1.0 Title Page

Post Marketing Observational Study
PROTOCOL

Amendment 1

(Protocol ID PUFA5004)

A PROSPECTIVE OBSERVATIONAL PROGRAM USING DIGITAL TECHNOLOGY TOOLS TO ENHANCE PATIENT ADHERENCE TO OMACOR THERAPY (DIAPAsOn)

Product Name:	Omacor (Omega-3 triglycerides [EPA/DHA=1.2/1 - 90%])	
Type of Study:	Observational	
Date of the Protocol:	August 21, 2017	
Date of the Amendment 1:	12th February 2018	
Sponsor	**Abbott Laboratories** 125171, Moscow Russian Federation, Leningradskoe shosse, 16A, bld. 1, Metropolis Business Center	Tel.: + 7 495 258 4280 Fax: +7 495 258 4281

This study will be conducted in compliance with this protocol.

Confidential Information

No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

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3.0 Reason for amendment

Discrepancy between Protocol inclusion criteria and routine clinical practice.

The Investigators informed that it's impossible to match inclusion criteria that patient should have been taking Omacor for at least 3 days at the time of enrollment into the program (inclusion criteria #3) because patients usually return to the physician not earlier than 1 month after treatment administration.

4.0 Changes

The changes were made in the inclusion criteria #3 and corrected throughout the Protocol. The changes were summarized in the table below:

Section, page	**Previous version**	**New version**
6.1.1 Inclusion Criteria, page 8	3. Patients having been prescribed Omacor (Omega-3 triglycerides [EPA/DHA = 1.2/1 - 90%]) for at least 6 months AND who have been taking Omacor ***for 10±7 days*** at the time of enrollment into the program.	3. Patients having been prescribed Omacor (Omega-3 triglycerides [EPA/DHA = 1.2/1 - 90%]) for at least 6 months AND who have been taking Omacor ***no more than 14 days*** at the time of enrollment into the program.
6.5 Study Conduct, Figure 1. The program flow-chart, page 12	Patients who have been receiving Omacor ***for 10 ± 7 days***	Patients who have been receiving Omacor ***no more than 14 days***

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3.0 Rationale

This study is a prospective observational program within the frames of which Omacor (Omega-3 triglycerides [EPA/DHA = 1.2/1 - 90%]) is prescribed to patients with a history of myocardial infarction within a routine procedure as a part of the combination therapy (in combination with statins, antiaggregants, beta-blockers, angiotensin-converting enzyme inhibitors (ACE)) and/or to patients with hypertriglyceridemia. The population of observed patients will be limited to those who were prescribed Omacor for the first time or not earlier than 3 months after the last dose of Omacor and course of administration is at least 6 months.

This program is conducted to assess the effectiveness of the use of digital technology tools to enhance the adherence of patients with a history of myocardial infarction and/or hypertriglyceridemia, as well as to assess the impact of the use of digital technology tools on the effectiveness of treatment and improvement of the quality of life of these patients.

The primary objective of the program is to assess patient adherence to therapy with Omacor. Adherence is defined as the extent to which a person's behavior in taking medication corresponds with agreed recommendations from a health care provider (World Health Organization, 2003) that expects patient active involvement into treatment process and strong relationship between patient and physician. In this study adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor in period divided by the number of days in period.

Secondary objectives include assessment of the reasons for discontinuation of Omacor, assessment of the quality of patients' life and assessment of health outcome during the study.

Additional tasks of the program include a description of the target patient population prescribed with Omacor, as well as raising patients' awareness about the disease.

4.0 Study Objective(s)

Primary objective

1. To assess adherence to therapy with Omacor in post-MI patients or patients with hypertriglyceridemia.

Secondary objectives

1. To evaluate the reasons for the termination of therapy with Omacor.
2. To evaluate the quality of life of patients during the program.
3. To evaluate health outcomes in patients group during the program.

Primary endpoints

1. Mean adherence rate at the end of the study (Visit 3).
   Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor® in period divided by the number of days in period.
2. Mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] at the end of the study (Visit 3).

