PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

Study title:	Multicenter, Open-Labeled, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for the Treatment of Patients with Chronic Hepatitis B with delta agent for 24 weeks in Combination with Tenofovir to Suppress Hepatitis B Virus Replication Vs. the Administration of Tenofovir to Suppress Hepatitis B Virus Replication"
Protocol No.	MYR 202
Version and date of this Patient Information Sheet	Version 8.0 dated September 28, 2017
Study sponsor:	Hepatera LLC, Russia
Study doctor: Full name:	_____ _____
Study site: Name: Address: Telephone:	_____ _____ _____ _____ _____ _____ _____ _____

Patient No.: _____
Patient's initials: _____

PATIENT INFORMATION

Dear Patient,

You are invited to volunteer for participation in a clinical study of a new drug for the treatment of chronic hepatitis B with delta agent.
Before you agree to participate in this study, it is important that you read and understand the following explanation of the objectives, procedures, benefits, risks, inconveniences and cautions for this study. This document also describes the alternative treatments that are available to you and your right to stop participating in the study at any time.
Please read the information below and discuss it with the study doctor. Take your time and ask your study doctor as many questions on the study as you like. If it is difficult for you to make a decision, you can take this information sheet and informed consent form with you home for the time you need to discuss it with family members, relatives, close people and friends. If you see any words or information that you do not understand, your study doctor will explain them to you. Reading this form and talking to the study doctor can help you make a decision on the participation in this study.
If you are not completely honest with your study doctor when discussing your health, you may harm yourself by participating in this study.
If you decide to participate in the study, you need to personally write your full name and data on page 25, the name and initials of the study doctor who discussed with you the participation in the study on page 26, and your signature and date on page 26. You also need to write your initials and the number provided by the study doctor on each page of two copies of this document. You will receive one signed and dated copy. This will serve as confirmation that you have been informed about the purpose of the study and its procedures, and that you agree to the terms and conditions of the study, but this does not deprive you of any legal rights. You need to sign this form prior to the performance of any study procedures.

DO I HAVE TO TAKE PART IN THIS STUDY?

Only you can decide whether to participate or not. You can stop participating in the study at any time. Your decision will in no way affect any medical care provided to you in the future. If you refuse to continue to participate in the study, the sponsor company or its partners will still have access to the data obtained prior to your withdrawal.

SUMMARY OF THE CLINICAL STUDY

You are invited to take part in a Phase II / III clinical study of a new drug, Myrcludex B, a lyophilisate for preparation of solution for injections. This study is of a research and experimental nature. You are asked to participate in this study because you have been diagnosed with chronic hepatitis B with delta agent. This disease affects your health and causes you inconvenience in everyday life. Lack of treatment may lead to the progression of the disease, which may result in death.
This clinical study combines two phases (phase II and phase III):
Phase II is a research study to evaluate the efficacy and safety of Myrcludex B in patients with chronic hepatitis B with delta agent and to compare the results of treatment with Myrcludex B *in <u>three</u> doses* with the control group receiving therapy with Tenofovir against the hepatitis B virus.
Phase III is a research study to evaluate the efficacy and safety of the most effective and safe dose of Myrcludex B in patients with chronic hepatitis B with delta agent selected on the basis of analysis of the results of treatment of patients in Phase II, and to compare the results of treatment with Myrcludex B *<u>in the optimal dose</u>* to the control group receiving therapy with Tenofovir.
This means that the clinical study will start from Phase II and then move to Phase III after the completion of the therapeutic and diagnostic measures provided for in Phase II.
The study drug will be administered along with Tenofovir.
This study is open, that is, after the allocation to groups both you and the investigator will know at which dose you will receive the drug. Thus, the information about the treatment you receive will be available to your investigator.
The study drug will be administered for 24 weeks, every day, preferably at the same time. For 48 weeks, you will receive Tenofovir no matter which group you are assigned to.

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In phase II of the study, it is planned to obtain data from 120 patients aged from 18 years to 65 years inclusive, who will be randomly assigned to one of the 4 treatment groups in the ratio of 1:1:1:1.
Group A (30 patients): Myrcludex B 2 mg/day subcutaneously for 24 weeks + Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.
Group B (30 patients): Myrcludex B 5 mg/day subcutaneously for 24 weeks + Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.
Group C (30 patients): Myrcludex B 10 mg/day subcutaneously for 24 weeks + Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.
Group D (30 patients): therapy with Tenofovir for 48 weeks.
The number of patients to participate in phase III will be calculated on the basis of the data of the Interim Report prepared in phase II. Randomization (random allocation of patients to one of the treatment groups) will be made in 2 groups in the ratio of 1:1.
Group I: Myrcludex B in optimal dosage subcutaneously for 24 weeks + Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.
Group II: Therapy with Tenofovir for 48 weeks.
The study will be conducted in several study sites in Russia. Your participation in the study (monitoring of your condition) will last no more than 64 weeks (including the screening period).

SUMMARY OF THE STUDY DRUG CHARACTERISTICS

Myrcludex B is an antiviral drug and is planned to be used for the treatment of chronic hepatitis B with delta agent.
In earlier clinical studies, Myrcludex B showed good tolerability and efficacy in the treatment of hepatitis B with delta agent.
Myrcludex B will be used in the form of a lyophilized powder for injections, which will be diluted with 1 ml of water for injections before use.

Composition:
Active ingredient: Myrcludex-B acetate, 2.0 mg/vial, 5.0 mg/vial.
Excipients: water for injection, sodium carbonate, sodium bicarbonate, mannitol, hydrochloric acid and sodium hydroxide used to dissolve the drug before aseptic filling and lyophilization. The excipients used are of pharmaceutical grade.
In phase II of this clinical study, Myrcludex B will be administered at doses of 2, 5 and 10 mg/day subcutaneously for 24 weeks along with the administration of Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.
In phase III of this clinical study, Myrcludex B will be administered at an optimal dose subcutaneously (the optimal dose will be determined according to the results of phase II) for 24 weeks along with the administration of Tenofovir, followed by 24 weeks follow-up against the background of therapy with Tenofovir.

OBJECTIVES OF THE STUDY

The primary objective of Phase II of this clinical study is to evaluate the efficacy of Myrcludex B (Hepatera LLC, Russia) against the background of therapy for chronic hepatitis B with delta agent and to compare the results of Myrcludex B therapy *in three doses* with the control group receiving Tenofovir therapy.
The secondary objectives of Phase II of the study are to assess the side effects of Myrcludex B, to assess the pharmacokinetics (drug concentration in the blood, including studying the effect of Myrcludex B on the activity of the liver enzyme system) and immunogenicity (production of antibodies to the drug).
The primary objective of Phase III of this clinical study is to evaluate the efficacy of Myrcludex B (Hepatera LLC, Russia) against the background of therapy for treating chronic hepatitis B with a delta agent and to compare the results of Myrcludex B therapy *in the most optimal dose* with the comparison group receiving Tenofovir.
The secondary objectives of the III phase of the study are to assess the safety and tolerability of the drug Myrcludex B when administered in the optimal dose, to assess the pharmacokinetics (drug concentration in the blood) and immunogenicity (production of antibodies to the drug).
In addition, we want to learn more about your disease and the response of your body to the study drug by identifying some “biomarkers”. “Biomarkers” are various types of substances/indicators in the blood that are associated with the disease and/or your response to the administration of the study drug.

