All-Russian Public Organization «Russian Scientific Liver Society» (RSLS)
Akademicheskaya str., 4 B, office 1a, 127299, Moscow, Russia
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CLINICAL TRIAL REGISTRATION STATEMENT

Russian Scientific Liver Society (RSLS) at the meeting of the board of the RSLS registered non-interventional observational program "Experience of administration of the drug Ursosan® (ursodeoxycholic acid) for the prevention of atherosclerosis and liver fibrosis in real clinical practice for patients with non-alcoholic fatty liver disease".

Date of registration: September 19, 2017.
Protocol No. RSLS-CT-2017-15
Ind No. 327-93
Investigational product name: Ursodeoxycholic acid UDCA (Ursosan®) PRO.MED.CS Marketing.
Trial phase: IV (post-marketing).
The grant is provided by JSC "PRO.MED.CS Marketing" 2, Ugreshskaya str., 115088, Moscow, Russia
Principal investigator name and contact information: Marina V. Maevskaya e-mail: liver.orc@mail.ru
tel. +7 (903) 779 44 03
Coordinating center: 1s1, Pogodinskaya str., 119881, Moscow, Russia.
Duration of patient participation and study duration: Screening 01.10.2017 – 01.04.2018; Treatment 08.10.2017 – 15.10.2018.
The scientific supervisor of the Program is Academician of the Russian Academy of Sciences, Professor, MD Vladimir T. Ivashkin.

Vice president RSLS Pavlov Chavdar S.

Protocol No. 5-P / 2017
of the Russian Scientific Liver Society (RSLS) Ethics Committee meeting

September 12, 2017, Moscow

The start time of the meeting: 10 hours and 30 minutes

In accordance with the 1975 Helsinki Declaration, revised in 2013;
"The Constitution of the Russian Federation";
Federal Law No. 323-ФЗ "On the Fundamentals of Public Health Protection in the Russian Federation"; art. 36.1; National Standard of RF ГОСТ Р 52379-2005 « Good clinical practice » GCP (2005 г.) Good Clinical Practice;
National Standard of RF ГОСТ-Р ИСО 14155-2014 «Clinical trials. Good clinical practice»;
Federal Law «About the circulation of medicines» of 12.04.2010 № 61-ФЗ art. 40;
By order of the Ministry of Health of RF «About the Ethics Committee of the Ministry of Health of the Russian Federation» № 435н;
Federal Law «About personal data» № 152-ФЗ; Recommendations of the Ethics Committee that reviews WHO biomedical research and EF GCP;
Recommendations of the Council of Europe Steering Committee on Bioethics for members of Ethics Committees.

at the meeting of the RSLS Ethics Committee:
chairman of the Ethics Committee - Beniashvili Allan G. (PhD, Senior Researcher of the Laboratory of Psychopharmacology, FGBNU Scientific Center for Mental Health); Ethics Committee members - Zharkova Maria S. (PhD, Head of the Hepatology Department of the V. H. Vasilenko Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University) Ministry of Health of Russia); Morozova Margarita A. (MD, Head of the Laboratory of Psychopharmacology, FGBNU Scientific Center for Mental Health); Tikhonov Igor N. (gastroenterologist, hepatologist, assistant of the Department of Propaedeutics of Internal Diseases of the I. M. Sechenov First Moscow State Medical University); Bueverov Aleksey O. (MD, Professor of the Department of Medical and Social Expertise, Emergency and Polyclinic Therapy, IPO, Sechenov First Moscow State Medical University (Sechenov University) Ministry of Health of Russia); Palgova Lyudmila K. (MD, Professor of the Scientific-Clinical and Educational Center of Gastroenterology and Hepatology of the Institute of High Medical Technologies of St. Petersburg State University); Klimova Elena A. (MD, Professor of the Department of Infectious Diseases and Epidemiology, Evdokimov Moscow State Medical and Dental University, Ministry of Health of the Russian Federation); Geyvandova Natalia I. (MD, Professor of the Department of Hospital Therapy, Stavropol State Medical University).

Discussed the open international non-comparative study "Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with non-alcoholic fatty liver disease-USPEH" Protocol No. RSLS-CT-2017-15, Ind No.327-93.

An ethical review of the following documents was carried out:

1 statement of Maevskaya M. V. addressed to the Chairman of the LEC,
2 Clinical research protocol,

3 Informed consent form,
4 Case report form,
5 Concomitant medication log,
6 Medication log,
7 Adverse event (ae) report form,
8 CV of the researcher,
9 Certified copies of documents (diploma, certificates, category) confirming the qualification and specialization of the researcher,
10 The Treaty of grant by JSC "PRO.MED.CS Marketing" No.9-ПМЦ of 19.09.2017.

On the basis of which LEC concludes:

- the conditions of the study correspond to the generally accepted norms of morality,
- the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the research participants are met;
- there is no risk for the research subject;
- study participants are informed about the goals, methods, expected benefits of the study and the risks and inconveniences associated with participating in the study;
- the subject's consent to participate in the research was obtained.

According to the results of the ethical examination of the claimed research, its compliance with all the above-mentioned legislative requirements and regulatory documents was recognized.

DECIDED: Approve of the open international non-comparative study "Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with non-alcoholic fatty liver disease-USPEH" Protocol No. RSLS-CT-2017-15, Ind No.327-93.

Chairman of the Ethics Committee Beniashvili Allan G.

Secretary of the Ethics Committee Tikhonov Igor N.

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CLINICAL RESEARCH PROTOCOL

Ursodeoxycholic acid as a meanS of Preventing athErosclerosis, steatosis, and liver fibrosis in patients with nonalcoHolic fatty liver disease – USPEH
The grant is provided by JSC "PRO.MED.CS Marketing"

Protocol No.	RSLS-CT-2017-15	**Version No.**	1.1
Ind No.	327-93	**Date**	19.09.2017
Investigational Product Name	Ursodeoxycholic acid UDCA (Ursosan®) PRO.MED.CS Marketing		
Trial phase	IV (post-marketing)		
Sponsor(s), name and address	The grant is provided by JSC "PRO.MED.CS Marketing" 2, Ugreshskaya str., 115088, Moscow, Russia		
Funding organization	no		
Principal investigator name and contact information	Marina V. Maevskaya e-mail: liver.orc@mail.ru tel. +7 (903) 779 44 03		
Coordinating center (if applicable)	1s1, Pogodinskaya str., 119881, Moscow, Russia		

Approved by:

Principle investigator — September 19, 2017 — Date

Moscow
Site

PROTOCOL AGREEMENT

I have read and understand the protocol below. In my capacity as Investigator, my duties include making sure of the safety of the study participants enrolled by supervising them and providing JSC "PRO.MED.CS Marketing" with complete and timely information. This information will be provided as outlined in this study protocol. All the information relating to this study will be held in strict confidence and these confidentiality requirements apply to all staff at this study site or involved with this study. I agree to maintain the procedures required to perform this study in accordance with Good Clinical Practice principles and to abide by the terms of this protocol. I agree to maintain the principles of the 1975 Helsinki Declaration, revised in 2013.