Secondary endpoints

1. The percentage of patients who have chosen each of the suggested reasons for therapy termination.
2. The average score on each of 8 scales of SF-36 quality of life questionnaire at Visit 2 and Visit 3 vs. the baseline (Visit 1).
3. Change of lipid profile parameters at Visit 2 and Visit 3 vs. the baseline (Visit 1).
4. Number of hospitalizations due to cardio-vascular reasons during 6 months of the program.
5. Number of new cases of stenocardia during 6 months of the program.
6. Number of non-fatal myocardial infarction cases during 6 months of the program.
7. Number of cases of cardio-vascular death during 6 months of the program.
8. Mean adherence rate at Visit 2.
9. Change of mean adherence rate by end of the study (Visit 3) versus Visit 2.
10. The percentage of patients with adherence rate <0,5, 0,5-0,7, ≥0,8 at Visit 2 and Visit 3.
11. Mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] at Visit 1, Visit 2.
12. Change of mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] at Visit 2 and Visit 3 versus baseline (Visit 1).

Experimental endpoints

1. The average number of days when Omacor was taken during observational study period of 6 months. The last day of drug product administration is defined as date of last Omacor dose or last subject visit within this program whatever is earlier.
2. Correlation between primary endpoints and patients' social characteristics (gender, age, employment status, education level, marital status).
3. The percentage of patients who assess the drug product usability as very good, good, moderate and poor after 1 month of Omacor treatment.

For endpoints which are applicable, further analysis will be performed in subgroups of patients with the different medication adherence rate: <0,5, 0,5-0,7, ≥0,8 at Visit 2 and Visit 3. Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor in period divided by the number of days in period.

Additional objectives of the program include a description of the target patient population prescribed with Omacor, as well as raising patients' awareness about the disease.

4.1.1 Inclusion Criteria

1. Men and women ≥ 18 years of age.
2. Patients with history of myocardial infarction not earlier than 6 months ago.
   AND/OR
   Patients with diagnosis of hypertriglyceridemia.
3. Patients having been prescribed Omacor (Omega-3 triglycerides [EPA/DHA = 1.2/1 - 90%]) for at least 6 months
   AND
   who have been taking Omacor for 10±7 days at the time of enrollment into the program.
4. Patients who can, in the opinion of the Investigator, himself or through immediate relatives's help complete electronic system of data collection through mobile application or web-browser.
5. Patients who have signed the consent to participate in this program before entering their data in the eCRF and who understand their right to discontinue the program at any time.

4.1.2 Exclusion Criteria

1. Patients taken medicines (except for Omacor) or nutrition supplements containing omega-3 in any proportions at the time of enrollment into the program
   OR
   it has been less than 3 months since last dose of medicines or nutrition supplements containing omega-3 taken.
2. Female patients during pregnancy or breastfeeding.
3. Patients with increased sensitivity to the active substance, excipients, and soy.
4. Patients with exogenous hypertriglyceridemia (type I hyperchylomicronemia).

5. Participation in any other clinical or non-clinical study/program at present or within the latest 30 days.
6. Patients with any other clinical states that make him/her ineligible for the program on the study doctor's opinion based on clinical assessment.

4.2 Number of Patients to be Enrolled

In total, the program will include 3000 patients from approximately 150-200 sites (300 physicians) in the Russian Federation. The number of patients enrolled by each physician/site will be limited in order to avoid a situation when 1 large site affects results, thus having a negative impact on the representativeness.

4.3 Study Duration

The observation period will last from the enrollment in the program during Visit 1 until Visit 3 (Month 6 ±30 days). **Discontinuation of the drug product administration by the patient is not the reason for exclusion of the patient from the study.**

A decision on the duration of treatment is made by the attending physician at his/her discretion in accordance with the valid approved Instruction and the routine clinical practice but this program will include patients who are prescribed Omacor for at least 6 months. It is expected that the enrollment period will be approximately 3 months. The overall duration of the program is about 9 months.

4.3.1 Product Supply

Since this is a non-interventional observational program and the drug product is prescribed within the frames of a routine clinical practice, Abbott does not provide Omacor. The treatment should be prescribed in accordance with the current Instruction for Medical Use and local recommendations.