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WHAT DO I HAVE TO DO IF I AGREE TO PARTICIPATE IN THE STUDY?
If you agree to participate, and the study doctor confirms your eligibility for the study, you will be randomly assigned to one of the following groups (depending on the phase of the study in which you will be invited to participate):

- Phase II:

Group A (30 patients): Myrcludex B 2 mg/day subcutaneously (s.c.) for 24 weeks + Tenofovir; 24 weeks follow-up against the background of therapy with Tenofovir;
Group B (30 patients): Myrcludex B 5 mg/day subcutaneously (s.c.) for 24 weeks + Tenofovir; 24 weeks follow-up against the background of therapy with Tenofovir;
Group C (30 patients): Myrcludex B 10 mg/day subcutaneously (s.c.) for 24 weeks + Tenofovir; 24 weeks follow-up against the background of therapy with Tenofovir;
Group D (30 patients): Tenofovir for 48 weeks;

- Phase III:

Group I: Myrcludex B in optimal dosage subcutaneously for 24 weeks + Tenofovir, with 24 weeks follow-up against the background of therapy with Tenofovir.
Group II: Tenofovir for 48 weeks.

You are invited to participate in:
[__] Phase II of this clinical study;
[__] Phase III of this clinical study.

Regardless of whether you are assigned to one of the Myrcludex B treatment groups, you will be prescribed treatment with Tenofovir to suppress the hepatitis B virus.
Participation in this study involves periods of hospitalization (if you agree to participate in an additional pharmacokinetic study) and outpatient clinic visits.
If you have not taken any nucleoside/nucleotide analogues before or have taken these drugs for less than 12 weeks up to this point, you will need to undergo a 12-week course of pre-therapy with Tenofovir. The respective drugs will be provided by the sponsor for free.
You will need to inform your study doctor if your health condition changes and you need to take other medications.

Moreover, during the study and for 3 months after taking the last dose of the study drug, you will need to follow effective methods of contraception, which are described below. In the event of a pregnancy (in a female patient or female partner of a study participant) during the study period or within 30 days after taking the last dose of the study drug, you will need to inform the study doctor about it.

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STUDY DESIGN AND PROCEDURES

The schedule of your visits is very important, and you should try to comply the pre-arranged schedule. In case of your participation in both Phase II and Phase III of this study, in addition to taking the drug, you will need to visit your doctor 15 times if you do not need a 12-week course of pre-therapy, or 17 times if you are prescribed the pre-therapy, as well as a series of examinations that will help us make the correct diagnosis, as well as monitor the course of your treatment. The procedures at each visit will take you 1 to 3 hours.

You will undergo the following examinations:

1. **Physical examination** involves examination of all organ systems and body parts by your study doctor to obtain complete information about your health.

2. **Evaluation of anthropometric data (measuring body height and weight).**

3. **Evaluation of vital functions** includes the measurement of body temperature, heart rate, and arterial pressure.

4. **Collecting anamnesis and demographic data.** The doctor will write down your personal data (date of birth, gender, race), ask you about your earlier health condition and ask some other questions of a medical nature.

5. **Electrocardiography (ECG)** is a painless procedure to record the electrical activity of the heart, which will be performed to monitor the safety of your health. You will be asked to lie down in order to fix the electrodes with a sticky coating on the clean surface of the skin with no hair. Twelve electrodes will be placed on various parts of your body: chest, arms and legs. You will have to lie still for 10-15 minutes. Since the ECG is performed without penetration into the body and without the use of dyes or X-rays, the procedure is safe.

6. **Blood sampling** is necessary for the following laboratory tests: general blood analysis, biochemical blood analysis, assessment of the blood coagulation system, determination of biomarkers and determination of the drug concentration in the blood. The total amount of blood taken throughout the study will be at least 648 ml. With the appointment of a 12-week preliminary course of treatment with Tenofovir, the volume of blood collected will increase by approximately 30 ml. With the participation in an additional pharmacokinetic study of Myrcludex B and systemic (total) metabolic activity of CYP3A (within phase II), the volume of blood collected will increase by approximately 280 ml.
In the case of clinically significant abnormality of the laboratory test results or if it is not possible to analyze the sample taken (for example, in the case of hemolysis, damage during transportation, etc.), additional blood volume may be required for repeated tests.
If it is necessary to conduct repeated blood tests or control the safety of the study therapy, you may be invited to the study site for additional tests. After an unplanned visit, the next visit will be held according to the previously approved schedule in accordance with the protocol.

7. **Clinical and biochemical blood tests, evaluation of the blood coagulation system (coagulogram)** will be conducted to assess the safety of your participation in the study.

8. **The blood test for alpha-fetoprotein (AFP)** will be conducted for all patients at the screening stage. The analysis is performed in a central laboratory to exclude hepatocellular carcinoma.

9. **The content of bile acids in the blood.** The bile acid test is used to control the effects of the study drug.

10. **HDV RNA.** Determination of RNA of hepatitis D virus in blood serum by the method of polymerase chain reaction (PCR) in the “real time” mode.

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11.HBV DNA. Determination of DNA of hepatitis B virus in blood serum by the method of polymerase chain reaction (PCR) in the "real time" mode.

12.HBV and HDV genotyping. It is carried out to determine the genotype of hepatitis B and D viruses by the method of sequencing (determination of the amino acid or nucleotide sequences of viral RNA or DNA).

13.HBsAg, HBeAg - Markers of infection with hepatitis B virus.

14.Analysis of immunogenicity. The enzyme immunoassay for the determination of antibodies to Myrcludex B will be carried out only in groups of patients who received the therapy with Myrcludex B.

15.NTCP polymorphism. Determination of the type of receptors on the liver cell.

16.Analysis for fibrosis serum marker. Conducted to assess the progression of fibrosis.

17.Additional pharmacokinetic study. In this study included in Phase II, 30 patients will take part (10 patients from each of the groups A, B and C). The pharmacokinetic (PK) study will be performed for the following purposes:

1) Evaluation of the concentration of Myrcludex B in the blood
Blood sampling to determine the concentration of the study drug in the blood (within Phase II of the study) is necessary for the secondary research objective of Phase II of the study. During the first day of treatment before the first injection of Myrcludex B and at certain time intervals (14 days after the first injection of the drug) after the administration of the drug, you will be taken 14 blood samples of 4 ml each. Over the entire study period, to determine the concentration of the study drug in the blood, you will have 112 ml of blood collected (if applicable).