Protocol No.	RSLS-CT-2017-15	**Protocol date**	September 19, 2017
Protocol title	**U**rsodeoxycholic acid as a mean**S** of **P**reventing ath**E**rosclerosis, steatosis and liver fibrosis in patients with nonalco**H**olic fatty liver disease – USPEH		

Russia	City: Moscow
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Protocol Synopsis

Project title	An open international noncomparative study with the code USPEH – **U**rsodeoxycholic acid as a mean**S** of **P**reventing ath**E**rosclerosis, steatosis, and liver fibrosis in patients with nonalco**H**olic fatty liver disease
Sponsor(s)	The grant is provided by JSC "PRO.MED.CS Marketing"
Funding organization	no
Website	https://rsls.ru/ru/for-specialists/nablprog
Rationale	Up to 30-35% of the population suffers from Nonalcoholic fatty liver disease (NAFLD). Among the NAFLD risk factors, obesity is considered to be one of the key factors. Such a high morbidity puts this disease among the most important diseases in primary health care. NAFLD is often associated with cardiovascular diseases (CVDs), which have become the main cause of decreased life expectancy in patients. In a number of studies, it has been noted that hepatic steatosis is an early predictor of coronary atherosclerosis and is associated with an increase in carotid intima-media thickness (CIMT). Experimental and clinical studies have shown the anti-inflammatory, antiapoptotic, antifibrotic, and cytoprotective effects of ursodeoxycholic acid (UDCA). Moreover, clinical studies have shown normalization of alanine transaminase (ALT), aspartic transaminase (AST), and gamma-glutamyl transpeptidase (GGT) levels, as well as a decrease in liver fibrosis severity. In addition, UDCA has a positive effect on dyslipidemia by lowering total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels and increasing high-density lipoprotein (HDL) levels. This effect may be associated with the CVD risk change.
Study design	An open international noncomparative study.
Primary objective(s)	Following parameters assessed at the end of the 6-month treatment for the total sample and for men and women separately: – liver function tests (LFT: ALT, AST, and GGTP), – lipid profile (TC, LDL, HDL, and TG), – fatty liver index (FLI), – NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index for liver fibrosis, – 10-year and lifetime Atherosclerotic Cardiovascular Disease (ASCVD) risk, and – CIMT.
Secondary objective(s)	Following parameters assessed at the end of the 6-month treatment for the subgroups with and without weight loss > 5% from baseline: – LFT: ALT, AST and GGTP,

	– lipid profile (TC, LDL, HDL, and TG), – FLI, – NFS, FIB-4, – 10-year and lifetime ASCVD risk, and – CIMT.
Number of patients	210 patients with NAFLD
Patient selection criteria	**Inclusion criteria** – surveillance in primary health care settings, – use of personal data in accordance with the legislation of the participating countries, – age over 18 years, – proven NAFLD case based on abdominal US, – FLI index value > 60, – the physician's decision to prescribe UDCA regardless of the patient's inclusion in the study, and – availability of the patient's written informed consent to participate in the program. **Non-inclusion criteria** – pregnancy, – hepatic decompensation (serum albumin ≤ 35 g/L, international normalized ratio ≥ 1.2, platelets < 150×10^9/L), – UDCA allergy, – presence of atherosclerotic complications, – use of statins, – use of other drugs that could potentially affect the studied parameters, – use of medications in past medical history associated with secondary hepatic steatosis development (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproic acid, and antiretroviral drugs), – unhealthy alcohol use (40 g ethanol per day for men and 20 g ethanol per day for women), – scores on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire > 8 for both men and women, – type 1 diabetes mellitus; parenteral nutrition; fasting; and presence of a secondary etiology of liver disease (viral, metabolic, autoimmune, cholestatic, or drug etiology). **Exclusion criteria** – a patient's decision to discontinue participation in the study at any stage, – acute hepatocellular or cholestatic injury that occurred during the study: increased ALT, AST, GGT, or alkaline phosphatase levels by two or more times; and – the need to take other drugs that potentially affect the studied parameters, arising during the study.

Product, dose, and route of administration	Daily UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight per os for 6 months. In addition, total sample was given standard recommendations to modify their lifestyle and diet: strength or aerobic exercise for at least 150 min per week, Mediterranean diet, and consumption of no more than 1500 kcal/d.
(Control) product, dose, and route of administration	not provided by the protocol
Duration of patient participation and study duration	
Screening	01.10.2017 – 01.04.2018
Treatment	08.10.2017 – 15.10.2018
Follow-up	post-study follow-up is not provided by the protocol

1. STUDY TEAM

Role	**Name, surname**	**Title**	**Affiliation**	**Contact information**
The scientific supervisor	Vladimir T Ivashkin	Full Prof, M.D.	Department of Internal Medicine Propaedeutics, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia	e-mail: liver.orc@mail.ru tel. +7 (985) 924 94 16
Coordinator	Marina V Maevskaya	Prof, M.D.	Department of Internal Medicine Propaedeutics, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia	e-mail: liver.orc@mail.ru tel. +7 (903) 779 44 03
Investigator	Evgeny V Chesnokov	Prof, M.D.	Tyumen State Medical University, Tyumen, Russia	e-mail: e.v.chesnokov@mail.ru tel. +7 (909) 184 61 11
Investigator	Irina Yu Pirogova	Prof, M.D.	Head at the CMC “Lotus” Center for Gastroenterology	e-mail: irina_pirogova@inbox.ru tel. +7 (919) 339-56-61

			and Hepatology, Chelyabinsk, Russia	
Investigator	Alexandr V Nersesov	Prof, M.D.	Head of the Gastroenterology Department S. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan	e-mail: alexander.nersesov@gmail.com tel. +7 (701) 799 82 12
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Statistical processing	Maria Yu Nadinskaia	Ph.D in Medicine, Associate Professor	Department of Internal Medicine Propaedeutics, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia	e-mail: marianad@ramler.ru tel. +7 (926) 306-39-99

2. STUDY OBJECTIVES

Primary Objectives

Following parameters assessed at the end of the 6-month treatment for the total sample and for men and women separately:

- LFT: ALT, AST and GGT,
- lipid profile: TC, LDL, HDL, and TG,
- FLI,
- NFS, FIB-4,
- 10-year and lifetime ASCVD risk, and
- CIMT.

Hypothesis:

A 6-month UDCA treatment reduces ALT, AST, and GGT levels, improves lipid profile (decreases TC, LDL, and TG; increases HDL), and decreases FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT independently of sex.

Secondary Objectives

Considering that the patients were given dietary and lifestyle recommendations, it was assumed that some patients would lose weight by the end of the study, which in itself could affect the parameters studied. Based on this assumption, a subgroup analysis with and without weight loss > 5% from baseline will be planned.

Following parameters assessed at the end of the 6-month treatment for the subgroups with and without weight loss > 5% from baseline:

- LFT: ALT, AST and GGT,
- lipid profile: TC, LDL, HDL, and TG,
- FLI,
- NFS, FIB-4,
- 10-year and lifetime ASCVD risk, and
- CIMT

Hypothesis:

A 6-month UDCA treatment reduces ALT, AST, and GGTP levels, improves lipid profile (decreases TC, LDL, and TG; increases HDL), and decreases FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT independently of weight loss >5% from baseline.

3. BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is currently the leading cause of liver disease and liver transplantation in developed countries; the number of people with this pathology is steadily growing [1]. NAFLD-related morbidity in the world is approximately 25%, being the highest in Middle Eastern and South American countries, while in Europe and Asia, the morbidity is approximately the same [2].

According to the DIREG 1, DIREG_L_01903 and DIREG 2 studies, up to 27% of the population suffers from NAFLD in Russia [3]. Among the NAFLD risk factors, obesity is considered to be one of the key factors. Such a high morbidity puts this disease among the most important diseases in primary health care.

NAFLD is often associated with cardiovascular diseases (CVDs), which have become the main cause of decreased life expectancy in patients [4]. According to one prospective study with over almost three decades of follow-up, 30% of deaths in patients with NAFLD were due to CVD, and 19% were due to liver disease [5].

The gold standard methods for the diagnosis of NAFLD are liver biopsy, proton magnetic resonance spectroscopy, and quantitative fat/water selective magnetic resonance imaging.

An ultrasound examination (US), a less expensive and more accessible method, is preferred for hepatic steatosis detection in primary health care settings. NAFLD is diagnosed after steatosis secondary causes are excluded. At all stages of the disease, the following validated scales are used: the fatty liver index (FLI), nonalcoholic fatty liver disease fibrosis score (NFS), and liver fibrosis index (FIB-4) [6].