4.3.2 Description of Activities

After enrollment in the program, patients will visit the study site once again to assess their state approximately 3 months and 6 months later. Some of these data will be entered by the patients themselves using their personal account in the electronic system of the program.

5.0 Pharmacovigilance-Relevant Information

5.1 Definitions

5.1.1 Adverse Drug Reaction (ADR)

The **adverse drug reaction (ADR)** is defined as a response to a medicinal product which is noxious and unintended. In this context, the response means that a causal relationship between the drug product and the adverse event is, at least, rationally possible. Adverse drug reactions may occur as a result of the drug product administration both within the frames of the officially registered Instruction or in the case of the off-label use, or as a result of exposure at the workplace. Cases of the off-label use include administration of the drug product for unregistered indications, overdose, misuse, abuse, and medication errors.

If an adverse drug reaction meets any of the following criteria, it is considered **a serious adverse drug reaction (SADR):**

Patient's death - an adverse reaction that leads to patient's death.

Life threatening reaction is an adverse reaction that would lead to the immediate death, on investigator's opinion, if a medical intervention has not been made. This does not include events which would have been fatal in a more severe form.

Hospitalization - an adverse reaction that led to admission to the hospital for any period of time. This does not include visits to the emergency departments or outpatient's clinic.

Prolongation of hospitalization - an adverse reaction that occurs in a study subject during the hospitalization and prolongs the patient's stay in the hospital.

Congenital abnormality/malformation - an abnormality identified at birth or after it, or any defect that leads to the fetal loss.

Persistent or significant disability/incapacity - an adverse reaction that leads to a condition which significantly interferes with daily activities of a program participant.

Important medical event requiring medical or surgical intervention to prevent serious outcome is an important from a medical point of view adverse event that at first may not be life-threatening or result in death or hospitalization, but, on the basis of a medical conclusion, it may endanger the patient and require medical or surgical intervention to prevent any of the outcomes listed above (for example, the death of the subject, threat to his/her life, hospitalization, prolongation of hospitalization, congenital abnormality/malformation or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring an

intensive care in the emergency unit or domiciliary, abnormal changes in the blood or convulsions that do not result in hospitalization or the development of drug addiction or drug abuse.

5.1.2 Other Pharmacovigilance- relevant information

In the context of this Protocol, "other safety-related data" means:

- cases related to the exposure of the drug product during pregnancy (related to the mother, the father or the fetus) with the development of an adverse drug reaction or without it;
- transmammary exposure of the drug product on the infant (transmission through the breast milk) with the development of an adverse drug reaction or without it;
- overdose with the development of an adverse drug reactions or without it;
- abuse or misuse (for example, use without clinical reasons) with the development of an adverse drug reaction or without it;
- medication errors (for example, any event that may cause or lead to inappropriate use of the drug product or harm a patient, despite the fact that the treatment is monitored by a healthcare professional, patient, or consumer) with the development of an adverse drug reaction or without it;
- unexpected therapeutic or clinical benefit of the drug product administration;
- any failure in the expected pharmacological effect (for example, "reports on the lack of efficacy");
- supposed transfer of the infectious agent through the drug product;
- off-label use with the development of an adverse drug reaction or without it;

unintentional, accidental exposure or exposure at the workplace with the development of an adverse drug reaction or without it.

5.2 Serious AE/ADR Collection Period

Adverse drug reactions, serious adverse drug reactions and other safety-related information will be reported to Abbott from the inclusion of the patient in the program during Visit 1 until Visit 3. All adverse reactions, observed in a patient outside the frames of this program should be reported to regulatory authorities by a physician in accordance with the legislation of the Russian Federation and the local practice of the healthcare institution.

5.3 Reports on ADR, SADR and other safety-related data

In the case of an adverse drug reaction, serious adverse drug reaction and reporting of other safety-related data, a physician must notify the contact person in Abbott mentioned below within 24 hours after getting acquainted with this information.

