical recommendations.

Number of study sites

6 (Kazan, Novosibirsk, Omsk, Samara, St. Petersburg, Ufa).

Patient number	The target patient number is 12,000.
Study period	Development and approval of the project materials (protocol, electronic database): March 31, 2017. Start-up meeting: April 2017. Preparation, printing and delivery of the project materials: April 30, 2017. First patient in: May 1, 2017. Last patient in: April 30, 2018. End of data collection for the main part of the program: October 30, 2018. Analysis of the results and preparation of the final study report on the main part of the program: December 31, 2018. End of data collection for the 6-month extension phase: April 30, 2019. Analysis of the results and preparation of the final study report: June 30, 2019.
Study condition	Cardiovascular risk factors. Special attention will be given to lipid level assessments.
Study treatment	Statins included into the list of life-saving and essential drugs and administered for correction of lipid spectrum to prevent cardiovascular disorders in the real world medical setting.
Ethical and regulatory aspects	The state registration of the project is planned to be done in the Federal State Research Institution "Center of Informational Technologies and Executive body systems" of the Ministry of Education and Science of the Russian Federation, in accordance with the Act of the Government of the Russian Federation №279 from March 31, 2009. It is planned to establish a Research and Advisory Committee for the project. It is planned that the study materials will be approved by an Intercollegiate Ethics Committeем. Personal data management in the project will be done in accordance with the Federal Law 152-F3 from July 27, 2006 (version of June 4, 2014). The Russian Society for Prevention of Non-Communicable Diseases and the League of Clinical Research will receive blinded data on the study subjects, i.e. the participating study sited will implement the blinding procedure on personal data (Art. 3, par.9, 152-F3). To improve data quality, monitoring activities will be implemented in the main part of the program, in accordance with normative requirements on performance of research as follows: • The National Standard of the Russian Federation from

27.09.2005 GOST R 52379-2005 “Good Clinical Practice”,

- The Decree of the Ministry of Health and Social Development of Russia №757n from 26.08.2010 г. “On approval of the Order of pharmacovigilance monitoring of safety of pharmaceuticals for medical use, registration of adverse effects, serious adverse reactions, unexpected adverse reactions during the use of pharmaceuticals for medical use”.

The monitoring will be performed by an independent third party (a contract research organization) and will include (but not limited to) visits of study monitors to study sites and check-ups of the study materials.

Criteria and methodology of medical chart selection for further screening

- Total cholesterol ≥5 mmol/L
- Additional risk factors identified during previous screening:
  - age 40-65 years
  - arterial hypertension (SBP>140 mmHg, DBP>90 mmHg) or antihypertensive treatment
  - history of dyslipidemia
  - smoking
  - overweight or obesity (BMI ≥25,0)
  - diabetes mellitus
  - chronic renal disease.

Inclusion criteria

Data on the following subjects is planned to be collected in the project:

- Aged from 40 to 65 years inclusively
- With a high (≥5%) cardiovascular risk measured by SCORE[1] and low density lipoprotein (LDL) levels of ≥2,5 mmol/L,
  or
  with a very high (≥10%) cardiovascular risk measured by SCORE and LDL levels ≥1,8 mmol/L
  or
  With atherosclerotic stenosis of brachiocephalic arteries of >50% in the absence of cerebrovascular disease[2]

Exclusion criteria

- No contraindications to statin treatment and not taking stating at study entry.

- History of the following clinically significant events and conditions:
  (а) myocardial infarction
  (б) stroke
  (в) transient ischemic attack
- Presence of the following diseases at the time of a statin administration:

[1] SCORE: Systematic COronary Risk Evaluation.

[2] If atherosclerosis of brachiocephalic arteries has been confirmed either by data obtained from the source medical documentation or identified during the work-up within routing medical care of the medical institution; decision to perform such a work-up can be made by a doctor and is unrelated to performance of the given research project.

(a) ischemic heart disease
(б) heart failure
(в) peripheral artery atherosclerosis
(г) atherosclerotic stenosis of brachiocephalic arteries with cerebrovascular disease[3].

Subjects must give their consent for processing of their personal data for the purposes of this scientific project.