Validated scales are also used to assess the CVD risk in patients with NAFLD. To accomplish this task, the Atherosclerotic Cardiovascular Disease (ASCVD) 2013 Risk Calculator and the Framingham Risk

Score (2008) are used. In a number of studies, it has been noted that hepatic steatosis is an early predictor of coronary atherosclerosis and is associated with an increase in carotid intima-media thickness (CIMT) [7].
There is currently no approved standard therapy for NAFLD. The main factor in successful treatment is weight loss, which is a key link in both NAFLD itself and CVD pathogenesis [8]. Among the NAFLD drug treatments, those that affect various disease pathogenesis links may be considered, including increased sensitivity to insulin (pioglitazone, rosiglitazone and liraglutide), lipid-lowering agents (statins), and antioxidant and cytoprotective drugs such as ursodeoxycholic acid (UDCA), vitamin E, obeticholic acid, and omega-3 fatty acid-polyunsaturated fatty acids [9].
Experimental and clinical studies have shown the anti-inflammatory, antiapoptotic, antifibrotic, and cytoprotective effects of UDCA [10-17]. Moreover, clinical studies have shown normalization of alanine transaminase (ALT), aspartic transaminase (AST), and gamma-glutamyl transpeptidase (GGTP) levels, as well as a decrease in liver fibrosis severity [18-24]. In addition, UDCA has a positive effect on dyslipidemia by lowering total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels and increasing high-density lipoprotein (HDL) levels. This effect may be associated with the CVD risk change. The average dose UDCA in most studies is 15 mg/kg daily oral.

4. STUDY DESIGN

The study design is an open international noncomparative trial in primary health care settings.
The study population includes patients with NAFLD, being treated in primary care settings.
The primary outcomes that will be assessed at the end of the 6-month treatment are as follows: LFT, lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT.
Subgroups analysis will be performed at the end of the 6-month treatment for patients with and without weight loss > 5% from baseline by assessing the following parameters: LFT, lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT. Total sample size: 210 patients with NAFLD.

Table 1. Sample size

Location	**Patients, n**
Russian Federation	150
Moscow	50
Tyumen	50
Chelyabinsk	50
Kazakhstan	50
Almaty	20
Astana	15
Shymkent	15
Uzbekistan, Tashkent	10
TOTAL	**210**

Period of screening: 01.10.2017 – 01.04.2018. The screening duration is from 1 to 2 weeks for each patient. Period of treatment: 08.10.2017 – 15.10.2018. The treatment duration is 6 months for each patient. A post-study follow-up is not provided.

Intervention

The patients who will be included in the study will receive daily UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight for 6 months. In addition, all patients will be given standard recommendations to modify their lifestyle and diet: strength or aerobic exercise for at least 150 minutes per week, Mediterranean diet, and consumption of no more than 1500 kcal/day [25].

5. PATIENT INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- surveillance in primary health care settings,
- use of personal data in accordance with the legislation of the participating countries,
- age over 18 years,
- proven NAFLD case based on abdominal US,
- FLI index value > 60,
- the physician's decision to prescribe UDCA regardless of the patient's inclusion in the study, and
- availability of the patient's written informed consent to participate in the program.

Non-inclusion criteria

- pregnancy,
- hepatic decompensation (serum albumin ≤ 35 g/L, international normalized ratio ≥ 1.2, platelets < 150×10^9/L),
- UDCA allergy,
- presence of atherosclerotic complications,
- use of statins,
- use of other drugs that could potentially affect the studied parameters,
- use of medications in past medical history associated with secondary hepatic steatosis development (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproic acid, and antiretroviral drugs),
- unhealthy alcohol use (40 g ethanol per day for men and 20 g ethanol per day for women),
- scores on the AUDIT questionnaire > 8 for both men and women,
- type 1 diabetes mellitus; parenteral nutrition; fasting; and presence of a secondary etiology of liver disease (viral, metabolic, autoimmune, cholestatic, or drug etiology).

Exclusion criteria

- a patient's decision to discontinue participation in the study at any stage,
- acute hepatocellular or cholestatic injury that occurred during the study: increased ALT, AST, GGT, or alkaline phosphatase levels by two or more times; and
- a need to take other drugs that potentially affect the studied parameters, arising during the study.

6. STUDY ENROLLMENT PROCEDURES

The study enrolls patients admitted to the primary health care settings. The patients who met all inclusion and exclusion criteria based on the Case Report Forms are enrolled by the Principal investigator. If any patient decides at any stage of the study to discontinue participation or has the need to take other drugs that could potentially affect the studied parameters, the data will be

recorded in the Case Report Forms and he or she will be excluded from the study. Patients will also be excluded from the study if they develop an acute hepatocellular or cholestatic injury that occurred during the study: an increase in ALT, AST, GGT, or alkaline phosphatase levels two or more times after 3 months of treatment or at any time. This information should be recorded immediately in the Case Report Form, and the Principal investigator will make a decision regarding patient exclusion.
The possible association between these abnormalities and drug use or other medical condition or intervention will be determined, and the severity of abnormalities will be assessed according to WHO-UMC[1] guidelines.

7. STUDY INTERVENTION, DURATION, AND ROUTE OF ADMINISTRATION

Intervention: daily UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight for 6 months. In addition, all patients will be given standard recommendations to modify their lifestyle and diet at every visit: strength or aerobic exercise for at least 150 minutes per week, Mediterranean diet, and consumption of no more than 1500 kcal/day [25].

The drug is bought by the patient. The patient maintains records of the drug use. The patients attended more than 80% of the study and taken more than 80% of the total drug dose are supposed to have completed the entire therapy protocol.
Other drugs that could potentially affect the studied parameters must not be administered. The patient needed to take such drug is excluded from the study.

8. STUDY PROCEDURES

Study Evaluation Schedule
The study will include Screening visit, Visit 1 (baseline), Visit 2 (3 months after the treatment initiation), and Visit 3 - Final visit (6 months after the treatment initiation)

Table 2. Study Evaluation Schedule

Assessment	Screening	0 Visit 1 (Baseline)	3 months of the treatment Visit 2	6 months of the treatment Visit 3 (Final)
Informed Consent	X			
Demographics	X			
Medical History	X			
General Physical Exam (including weight, BMI, waist circumference)	X	X	X	X
Complete blood count	X			X
LFT: ALT, AST, GGTP	X		X	X
Lipid profile: TC, LDL, HDL, TG	X			X

[1] "The use of the WHO-UMC system for standardised case causality assessment" URL: https://www.who.int/publications/m/item/WHO-causality-assessment (date accessed 15.07.2017)

Other biochemical parameters: creatinine, fasting glucose	X			X
FLI	X			X
NFS	X			X
FIB-4	X			X
CIMT	X			X
ASCVD, 10-year risk, lifetime risk	X			X
Medication log		X	X	X
Concomitant medication log		X	X	X
Adverse events form		X	X	X

The body weight, BMI, WC, and LFT will be evaluated at baseline (initial assessment), 3 months and 6 months (final assessment) of the treatment. The lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT will be assessed at baseline and the end of treatment (Table 2, Figure)

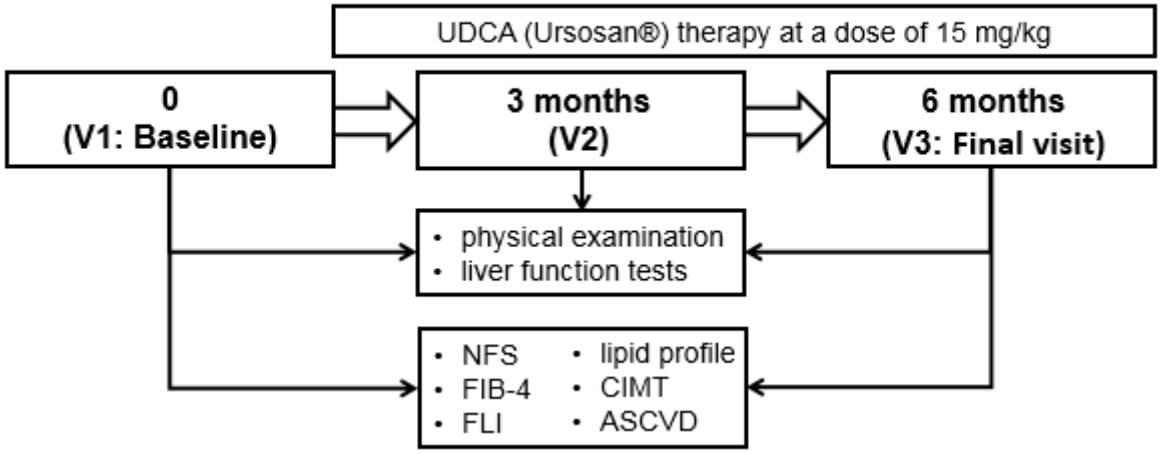

Figure. Scheme of the study. V: visit, UDCA: ursodeoxycholic acid; NFS: nonalcoholic fatty liver disease fibrosis score; FIB-4: liver fibrosis index; FLI: fatty liver index; CIMT: carotid intima-media thickness: ASCVD: Atherosclerotic Cardiovascular Disease

9. SAFETY ASSESSMENT

Definitions

Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal;

- is associated with a serious adverse event;
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests;
- is considered by the investigator to be of clinical significance.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal;
- life-threatening;
- requires or prolongs hospital stay;
- results in persistent or significant disability or incapacity;
- a congenital anomaly or birth defect;
- an important medical event.