6.0 Ethics and Quality

Patient's written consent to the use and/or disclosure of personal and/or medical information must be obtained before his/her inclusion in the program and patients who are not yet ready to express such written consent will not be included in the program. However, all reasonable efforts will be made to avoid the disclosure of personal information (such as name, address, etc.).

The program will be carried out in accordance with the Protocol, principles of the International Conference on Harmonization, ethical standards based on the Declaration of Helsinki, and all applicable local requirements.

As it is known, the main purpose of the observational/noninterventional studies is to obtain information about everyday clinical practice which is not subjected to any external influences. Since it is not always possible to distinguish between "clinical practice" and "intervention", for example, there is still no clear understanding whether the use of questionnaires and patient diaries violates the principle of non-intervention, then the final decision is made by the Ethics Committee [8].

Taking into account the facts mentioned above, the Protocol and relevant documents related to the program will be submitted to the Ministry of Healthcare of the Russian Federation to make a decision to determine the type of study applied in this program; it will also decide whether the requirements of the Russian legislation listed in the Federal law No. 61 "On Drug Circulation" dd April 12, 2010 may be applied to this program.

Program documents will also be submitted to the Independent Ethics Committee (IEC), Intercollegiate Ethics Committee (119002 Moscow, Gagarinsky lane, 37), and, when necessary, to the Local Ethics Committees (LEC) in the study sites. Enrollment of patients will begin only after receiving a written approval from the IEC.

All data will be collected and processed in a manner that does not disclose the identity of individual patients and, therefore, patient confidentiality will be maintained at any time.

The study doctor will be responsible for ensuring that the quality control and quality control system which ensure the implementation of the program and collection, documentation and reporting in accordance with the Protocol, accepted standards of Good Clinical Practice (GCP) and all applicable local laws and requirements are implemented.

Members of the clinical research team in the Russian branch of Abbott will monitor completeness and correctness of data in electronic CRFs after they have been completed in the EDC. Any discrepancy/contradiction will be brought to the attention of the study site in order to be corrected. All necessary corrections will be entered to the database in accordance with the applicable procedures of the EDC.

7.0 Data Analysis Plans

This section describes the basic information about statistical data analysis within the frames of this observational program.

General principles

Since this is an open-label non-randomized non-interventional observational program, methods of descriptive summary statistics will primarily be applied. Quantitative variables are represented as the number of patients, the mean, standard deviation, median, 1st and 3rd quartile, the minimum and maximum values. Qualitative variables are presented in the form of the number and percentage of patients in each category. In addition, for the estimated parameters, bilateral 95% confidence intervals will be calculated. Statistical significance will be calculated for all variables. Plots may be made for a visual representation of the findings, if necessary.

Calculation of a sample size

The main objective of the program is a research and does not aim at verification of any hypothesis, so no formal sample size calculation has been carried out. It is planned to include 3000 patients in 150-200 centers (300 physicians): this sample size is sufficient for adequate scientific assessment of findings.

Population for data analysis

Per Protocol Population will include those patients who have completed at least Visit 2. This population will be used to assess the effectiveness. If the patient discontinues the treatment, the follow-up continues until expiration of 6 months from the date of initiation of Omacor. And for such patients the level of compliance is also calculated.

The endpoints which are applicable will be evaluated in subgroups of patients with the different medication adherence rate: <0,5, 0,5-0,7, ≥0,8 at Visit 2 and Visit 3. Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor in period divided by the number of days in period.

Safety Population will include those patients who have completed at least 1 Visit, i.e. they have been taking Omacor for not less than 3 days. This population will be used for reporting on ADR, SADR, and other safety-related data.

Analysis of the primary endpoint

1. Mean adherence rate will be determined at the end of the study (Visit 3). Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor® in period divided by the number of days in period.
2. Mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] will be determined at the end of the study (Visit 3).

Summary of demographics and baseline characteristics

Demographic and baseline characteristics will be summarized by methods of descriptive summary statistics described above, and are presented for populations of all patients included in the study.

Data on the cardiological anamnesis will be presented in the form of the number and percentage of patients in each MedDRA system-organ class (SOC) and preferred terms (PT).