2) Evaluation of the systemic (general) metabolic activity of the liver enzyme system prior to prescribing the study drug and during therapy with Myrcludex B. To study the metabolic activity of the liver enzyme system, you will be injected with a microdose (low dose that does not result in any therapeutic effect and has no negative effect on the body) of Midazolam (MDZ) and a study of its concentration in the blood will be conducted. Thus, the activity of the liver enzyme system will be evaluated by the concentration of Midazolam in the blood.
In clinical practice, in therapeutic doses, Midazolam is used in patients with sleep disorders, for premedication and sedation, as well as induction of anesthesia.

A 10 μg microdose of Midazolam will be administered with 20 ml of physiological sodium chloride solution intravenously before the administration of Myrcludex B. The duration of the solution administration is 5 minutes.
Blood sampling to study the concentration of Midazolam in the blood will be carried out in ***3 stages:***
– Day (-13) – Day (-12) [Visit 04] separately from the administration and PK study of Myrcludex B;
– Day 1 – Day 2 [Visit 1] together with the administration and PK study of Myrcludex B;
– Day 14 – Day 15 [Visit 3] together with the administration and PK study of Myrcludex B.
On Day (-13-12), the pharmacokinetics of Midazolam will be studied prior to the beginning of therapy with Myrcludex B at the following time points: before the administration of MDZ and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, 24:00 (h:min) after the administration of MDZ.
To study the pharmacokinetics of MDZ on Day 1 and Day 14, Midazolam is administered before the administration of Myrcludex B study drug and blood is taken (except for the zero time point) after Myrcludex B has been administered. The time for taking blood samples for the MDZ PK analysis: prior to the administration of MDZ and Myrcludex B and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, 24:00 (h:min) after the administration of Myrcludex B. The total volume of blood to be collected from you during the entire period of your participation in the additional pharmacokinetic study to evaluate the concentration of Myrcludex B and Midazolam in the blood will be 280 ml.

18.The main pharmacokinetic study. Blood sampling to determine the concentration of the study drug in the blood (as part of Phase II of the study) is necessary for a more accurate study of the possible cumulation of the drug (i.e. accumulation of Myrcludex B in the human body). During the entire period of the study, blood samples will be taken from all patients receiving Myrcludex B 7 times in a total volume of 28 ml. Blood sampling will be carried out 1 hour +/- 15 min after the drug administration.

19.Taking urine samples. Urine samples for general analysis will be collected to control the safety of your condition.
For women of childbearing age, a urine pregnancy test is provided.

20.Liver biopsy and fibroelastometry. Biopsy is performed to determine the extent of the inflammatory process and the stage of liver fibrosis. An immunohistochemical analysis of HDV-positive cells will also be carried out. Part of the biopsy sample will be frozen for analysis of intrahepatic parameters. A liver biopsy is performed as follows: 1 - The patient lies down on his/her back and puts his/her right arm over his/her head. During the biopsy sampling you may not move; 2 - To ensure your psychological comfort you may be offered to take a mild sedative; 3 - Before the procedure, the puncture site is disinfected and anesthetized, after which a small incision is made and a biopsy needle is inserted through it, and a small piece of liver tissue is taken. The procedure itself occurs very quickly, usually in tenths of a second. After the liver biopsy, you will be under the supervision of the medical staff for four hours, because you may experience discomfort and pain, and you may need to take pain medication. For eight hours after the procedure, you are not recommended to drive or resume activities related to the operation of complex machinery. During the day after the biopsy, you should not play sports.
By decision of your study doctor, instead of a liver biopsy, you may have to undergo **fibroelastometry** – an examination of the liver that is not accompanied by body punctures and performed with the help of special equipment (fibroscan). The procedure for this examination resembles ultrasonography: the condition of the liver will be assessed using a special sensor.
Fibroelastometry and biopsy procedures can be performed directly at the study site, or, if this is not possible, at an authorized medical institution that has the proper equipment and qualified personnel.

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21.Evaluation of recent and concomitant therapy will be carried out throughout the study. Your study doctor will regularly inquire in and keep a record of what medicines you are taking and what other types of treatment you are receiving. This information will help assess the relationship of adverse events detected in you with the use of the study drug. In addition, information will be collected on whether you have ever been administered interferon for the treatment of hepatitis, regardless of the duration of treatment, and if so, with what drugs and when.

22.Records of adverse events will be kept throughout the study in order to monitor the safety of your health and assess the safety of the use of the study drug. Adverse events are any adverse symptoms, complaints or illnesses that you may experience during this study.

23.Inclusion/exclusion criteria will be evaluated prior to randomization. The study doctor may ask you additional questions to clarify these criteria.
For more information about the research procedures, you can ask your doctor. You can ask him/her any questions concerning this study.

DURATION OF YOUR PARTICIPATION IN THE STUDY
Your participation in the Phase II study (monitoring your condition after the administration of the first dose of the study drug - Myrcludex B or Tenofovir) will last 48 weeks. Within 24 weeks, you will receive Myrcludex B (in the case of randomization into groups A, B or C) or therapy of hepatitis B with Tenofovir (in the case of randomization into group D). After that, patients of all groups will receive therapy with Tenofovir for another 24 weeks. The total participation in the study will take you no more than 52 ± 3 weeks (including the screening period) if you do not need a 12-week course of pre-therapy with Tenofovir, and no more than 64 ± 3 weeks (including a screening period of up to 28 days) if you will be prescribed such course.
If you participate in Phase III of this clinical study, then monitoring of your condition after the administration of the first dose of the study drug - Myrcludex B or Tenofovir will last 48 weeks. Within 24 weeks, you will receive Myrcludex B (in case of randomization into group I) or Tenofovir (in case of randomization into group II). After that, patients of all groups will receive therapy with Tenofovir for another 24 weeks. The total participation in the study will take you no more than 52 ± 3 weeks (including the screening period of up to 28 days) if you do not need a 12-week course of pre-therapy with Tenofovir and no more than 64 ± 3 weeks (including the screening period) if you are prescribed such course.
You can withdraw from the study at any time without explaining the reasons for refusing to further participate in it. However, in the event that you decide to withdraw from the study, we recommend that you first talk with the study doctor.
The doctor conducting the study may exclude you from it at any time, if he considers that the best option for you is to stop taking the study drug. The reasons for this decision may be the following:

- This is in your interests (for example, for safety reasons);
- You are female and expecting a baby (the pregnancy occurred during the study);
- The clinic staff found out that, along with the study drug, you received any other treatment prohibited by the study protocol.

You may also be excluded from the study for administrative reasons:

- If you violate the visit schedule, or
- If you take Myrcludex B or drug therapy for hepatitis B in larger or smaller quantities than is provided for by the protocol.