Data to be collected

- Demographic characteristics
  (a) gender
  (b) age (full years by the time when written informed consent is signed)
- cardiovascular risk factors:
  (a) hypercholesterolemia (based on the results of lipid tests, see below)
  (b) smoking status (yes/no)
  (c) blood pressure (systolic blood pressure, mmHg; diastolic blood pressure, mmHg)
  (d) diabetes mellitus (yes/no)
  (e) height (at Visit 1) and weight (at all visits) for calculation of body mass index (BMI)
- blood lipids (all in mmol/L):
  (a) total cholesterol
  (b) low density lipoprotein cholesterol
  (c) high density lipoprotein cholesterol
  (d) triglycerides
- treatment administered for prevention of cardiovascular disease:
  (a) statin prescribed for prevention of cardiovascular disease (name; original /generic; dose mg/daily)
  (b) other treatments prescribed for prevention of cardiovascular disease (name; original /generic)
  (c) if a drug is withdrawn, the reason for withdrawal:
  - by prescribing physician due to low efficacy;
  - by prescribing physician due to poor tolerance;
  - by another physician due to any reason;
  - unavailability of the drug;
  - patient's decision;
  - other reasons
  (d) duration of statin therapy, months,
  (e) proportion of subjects who continue to take statin by the end of the main part of the program (6 mo) and by the end of the 6-mo extension of the main program (12 mo)
  (f) Morisky-Green test, scores (see Appendix 1).

- development of one of the following conditions (disorders) during the trial:
  (a) myocardial infarction (yes; no)
  (b) stroke (yes; no)
  (c) transient ischemic attack (yes; no)

[3] If cerebrovascular disease is present, statin administration cannot be considered as primary prevention.

(d) ischemic heart disease (yes; no)
(e) heart failure (yes; no)
(f) atherosclerosis of brachiocephalic arteries (yes; no)
(g) hospitalization (yes; no; if yes, due to a cardiovascular disease or due to another reason)
(h) emergency call (yes; no; if yes, due to a cardiovascular disease or due to another reason)
(i) revascularization (yes; no)
(j) death (if yes, due to a cardiovascular disease or due to another reason).

Time points of assessments

In this study data obtained in the real world medical practice will be analyzed. It is assumed that subjects will be assessed and treated according to the usual practice of their medical centers and at a physician's discretion.
It is desirable that the standard medical practice of the participating study sites involves regular assessment of patients who have been administered statins for improvement of their lipid spectrum to prevent cardiovascular diseases. It is assumed that patients to whom a statin has been prescribed for prevention of cardiovascular diseases should be assessed approximately at 1 to 2, 3 to 4, 5 to 6, and 11 to 12 months to monitor their treatment compliance, potential treatment modifications, course of their cardiovascular risks or cardiovascular disorders.

Since this research project is aimed to assess the examination and treatment of patients in the real world medical practice, the study organizers will not set any concrete time points at which patients should make their visit to the doctor. The type of the follow-up should correspond to that adopted in the medical institution.

At the same time, it is desirable that during the main part of the program those subjects that have been prescribed a statin, would see their doctors three time, approximately at 1 to 2, 3 to 4, and 5 to 6 mother after initiation of statin treatment. Those participating in a 6-month extension of the main part of the program are recommended to be assessed at 11 to 12 months after initiation of statin treatment.

Data management and analysis

Remote input of data (data into the electronic database will be entered by the participating physicians from the workplace). Data will be entered in depersonalized form.
The methods of descriptive statistics will be used for the whole population for all the indicators studied.

For those categories for which it is possible (for example, "high-density lipoprotein cholesterol"), the data will be reduced to time points "after 2 months"; "in 3 months"; "in 6 months"; "in 12 months", using the method move forward the last observation data (Last Observation Carried Forward, LOCF).

In addition, using descriptive statistics methods, all the studied indicators will be analyzed separately for the following populations:

- population in which a set of preventive measures was carried out (in-

depth medical advice to patients about taking therapy, sms reminders about the need to follow the doctor's prescription)
- population in which a set of preventive measures was not carried out.

Using the methods of comparative statistics, the following variables will be compared:
- Change in the lipid spectrum of the blood during the study period:

(A) in the whole population
(B) in a population in which a set of preventive measures was carried out (in-depth medical advice to patients about taking therapy, sms-reminders about the need to follow the doctor's prescription)
(C) in a population in which a set of preventive measures was not carried out.

In addition, using the methods of comparative statistics, the following indicators will be compared:
- reasons for withdrawal of therapy
- duration of statin therapy: between groups; for each trade name
- Percentage of patients who continued to receive statins at the end of the main part of the program (6 months): between groups; for each trade name
- Percentage of people who continued to receive statins at the end of the 6-month continuation of the main part of the program (12 months): between groups; for each trade name
- results of Moriski-Green test
- blood pressure
- smoking status
- change in body mass index
- development of one of the following conditions (occurrence of the following diseases, development of the following events) during the study period:

(A) myocardial infarction
(B) stroke
(C) transient ischemic attack
(D) ischemic heart disease
(E) heart failure
(E) atherosclerosis of brachiocephalic arteries
(G) atherosclerotic disease of peripheral arteries
(H) hospitalization
(I) call an ambulance
(K) revascularization
(K) death,

in a population in which a set of preventive measures was carried out (in-depth medical advice to patients about the admission of therapy, sms-reminders about the need to follow the doctor's prescription), and in a population in which a set of preventive measures was not carried out.