Secondary endpoints

1. The percentage of patients who have chosen each of the suggested reasons for therapy termination will be determined.
2. The average score on each of 8 scales of SF-36 quality of life questionnaire at Visit 2 and Visit 3 vs. the baseline (Visit 1) will be determined.
3. The average values of lipid profile at Visit 2 and Visit 3 vs. the baseline (Visit 1) will be determined.
4. Number of hospitalizations due to cardio-vascular reasons during 6 months of the program will be determined.
5. Number of new cases of stenocardia within 6 months of the program will be determined.

6. Number of cases non-fatal myocardial infarction cases during 6 months of the program will be determined.
7. Number of cases of cardio-vascular death within 6 months of the program will be determined.
8. Mean adherence rate will be determined at Visit 2. Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor® in period divided by the number of days in period.
9. Change of mean adherence rate by end of the study (Visit 3) versus Visit 2 will be determined.
10. The percentage of patients with adherence rate <0,5, 0,5-0,7, ≥0,8 will be determined at Visit 2 and Visit 3.
11. Mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] will be determined at Visit 1, Visit 2.
12. Change of mean score of National questionnaire of treatment compliance (edited by Fofanova T.V. et al.) [9] at Visit 2 and Visit 3 versus baseline (Visit 1) will be determined.

Experimental endpoints

1. The average number of days when Omacor was taken during observational study period of 6 months will be determined. The last day of drug product administration is defined as date of last Omacor dose or last subject visit within this program whatever is earlier.
2. Correlation between primary endpoints and patients' social characteristics (gender, age, employment status, education level, marital status) will be determined.
3. The percentage of patients who assess the drug product usability as very good, good, moderate and poor will be determined after 1 month of Omacor treatment.

For endpoints which are applicable, further analysis will be performed in subgroups of patients with the different medication adherence rate: <0,5, 0,5-0,7, ≥0,8 at Visit 2 and Visit 3. Adherence rate will be calculated as the sum of days when patient taken the full prescribed dose of Omacor in period divided by the number of days in period.

Additional objectives of the program include a description of the target patient population prescribed with Omacor in addition to the standard therapy, as well as raising patients' awareness about the disease.

General Definitions and Abbreviations

Since this is an open, non-randomized non-interventional observational program, the methods of descriptive summary statistics will primarily be used. Quantitative variables will be presented as number of patients (N), mean (Mean), standard deviation (SD), median (Median), 1st quartile, 3rd quartile, minimum (Min) and maximum values (Max). Qualitative variables will be presented in terms of the number and rate of patients in each category and two-sided 95% confidence intervals will be calculated. Statistical significance (p-value) will be calculated for all comparisons (Visit 2 – Visit 1, Visit 3 – Visit 1). No formal conclusions can be drawn from these comparisons as no hypotheses were defined upfront to be tested. If necessary, charts can be prepared for the visual presentation of the results.

Individual patient lists (listings) will be formed for raw data processing.

Analysis of data on ADR, SADR and other safety-related data

All data on ADR, SADR and other safety-related data will be reported separately for each patient, i.e. patients will be counted, but not the reactions. It means that if a patient has the same reaction repeatedly, the reaction will be counted only once. Repeated reactions in one patient will be summarized in accordance with the following rule: if a patient has experienced the same reaction more than once, this reaction will receive the highest degree of severity, the most close relationship with the drug product and the earliest onset date.

All data on ADR, SADR and other safety-related data will be summarized and evaluated regardless of whether they have been reported in accordance with the Protocol or received from spontaneous reports.

8.0 Final Report and Publications

The final report will be written upon completion of the program. This report will contain a description of the program objectives, the methodology of the program and its results and conclusions. Completed eCRFs and the report on the program should be treated as a confidential property of Abbott Laboratories and may not be transferred to third parties in any form (publications or presentations) without obtaining the written approval of Abbott Laboratories. The results of this program can be published by Abbott Laboratories or any of the participating investigators after receiving a written approval from Abbott Laboratories.

9.0 References

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