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SCHEDULE OF VISITS

The schedule of visits is the same for Phases II and III

Screening (Visit 01):

In order to determine whether you are eligible the study, after you have agreed to participate in the study, you need to undergo the following tests and procedures. The procedures of this visit can take you about 1-3 hours. In some cases, the study doctor may ask you to come on an empty stomach. Screening procedures are the same for Phases II and III and include:

- Collection of baseline information (demographic data, data on participation in other studies, etc.);
- Collection of medical history;
- Physical examination;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Collection of anthropometric data (measurement of body height and weight);
- The following laboratory and instrumental tests:
  - Complete Blood Count;
  - Blood clotting test;
  - Blood chemistry;
  - Clinical urine analysis;
  - 12-lead ECG;
  - Serological blood test (HIV, hepatitis B, C and B with delta agent);
  - Urine drug screen;
  - Breath test for alcohol;
  - Test for AFP (alpha-fetoprotein, analysis necessary to exclude a liver tumor);
  - HDV RNA;
  - HBeAg and antibodies to HBeAg;
  - HBsAg (nonquantitative determination)
  - For female patients – urine pregnancy test;
- Abdominal ultrasound;
- Liver biopsy (or fibroelastometry, depending on the decision of the study doctor);
- Evaluation of inclusion and exclusion criteria;
- Registration of Serious Adverse Events;
- Collection of data on concomitant therapy, as well as on previous therapy for hepatitis with interferon preparations, regardless of the remoteness of treatment**.**

The period of pre-therapy with Tenofovir (Visits 02-04):

If you were prescribed a 12-week course of pre-therapy with Tenofovir, you will need to come to the study site twice: for the first time - no later than 84 days before the expected date of the randomization visit, for the second - no later than 14 days before the expected date of the randomization visit. In addition, 4 weeks before the randomization visit, you will need to answer a number of doctor's questions by phone. The doctor will agree with you on the date and time of the call.

The procedures of the first visit within the period of pre-therapy with Tenofovir (Visit 02) are performed on an outpatient basis. These procedures may take you about 1 to 3 hours. In some cases, the study doctor may ask you to come on an empty stomach. The procedures of Visit 02 include:

- Physical examination;
- Body weight measurement;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- The following laboratory and instrumental tests:
  - Complete blood count and blood clotting test - if more than 14 days have passed since the previous blood sampling;
  - Blood chemistry;
  - HDV RNA;

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- HBV DNA and HBsAg;
- HBV/HDV genotyping (frozen specimens) is performed in patients who have been pre-treated with Tenofovir;
- Resistance test (frozen specimens) is performed in patients who have been prescribed pre-therapy with Tenofovir;

- Registration of Serious Adverse Events;
- Collection of data on concomitant therapy;
- Issuance of Tenofovir in the amount necessary for a 12-weeks therapy course;

In addition, you will agree with the doctor on the date and time of the phone call, which must be made no later than 8 weeks from the date of Visit 02.
During the phone call (remote Visit 03), you will need to answer several questions of the doctor regarding your health condition, as well as calculate the amount of used and unused drug and pass this information to the doctor. During the phone call, the doctor will remind you to come to Visit 04 at the study site and set a date for this visit.
The procedures of Visit 04 (a visit at the study site, in outpatient mode, 14 days prior to the scheduled randomization visit) These procedures may take you about 1 to 3 hours. In some cases, the study doctor may ask you to undergo the tests on an empty stomach. The procedures of this visit include:

- Physical examination;
- Body weight measurement;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- The following laboratory and instrumental tests:
  - Complete blood count;
  - Blood clotting test;
  - Blood chemistry;
  - <u>For female patients</u> – urine pregnancy test;
- Re-evaluation of inclusion and exclusion criteria;
- Only for patients participating in the additional pharmacokinetic study <u>in Phase II</u>: hospitalization in the evening before blood sampling (Day (-14)). Taking blood samples before the administration of Midazolam and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, **24:00 on the next day** (h:min) after the administration of Midazolam (Days (-13) and (-12)).
- Registration of Serious Adverse Events;
- Calculation by the doctor of used and unused Tenofovir;
- Evaluation by the doctor of compliance with the prescribed therapy;
- Collection of data on concomitant therapy**.**

Visit 1: Randomization and Beginning of Therapy: this visit is conducted after the end of the screening procedures or the period of pre-therapy with Tenofovir and confirmation of your eligibility for the study. The visit procedures will take about 1-3 hours.
During this visit, after completing the planned procedures, you will be randomly assigned to one of the four therapy groups (in Phase II) or to one of the 2 therapy groups (in Phase III).
The treatment and the visits will take place on an outpatient basis, in the same way for Phases II and III. Only patients participating in the additional pharmacokinetic study (in Phase II) will be hospitalized three times at the study site. For the first time, they will be hospitalized in the evening 2 weeks prior to randomization and leave the center the next morning after the administration of Myrcludex B (approximately 24 hours after the administration of Myrcludex B). For the second time, the patients will be hospitalized before the beginning of therapy with the study drug (after randomization) and will be discharged the next day after the daily blood sampling. Then (for the third time) the patients will be hospitalized on the evening before the 14th day of the study and will be discharged the next day after daily blood sampling.
The following procedures and measurements will be carried out during this visit:

- Physical examination;
- Body weight measurement;
- Final evaluation of inclusion/exclusion criteria;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-

dominant hand), and heart rate;

- The following laboratory and instrumental tests:
  - Complete blood count;
  - Blood clotting test;
  - Blood chemistry;
  - Test for total bile acids in the blood;
  - The content of bile acids in the blood;
  - Clinical urine analysis;
  - HDV RNA;
  - HBV DNA and HBsAg;
  - HBV/HDV genotyping (frozen specimens) is performed in patients who were NOT prescribed pre-therapy with Tenofovir;
  - Resistance analysis (frozen samples) is performed in patients who were NOT prescribed pre-therapy with Tenofovir;
  - Immunogenicity;
  - Serum fibrosis marker;
  - NTCP polymorphism;
  - Breath test for alcohol;
  - For female patients – urine pregnancy test;
- Registration of Adverse Events
- Collection of data on concomitant therapy
- Randomization;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir;
- Issuance of patient diaries;
- *For patients participating in the additional PK sub-study (sub-study of pharmacokinetics of Myrcludex B) in Phase II: hospitalization in the evening before blood sampling. Taking blood samples immediately before the administration of Myrcludex B and Midazolam and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00,* ***24:00 on the next day*** *(h:min) after the administration of Myrcludex B.*

- For patients participating in the additional PK study (study of the systemic metabolic activity of CYP3A) in Phase II: hospitalization in the evening before blood sampling (Day (-1)). Taking blood samples before Midazolam administration and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, **24:00 on the next day** (h:min) after the administration of Myrcludex B (Days 1-2).

- *Blood sampling for the main pharmacokinetic study. For patients who are not participating in the PK study, a blood sampling time point is scheduled at the randomization visit (1 hour +/- 15 min after the administration of Myrcludex B).*

Your treatment will begin at this visit. The study doctor will teach you the technique of subcutaneous administration of the drug, as well as filling-in the patient's diary. Separately, you will be provided with training documents. At this visit, in the presence of the doctor, you will make a subcutaneous injection of the study drug and take Tenofovir. Later on, the injection of the study drug and taking of Tenofovir should be carried out every 24 hours ± 1 hour. At that, you can adjust the administration of the second and subsequent doses of the study drug to the schedule convenient for you, which should be reflected in the patient's diary. The administration of subsequent doses of the drug should be carried out every 24 ± 1 hours from the scheduled time.