At the end of the study, a final report will be prepared in Russian.

General description of the study

6 centers of medical prevention (MSC), located in different regions of Russian Federation will take part in this project, in cooperation with other medical and preventive institutions.

During the **first** phase of the project (screening 1) is expected to be screened in the existing health care institutions of primary health care databases (patients, healthy individuals) and identify individuals;
(a) not currently suffering from cardiovascular disease (diseases), which are exclusion criteria for this scientific program,
(b) do not have the history of conditions (diseases), which are exclusion criteria in this scientific program,
(c) not receiving statin for the prevention of cardiovascular disease,
(d) having risk factors for cardiovascular disease.

Sufficient number of subjects should be screened in each center to include 2,000 patients who meet the inclusion and exclusion criteria in the project.

During the **second** phase of the project (screening 2) subjects will be invited to the study centre in medical prevention and treatment-and-prophylactic institutions (MPI), or to physician to confirm that subject:
(a) does not currently suffer from cardiovascular disease (diseases), which are exclusion criteria for this scientific program,
(b) does not have a history of conditions (diseases), which are exclusion criteria for this scientific program,
(c) does not receive statins for the prevention of cardiovascular diseases,
(d) has risk factors for cardiovascular disease,
(e) has reasonable indications for determining the lipid spectrum.

During the **third** phase of the project (screening 3) subjects who were selected during the second phase, will be determined lipid profile by express test. Persons with lipid metabolism disorders, which are indications for prescribing vital and essential statins for the prevention of cardiovascular diseases, are prescribed statins in accordance with standard practice of medical institution.

Following the appointment of statin subject signs an informed consent for processing of personal data. From this moment, the subject is considered included in the scientific research.

It is necessary to include 2,000 patients in each center that meet the inclusion and exclusion criteria.

During the **fourth** phase (the main part of the program - observation):
(a) all subjects will be consulted about the prevention of cardiovascular diseases and the use of medicines for this purpose
(b) subjects will be randomized (using the CRStat system) in two groups in a ratio 1: 1; in one of the groups will be carried out a profound consultation (different from standard practice for this medical institution) on the importance of primary prevention of cardiovascular diseases, including preventive reception of statins
(c) subjects in profound consultation group will receive regular reminders (2 times a month) via SMS and calls to check maintenance the doctor's recommendations and follow-up visit to study centre
(d) subjects will come for final examinations (consultations) to study doctor.

During the **fifth** phase (6-month continuation of the program - observation):
(a) subjects in profound consultation group will receive regular reminders (2

	times a month) via SMS and calls to check maintenance the doctor's recommendations and follow-up visit to study centre (b) subjects will come for the final examination (consultation) to study doctor. It is desirable that medical prevention and treatment-and-prophylactic institutions (MPI) take part in the program, in witch standard medical practice involves periodic surveys of persons receiving statins for lipid correction and for prevention of cardiovascular disease: approximately in 1-2, 3-4, 5-6 and 11 -12 months after beginning of statin therapy.
Potential medical, social and economic consequences of the project	The results of the project (medical statistical and pharmaco-epidemiological) will be presented to the Russian medical community and healthcare institutions in order to: (a) draw attention to the problem of primary prevention of cardiovascular diseases, (b) based on the analysis of the results of the study help healthcare professionals and healthcare providers to choose the right line for treatment people with high cardiovascular risks, including timely administration of statins, (c) demonstrate the advantages of complex preventive measures (profound consultation about necessity of maintenance the doctor's recommendations; sms reminders about the need to follow the doctor's prescription), having the aim of reducing the number of cardiovascular diseases in Russian Federation. In order to promote the development of modern approaches to the prevention of cardiovascular diseases, to demonstrate to a wide range of doctors the benefits of timely prescription of statins for primary prevention of cardiovascular diseases, during the project it is planned to hold meetings, conferences, roundtables on the prevention of cardiovascular diseases with the aim of discussing the progress of scientific research in Russia and abroad, as well as the participation of physicians in the work of international congresses and conferences with the purpose of increasing their own knowledge and further transfer of this knowledge to Russian specialists.

References

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