All adverse events that do not meet any of the criteria for serious should be regarded as non serious adverse events.

Adverse Event Reporting Period

For this study, the study treatment follow-up is defined as 7 days following the last administration of study treatment.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- the laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- the abnormality suggests a disease and/or organ toxicity
- the abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Most common adverse reactions reported with the use of ursodiol during worldwide postmarketing and clinical experience (≥1%) and can be revealed by physical examination on follow-up are, in alphabetical order: abdominal discomfort, abdominal pain, alopecia, diarrhea, nausea, pruritus, and rash [27].

Recording of Adverse Events

At each contact with the patient, the investigative team will seek information on adverse events by specific questioning and, as appropriate, by examination. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

10. INTERVENTION DISCONTINUATION

A patient may be discontinued from the study at any time if the patient or the Investigator feels that it is not in the patient's best interest to continue.
The following is a list of possible reasons for study treatment discontinuation:

- a patient's decision to discontinue participation in the study at any stage,
- acute hepatocellular or cholestatic injury that occurred during the study: increased ALT, AST, GGT, or alkaline phosphatase levels by two or more times; and
- the need to take other drugs that potentially affect the studied parameters, arising during the study
- patient withdrawal of consent
- patient is not compliant with study procedures
- Adverse Event that in the opinion of the Investigator would be in the best interest of the patient to discontinue study participation
- protocol violation requiring discontinuation

All patients are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Investigator to provide a reason for patient withdrawals. If a patient is withdrawn from treatment due to an Adverse Event, the patient will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. The Investigator must make every effort to contact patients who are lost to follow-up. Attempts to contact such patients must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

11. STATISTICAL AND ANALYTICAL CONSIDERATIONS

We expect that a 6-month UDCA therapy will improve LFTs, lipids and reduce FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT both in men and women.
Each patient will be assessed according to the following parameters: weight, height, body mass index, waist circumference (WC), smoking, alcohol consumption (AUDIT), metabolic syndrome criteria according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [26], complete blood count and l*iver* function *tests*, and lipid profile.
FLI index will be calculated using the formula FLI. The noninvasive liver fibrosis assessment will be carried out using the NFS score. Another method for liver fibrosis assessment will be provided is the calculation of the fibrosis index FIB-4. The risk of developing complications from the cardiovascular system will be assessed using the ASCVD 2013 calculator. The CIMT will be assessed with a standard method in accordance with the European Society of Cardiology recommendations.
The studied parameters will be investigated three times: initially and at 3 and 6 months after the start of the study. All data will be entered into the patient's Case Report Form.
As the primary study endpoint, we will assess the change in ALT, AST, GGT levels, lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT before and after 6 months of UDCA therapy and compare the results obtained and men and women.
As the secondary study endpoint, we will compare the change in ALT, AST, GGT levels, lipid profile, FLI, NFS, FIB-4, 10-year and lifetime ASCVD risk, and CIMT before and after 6 months of UDCA therapy in subgroups with and without weight loss > 5% from baseline.

Data will be presented as absolute and relative indicators, mean ± standard deviation for normally distributed values and for the rest of the values, as median (Me) and the 25th and 75th percentiles - interquartile range (IQR). To test statistical hypotheses, the Wilcoxon test, paired *t*-test, Fisher's exact test, and Pearson's chi-squared test will be used. The critical value of the statistical significance level, when testing the null hypotheses, will be qual to 0.05. Statistical analysis will be performed using SPSS Statistics v.23.0 (IBM Corporation, USA).

12. DATA COLLECTION

All personal data will be used in accordance with the legislation of the participating countries.

Confidentiality
Information about study patients will be kept confidential and managed according to the requirements of the Federal Law of 27 July 2006 N 152-FZ on Personal Data which is similar to the Health Insurance Portability and Accountability Act of 1996.

Those regulations require a signed patient authorization informing the patient of the following:
- what protected health information will be collected from patients in this study;
- who will have access to that information and why;
- who will use or disclose that information;
- the rights of a research patient to revoke their authorization for use of their protected health information.

In the event that a patient revokes authorization to collect or use protected health information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled study period.

Data will be collected at the following points: immediately prior to treatment initiation, 3 and 6 months post-treatment. Data will be collected using the Case Report Forms and entered into a database created on the basis of Excel spreadsheets (Microsoft, USA) by two investigators independently. In case of data discrepancies, the indicators will be manually checked from the Case Report Forms.
Baseline data will be collected in primary health care settings prior to treatment (Visit 1), follow up data will be also collected in primary health care settings 3 (Visit 2) and 6 (Visit 3: Final visit) months after treatment.

Case Report Forms
The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.
If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

Records Retention
The investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or

contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

12. PARTICIPANTS RIGHTS

All consents will be stored in well-marked binders in locked file cabinets located in private offices. Databases with identifying information will be secure as they will be password protected and encrypted. Staff will be trained in confidentiality issues.
All data and study forms will be in secured locations (locked room or cabinet) and access is limited to study personnel. Patient names are not used; instead a name code is assigned upon enrollment. Release of data to persons or organizations outside study personnel will require written consent of the patient.

14. PUBLICATION

Results will be submitted for publication or data disseminated via meeting abstracts after approval by the Principal investigator and all authors/involved investigators.

15. REFERENCES

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16. ADDITIONAL DOCUMENTS

1. Informed consent form
2. Case report form
3. Medication log
4. Concomitant medication log
5. Adverse event (ae) report form

CASE REPORT FORM

For Clinical Research Protocol

Ursodeoxycholic acid as a meanS of Preventing athErosclerosis, steatosis and liver fibrosis in patients with nonalcoHolic fatty liver disease – USPEH

Protocol Number: RSLS-CT-2017-15

Individual Number: 327-93

Moscow

All-Russian Public Organization «Russian Scientific Liver Society» (RSLS)
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INCLUSION CRITERIA

Subjects who meet the following criteria may be included in the study. Did the subject meet the following criteria requirements for inclusion? (✓Yes or No)		**Yes**	**No**
01	The subject is male or female over 18 years of age.		
02	The subject has proven nonalcoholic fatty liver disease (NAFLD) case based on US abdominal data.		
03	The subject has fatty liver index (FLI) index value > 60.		
04	The physician decides to prescribe ursodeoxycholic acid (UDCA) regardless of the patient's inclusion in the study.		
05	The subject is able and willing to provide written informed consent.		
06	The subject agrees to comply with the requirements of the protocol and complete study measures.		

NON-INCLUSION CRITERIA

The following will non include potential subjects in the study. Does the subject have any of the following? (✓Yes or No)		**Yes**	**No**
01	The subject is a female who is pregnant or lactating.		
02	The subject has hepatic decompensation. Any of these: serum albumin ≤ 35 g/L, international normalized ratio ≥ 1.2, platelets < 150×10^9/L.		
03	The subject has UDCA allergy in past medical history.		
04	The subject has presence of atherosclerosis complications		
05	The subject use of statins.		
06	The subject use of other drugs that potentially affect the studied parameters.		
07	The subject use of medications in past medical history associated with secondary hepatic steatosis development (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproic acid, and antiretroviral drugs);		
08	The subject has type 1 diabetes mellitus; parenteral nutrition; fasting; and presence of a secondary etiology of liver disease (viral, metabolic, autoimmune, cholestatic, or drug etiology).		