The doctor will also instruct you that if you miss a dose of the study drug, you should follow the following algorithm: if you remembered about the missed dose no later than 4 hours after the time scheduled at the randomization visit, the dose should be administered. On the next day, the dose should be administered at the scheduled time. If more than 4 hours have passed after the scheduled time, the dose should not be administered, it should be considered as missed, and on the next day, you should self-administer the next dose at the scheduled time. The fact of missing a dose should be recorded in the patient's diary, and you will also need to inform the investigator about the missed dose by phone.

The procedures and evaluations in the treatment period will be the same for Phases II and III.

Patient No.: _____
Patient's initials: _____

Visit 2: Treatment week 1 /Day 8 ± 2: The procedures of this visit will take about 1 to 2 hours.
The following procedures will be performed at Visit 2:

- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Registration of AE;
- Accounting of study drugs and assessment of compliance with the prescribed therapy.

At this visit, you will have to provide the filled-in diary so that the doctor can check the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

Visit 3: Treatment Week 2 / Day 15 ± 2:
The following procedures will be performed at Visit 3:

- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Registration of AE;
- *For patients participating in the additional PK sub-study (sub-study of pharmacokinetics of Myrcludex B) in Phase II: hospitalization in the evening before blood sampling. Taking blood samples immediately before the administration of Myrcludex B and Midazolam and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00,* ***24:00 on the next day*** *(h:min) after the administration of Myrcludex B.*
- For patients participating in the additional PK study in Phase II: hospitalization in the evening before blood sampling (Day 13). Taking blood samples before Midazolam administration and 00:05; 00:15; 00:30; 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, **24:00 on the next day** (h:min) after the administration of Myrcludex B (Days 14-15).

At this visit, you will have to provide the filled-in diary so that the doctor can check the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

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Visit 4: Treatment week 4 / Day 28 ± 2:
The following procedures will be performed at this visit:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- Urine analysis;
- For female patients – urine pregnancy test;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBsAg;
- Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Registration of AE;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir.

If you receive the study drug, then at this visit you will need to return unused vials of the drug in order for the doctor to verify the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.
Also, at this visit you will have to return the unused drug for the treatment of hepatitis B.

Visit 5: Treatment week 8 ± 2 days:
The following procedures will be performed at this visit:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- For female patients – pregnancy test;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBsAg;
- Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
- Registration of AE;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir.

At this visit, you will have to return all unused drugs, as well as the used and unused vials with Tenofovir so that the doctor can verify the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

Visit 6: Treatment week 12 ± 2 days:
The following procedures will be performed at Visit 6:
- Physical examination;
- Body weight measurement;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- 12-lead ECG;
- Complete blood count, coagulogram;
- Blood chemistry;
- Urine analysis;
- For female patients – pregnancy test;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBV DNA;
- HBsAg;
- Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
- Immunogenicity;
- Registration of AE;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir.

At this visit, you will have to return all unused drugs, as well as the used and unused vials with Tenofovir so that the doctor can verify the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

Visit 7: Treatment week 16 ± 2 days:
The following procedures will be performed at this visit:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- For female patients – pregnancy test;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBsAg;
- Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
- Registration of AE;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir.

At this visit, you will have to return all unused drugs, as well as the used and unused vials with Tenofovir so that the doctor can verify the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

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Visit 8: Treatment week 20 ± 2 days:
The following procedures will be performed at Visit 8:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- For female patients – pregnancy test;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBsAg;
- Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
- Registration of AE;
- Collection of data on concomitant therapy;
- Assessment of the correctness of filling-in of patients' diaries;
- Accounting of study drugs and assessment of compliance with the prescribed therapy;
- Issuance of the study drug for 28 days;
- Issuance of Tenofovir.

At this visit, you will have to return all unused drugs, as well as the used and unused vials with Tenofovir so that the doctor can verify the patient's diary entries and enter the data on compliance with the therapy. Copies of the filled-in patient diary pages will be stored at the study site.

Visit 9: Treatment week 24 ± 2 days: End of therapy with the study drug
The following procedures will be performed at this visit:
- Physical examination;
- Body weight measurement;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- 12-lead ECG;
- The following laboratory and instrumental tests:
  - Complete blood count;
  - Blood clotting test;
  - Blood chemistry;
  - Total bile acids in the blood;
  - The content of bile acids in the blood;
  - General urine analysis;
  - HDV RNA;
  - HBV DNA and HBsAg;
  - Blood sampling for the main pharmacokinetic study (1 h ± 15 min after administration of Myrcludex B);
  - HBeAg and antibodies to HBeAg (only in patients with a positive HBeAg result at screening);
  - Resistance test;
  - Immunogenicity;
  - Serum fibrosis marker;
  - For female patients – urine pregnancy test;
- Liver biopsy (or fibroelastometry, depending on the decision of the study doctor);
- Registration of AE;
- Evaluation of compliance with the prescribed therapy;
- Collection of data on concomitant therapy;
- Issuance of Tenofovir for 56 days;
- Assessment of the correctness of filling-in of patients' diaries.

At this visit, you will need to return all the unused drug, as well as the used and unused vials with Tenofovir

so that the doctor can verify the patient's diary entries and enter the data on compliance with the therapy.

Follow-up period (FUV – follow up visits)
Upon completion of the treatment period begins the 24-weeks follow-up period, the procedures of which are the same for Phases II and III. During the follow-up period you will continue to take Tenofovir.
FUV-1: FU Week 1 – Study Week 25 ± 3 days:
FUV-2: FU Week 2 – Study Week 26 ± 3 days:
The following examinations will be performed at visits FUV-1 and FUV-2:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- Registration of Adverse Events;
- Collection of data on concomitant therapy.

FUV-3: FU Week 4 – Study Week 28 ± 3 days:
The following procedures will be performed at this visit:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- HDV RNA;
- HBsAg (frozen samples);
- Collection of data on concomitant therapy;
- Registration of Adverse Events;
- Issuance of Tenofovir for 56 days.

At this visit, you will have to return the packages of the used drug so that the doctor can record the data on compliance with the therapy.

FUV-4: FU Week 12 – Study Week 36 ± 3 dais:
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-dominant hand), and heart rate;
- Complete blood count, coagulogram;
- Blood chemistry;
- Urine analysis;
- HDV RNA;
- HBV DNA, HBsAg;
- Immunogenicity;
- Collection of data on concomitant therapy;
- Registration of Adverse Events;
- Issuance of Tenofovir for 56 days.

At this visit, you will have to return the packages of the used drug so that the doctor can record the data on compliance with the therapy.

FUV-5: FU Week 24 – Study Week 48 ± 3 days: Final visit of the study
At this visit, you will have to return the packages of the used and unused Tenofovir so that the doctor can record the data on compliance with the therapy.
The following final procedures will be performed at this visit:
- Physical examination;
- Body weight measurement;
- Measurement of vital functions: blood pressure (in the sitting position after 5 minutes of rest on the non-

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dominant hand), and heart rate;
- 12-lead ECG;
- Complete blood count, coagulogram;
- Blood chemistry;
- Urine analysis;
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBV DNA;
- HBsAg;
- HBeAg and antibodies to HBeAg (only in patients with a positive HBeAg result at screening);
- Immunogenicity;
- Serum fibrosis marker;
- Collection of data on concomitant therapy;
- Registration of Adverse Events;
- Accounting of the drug.

Unscheduled visit / Early withdrawal visit
At the discretion of your study doctor, you can be invited to an unscheduled visit to the study site at any time during the study. If your study doctor decides that your further participation in the study is not appropriate, you can be excluded from the study, and you will be prescribed another necessary therapy, according to the doctor's professional judgment. However, you will be required to undergo the following procedures to assess the safety of the therapy:
- Registration of adverse events;
- Physical examination;
- Body weight measurement;
- Assessment of vital functions;
- Complete Blood Count, coagulogram;
- Blood chemistry (complete set);
- Total bile acids in the blood;
- The content of bile acids in the blood;
- HDV RNA;
- HBV DNA;
- HBsAg;
- Urine analysis;
- Collection of data on concomitant therapy.

You will be asked to inform the study personnel during the study about any changes in your condition that you experienced during the study, and to inform the study personnel about any drugs you take.

PATIENT RESPONSIBILITIES
In order to participate in this study, you must give your consent to all procedures and study visits.
Only you may use the study drug, and you should keep the study drug out of the reach of children, as well as other persons other than the personnel of the study site.
Your responsibilities as a patient in the study include the following:
- You will come to study visits, follow the instructions of the doctors and take the study drug according to the instructions. Inform the study site if you cannot come to a scheduled visit.
- Provide true information about your medical history and current health status.
- Inform your attending physician about whether you participated in any study within the previous 30 days or whether you are participating in any other study now.
- It is important that you tell your attending physician about any changes in your health status, regardless of whether you think that they are related or not to the administration of the study drug.
- Contact your attending physician immediately if you experience any undesirable sign or symptom.
- You must also inform your attending physician about any drugs you are currently taking. This applies to both drugs prescribed by your doctor and medicines sold over-the-counter (for example, at a pharmacy or

health food store, including herbal medicines and vitamin supplements). Your study doctor will tell you if you can keep taking these drugs.

- You must to inform your attending physician in advance about any planned changes in the administration of your current drugs or starting new ones, even if they are prescribed by another doctor. Always follow the instructions of your attending physician during the study.
- You will be given a study patient card with all the necessary information about this study, which you can use for emergency contact with your attending physician. You will need to carry this card with you throughout your participation in the study. It will also contain information about the experimental drug Myrcludex B you receive as part of your participation in this study. If you have questions or you need any additional information, contact your study doctor.
- You will be given a patient diary in which you will need to enter information about the administration of the drugs; you will be required to bring the completed diary to the visits at the study site.
- Follow the instructions of the attending physician, including recommendations on diet and physical activity.
- Female patients of childbearing age, as well as male patients, must consent to use effective contraception defined as a double barrier method, a single barrier method in combination with a spermicide, intrauterine device or female oral contraceptives. Effective contraception should be applied during 30 days before the start of the study, throughout the study and for 3 months after its completion. If you are female and become pregnant or suspect pregnancy, or if you are male and your partner becomes pregnant during your participation in the study, you should immediately inform your doctor. If you are a woman of childbearing age, your study doctor will tell you whether the drugs you are taking can affect the efficacy of your contraceptives, and whether you should use another method.

HANDLING OF BIO SAMPLES

Samples and, if applicable, data obtained may be re-analyzed in the future by the sponsor company or its affiliates, subsidiaries and authorized companies, employees, partners or third parties potentially using the new technology. Based on the permission of the Ministry of Health of the Russian Federation, the samples will be exported to Germany for study. This process is not limited by time frame. You agree that we are entitled to re-examine the samples and any other data.

In addition, samples and such data may be used in future studies of Myrcludex B, your health or other medical issues. This process is not limited by time frame. You consent to the use of your samples and all data obtained in such future studies.

Blood samples taken for routine laboratory tests and disease assessments will be used only as part of this study, and upon completion of the study all unused samples will be destroyed. These samples will not be stored for possible future use outside the scope of this study. If these provisions change, it will first be necessary to obtain your consent before conducting any research. You have the right to refuse this.

Bio samples can be stored by Hepatera LLC for up to 5 years after completion of the study. After this period, the samples will either be destroyed, or a new approval of additional sample storage period will be requested from the Council of Ethics / Ministry of Health (CE/MOH) of the Russian Federation. It is possible that the samples will be re-analyzed during this period. This may include analysis of newly identified markers and/or repeating the initial analysis using new improved technologies.

If you revoke your consent to the storage of your samples, the results of all analyzes performed up to this time can be saved in accordance with legal and regulatory requirements. You can request the destruction of all remaining samples that can be identified as belonging to you.

HAS THIS STUDY RECEIVED ETHICAL APPROVAL?

The protocol of this clinical study was submitted to the Council of Ethics of the Ministry of Health and the Local Ethics Committee (LEC), who both gave their written approval to conduct this study. Also, the permission of the Ministry of Health of the Russian Federation to conduct this study. The structure of the study complies with the regulatory documents of the Ministry of Health and other regulatory bodies of the Russian Federation on clinical studies, as well as the World Medical Association's Declaration of Helsinki, which contain recommendations for doctors on biomedical research involving human subjects. You can get a copy of these documents from your study if you want to read them.

POSSIBLE RISKS, SIDE EFFECTS AND INCONVENIENCES

In studies like this, it is impossible to foresee all possible risks or side effects. The response of each patient to

the study drug, device, or procedure may vary. You may experience a side effect, or you may have an increased risk of developing symptoms, diseases, and/or complications that your study doctor or study sponsor cannot predict. If such a side effect occurs, you should immediately inform your study doctor.
In order to ensure your safety, you must also inform your study doctor about all the drugs you are taking.
The results of clinical studies have shown that Myrcludex B is well tolerated.
Based on the data collected during the conduct of clinical studies to date, the predicted side effects are local skin reactions, such as redness, itching, or inflammation.
The drug for the treatment of chronic hepatitis B used in the study, Tenofovir, has been used in clinical practice for many years and is well tolerated.
The most frequent adverse reactions are a decrease in the level of phosphates in the blood, dizziness, abnormalities in the gastrointestinal tract, headache, and fatigue.
If you are not completely honest with your study doctor and study personnel in matters relating to the side effects that you may have, you may harm yourself by participating in this study.