09	The subject has unhealthy alcohol use (40 g ethanol per day for men and 20 g ethanol per day for women)		
10	The subject's score on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire is > 8 for both men and women		

EXCLUSION CRITERIA

The following will exclude potential subjects from the study. Does the subject have any of the following? (✓Yes or No)		**Yes**	**No**
01	A patient's decision to discontinue participation in the study at any stage.		
02	The subject need to take other drugs that potentially affect the studied parameters, arising during the study		
03	The subject has acute hepatocellular or cholestatic injury that occurred during the study. Any of these: increased ALT, AST, GGT, or alkaline phosphatase levels by two or more times after 3 months of the treatment		

INFORMATION SESSION

Date of Information Session	Did the subject attend the Information Session?	Comments
/ / DD/MM/YYYY	☐ Yes ☐ No (explain, if No)	

SUBJECT ELIGIBILITY

Date the subject signed the informed consent form:	/ / DD/MM/YYYY
Did the subject meet all of the inclusion/ don't meet non-inclusion criteria?	☐ Yes ☐ No

If the subject did not meet all of the inclusion or meet some non-inclusion criteria, provide criterion number and explanation below.

Category	Inclusion/non-inclusion criteria No.	Explanation	Exemption Granted?	If Yes, Date Granted
☐ Inclusion ☐ non-inclusion			☐ Yes ☐ No	/ / DD/MM/YYYY
☐ Inclusion ☐ non-inclusion			☐ Yes ☐ No	/ / DD/MM/YYYY
☐ Inclusion ☐ non-inclusion			☐ Yes ☐ No	/ / DD/MM/YYYY

SCREENING

DEMOGRAPHICS

Date	**Date of Birth**	**Sex**
/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ Male ☐ Female

BODY MEASUREMENTS

Were body measurements collected?		**Date**
☐ Yes ☐ No		/ / DD/MM/YYYY
Parameter	**Unit**	**Result**
Height	m	
Weight	kg	
Waist circumference	cm	
Obesity	0 – 4 stage	

VITAL SIGNS

Were vital signs collected?	**Date**	**Was Subject seated for 5 minutes?**
☐ Yes ☐ No	/ / DD/MM/YYYY	☐ Yes ☐ No
Parameter	**Unit**	**Result**
Glasgow coma scale score	score	
Systolic blood pressure	mmHg	
Diastolic blood pressure	mmHg	
Heart rate	beats/minute	
Respiratory rate	breaths/minute	
Body temperature	ºC	

LABORATORY EVALUATIONS

Were the scheduled laboratory samples obtained?			**Date**
☐ Yes ☐ No			/ / DD/MM/YYYY
Evaluation: Blood Tests			
Test / Parameter	**Unit**	**Result**	**Comment**
COMPLETE BLOOD COUNT			
Red blood cell (RBC)	trillion cells/L		
Hemoglobin	grams/L		
Hematocrit	percent		
White blood cell count (WBC)	billion cells/L		
Platelet count	billion/L		
LIVER FUNCTION TESTS			
Alanine transaminase (ALT)	U/L		
Aspartate transaminase (AST)	U/L		
Alkaline phosphatase (ALP)	U/L		
Gamma-glutamyltransferase (GGT)	U/L		
Albumin	g/L		
total protein	g/L		
Bilirubin total	µmol/L		
Bilirubin direct	µmol/L		
International normalized ratio			
OTHER BIOCHEMICAL PARAMETERS			

Creatinine	µmol/L		
Fasting glucose	mmol/L		
LIPID PROFILE			
Total cholesterol (TC)	mmol/L		
High-density lipoprotein (HDL)	mmol/L		
Low-density lipoprotein (LDL)	mmol/L		
Triglycerides (TG)	mmol/L		

URINE PREGNANCY TEST

Result		
☐ Positive	☐ Negative	☐ N/A, Male or Woman of Non-childbearing Potential

12-LEAD ELECTROCARDIOGRAM REPORT

Was ECG performed?	**Was subject supine at Least 5 Minutes?**	**Date** _____/__/_____ DD/MM/YYYY
☐ Yes ☐ No	☐ Yes ☐ No	
ECG Interpretation: ☐ Normal ☐ Abnormal		
comments regarding abnormal findings:		

MEDICAL HISTORY

Does the subject have any relevant medical history?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Type 1 diabetes mellitus	☐ Yes ☐ No		
Parenteral nutrition	☐ Yes ☐ No		
Fasting	☐ Yes ☐ No		
Presence of a secondary etiology of liver disease. Any of etiology: viral, metabolic, autoimmune, cholestatic, or drug.	☐ Yes ☐ No		
Coronary artery disease	☐ Yes ☐ No		
Carotid artery disease	☐ Yes ☐ No		
Peripheral artery disease	☐ Yes ☐ No		
Aneurysms	☐ Yes ☐ No		
Chronic kidney disease	☐ Yes ☐ No		
Other diagnosis	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
4.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
5.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
6.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

Consider the following systems when performing the assessment:

– Allergies – Skin – Musculoskeletal	– Respiratory – Cardiovascular – Gastrointestinal	– Genitourinary – Hematologic – Endocrine – Neurological

DRUG HISTORY

Does the subject take any medications?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
The subject has UDCA allergy	☐ Yes ☐ No		
Medications in past medical history or ongoing:			
amiodarone	☐ Yes ☐ No		
methotrexate	☐ Yes ☐ No		
tamoxifen	☐ Yes ☐ No		
glucocorticoids	☐ Yes ☐ No		
valproic acid	☐ Yes ☐ No		
antiretroviral drugs	☐ Yes ☐ No		
statins	☐ Yes ☐ No		
Other medications that potentially affect the studied parameters	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
4.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
5.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

SMOKING HISTORY

Was Smoking History collected? ☐ Yes ☐ No	**Date** / / DD/MM/YYYY	
Parameter	**Result**	**Comments**
Age subject began smoking daily		
Average number of cigarettes smoked per day over the past year		

PHYSICAL EXAMINATIONS

Does the subject have any abnormal findings? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY

Findings
1.
2.
3.
4.
5.
6.
7.

Consider the following systems when performing the assessment:

– General Appearance – Skin – Extremities	– Respiratory – Cardiovascular – Gastrointestinal	– Genitourinary – Hematologic – Endocrine – Neurological

CURRENT STATUS OF DRINKING BEHAVIORS

Was drinking behaviors status collected? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY

Parameter	**Unit**	**Result**	**Comments**
Amount of ethanol per day	g		
Subject's score on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire	score		

SIGNS OF DECOMPENSATED LIVER DISEASE

Were all these parameters collected? ☐ Yes ☐ No	**Date** ____/____/____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	
1. Platelets	$\times 10^9$/L		< 150×10^9/L ☐ Yes ☐ No
2. Serum albumin	g/L		≤ 35 g/L ☐ Yes ☐ No
3. International normalized ratio			≥ 1.2 ☐ Yes ☐ No

ULTRASOUND OF ABDOMEN

Was ultrasound of abdomen performed? ☐ Yes ☐ No	**Date** ____/____/____ DD/MM/YYYY	
Parameter	**Result**	**Comments**
1. Renal cortex appearing relatively hypoechoic compared to the liver parenchyma	☐ Yes ☐ No	
2. Absence of the normal echogenic walls of the portal veins and hepatic veins	☐ Yes ☐ No	
3. Poor visualization of deep portions of the liver	☐ Yes ☐ No	
4. Poor visualization of the diaphragm	☐ Yes ☐ No	
5. Signs of portal hypertension	☐ Yes ☐ No	
6. Signs of cholestasis	☐ Yes ☐ No	

FATTY LIVER INDEX

Were all these parameters collected? ☐ Yes ☐ No	**Date** ____/____/____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
1. Body mass index	Kg/m^2		
2. Waist circumference	cm		
3. Triglycerides	mmol/l		
4. Gamma-glutamyl transpeptidase	U/l (reference range 15-41)		
FLI			**FLI > 60** ☐ Yes ☐ No

NFS: NON-ALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE

Were all these parameters collected? ☐ Yes ☐ No	**Date** ____/____/____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
BMI	kg/m^2		
Impaired fasting glucose / diabetes	Yes / no		
Platelet count	billion/L		
Albumin	g/L		
AST	U/l		
ALT	U/l		
NFS			**NFS > 0.675** ☐ Yes ☐ No

FIBROSIS-4 (FIB-4) INDEX FOR LIVER FIBROSIS

Were all these parameters collected? ☐ Yes ☐ No	**Date** / / DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
Platelet count	billion/L		
AST	U/l		
ALT	U/l		
FIB-4			**FIB-4 > 3.25** ☐ Yes ☐ No

METABOLIC SYNDROME, NCEP ATP III

Date			/ / DD/MM/YYYY
≥ 3 criteria			☐ Yes ☐ No
Parameter	**Unit**	**Result**	**Criteria**
Waist circumference	cm		☐ Yes ☐ No
Fasting glucose	mmol/L		☐ Yes ☐ No
Triglycerides (TG)	mmol/L		☐ Yes ☐ No
High-density lipoprotein (HDL)	mmol/L		☐ Yes ☐ No
Blood pressure Systolic / Diastolic	mmHg		☐ Yes ☐ No

SONOGRAPHIC ASSESSMENT OF COMPLEX INTIMA-MEDIA THICKNESS

Was the CIMT measured from both sides?? ☐ Yes ☐ No	**Date** / / DD/MM/YYYY		
Side	**Unit**	**Result**	**Comments**
Right	mm		
Left	mm		

CARDIOVASCULAR DISEASE RISK ASSESSMENT BY ASCVD 2013 CALCULATOR

Were all these parameters collected? ☐ Yes ☐ No	**Date** / / DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
Sex	Male / women		
Race	White African Other		
Smoker	Yes / no		
Diabetes	Yes / no		
Total cholesterol (TC)	mmol/L		
High-density lipoprotein (HDL)	mmol/L		
Systolic blood pressure	mmHg		
Treatment for hypertension	Yes / no		
ASCVD 10-year risk			
ASCVD lifetime risk			

VISIT 1 (BASELINE, WEEK 0)

CURRENT STATUS OF DRINKING BEHAVIORS

Was drinking behaviors status collected? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Amount of ethanol per day	g		
Subject's score on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire	score		

BODY MEASUREMENTS

Were body measurements collected?		**Date**
☐ Yes ☐ No		_____/__/_____ DD/MM/YYYY
Parameter	**Unit**	**Result**
Height	m	
Weight	kg	
Waist circumference	cm	
Obesity	0 – 4 stage	

VITAL SIGNS

Were vital signs collected?	**Date**	**Was Subject seated for 5 minutes?**
☐ Yes ☐ No	/ / DD/MM/YYYY	☐ Yes ☐ No
Parameter	**Unit**	**Result**
Glasgow coma scale score	score	
Systolic blood pressure	mmHg	
Diastolic blood pressure	mmHg	
Heart rate	beats/minute	
Respiratory rate	breaths/minute	
Body temperature	ºC	

VISIT 2 (3 MONTHS OF THE TREATMENT)

CURRENT STATUS OF DRINKING BEHAVIORS

Was drinking behaviors status collected? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Amount of ethanol per day	g		
Subject's score on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire	score		

BODY MEASUREMENTS

Were body measurements collected?		**Date**
☐ Yes ☐ No		_____/__/_____ DD/MM/YYYY
Parameter	**Unit**	**Result**
Height	m	
Weight	kg	
Waist circumference	cm	
Obesity	0 – 4 stage	

VITAL SIGNS

Were vital signs collected?	**Date**	**Was Subject seated for 5 minutes?**
☐ Yes ☐ No	/ / DD/MM/YYYY	☐ Yes ☐ No
Parameter	**Unit**	**Result**
Glasgow coma scale score	score	
Systolic blood pressure	mmHg	
Diastolic blood pressure	mmHg	
Heart rate	beats/minute	
Respiratory rate	breaths/minute	
Body temperature	ºC	

MEDICATION LOG: SPECIAL FORM

Has the subject completed a special form?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Medications that potentially affect the studied parameters	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
4.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
5.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

CONCOMITANT MEDICATIONS: SPECIAL FORM

Has the subject completed a special form?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Medications that potentially affect the studied parameters	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

ADVERSE EFFECT: SPECIAL FORM

Have there been any serious side effects?	**Date**
☐ Yes ☐ No	/ / DD/MM/YYYY
In the event of the development of AE, was a special form filled in?	
☐ Yes ☐ No	/ / DD/MM/YYYY

EXCLUSION CRITERIA

The following will exclude potential subjects from the study. Does the subject have any of the following? (✓Yes or No)		**Yes**	**No**
01	A patient's decision to discontinue participation in the study at any stage.		
02	The subject need to take other drugs that potentially affect the studied parameters, arising during the study		
03	The subject has acute hepatocellular or cholestatic injury that occurred during the study. Any of these: increased ALT, AST, GGT, or alkaline phosphatase levels by two or more times after 3 months of the treatment		
	DATE OF EXCLUSION	/ / DD/MM/YYYY	

VISIT 3 (6 MONTHS OF THE TREATMENT, FINAL VISIT)

CURRENT STATUS OF DRINKING BEHAVIORS

Was drinking behaviors status collected? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Amount of ethanol per day	g		
Subject's score on the AUDIT (Alcohol Use Disorders Identification Test) questionnaire	score		

BODY MEASUREMENTS

Were body measurements collected?		**Date**
☐ Yes ☐ No		_____/__/_____ DD/MM/YYYY
Parameter	**Unit**	**Result**
Height	m	
Weight	kg	
Waist circumference	cm	
Obesity	0 – 4 stage	

VITAL SIGNS

Were vital signs collected?	**Date**	**Was Subject seated for 5 minutes?**
☐ Yes ☐ No	/ / DD/MM/YYYY	☐ Yes ☐ No
Parameter	**Unit**	**Result**
Glasgow coma scale score	score	
Systolic blood pressure	mmHg	
Diastolic blood pressure	mmHg	
Heart rate	beats/minute	
Respiratory rate	breaths/minute	
Body temperature	ºC	

LABORATORY EVALUATIONS

Were the scheduled laboratory samples obtained?			**Date**
☐ Yes ☐ No			/ / DD/MM/YYYY
Evaluation: Blood Tests			
Test / Parameter	**Unit**	**Result**	**Comment**
COMPLETE BLOOD COUNT			
Red blood cell (RBC)	trillion cells/L		
Hemoglobin	grams/L		
Hematocrit	percent		
White blood cell count (WBC)	billion cells/L		
Platelet count	billion/L		

LIVER FUNCTION TESTS			
Alanine transaminase (ALT)	U/L		
Aspartate transaminase (AST)	U/L		
Alkaline phosphatase (ALP)	U/L		
Gamma-glutamyltransferase (GGT)	U/L		
Albumin	g/L		
total protein	g/L		
Bilirubin total	µmol/L		
Bilirubin direct	µmol/L		
International normalized ratio			
OTHER BIOCHEMICAL PARAMETERS			
Creatinine	µmol/L		
Fasting glucose	mmol/L		
LIPID PROFILE			
Total cholesterol (TC)	mmol/L		
High-density lipoprotein (HDL)	mmol/L		
Low-density lipoprotein (LDL)	mmol/L		
Triglycerides (TG)	mmol/L		

MEDICAL HISTORY

Does the subject have any relevant medical history?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Type 1 diabetes mellitus	☐ Yes ☐ No		
Parenteral nutrition	☐ Yes ☐ No		
Fasting	☐ Yes ☐ No		
Presence of a secondary etiology of liver disease. Any of etiology: viral, metabolic, autoimmune, cholestatic, or drug.	☐ Yes ☐ No		
Coronary artery disease	☐ Yes ☐ No		
Carotid artery disease	☐ Yes ☐ No		
Peripheral artery disease	☐ Yes ☐ No		
Aneurysms	☐ Yes ☐ No		
Chronic kidney disease	☐ Yes ☐ No		
Other diagnosis	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
4.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
5.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
6.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

Consider the following systems when performing the assessment:

– Allergies – Skin – Musculoskeletal	– Respiratory – Cardiovascular – Gastrointestinal	– Genitourinary – Hematologic – Endocrine – Neurological

PHYSICAL EXAMINATIONS

Does the subject have any abnormal findings? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY
Findings	
1.	
2.	
3.	
4.	
5.	
6.	
7.	

Consider the following systems when performing the assessment:

– General Appearance – Skin – Extremities	– Respiratory – Cardiovascular – Gastrointestinal	– Genitourinary – Hematologic – Endocrine – Neurological

FATTY LIVER INDEX

Were all these parameters collected? ☐ Yes ☐ No	**Date** _____/__/_____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
1. Body mass index	Kg/m^2		
2. Waist circumference	cm		
3. Triglycerides	mmol/l		
4. Gamma-glutamyl transpeptidase	U/l (reference range 15-41)		
FLI			**FLI > 60** ☐ Yes ☐ No

NFS: NON-ALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE

Were all these parameters collected? ☐ Yes ☐ No	Date / / DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
BMI	kg/m^2		
Impaired fasting glucose / diabetes	Yes / no		
Platelet count	billion/L		
Albumin	g/L		
AST	U/l		
ALT	U/l		
NFS			**NFS > 0.675** ☐ Yes ☐ No

FIBROSIS-4 (FIB-4) INDEX FOR LIVER FIBROSIS

Were all these parameters collected? ☐ Yes ☐ No	Date / / DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
Platelet count	billion/L		
AST	U/l		
ALT	U/l		
FIB-4			**FIB-4 > 3.25** ☐ Yes ☐ No

METABOLIC SYNDROME, NCEP ATP III

Date			/ / DD/MM/YYYY
≥ 3 criteria			☐ Yes ☐ No
Parameter	**Unit**	**Result**	**Criteria**
Waist circumference	cm		☐ Yes ☐ No
Fasting glucose	mmol/L		☐ Yes ☐ No
Triglycerides (TG)	mmol/L		☐ Yes ☐ No
High-density lipoprotein (HDL)	mmol/L		☐ Yes ☐ No
Blood pressure Systolic / Diastolic	mmHg		☐ Yes ☐ No

SONOGRAPHIC ASSESSMENT OF COMPLEX INTIMA-MEDIA THICKNESS

Was the CIMT measured from both sides?? ☐ Yes ☐ No	**Date** / / DD/MM/YYYY		
Side	**Unit**	**Result**	**Comments**
Right	mm		
Left	mm		

CARDIOVASCULAR DISEASE RISK ASSESSMENT BY ASCVD 2013 CALCULATOR

Were all these parameters collected? ☐ Yes ☐ No	**Date** ____/____/____ DD/MM/YYYY		
Parameter	**Unit**	**Result**	**Comments**
Age	years		
Sex	Male / women		
Race	White African Other		
Smoker	Yes / no		
Diabetes	Yes / no		
Total cholesterol (TC)	mmol/L		
High-density lipoprotein (HDL)	mmol/L		
Systolic blood pressure	mmHg		
Treatment for hypertension	Yes / no		
ASCVD 10-year risk			
ASCVD lifetime risk			

MEDICATION LOG: SPECIAL FORM

Has the subject completed a special form?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Medications that potentially affect the studied parameters	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

CONCOMITANT MEDICATIONS: SPECIAL FORM

Has the subject completed a special form?	**Date**		
☐ Yes ☐ No	/ / DD/MM/YYYY		
Medications that potentially affect the studied parameters	**Date of Onset**	**Date of Resolution**	
1.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
2.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing
3.	/ / DD/MM/YYYY	/ / DD/MM/YYYY	☐ ongoing

ADVERSE EFFECT: SPECIAL FORM

Have there been any serious side effects?	**Date**
☐ Yes ☐ No	/ / DD/MM/YYYY
In the event of the development of AE, was a special form filled in?	
☐ Yes ☐ No	/ / DD/MM/YYYY

INFORMED CONSENT

Study title	**U**rsodeoxycholic acid as a mean**S** of **P**reventing ath**E**rosclerosis, steatosis, and liver fibrosis in patients with nonalco**H**olic fatty liver disease		
Protocol No.	RSLS-CT-2017-15	Ind No.	327-93
Informed consent for	participant patients		
Version	1.1.	Date	19.09.2017
Name of research organization	All-Russian Public Organization «Russian Scientific Liver Society» (RSLS) Akademicheskaya str., 4 B, office 1a, 127299, Moscow, Russia E-mail: inf@rsls.ru www.rsls.ru		
Principal investigator name and contact information	Marina V. Maevskaya, Prof, M.D. Vice president All-Russian Public Organization «Russian Scientific Liver Society» (RSLS) Department of Internal Medicine Propaedeutics, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia e-mail: liver.orc@mail.ru tel. +7 (903) 779 44 03		
Name of sponsor	The grant is provided by JSC “PRO.MED.CS Marketing”		

You will be given a copy of the full Informed Consent form for your records.

Introduction

This research is on nonalcoholic fatty liver disease (NAFLD) therapy. I will give you information on this study and invite you to be part of this research. You do not have to decide today if you will participate. You may speak with anyone you wish before you decide if you want to participate. As we go through this information sheet, if there are words or terms you do not understand, please stop me and I will explain them to you. If you think of questions later, you can also ask them of me or anyone on the study.

Purpose of the research

NAFLD is currently the leading cause of liver disease and liver transplantation in developed countries; the number of people with this pathology is steadily growing. NAFLD is often associated with cardiovascular diseases (CVDs), which have become the main cause of decreased life expectancy in patients. There is currently no approved standard therapy for NAFLD. Among the treatments, ursodeoxycholic acid (UDCA) has shown the anti-inflammatory, antiapoptotic, antifibrotic and cytoprotective effects.

The purpose of this study is to evaluate the effects of UDCA on liver steatosis and fibrosis, atherogenesis, and CVD risk in NAFLD patients.

Type of research intervention

You will receive daily UDCA (Ursosan®) therapy at a dose of 15 mg/kg body weight for 6 months. In addition, you will be given standard recommendations to modify lifestyle and diet: strength or aerobic exercise for at least 150 minutes per week, Mediterranean diet, and consumption of no more than 1500 kcal/day.

In this study, you will have four visits: a recruitment visit, baseline visit, and two follow-up visits (one at 3 months and another final visit at 6 months).

Participant selection

You are invited to participate in this study because you are supposed to meet inclusion and exclusion criteria.

Voluntary participation

Your participation in this study is completely voluntary: If you decide not to participate, you will receive all the medical care you may need and your relationship with the medical team that treats you will not be affected. In the case that, during the study, any problem or circumstance relevant to your health care is detected, you will be informed about it and you will be advised on the most appropriate measures for its treatment and control. We do not expect there to be any additional risk from your participation in this study. You may change your mind later and stop participating even if you agreed earlier

Description of the process

During the research you make three visits to the clinic.

- In the first (Screening) visit you will be asked about complaints and symptoms, smoking, and alcohol consumption and examined by a doctor. We will measure your weight, height, body mass index, and waist circumference. A small amount of blood will be taken from your arm with a syringe. This blood will be tested for complete blood count, liver function tests, and lipid profile. B-mode ultrasonography will also be used to assess the carotid intima-media thickness.
- If you meet all inclusion and exclusion criteria, you will be administered the test drug (baseline visit).
- At the next visit, which will be three months later, you will again be asked some questions about your health, examined, and blood test will be taken.
- After next three months (Final visit), you will come back to the clinic for examination, blood test, and ultrasonography.

Duration

The research takes place over 6 months in total. During that time, it will be necessary for you to come to the primary health care setting 4 times: at screening visit, baseline visit, follow-up visit, and final visit. At the end of six months, the research will be finished.

Side effects

This drug can have some unwanted effects. Mostly, it can cause abdominal discomfort, abdominal pain, alopecia, diarrhea, nausea, pruritus, and rash.
It is possible that it may cause some problems that we are not aware of. However, we will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of the drug. If this is necessary, we will discuss it together with you and you will always be consulted before we move to the next step.

Risks

During the study, any problem or circumstance relevant to your health care is detected, you will be informed about it and you will be advised on the most appropriate measures for its treatment and control. We do not expect there to be any additional risk from your participation in this study.

Benefits

According to other studies, we expect the improvement in your liver function tests and lipid profile. We also expect a weight loss of 5-10% of your total weight. As a result, we suggest reducing the liver steatosis. In any case, the data collected in it may lead to a better understanding of the treatment of NAFLD and your participation is likely to help us find the answer to the research question.

Reimbursements

You will not be given any money or gifts to take part in this research.

Confidentiality

Your consent is requested for the use of your data for the development of this project. Both personal data (age, sex, race), as well as health data, will be collected using a coding procedure. Only the researcher and / or responsible doctor may relate these data to you, being responsible for keeping the consent document. The information will be processed during the analysis of the results obtained and will appear in the final reports. It will be never possible to identify you, guaranteeing the confidentiality of the information obtained, in compliance with current legislation.

Results

The knowledge that we get from doing this research will be shared with you through emails before it is made widely available to the public. Confidential information will not be shared. After these emails, we will publish the results in order that other interested people may learn from our research.

Right to refuse or withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way

Alternative to participation

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the clinic

Who to contact?

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Role	Name, surname	Title	Affiliation	Contact information
Principal investigator	Marina V Maevskaya	Prof, M.D.	Department of Internal Medicine Propaedeutics, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia	e-mail: liver.orc@mail.ru tel. +7 (903) 779 44 03
Investigator	Evgeny V Chesnokov	Prof, M.D.	Tyumen State Medical University, Tyumen, Russia	e-mail: e.v.chesnokov@mail.ru tel. +7 (909) 184 61 11
Investigator	Irina Yu Pirogova	Prof, M.D.	Head at the CMC "Lotus" Center for Gastroenterology and Hepatology, Chelyabinsk, Russia	e-mail: irina_pirogova@inbox.ru tel. +7 (919) 339-56-61
Investigator	Alexandr V Nersesov	Prof, M.D.	Head of the Gastroenterology Department S. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan	e-mail: alexander.nersesov@gmail.com tel. +7 (701) 799 82 12
Investigator	Akzhan Konysbekova	Prof, M.D.	Scientific Research Institute of Cardiology and Internal Diseases, Almaty, Kazakhstan	e-mail: u_akzhan@mail.ru tel. +7 (701) 734-55-31
Investigator	Aigul M Raissova	Prof, M.D.	Scientific and Research Institute of Cardiology and Internal Diseases. Almaty, Kazakhstan	e-mail: ram-79@mail.ru tel. +7 (777) 217-54-10
Investigator	Elena B Zueva	Prof, M.D.	Tashkent Medical Academy, Tashkent, Uzbekistan	e-mail: zueva345@mail.ru tel. + (998) 90 925 07 14

Statement of consent

I have read the study information, or it has been read to me. The risks of the procedure have been explained to me and are also identified in this documentation. Any questions I have about the intervention, its benefits, and its risks have been explained to my satisfaction. I give my informed consent to voluntarily participate in this research.

Print name of participant

Signature of participant Date

Statement by witness

I have witnessed the reading of the consent form to this possible participant, and they have had the opportunity to ask questions. I confirm that this individual has given their consent freely.

Print name of witness

Signature of Witness Date

Statement by the researcher taking consent

I have accurately read the information sheet to the potential participant and have ensured, to the best of my ability, that they understand the research study. I confirm that the participant was given adequate opportunity to ask questions about the study and I provided them answers to the best of my ability. I conform that this individual has not been coerced into providing consent, and their consent has been given willingly and freely.

Print name of researcher

Signature of researcher Date

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “____” “____” “____” Surname First name Patronymic

ADVERSE EVENT (AE) REPORT FORM

Study title	Ursodeoxycholic acid as a meanS of Preventing athErosclerosis, steatosis, and liver fibrosis in patients with nonalcoHolic fatty liver disease – USPEH				
Protocol no.	RSLS-CT-2017-15	Ind No.	327-93	Date	____/____/____ DD/MM/YYYY

Adverse Event	Start date dd-mm-yyyy	Stop date dd-mm-yyyy	Severity	Relationship	Action taken	Outcome of AE	Expected (y/n)	*SAE (y/n)

Participant had no adverse events (to be completed at the end of study):

☐ NONE

*Fill out SAE form if Yes is answered.

Print Name of Principal Investigator **Signature of Principal investigator** **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** "_____" "_____" "_____" Surname First name Patronymic

ADVERSE EVENT (AE) REPORT FORM KEY

Code	Severity	Relationship	Action taken	Outcome of AE
00		Not related	None	
01	Mild	Unlikely related	Does modification	Resolved
02	Moderate	Possibly related	Medical intervention	Recovered with minor sequelae
03	Severe	Probably related	Hospitalization	Recovered with major sequelae
04	Life-threatening	Definitely related	Intervention discontinued	Ongoing treatment
05			Other, describe	Condition worsening
06				Death
07				Unknown

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “____” “____” “____” Surname First name Patronymic

MEDICATION LOG
UDCA (URSOSAN®) therapy at a dose of 15 mg/kg orally divided into three doses

Weght, kg		**Individual dose**	

1st month of treatment

Date dd/mm/yy	**Medication**	**A.M. (✓Yes or No) Number of capsules ☐**	**Noon (✓Yes or No) Number of capsules ☐**	**P.M. (✓Yes or No) Number of capsules ☐**
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			
	UDCA (Ursosan®)			

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “_____” “_____” “_____” Surname First name Patronymic

2nd month of treatment

Date dd/mm/yy	Medication	A.M. (✓Yes or No) Number of capsules ☐	Noon (✓Yes or No) Number of capsules ☐	P.M. (✓Yes or No) Number of capsules ☐
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			
	UDCA (Ursosan®)			

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “_____” “_____” “_____” Surname First name Patronymic

3rd month of treatment

Date dd/mm/yy	Medication	A.M. (✓Yes or No) Number of capsules ☐	Noon (✓Yes or No) Number of capsules ☐	P.M. (✓Yes or No) Number of capsules ☐
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	Investigator:	Subject Number:
Individual Number: 327-93	Country: City:	Subject Initials: “_____” “_____” “_____” Surname First name Patronymic

Weght, kg		Individual dose	

4th month of treatment

Date dd/mm/yy	Medication	A.M. (✓Yes or No) Number of capsules ☐	Noon (✓Yes or No) Number of capsules ☐	P.M. (✓Yes or No) Number of capsules ☐
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “____” “____” “____” Surname First name Patronymic

5th month of treatment

Date dd/mm/yy	Medication	A.M. (✓Yes or No) Number of capsules ☐	Noon (✓Yes or No) Number of capsules ☐	P.M. (✓Yes or No) Number of capsules ☐
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “_____” “_____” “_____” Surname First name Patronymic

6th month of treatment

Date dd/mm/yy	Medication	A.M. (✓Yes or No) Number of capsules ☐	Noon (✓Yes or No) Number of capsules ☐	P.M. (✓Yes or No) Number of capsules ☐
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
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	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			
	UDCA (Ursosan®)			

Compliance with the daily dose Total Prescribed Daily Dose / Dose Taken		%	Compliance with the duration of treatment duration of taking at least 80% of prescribed dose per day / total duration of treatment		%

Signature of investigator **Date**

Protocol Number: RSLS-CT-2017-15	**Investigator**:	**Subject Number:**
Individual Number: 327-93	**Country:** **City:**	**Subject Initials:** “____” “____” “____” Surname First name Patronymic

CONCOMITANT MEDICATION LOG

Ask Participant: Are you currently taking any medications?

No.	Medication	Indication	Dose, units	Freq	Form	Route of administration	Start date dd/mm/yyyy	End date dd/mm/yyyy	Medication could potentially affect the studied parameters
1									☐ Yes ☐ No
2									☐ Yes ☐ No
3									☐ Yes ☐ No
4									☐ Yes ☐ No
5									☐ Yes ☐ No
6									☐ Yes ☐ No
7									☐ Yes ☐ No
8									☐ Yes ☐ No
9									☐ Yes ☐ No
10									☐ Yes ☐ No

Signature of investigator **Date**