Other risks and inconveniences
In addition, the procedures performed during the clinical study may also pose a risk or cause discomfort.
The puncture and/or catheterization of veins for blood sampling may be painful; at the puncture site, may occur bleeding and formation of a hematoma (bruising), which in rare cases leads to thrombosis (vein clogging by thrombus) or thrombophlebitis (thrombosis combined with vein inflammation) and/or peripheral nerve damage (numbness). In the event of adverse events, the catheter will be immediately removed, and further blood collection will be carried out through single punctures.
Measurement of blood pressure may cause a feeling of pressure and mild soreness at the site of the cuff when it is pumped up, as well as the formation of small subcutaneous bruises in case of repeated measurements of blood pressure during the day.
During electrocardiography (ECG), you may experience skin rash or irritation where the sticky gel is applied and where ECG electrodes are placed. Some male volunteers may need to have small areas of chest hair shaven to properly attach the electrodes.
Women of childbearing age and men need to use effective methods of contraception throughout their participation in the study. An effective contraceptive method is a method the failure rate of which is no higher than 1%. In this study, acceptable methods of contraception are the methods listed in the Patient Responsibilities section above.
It is you, and not your partner, who are responsible for preventing pregnancy. If necessary, consult your study doctor on the method of contraception most appropriate for you among those listed above.
Before the beginning of the study, women of childbearing age will be tested for pregnancy (urine test using test strips). Women who suspect that they may be pregnant should report this to the study doctor.
Women should not take part in the study during pregnancy or breastfeeding.
Sexually active men need to use reliable methods to prevent pregnancy in their partners.
Throughout the study, your doctor will notify you of any new information that may be available and may affect your decision to continue your participation in the study.

Unknown risks
You may experience side effects or inconveniences that are not listed in this form or may not yet be known. You may experience new side effects. If you have any problems, immediately inform your study doctor or study personnel.

The influence of the study drug on driving vehicles and operating machinery requiring increased concentration of attention
Care should be taken when driving vehicles and operating machinery during therapy with the study drug, since the drug may cause dizziness.

OTHER DRUGS
There are certain drugs that you should not take while participating in this study. Your study doctor will tell you about them and provide you with a list of prohibited drugs. If another doctor prescribes you any of these drugs, please notify your study doctor before taking any of these drugs during your participation in the study.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY

Patient No.: _____
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You are not obliged to participate in this study to receive treatment for chronic hepatitis B with delta agent. You may be prescribed other available drugs. A study doctor can discuss with you the risks and benefits of alternative treatment options.

POSSIBLE BENEFITS FROM PARTICIPATION IN THIS STUDY

During the study, you will be under close supervision of a qualified doctor as well as other medical personnel. Your condition will be regularly evaluated. You may or may not directly benefit from participation in this study. It is possible that your condition will improve, remain the same or worsen.
Your participation in the study may be beneficial for other patients with chronic hepatitis B with a delta agent.

COST OF PARTICIPATION AND REIMBURSEMENT OF EXPENSES

All procedures associated with the study, the issuance of the study drug, medical examinations, laboratory tests, and pregnancy tests will be completely free for you. The drugs used in this study - Myrcludex B and Tenofovir - will be provided to you for free. Thus, participation in the study will be free for you.

PAYMENT FOR PARTICIPATION

Remuneration for participation in this study is not provided.
During the study, patients of Group D may be individually reimbursed for the reasonable costs of public transport related to attending scheduled visits at study sites, provided that there are no deviations from the visits schedule.
After the completion of the study according to the protocol, the Sponsor of the study will donate Myrcludex B for this group of patients in the prescribed maximum effective and safe dosage, in an amount sufficient for a 24-weeks course of treatment.

IMPORTANT! The drug will be provided after registration of the drug in the Russian Federation.

INSURANCE AGAINST POSSIBLE HARM TO HEALTH

Your safety during this study is the responsibility of the principal investigator of this study site. In the event that an adverse reaction develops in you, the principal investigator and his staff will provide you with free qualified medical assistance and will do everything possible for your treatment.
If you agree to participate in this study, your participation in this study will be insured in accordance with the Federal Law dated April 12, 2010 No. 61-FZ “On Drug Circulation”, Resolution of the Government of the Russian Federation No. 714 “On Approval of the Standard Rules for Mandatory Insurance of Life and Health of Patients Participating in Clinical Studies of Drugs” dated September 13, 2010 and Resolution of the Government of the Russian Federation No. 393 “On Amendments to the Standard Rules for Mandatory Insurance of Life and Health of Patients Participating in Clinical Studies of Drugs” dated May 18, 2011.
Attached to this document is an original certificate of insurance and a leaflet describing the insurance conditions stipulated by the certificate as well as your actions in case of harm to health. You will receive the original certificate of insurance along with the leaflet, and a copy of the certificate will be kept in the insurance company. In order to ensure anonymity, your personal data in the certificate will be replaced with the Individual Patient Identification Code, which will be assigned to you in the study in the form established in the Russian Federation, and which is indicated at the end of this document. In the event of harm to your health associated with this clinical study, INGOSSTRAKH Open Insurance Company undertakes to reimburse all costs for the necessary medical examinations and treatment, the need for which will arise as a result of direct exposure to the study drug and the comparison drugs and/or medical procedures performed according to the study protocol.
This study does not provide for any additional types of voluntary insurance or other options for treatment and/or compensation in the event of a patient’s death or harm to the patient’s health caused in this study.
Please note that if you have a valid voluntary health insurance (VHI) policy, participation in a clinical study may violate the terms of this policy and deprive you of the rights to receive medical assistance under VHI. If you have a valid VHI certificate, please read the insurance terms and conditions set out in it.

For more information, please contact: INGOSSTRAKH Open Insurance Company, 41 Lesnaya Street, 127994 Moscow, Russia
Department for loss adjustment, insurance of property and liability.

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Tel/fax: 8 (495) 641-41-01, 725-73-25, 234-36-00.

If you believe that you were treated unethically during the study, or that your rights as a patient were violated, please contact the Council of Ethics, whose contacts are given below.
The sponsor bears no responsibility for any losses, harm and/or damage that may be caused to you, if such losses are caused by:

- Taking a prohibited drug during the study;
- Deviation, on your part, from the study protocol, this patient information sheet (informed consent form), the requirements of the study and/or any instructions given to you by your study doctor;
- Action or inaction of a third party in response to an adverse event or reaction to the study drug.

During your participation in a clinical study, you may not participate in another study. If you need to receive any medical assistant that is not related to this study, you should inform your study doctor.

CONFIDENTIALITY OF PERSONAL INFORMATION

Records made during the study are called study records. Records that will be collected, used and transferred to other persons in this study may include a study record about you, your data from medical records, results of laboratory, diagnostic and other tests, results of analyzes of stored bio samples (blood, urine, biopsy), and clinical and research observational data obtained during your participation in the study. Primary records will be kept at the study site.
As part of this study, your study doctor and personnel will make records about your health, which will include your name and other personal information. Authorized representatives of Hepatera LLC, the Council of Ethics and the Federal Service for Supervision of Health and Social Development of the Russian Federation may have access to this data. Copies of research records that will not contain your name can be provided to Hepatera LLC, Councils of Ethics and laboratories that can be involved in conducting this study.
The sponsor may send a copy of the impersonated records to the Federal Service for Supervision of Health and Social Development of the Russian Federation or other regulatory authorities, for example, state regulatory authorities of other countries.
Information on the study and the results of this study can be presented at conferences or published in scientific magazines. Presentations and publications will not include your name or information which allows to establish your identity.
For your safety, the study doctor should inform the health care provider, who usually provides you with medical assistance, about your participation in this study, if your study doctor is not this health care provider. Please discuss any questions about this with your study doctor.
You have the right to receive information on the results of all laboratory tests of biological samples that you have submitted, and on your health condition.

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GETTING ANSWERS TO YOUR QUESTIONS ON THE STUDY

You can ask questions on this form or on the study at any time. You may have questions about the study, about the harm associated with the study, or about payment during the study. You may have other questions. You should contact your study doctor or the personnel participating in the study to discuss any questions or concerns. To ask questions related to this study, as well as to report on the harm associated with the study, or to obtain information on research procedures, please contact your study doctor:

Last name, First name, Patronymic of the doctor _____
_____

Telephone: _____

If you feel that your rights as a study participant have been violated, or if you have questions related to the ethical aspects of this study, then you should contact the representative of the Local Ethics Committee
_____
_____

Tel._____

Address: _____
_____

This committee is a group of people from scientific and other fields who carry out initial and further supervision of the study from the point of view of ethical principles in order to ensure the safety and well-being of patients.

If you have questions about this study, you should first discuss them with your study doctor or representative of the Local Ethics Committee. After you have discussed them with your study doctor or the local ethics committee, and have not received a satisfactory answer, you can contact the Council of Ethics of the Ministry of Health:

Council of Ethics of the Ministry of Health:
Rakhmanovsky Lane 3, GSP 4, 127994 Moscow,
Telephone: (495) 625-44-21.

If you have any questions to the company sponsoring the study, you can contact the representative office of the company:

Verkhnyaya Radischevskaya Street 12/19, bldg. 1, 1109240 Moscow. Tel. +7 (495) 726-52-53.

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Patient's initials: _____

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. Anyone who is invited to participate in the study may refuse it. No one is obliged to participate in the study. If you agree to participate in the study, you can withdraw from it at any time. You are not required to explain the reason. No doctor may discriminate you or treat you differently if you decide not to participate in the study or decide later to discontinue your participation. If you withdraw from the study, it is in your interest to inform the study personnel and to follow their instructions.

NEW INFORMATION ABOUT THE STUDY

The information provided in this form reflects available knowledge about the study at the time of its signing. If during the study we become aware of any new information that may affect your decision to continue to participate in the study, you will be informed by your study doctor.

DATA PROTECTION

By signing this form, you give express permission to inspect, transfer and process medical information about you, as described in the *Confidentiality of Personal Information* section and as described below:

- Representatives of the sponsor (monitors, study managers, auditors, other authorized persons) and representatives of the abovementioned regulatory authorities can study medical information about you with direct access to medical records.
- Study data, including anonymous medical information about you, can be processed, i.e. they will be collected, entered into a computer database, verified, analyzed, printed and will be reported in due course for legitimate scientific purposes, including use in future medical or pharmaceutical research.
- Study data may be transferred for processing to other countries, including countries not covered by the European Privacy Directive.
- You can access medical information about you in accordance with the laws of the Russian Federation.
- The sponsor will not disclose information about your health status to insurance companies, unless required by law. In this case, you will be asked to provide a separate written consent to this. If you decide to revoke your consent to use your health information after it is provided to the Sponsor, from then on no such data will be transmitted by the Sponsor to any third party, including the insurance company. Data transmitted prior to revocation of consent, are not subject to return.

If you do not want your data to be used for the study as described above, you should refuse to participate in the study.

In case of your early withdrawal from the study, including because of your refusal to further participate in the study, the data collected in the study before you leave it, however, can be processed along with other data obtained as part of this clinical study.

For more information about the procedures for transmission of medical data from the study, please contact your study doctor. You can ask him/her any questions on this study.

Patient No.: _____
Patient's initials: _____

PATIENT INFORMED CONSENT
to participation in clinical study

I, _____,
born on _____, tel.: _____,
have been informed by the study doctor about the nature of the planned study on the efficacy and safety of Myrcludex B (Hepatera LLC, Russia) in combination with Tenofovir.
By signing this document, I confirm the following:

• I have read and understood the contents of the patient information sheet of the above study and confirm that I had enough time to make a decision on participation in this study	*Patient's signature*
• I have received satisfactory answers to all the questions I asked	*Patient's signature*
• I voluntarily agree to take part in this scientific study, follow the study procedures and provide the information needed to the study doctor, nurses or other personnel upon request	*Patient's signature*
• I understand that I can withdraw from this study at any time without explaining the reason, and that this decision will not affect my medical care or my legal rights.	*Patient's signature*
• I have received one original copy of this Patient Information Sheet	*Patient's signature*
• If the study doctor is not my attending physician, I consent that my attending physician is informed about my participation in this study and asked for medical information about my health status	*Patient's signature*
• I consent to taking samples from me and use samples as described in this information sheet	*Patient's signature*
• I consent to use and transfer of my personal and medical data, as described in this Patient Information Sheet, and to: ✓ identification of information only with the help of my study participant identification number; ✓ analysis, processing and disclosure of the data to the sponsor, its branches and authorized representatives, auditors and monitors of the study for the purposes described in the study protocol; ✓ analysis or verification of the data by properly authorized organizations; ✓ publication and transmission of the data to regulatory authorities or health insurance organizations located in my country or in other countries; and to transmission of the data, if necessary, to any country where the laws on the protection of my personal data may be less strict.	*Patient's signature*
• I understand that I may also be asked for permission to contact me later to obtain my consent in connection with this study or any sub-study within it.	*Patient's signature*

I have signed and dated this information sheet, including patient information and informed consent form, on 26 pages in 2 copies; I have received 1 copy signed and dated by me personally and by the study doctor.

Investigator (full name) _____, who discussed with me the question of my participation in the study, gave me a thorough explanation of the nature, objectives and duration of the study. I had the opportunity to ask him/her questions regarding all aspects of the study.

I voluntarily agree to take part in the clinical study according to protocol No. MYR 202 "A multicenter, open-label, randomized clinical study of the efficacy and safety of 3 doses of Myrcludex B for treating patients with chronic hepatitis B with delta agent for 24 weeks in combination with the use of Tenofovir to suppress replication of hepatitis B virus compared to using Tenofovir to suppress the replication of hepatitis B virus." I have been informed that I can refuse to participate or withdraw from this study at any time.

Patient's signature: _____ Date _____

Patient No.: _____
Patient's initials: _____

I confirm that I explained in detail the purpose and possible risks of this study to the patient _____, and the patient had the opportunity to ask any questions about the nature, risks and benefits of his/her participation in the study.
Signature of the study doctor: _____ Date _____
* Full name of independent witness and/or legal representative (in block letters):
_____
Signature of the witness and/or legal representative: _____ Date _____
** If applicable*
(If the participant is illiterate, verbal consent must be obtained in the presence of an independent witness, confirmed by the signature of the witness)

The patient has been assigned an individual patient identification code: