CLINICAL STUDY PROTOCOL
No. MYR 202

«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"

Version: 7.0

Date: September 28, 2017

Test product: *Myrcludex B, lyophilisate for solution for injection.*

Sponsor: *Hepatera LLC, Russia*

Sponsor's Address: *109240, Moscow, Verkhnyaya Radishchevskaya Street, 12/19, bldg. 1*

Clinical phase: *II-III.*

Moscow, 2017

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 5

LIST OF ABBREVIATIONS 12

1. BACKGROUND INFORMATION 14
   - 1.1. Protocol Identification 14
   - 1.2. Contact Information about Sponsor 15
   - 1.3. Page of the Protocol Approval by Sponsor 16
   - 1.4. Contact Information about Clinical Centers and Investigators 17
   - 1.5. Investigator Agreement 19
   - 1.6. Contact Information about the Central Clinical Laboratory and Other Study Services 20

2. JUSTIFICATION OF STUDY 22
   - 2.1. Name and Description of the Study Drug 23
     - 2.1.1. Background information 23
   - 2.2. Summary of Preclinical and Clinical Studies 24
     - 2.2.1. Preclinical studies 24
     - 2.2.2. Clinical use of MXB 25
   - 2.3. Information on the Drug for Treatment of the Co-Infection with Hepatitus B virus 27
   - 2.4. Administration, Dosage and Duration of the Administration of the Investigational Medical Product 27
   - 2.5. Study Compliance with Regulatory Requirements 29
     - 2.5.1. List of Applicable Standards and Regulatory Requirements 29
     - 2.5.2. Clinical Center's Responsibilities 30
   - 2.6. Description of the Study Population 30
   - 2.7. Literary Sources and Data 31

3. STUDY OBJECTIVES AND ENDPOINTS 32

4. STUDY DESIGN 33
   - 4.1. Study Design Description 33
   - 4.2. Pharmacokinetic Study 39
     - 4.2.1. Pharmacokinetic Substudy (PK-substudy) 39
     - 4.2.2. Pharmacokinetic main study (PK-main study) 41
   - 4.3. Randomization 41
   - 4.4. Study Stages and Procedures 41
     - 4.4.1. Screening Procedures 42
     - 4.4.2. Procedures and evaluations during the period of pre-treatment period with tenofovir 42
     - 4.4.3. Randomization Visit 44
     - 4.4.4. Procedures and Evaluations during the Treatment Period 45
     - 4.4.5. Evaluation after the end of the treatment 49
   - 4.5. Premature Drop-out from the Study, Dose Interruption, Dose Correction 50
   - 4.6. Treatment of the Activation of an Inflammatory Process 51
   - 4.7. Detailed Description of the Study Procedures 51
   - 4.8. Study Completion, Suspension or Termination and Withdrawal of a Center or a Patient 56
     - 4.8.1. Study completion as per protocol 56
     - 4.8.2. Study Suspension or Termination 56
     - 4.8.3. Premature termination of a center's participation in the study 57
     - 4.8.4. Premature termination of a patient's participation in the study 57
   - 4.9. List of Data Registered Directly in the CRF 57

5. PATIENT SELECTION AND DROP-OUT 58
   - 5.1. Inclusion Criteria 58
   - 5.2. Exclusion Criteria 58
   - 5.3. Criteria for Premature Withdrawal of Patients from the Study 59

5.3.1. Withdrawal criteria 59
5.3.2. Data on the patients dropped out 60
5.3.3. Subject substitution 60
5.3.4. Follow-up of patients dropped out 60

6. PATIENT TREATMENT 61

6.1. Myrcludex B 61
6.1.1. Dosage form 61
6.1.2. Container Closure System 61
6.1.3. Drug Handling and Storage 61
6.2. Dose and Administration of Myrcludex B 61
6.3. Previous and Concomitant Medication 62
6.4. Excluded medication 64
6.5. Methods of Monitoring Patient Compliance 64

7. EFFICACY EVALUATION 65

7.1. Efficacy Criteria 65
7.2. Efficacy Parameter Evaluation Methods and Terms 65

8. SAFETY EVALUATION 67

8.1. Safety parameter evaluation criteria 67
8.2. Adverse Events 67
8.2.1. Definitions 67
8.2.2. Suspected unexpected serious adverse reaction (SUSAR (SUSAR) 69
8.2.3. Follow-up period and recordkeeping 69
8.2.4. Adverse event characteristics 69
8.2.5. Investigator's reports about serious adverse events 70
8.2.6. Emergency notification 70
8.2.7. Pregnancy 71
8.2.8. After-treatment reporting requirements 71
8.3. Laboratory Abnormalities and Other Deviations Classified as Adverse Events and Serious Adverse Events 71
8.4. Managing Toxic Reactions 72
8.4.1. Grade 1 to 2 laboratory abnormalities 72
8.4.2. Laboratory abnormality or Grade 3 clinical event 72
8.4.3. Laboratory abnormality or Grade 4 clinical event 72
8.5. Risks for Women of Childbearing Age and Risks during Pregnancy 73

9. STATISTICS 74

9.1. Documentation of Statistical Methods 74
9.1.1. General principles 74
9.1.2. Demographic and baseline characteristics 74
9.1.3. Efficacy analysis methods 74
9.1.4. Safety analysis methods 74
9.2. Scheduled Number of Subjects 75
9.3. Applicable Significance Level 76
9.4. Study Termination Criteria 76
9.5. Procedures for Accounting Missing Data not to be Analyzed 77
9.6. Procedures for Reporting Any Deviations from the Original Statistical Plan 77
9.7. Selection of participant for the statistical analysis 77

10. DIRECT ACCESS TO SOURSE DATA/DOCUMENTS 78

10.1. Access and Verification of Source Data and Records 78
10.2. Access to Additional Information 78

11. QUALITY CONTROL AND QUALITY ASSURANCE 78

11.1. Periodic Monitoring 78
11.2. Audit and Inspection 79

12. LEGAL AND ETHICAL ISSUES IN STUDY MANAGEMENT 81

12.1. General requirements 81
12.2. Ethical Conduct of the Study 81
12.3. Council on Ethics and Local Ethics Committee 81
12.4. Regulatory Approval 81
12.5. Periodic Informing of the Independent Ethics Committee 81
12.6. Notification to Regulatory Authorities 82
12.7. Information for the Patient and Informed Consent Form 82

13. DATA MANAGEMENT AND RECORDKEEPING 83

13.1. Clinical Study Documents 83
13.2. Presentation (Delivery) of Study Documents and Materials 83
13.3. Primary Documentation 83
13.4. Data Collection: Case Report Forms (CRFs) 84
13.5. Data Processing and Introduction of Amendments to eCRFs 84
13.6. Confidentiality of Patient Data 84
13.7. Investigator File (Study Documentation Log) 85
13.8. Data Archiving 85

14. FINANCING AND INSURANCE 85

15. PUBLICATION AND STUDY RESULT USAGE 87

16. FINAL REPORT 87

17. CONFIDENTIALITY 88

18. PROTOCOL AMENDMENTS AND/OR PROTOCOL REVIEW 88

19. REFERENCES 89

LIST OF FIGURES

Figure 1a. Graphical scheme of the Phase II clinical study. 34
Figure 2b. Graphical scheme of the Phase III clinical study. 35

LIST OF TABLES

Table 1. Study diagram for Phases II and III. 36
Table 2 Classification of Skin Adverse Events, Associated with the Study drug Injections 72

PROTOCOL SYNOPSIS

Protocol No.: MYR 202 **Study drug:** Myrcludex B

Study title:	Multicenter, Open-Labeled, Randomized Clinical Study of the 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
Clinical phase:	II-III phase.
Key information:	The HDV is a small RNA virus that needs auxiliary functions from the HBV for its assembly and multiplication, and that uses the HBV envelope to release the virus and infect new cells. Approximately 5-15% of cases of chronic HBV infection show the infection with HDV. Several studies have shown that chronic HDV infection leads to a more severe form of liver disease than chronic HBV monoinfection, accompanied by faster progression of fibrosis, an increased risk of hepatocellular carcinoma, and early decompensation in addition to fibroid induration. The recent study in Italy, in which patients with hepatitis D had been observed for 28 years, showed that 25% of patients with fibroid induration had HCC and that liver failure led to death in three-fifths of patients (Romeo et al, 2009). Fibroid induration and hepatic cancer develop 10-15 years earlier when there is a co-infection with HBV/HDV, and the 5-year mortality of co-infected patients is twice higher than that of the HBV-infected patients (Recommendations for the prevention, diagnosis and treatment of HBV infection in Germany, Cornberg et al. 2007). The current possibilities for treating patients with hepatitis D are extremely limited, since interferon-alpha allows to achieve complete suppression of HDV activity in a small part of patients only: wherein, the treatment is accompanied by significant side effects and is characterized by high cost. PEG-INF-a has also been used in small studies for the treatment of hepatitis D, leading to a sustained virology response in about 20% of patients. In addition, the nucleoside and nucleotide analogues used to treat HBV are ineffective in HDV treatment. There remains a critical unmet medical need for new drugs for the treatment of chronic HDV infection, since essentially there are no treatment options for 75% of patients with the co-infection with HBV/HDV.
Description of the patient population:	The study will include patients with chronic HDV infection with positive HDV RNA at the screening stage to confirm the effectiveness of the treatment with Myrcludex B in this category of patients. Primary data on the efficacy of Myrcludex B in the treatment of patients with chronic viral hepatitis B with delta agent were obtained in the Phase Ib / IIa clinical study. In the Phase Ib/IIa study, treatment with Myrcludex B resulted in the increase of HDV RNA and ALT levels in patients with HDV infection. Out of 24 subjects in the Phase Ib/IIa, 10 patients had cirrhosis or had already undergone the IF therapy. In this patient population with the most limited therapeutic options, the possibility of a positive response to the treatment with Myrcludex B was demonstrated. Thus, the present study will include patients suffering from chronic hepatitis B with delta agent in whom the prior IF therapy has been ineffective or, in the opinion of the investigating physician, is currently contraindicated (including cases of interferon intolerance in the past medical history), as well as patients with hepatic cirrhosis. Inclusion of such a patient population is justified both ethically and by the previous study results.
Number of patients:	<u>Phase II</u> Screening will be performed on 200 patients, 120 of them will be randomized to one of 4 treatment Arms in the ratio of 1:1:1:1. <u>Phase III</u> The number of patients required to be enrolled in phase III will be calculated on the basis of data of the Interim report on the Clinical Study Results performed as a part of phase II. In Phase III, patients will be randomized to one of 2 treatment Arms in the ratio of 1:1.
Study design:	<u>Justification of the Design</u> The following features of the study drug (Myrcludex B): − it is administrated to treat chronic hepatitis B with delta agent - the most severe form of viral hepatitis; − it has an orphan status in the European Union and the United States; − there is currently no effective standard treatment for chronic hepatitis B with delta agent; − it has the ability to simulate a dose / response reaction based on the viral kinetics determine the availability of the possibility of using a two-phase adaptive design for the planned clinical study, with its assignment to phase II / III.

	The possibility of using an adaptive design in clinical studies conducted on small patient populations, such as the population of patients with chronic hepatitis B with delta agent, is also described in the European Medicines Agency (EMA) [GUIDELINE ON CLINICAL STUDIES IN SMALL POPULATIONS. London, 27 July 2006. Doc. Ref. CHMP/EWP/83561/2005]. The methodology for the planned Phase II / III study is based on EMA guidelines [REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL STUDIES PLANNED WITH AN ADAPTIVE DESIGN. London, 18 October 2007. Doc. Ref. CHMP/EWP/2459/02]. This is a multicenter, open-labeled, randomized clinical study. Phase II Taking into account the dropout of patients at the stage of Screening, approximately 200 patients will undergo Screening procedures, and 120 of them will be randomized into 4 treatment Arms in the ratio of 1:1:1:1: **Arm A (30 patients**): Myrcludex B 2 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy. **Arm B (30 patients):** Myrcludex B 5 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy. **Arm C (30 patients):** Myrcludex B 10 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy. **Arm D (30 patients):** tenofovir treatment for 48 weeks. The main part of the study includes Screening period of 28 days (day -28/-1), a pre-treatment period for patients, for whoma pre-treatment periodwith tenofovir, of 84 days is indicated, baseline randomization visit (Day 1) and a 24-week study period., Follow-up period will be 24 weeks for all treatment arms. Screening During the screening period (up to 28 days before the first drug administration and also the period of preliminary therapy (if applicable)), the following examinations will be performed: informed consent form signing, physical examination, laboratory tests, serological tests (HIV, HCV antibodies), HCV RNA in patients with anti-HCV antibodies, antibodies to HDV, HDV RNA, evaluation of inclusion/exclusion criteria, ultrasound, urine pregnancy test, alcohol-breath test, urine drug screen (test strips). During the screening, patients will undergo a liver biopsy study, with the determination of the level of hepatic necroinflammation and fibrosis. An immunohistochemical analysis of HDV RNA-positive cells will be performed A part of the biopsy material will be frozen to determine intrahepatic parameters. No use of maintenance drugs (for example, to stimulate the growth of platelets) is allowed. A liver biopsy study may be replaced, by the decision of the Investigator, with transient elastometry (fibroscan). Tenofovir Pre-treatment Period All patients who meet inclusion/exclusion criteria and who have not been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatment will receive the protocol-specified nucleotide analogue, tenofovir, for 12 weeks prior to randomization. Randomization visit All patients who meet inclusion/exclusion criteria and who have been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatment or pre-treated with tenofovir as per the protocol will be invited to a randomization visit: the following examinations will be conducted: physical examination, weight measurements, safety laboratory tests, virology parameters, serum marker for fibrosis, immunogenicity, HBV and HDV genotyping and resistance analysis (in patients who have not underwent prior treatment with tenofovir). All evaluations performed during this visit should be qualified as the main parameters for safety monitoring and should not be qualified as the inclusion/exclusion criteria. During the randomization visit, after completion of all procedures specified in the protocol, patients will be randomized to one of 4 treatment Arms and will receive the study drug for the first 28 days of use. Treatment period A treatment with the study drug on combination with tenofovir, or with tenofovir alone, will last for 24 weeks, followed by a 24-week follow-up period. Treatment will be conducted in an outpatient setting (except hospitalization for pharmacokinetic study and liver biopsy). The follow-up period Follow-up period will last for 24 weeks. During this period, patients from all groups will receive treatment with tenofovir.

Evaluations

A detailed schedule of evaluations performed is presented in the study design.

Pharmacokinetic study of Myrcludex B and study of systemic (general) metabolic CYP3A activity:

1. Supportive pharmacokinetic study (PK-substudy)

1.1. Substudy of Myrcludex B pharmacokinetics

10 patients from Arms A, B and C (total 30) will participate in the pharmacokinetic substudy. On day 1-2 and on day 14-15 of the drug administration, the patients will be hospitalized to the appropriate study site for blood sampling for PK study.

Blood sampling time for the PK analysis: before the administration of Myrcludex B and MDZ, and in 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 (hh:min) after the administration of Myrcludex B.

1.2. Substudy of the systemic (general) metabolic CYP3A activity

It is also planned to study the P450 (CYP3A) cytochrome activity in 10 patients from Arms A, B and C (total 30), as a part the pharmacokinetic substudy (PK-substudy).

Performance of this substudy is due to the fact that CYP3A is involved in the metabolism of about 50% of currently registered drugs and is the most common isoenzyme from the cytochrome family with localization in liver and intestines.

To study the metabolic CYP3A activity in patients enrolled in the study, it is planned to use data on the pharmacokinetics of the benzodiazepine derivative, Midazolam (MDZ).

In clinical practice, MDZ is used in patients with sleep disturbance, for premedication and sedation, and as an initial narcosis. In the planned substudy, patients will be injected with MDZ intravenously (iv) in a microdose (10 μg) that is unable to have any therapeutic effect due to the fact that the MDZ microdose is significantly less than the no observed adverse effect level (NOAEL) in humans. [Hohmann N. et al. Midazolam microdose to determine systemic and pre-systemic metabolic CYP3A activity in humans // Br J Clin Pharmacol /2014/79:2/278–285].

The possibility of using MDZ as an agent for studying the systemic metabolic CYP3A activity is regulated by the EMA guidelines [EMA. Guideline on the investigation of drug interactions. 2012, Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf] и FDA [CDER. Guidance for industry drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations. 2012, Available at // http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm292362.pdf].

The introduction of MDZ and its PK study is planned during the following time intervals:

– day (-13) – day (-12) [Visit 04] apart from the injection and PK-study of Myrcludex B;
– day 1 – day 2 [Visit 1] together with the injection and PK-study of Myrcludex B;
– day 14 – day 15 [Visit 3] together with the injection and PK-study of Myrcludex B.

On day (-13-12), the PK of Midazolam is studied before starting the treatment with Myrcludex B at the following time points: before the injection of MDZ and in 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 (hh:min) after the injection of MDZ.

To study the PK of MDZ on day 1 and day 14, Midazolam is administered prior to the administration of the study drug Myrcludex B, and blood sampling (except for the zero line) is performed after the administration of Myrcludex B. The blood sampling for MDZ analysis: before the administration of MDZ and Myrcludex B and in 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 (hh:min) after the administration of Myrcludex B.

2. **Pharmacokinetic main study (PK-main study).** For a more accurate study of the possible cumulation of the study drug in all patients treated with Myrcludex B, blood sampling points for the pharmacokinetic study are assigned: Week 4, 8, 12, 16, 20, 24 (1 hour +/- 15 minutes after the drug administration). Patients not enrolled in the pharmacokinetic substudy are assigned with a blood sampling point at the randomization visit (1 hour +/- 15 minutes after the drug administration).

Duration of the Study

Up to 64 weeks, including screening

Phase III

The number of patients required to be enrolled in phase III will be calculated on the basis of data of the Interim report performed as a part of phase II. Patients will be randomized to one of 2 treatment groups in the ratio of 1:1.

	Group I: Myrcludex B in the optimal dosage /subcutaneously (s/c) for 24 weeks + tenofovir, with the 24-week follow-up on treatment with tenofovir. **Group II:** treatment with tenofovir for 48 weeks. The main part of the study includes Screening period of 28 days (Day -28/-1), pre treatment period for patients, for whom a pre-treatment periodwith tenofovir is indicated to, lasting up to 84 days, baseline randomization visit (Day 1) and a 24-week study period. the follow-up period will be 24 weeks for all treatment arms. Screening During the screening period (up to 28 days before the first drug administration), the following examinations will be performed: physical examination, laboratory tests, serological tests (HIV, HCV antibodies), HCV RNA in patients with anti-HCV antibodies, antibodies to HDV, HDV RNA, evaluation of inclusion/exclusion criteria. During the screening, patients will undergo a liver biopsy study, with the determination of the level of hepatic necroinflammation and fibrosis. An immunohistochemical analysis of HDV RNA-positive cells will be performed. A part of the biopsy material will be frozen to determine intrahepatic parameters. No use of maintenance drugs (for example, to stimulate the growth of platelets) is allowed. A liver biopsy study may be replaced, by the decision of the Investigator, with transient elastometry (fibroscan). Tenofovir Pre-treatment Period All patients who meet the inclusion / exclusion criteria and who have not been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatment will receive the protocol-specified nucleotide analogue, tenofovir, for 12 weeks prior to the randomization. Randomization visit All patients who meet inclusion / exclusion criteria and who have been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatment or pre-treated with tenofovir as per the protocol will be invited to a randomization visit: the following examinations will be conducted: physical examination, weight measurements, safety laboratory tests, virology parameters, serum marker for fibrosis, immunogenicity, HBV and HDV genotyping and resistance analysis (in patients who have not underwent prior treatment with tenofovir). All evaluations performed during this visit should be qualified as the main parameters for safety monitoring and should not be qualified as the inclusion/ exclusion criteria. During the randomization visit, after completion of all procedures specified in the protocol, patients will be randomized to one of the 2 treatment and will receive the study drug for the first 28 days of use. Treatment period A treatment with the study drug on combination with tenofovir, or with tenofovir alone, will last for 24 weeks, followed by a 24-week follow-up period. Treatment will be conducted in an outpatient setting. The follow-up period Follow-up period will last for 24 weeks. During this period, patients from all groups will receive treatment with tenofovir. Evaluations A detailed schedule of evaluations performed is presented in the study design. Duration of the Study Up to 64 weeks, including screening Interim and final data analysis as a part of Phase II When the last patient completes a 24-week treatment period as a part of Phase II clinical study, patients from all treatment arms will be analyzed for viral load based on PCR results for HDV RNA (negative PCR results for HDV RNA or decrease by ≥2 log from baseline at Week 24 will be considered as the primary endpoint). The results of this study will be used to draw up the Interim report on the results of the Phase II clinical study, herewith, all patients will continue to be treated with tenofovir. During the Interim analysis, the recruitment of new patients into the clinical study will be suspended. Based on the data from the Phase II Interim Report, the optimal (based on efficacy and safety analysis) dosage for the second part of the clinical study (corresponding to phase III) will be selected, and the required additional number of patients to be enrolled in Phase III will be calculated. When calculating the sample size, the correction for a plurality of comparisons (Pocock correction) will be taken into account with due regard to two statistical analyzes (at treatment week 24 of phase II and treatment week 24 of phase

	III). The results of the Phase II Interim analysis will be submitted to the Ministry of Health of the Russian Federation. If a statistically significant conclusion is obtained based on the results of phase II on the statistical superiority of study drug in chosen dosage over the control group with respect to the primary endpoint at the bilateral significance level of 5%, then the recruitment of patients into Phase III of the study will not be performed, and the statistical analysis will be performed as a part of the Interim Report on Phase II and the Final Report on the Clinical Study Results. When the last patient completes the follow-up period of the first part of the clinical study, the data on the treatment studied will be analyzed in all patients completing 48-week treatment period in phase II, the Final Report on the Results of the Phase II Clinical Study will be prepared and submitted to the regulatory authorities. <u>Interim and final data analysis as a part of Phase III</u> When the last patient completes a 24-week treatment period as a part of Phase III clinical study, patients from all treatment arms will be analyzed for viral load based on PCR results for HDV RNA. These results will be used for preparing the Interim report on the results of the Phase III clinical study, herewith, all patients will continue to be treated with tenofovir. Negative PCR results for HDV RNA or decrease by ≥2 log from baseline to Week 24 will be considered as the primary endpoint. The results of the Interim Report on the Results of the Phase III Clinical Study will be submitted to the regulatory authorities with the aim of the study drug marketing authorization. When the last patient completes the follow-up period of the second part of the clinical study, the results of the treatment studied will be analyzed in all patients who have completed the 48-week treatment period, the Final Report on the Clinical Study Results will be prepared and submitted to the regulatory authorities.
Endpoints:	**Criteria for efficacy parameter evaluation for phases II and III** **Primary endpoint:** ● The negative PCR result for HDV RNA or a decrease by ≥2 log from baseline to week 24. **Secondary endpoints:** ● The duration of the effect (no increase) on HDV RNA at Week 24 after treatment (study week 48) compared to the results obtained at the end of the treatment period (study week 24). ● The presence of a combined response: the negative PCR result for HDV RNA, or a decrease by ≥2 log and normalization of ALT at Week 24 compared to the results obtained before the treatment with the study drug. ● Changes in ALT values at Week 24 and Week 48 compared to results obtained before the treatment with the study drug. ● Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) according to the liver biopsy results or the lack of fibrosis progression based on transient elastometry (fibroscan) at Week 24 compared to the results obtained before the treatment with the study drug. ● Canges (no increase) in marker for fibrosis – alpha-2 macroglobulin in the serum at Week 24 and Week 48 compared to the results obtained before the treatment with the study drug. ● Changes in HBsAg (decrease levels, disappearance of HBsAg, HBsAg antibodies) at Week 24 and Week 48 compared to the results obtained before the treatment with the study drug. ● Changes in HBV DNA levels at Week 24 and Week 48 compared to the results obtained before the treatment with the study drug. **Criteria for safety parameter evaluation for phases II and III** ● Data on adverse events, physical examination, weight measurement, vital signs examination, 12-lead ECG, hematology, coagulation panel, blood chemistry, urinalysis, serum bile acid test. ● Antibody response to Myrcludex B.
Dosage strength:	<u>Study drug</u> <u>Phase II</u> A 2 mg dose was effective in the Phase IIa studies in patients with HDV. A 10 mg dose showed the most pronounced effect in the Phase Ib/IIa clinical studies in patients with chronic hepatitis B. <u>Phase III</u> The dosage strength will be selected based on the Phase II results. <u>The drug for the treatment of the concurrent infection with the hepatitis B virus</u> The drug for the treatment of the concurrent infection with hepatitis B virus – tenofovir, is approved for the

	treatment of chronic HBV infection. The dose of tenofovir will be selected according to the prescribing information.
Inclusion criteria (similar both for Phases II and III):	1. Age from 18 through 65 years at the time of granting of a written informed consent for the participation in the study. 2. Presence of HBsAg in serum within at least 6 months before the screening period. 3. Anti-HDV antibodies in serum within at least 6 months. 4. Positive PCR on HDV RNA in serum during screening. 5. Patients with hepatic cirrhosis, regardless of prior treatment with interferons. 6. Patients without hepatic cirrhosis in whom prior IF treatment was ineffective or, in the opinion of the investigator, is currently contraindicated (including cases of interferon intolerance in the past medical history)[1]. 7. Alanine aminotransferase index is >1 UNL, but less than 10 UNL. 8. Prior treatment with nucleotide / nucleoside analogues for at least 12 weeks prior to the expected initiation date of the treatment period with the study drug or patient's consent to take tenofovir for at least 12 weeks before the planned start of study treatment. 9. Negative urine pregnancy test in female subjects of childbearing age: 10. Inclusion criteria for women. • Menopause within at least 2 years, or • Surgical sterilization (complete hysterectomy or bilateral oophorectomy, or ligation of both fallopian tubes, staples, or other method of sterilization), or • No heterosexual contactsduring the study period, or • Consent to use a highly effective contraceptive method (a double barrier method or a combination of a barrier method with a hormonal or intrauterine contraceptive) during the study period and within 3 months after the last dose of the study drug 11. Men must agree to use a highly effective contraceptive method (double barrier methods or a combination of a barrier method and a hormonal or intrauterine contraceptive used by a female partner) and not be a sperm donor during the study period and within three months after the last dose of the study drug.
Exclusion **criteria (similar both for Phases II and III):**	1. The Child Pugh score should be B-C or above 6 points; 2. The co-infection with hepatitis C virus (HCV) or HIV. Patients with the presence of anti-HCV antibodies in the presence of negative HCV RNA at the stage of screening are considered acceptable to participate in the study; 3. Creatinine clearance is <60 ml/min; 4. Total bilirubin is> 34.2 μmol / L. Patients with an increased total bilirubin level may be included in the study after consulting with the Medical Research Monitor if it is clearly established that such an increase is an evidence of Gilbert's syndrome. 5. Malignant tumors in any organ system, including hepatocellular carcinoma, in the past or current history. 6. Systemic connective-tissue diseases. 7. Chronic heart failure of functional classes III-IV according to NYHA (New York Heart Association) classification. 8. Patients with uncontrolled arterial hypertension (BP> 150/100 mm Hg affected by the administration of antihypertensive drugs) during previous 3 months before the initiation of the clinical phase. 9. Patients with past or unstable concomitant diseases, or clinical conditions that prevent the inclusion of this patient in the study. 10. Patients with mental disorders or social circumstances that interfere with the requirements of the protocol. 11. Decompensated liver disease in the current or previous history, including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding esophageal varices; 12. WBC count is <3000 cells/mm^3;

[1] Enrollment of patients who have previously undergone IF treatment is possible not earlier than in 30 days after the last administration of interferon.

	13. Neutrophil count is <1500 cells/mm^3; 14. Platelet count is <60,000 cells/mm^3; 15. A patient takes illegal psychiatric drugs at the time of screening; 16. Treatment with Interferon within 30 days before screening; 17. Transplantation of a solid organ in the past history; 18. Patients who abuse alcohol now or have abused it for 6 months before the enrollment; 19. A history of a disease requiring regular use of systemic corticosteroids; 20. Pregnant and lactating women; 21. Participation in other clinical studies within 30 days before screening; 22. Patients who have received Myrcludex B as a part of previous studies.
Statistical analysis of the Phase II and III study results:	Primary efficacy analysis will be based on the following efficacy endpoint: • The negative PCR result on HDV RNA or decrease by ≥2 log10 at treatment week 24 compared to the data obtained before the initiation of treatment with the study drug. In Phase II, treatment arms will be compared using the Wald test for Superiority by Margin of 5%; 95% Clopper-Pearson confidence interval will also be calculated for treatment response rates (for each treatment arm). Each experimental treatment arm (Myrcludex B) will be compared to the control arm receiving tenofovir alone. Each Myrcludex B treatment arm will be compared to the control arm separately (Arm A vs Arm D, Arm B vs Arm D, Arm C vs Arm D). Hypotheses will be tested sequentially, using Bonferroni-Holm method. Null hypotheses will be defined for each prior test, and appropriate p-values will be calculated (based on data obtained in the study). After that, null hypotheses will be rejected in descending order of respective p-values for critical values of type I error (α), calculated as $\alpha/(k - i + 1)$, where k is the number of planned comparisons and i is the sequential number of the comparison . In Phase III, the hypothesis of statistical superiority will be tested with the help of the two-sided Fisher exact test for the primary efficiency index. Qualitative secondary endpoints (ALT normalization and disappearance of HBsAg/ seroconversion) will be analyzed using the Fisher's exact test. Quantitative secondary endpoints (serum fibrosis marker, HBsAg and HBV DNA) will be presented as absolute values and changes from baseline. To compare treatment arms on the basis of endpoints, two-sided Wilcoxon rank sum test will be employed with adjustment at the significance level of 0.0167. If the assumptions necessary for carrying out parametric approach are not violated (will be verified using graphical methods), parametric analogues of the above methods will be used: analysis of variance ANOVA/ analysis of covariance ANCOVA, the paired Student's t-test for dependent samples. Numerical safety data will be presented as summary tables of descriptive statistics for each treatment arms. Descriptive statistics will be provided for each numerical safety endpoint. AEs will be tabulated per treatment group and System Organ Class (SOC) at Preferred Term (PT) level of MedDRA. SAEs will be reported in form of narratives. Vital sign and laboratory data as well as change from baseline will be summarized (where applicable) by visit of assessment and by treatment group. In addition, shifts in laboratory parameters will be presented by treatment group.

LIST OF ABBREVIATIONS

AFP - alfa-fetoprotein.
ALT - alanine transaminase.
AST - aspartate transaminase.
UNL - upper normal level.
WFI - water for injection.
HPLC - high-performance liquid chromatography.
HPLC-MS - high-performance liquid chromatography with mass spectrometry.
HCC - hepatocellular carcinoma
NOAEL - no observed adverse effect level.
DLT - dose-limiting toxicity.
DNA - deoxyribonucleic acid.
EP - European Pharmacopoeia.
IL - interleukin.
IMP - investigational medicinal product.
INF-α - interferon-alpha.
SD - study drug.
CRF - case report form.
IC - ion chromatography.
CK - creatine kinase.
CT - computer tomography.
LDG - lactate-dehydrogenase.
IU - international unit.
MRI - magnetic resonance imaging.
GCP - good clinical practice.
IEC - Independent Ethics Committee.
AE - adverse event.
RH - relative humidity.
s/c - subcutaneously.
SAP - statistical analysis plan.
RIA - radioassay.
SCR - screening period.
C_{avg} - average concentration.
C_{max} - maximum concentration.
C_{min} - minimum concentration.
SOC - system organ class.
SOP - standard operating procedure.
SAE - serious adverse event.
cccDNA -cyclic covalently closed deoxyribonucleic acid.
ICF - informed consent form.
PK - pharmakokinetics.
TNFα - tumour necrosis factor α.
CHB - chronic hepatitis B.
CHD - chronic hepatitis B with delta agent.
AP - alkaline phosphatase.
ECG - electrocardiogram.
IRB - Institutional Review Board.
AUC_{0-t} - area under the curve from the moment of administration of the drug to the determined time point t.
AUC_{tau} - area under the curve during the dose interval.
CTCAE - Common Terminology Criteria for Adverse Events.

CRP - C-reactive protein.
DNMEASL - European Association for the Study of the Liver.
FDA - Food and Drug Administration.
GCP - Good Clinical Practice.
GGT - Gamma-glutamyl transferase.
GMP - Good Manufacturing Practice.
HBV - hepatitis B virus.
HBeAg - Hepatitis B envelope antigen.
HBsAg - Hepatitis B surface antigen.
HCC - hepatocellular carcinoma.
HCV - hepatitis C virus.
HDV - hepatitis Delta virus (D).
HED - human equivalent dose.
HLA - human leukocyte antigen.
ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
INR - international normalized ratio.
IMPD - investigational medical product dossier.
IWRS - Interactive Web Response System.
MCH - mean corpuscular haemoglobin.
MCHC - mean corpuscular hemoglobin concentration.
MCV - mean corpuscular volume.
MDZ – Midazolam.
MedDRA - Medical Dictionary for Regulatory Activities.
MRT - mean residence time.
MXB - Myrcludex B.
NCI - National Cancer Institute (USA).
NYHA - New York Heart Association.
NOAEL - no observed adverse effect level.
NOEL - no observed effect level.
NTCP - sodium-taurocholate cotransporting polypeptide.
PBMC - peripheral mononuclear blood cells.
PT - Preferred terms
SOC - System Organ Class
SUSAR - suspected unexpected serious adverse reaction.
TEC - target therapeutic effect concentration.
T_{max} - time to maximum concentration.
TMF - Study Master File (Clinical study Master File).
TRAE - Therapy related adverse event.
$T_{1/2}$ - terminal elimination half-life.

1. BACKGROUND INFORMATION

1.1. Protocol Identification

Title:	Multicenter, Open-Labeled, Randomized Clinical Study of the 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:	7.0
Date:	September 28, 2017

1.2. Contact Information about Sponsor

Sponsor:	Full name of the contact person: Yana Anatolievna Deloveri Position: Director General Name of the institution: Hepatera LLC, Russia Address: 109240, Moscow, Verkhnyaya Radishchevskaya Street, 12/19, bldg. 1 Tel./fax: +7 (495) 726-52-53 E-mail: deloveri@ammaxwell.ru.

1.3. Page of the Protocol Approval by Sponsor

<table>
<tr><td>Protocol No.:</td><td colspan="2">MYR 202</td></tr>
<tr><td colspan="3">The study «Multicenter, Open-Labeled, Randomized Clinical Study of the 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» has been approved for conducting in accordance with the Protocol, the principles of Good Clinical Practice and applicable regulatory requirements. The signatures of these persons guarantee that they have accepted the final version of the protocol:</td></tr>
<tr><td>Sponsor
Hepatera LLC</td><td>Sponsor's Representative 1
Full name: Yana Anatolievna Deloveri
Position: Director General
Name of the institution: Hepatera LLC, Russia
Address: 109240, Moscow, Verkhnyaya Radishchevskaya Street, 12/19, bldg. 1
Tel./fax: +7 (495) 726-52-53
E-mail: deloveri@ammaxwell.ru</td><td>……..
Date

……..
Signature</td></tr>
</table>

1.4. Contact Information about Clinical Centers and Investigators

1) List of medical organizations in which the MYR 202 clinical trial will be conducted:

Clinical Site 1	"Moscow Regional Research Clinical Institute n.a. M.F. Vladimirskiy", 61/2, Shchepkina str., 129110, Moscow, Russia
Principal Investigator	Pavel Olegovich Bogomolov, MD, PhD
Clinical Site 2	State Budgetary Institution of Healthcare "Stavropol Regional Clinical Hospital", 1, ulitsa Semashko, 355000, Stavropol, Russia
Principal Investigator	Nataliya Ioganovna Geyvandova, MD, DMSc
Clinical Site 4	State Budgetary institution of the Republic of Sakha (Yakutia) "Yakutsk Clinical Hospital" 677005, Republic of Sakha (Yakutia), Yakutsk, ul. Stadukhina, 81, build. 5
Principal Investigator	Snezhana Spiridonovna Slepcova
Clinical Site 5	State Budgetary Healthcare Institution "Moscow Clinical Scientific and Practical Center of the Department of Public Health of Moscow" 111123, Moscow, Highway Enthusiasts, 86
Principal Investigator	Igor Gennadievich Bakulin
Clinical Site 6	State Autonomous Healthcare Institution "Republican Clinical Infectious Diseases Hospital named after Prof. A.F. Agafonov "(SAHI RCID) 420138, Republic of Tatarstan, Kazan, Pobedy Avenue, 83
Principal Investigator	Ilsiyar Mansurovna Khaertunova
Clinical Site 12	State Budgetary Educational Institution of Higher Professional Education "South Ural State Medical university" of the Ministry of Healthcare of the Russian Federation, 2 Cherkasskaya str., 454052, Chelyabinsk, Russia
Principal Investigator	Olga Igorevna, Sagalova, MD, PhD, DMSc
Clinical Site 13	State Budget Health Institution of Moscow "Infectious Clinical Hospital No. 1 of the Moscow Healthcare Department" 125367, Moscow, Volokolamskoye road, 63
Principal Investigator	Marina Rusanova from January 13, 2017 (Elena Andreevna Nurmukhametova, till 13.01.2017)
Clinical Site 16	LLC "Clinic of Modern Medicine" 121293, Moscow, Ploschad Pobedi, 2, bldg. 1
Principal Investigator	Tatyana Vladimirovna Stepanova
Clinical Site 18	State Budgetary Educational Institution of Higher Professional Education "Novosibirsk State Medical University" of the Ministry of Health of the Russian Federation 630091, Novosibirsk, Krasny prospect, 52
Principal Investigator	Marina Fedorovna Osipenko
Clinical Site 19	Medical Company "Hepatolog" LLC, 36A, Serdobskaya str., 430063, Samara, Russia
Principal Investigator	Vyacheslav Gennadievich Morozov, MD, PhD, DMSc
Clinical Site 20	Federal budgetary research institution Central Research Institute of Epidemiology 111123, Russia, Moscow, ul. Novogireevskaya, house 3a
Principal Investigator	Vladimir Petrovich Chulanov

2) List of medical organizations participating in the pharmacokinetic supplementary study:

Clinical Site 1	"Moscow Regional Research Clinical Institute n.a. M.F. Vladimirskiy", 61/2, Shchepkina str., 129110, Moscow, Russia
Principal Investigator	Pavel Olegovich Bogomolov, MD, PhD
Clinical Site 12	State Budgetary Educational Institution of Higher Professional Education "South Ural State Medical university" of the Ministry of Healthcare of the Russian Federation, 2 Cherkasskaya str., 454052, Chelyabinsk, Russia
Principal Investigator	Olga Igorevna, Sagalova, MD, PhD, DMSc
Clinical Site 21	Private institution - educational organization of higher education "Medical University "Reaviz " 443001, Samara, ul. Chapaevskaya, 227
Principal Investigator	Kachkovsky Michael Arkadevich

1.5. Investigator Agreement

I do confirm that I have read and understood this protocol, the Clinical Investigation Brochure, including the potential risks and side effects of the drug, and other information about the medication and study provided by the Sponsor.

I do agree to perform this study in accordance with the requirements of this protocol, and also to protect patient's rights, safety, confidentiality and well-being in accordance with ethical requirements set out in the Declaration of Helsinki of the WMA, requirements of Federal Law No. 61-FZ dd. April 12, 2010 "On Medicine Circulation"; principles of the National Standard of the Russian Federation GOST 52379-2005 "Good Clinical Practice" (hereinafter GCP) and other regulatory requirements of the Russian Federation.

I do agree to make changes in the protocol only after notifying the Sponsor, unless it is necessary to protect safety, rights and well-being of patients. I fully understand that any changes made by an Investigator(s) without prior discussion with the Sponsor's representative will constitute a violation of the protocol, including any bridging studies or procedures performed by patients (other than those necessary for patients' well-being).

I do agree to perform or monitor the described study personally.

I do agree to inform patients that the drugs are used for research purposes; I will ensure the compliance with the requirements associated with the receipt of an informed consent, following the approval of the Council on Ethics and the local Independent Ethics Committee (IEC) and in accordance with the principles of the GCP.

In accordance with the principles of the GCP, I do agree to inform the Sponsor of the adverse events that have developed during the study.

I do agree to ensure that all employees, colleagues and parties involved in the study are informed of their obligations to comply with the arrangements described above.

I do agree to keep faithful and accurate records, as well as to provide these records for analysis in accordance with the principles of the GCP.

I will ensure that the local IEC, which operates in accordance with the requirements of the GCP, is responsible for conducting an ethical review, as well as for approving the clinical study. I do also agree to promptly inform the local IEC about all changes in research activities and all unexpected problems, including patient risk and other aspects. In addition, I will not make any changes to the study without the approval of the Council on Ethics/local IEC, except for necessary cases of eliminating the apparent unexpected threat to patients' health and safety.

I am ready to provide the direct access to primary documents and agree for the audit held by auditors from the Sponsor's representatives and the regulatory agencies. I do guarantee that the investigational product(s) supplied by the Sponsor will only be used in the manner as described in this protocol.

I do agree to comply with all other requirements regarding the liabilities of clinical investigators, as well as all other important requirements of the Good Clinical Practice.

Investigator:

Signature: _____

Full name: _____

Position: _____

Institution: _____

Address: _____

Date: _____ (dd.mm.yyyy)

1.6. Contact Information about the Central Clinical Laboratory and Other Study Services

1) Central laboratory №1 (Immunogenicity)

Prolytic GmbH

Alt Fechenheim 34
D-60386 Frankfurt am Main, Germany

Contacts:
Dr. Elizabeth Wilson, Email: Elizabeth.Wilson@prolytic.de
DM, Prof. Dorothee Krone, Email: Dorothee.Krone@prolytic.de
Tel:+49 (0) 69 4109 2534, Fax: +49 (0) 69 4269 4784

2) Central laboratory №2 (Virology)

Medizinische Hochschule Hannover
Department of Gastroenterology, Hepatology and Endocrinology (Klinik für Gastroenterologie, Hepatologie und Endokrinologi)

Carl-Neuberg_Straße 1
D-30625 Hannover, Germany

Contacts:
Dr. Patric Lehmann, Email: Lehmann.Patrick@mh-hannover.de
Dr. Birgit Bremer, Email: Bremer.Birgit@mh-hannover.de
Tel:+49 (0) 51 1532 3304

3) Central laboratory №3 (HDV and HBV genotyping, resistance, NTCP polymorphism, bile acids)

Universitätsklinikum Heidelberg
Department of Infectious Diseases, Molecular Virology University (Zentrum für Infektiologie, Abteilung für Molekulare Virologie)

Im Neuenheimer Feld 672
D-69120 Heidelberg, Germany

Contacts:
Dr. Katrin Schöneweis, Email: Katrin.Schoeneweis@med.uni-heidelberg.de
MD, Prof. Stephan Urban, Email: Stephan.Urban@med.uni-heidelberg.de

4) Central laboratory №4 (PK)

Universitätsklinikum Heidelberg
Department of Infectious Diseases, Molecular Virology University (Zentrum für Innere Medizine, Abteilung Klinische Pharmakologie und Pharmakoepidemiologie, Analytisch-Chemisches Labor)

Im Neuenheimer Feld 410
D-69120 Heidelberg, Germany

Contacts:
MSc, PhD., Juergen Burhenne, Email: Juergen.Burhenne@med.uni-heidelberg.de

5) Central laboratory №5 (biopsy study: immunohistochemical study, intrahepatic options)

Universitätsklinikum Hamburg-Eppendorf
Zentrum Innere Medizin (Zentrum Innere Medizin, I. Medizinische Klinik, AG Virushepatitis)

Büro: Raum 332, 3.OG, Haus O58
Martinistraße 52
20246 Hamburg, Germany

Contacts:
DM, Prof. Maura Dandri, Email: m.dandri@uke.de
Dr. Marc Lütgehetmann, Email: m.luetgehetmann@uke.uni-hamburg.de

6) Central laboratory №6 (reception and analysis of the samples on the content of bile acids in the blood plasma, of CBC, coagulogram, biochemical blood analysis, urine analysis, determination of alpha fetoprotein levels and markers of fibrosis (macroglobulin))

Independent Laboratory INVITRO

1, bld 33 Nagatinskaya street; 117105;
Moscow; Russia www.invitro.ru

Russia, 117105, Moscow,
Nahagatinskaya St., 1, building 33

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Tel. + 7 495 258 07 88, доб.5192 / + 7 905 705 11 89

7) Central laboratory № 7 (содержания отдельных желчных кислот в крови)

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Auerbachstr. 112
70376 Stuttgart, Germany

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Dr. rer. nat. Mathias Haag, Email: mathias.haag@ikp-stuttgart.de
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Phone +49 (0)711 / 8101-5429

2. JUSTIFICATION OF STUDY

Hepatitis D with delta agent is an inflammatory hepatic disease caused by the hepatitis D virus, which requires HBsAg for its replication. Hepatitis D virus (HDV) is a hepatotropic virus with a small RNA genome also containing delta antigen. The HDV is at all times associated with HBV infection, since HDV ribonucleoprotein is bundled in HBsAg. The HDV genome is a double-stranded RNA with 1680 bases, it is historically homogeneous with viroids or with RNA of satellite viruses affecting plants [1]. The HDag consists of 2 isoforms – a small 24 kD protein necessary for replication, and a larger 27 kD protein necessary for the virion formation [2]. There are eight genotypes of HDV, while virus of genotype 1 is the most common in the world and in Europe [3].

Hepatitis D virus is a highly pathogenic virus that causes acute and chronic hepatic injury. Despite the fact that incidents of benign disease have been described [4], patients with hepatitis D usually develop advanced liver disease, leading to compensated or decompensated cirrhosis. There is an evidence in the literature that unlike HBV, the HDV can lead to direct cytotoxicity, which can lead to the acceleration of fibrosis [5, 6]. However, the immune system plays an important role in the eradication of infected hepatocytes; the HDV viremia level has no direct connection to histological changes [7]. There are no histological signs that distinguish hepatitis B with delta agent from other forms of viral hepatitis. A biopsy sample taken from a patient with chronic hepatitis D shows signs of portal and periportal inflammation, fragmentary necrosis, often accompanied by fibrosis and cirrhosis. There is a pronounced intraglobular infiltration by mononuclear cells and degenerative changes in hepatocytes [8]. Clinically, hepatitis B with delta agentmay become acute or fulminant, the chronic infection can lead to symptomatic carriage and worsen rapidly to the chronic liver disease.

Chronic hepatitis B with delta agent develops in 70-90% of patients with HDV superinfection. A liver disease associated with HDV has a more progressive course, compared to the chronic hepatitis B, and can lead to cirrhosis in 10-15% of patients in 2 years [9]. Hepatitis B with delta agent is the most severe form of the viral hepatitis in human [10], accompanied by the progression of liver disease, development of cirrhosis and decompensation [11, 12]

A study conducted with a patient cohort observed for a long time in a specialized center showed a clear trend towards a decreased survivability of HBeAg-negative patients with HDV, compared to patients with HBV monoinfection [13]. In endemic populations with HDV infection, liver disease is a serious medical problem. In the study performed in Italy in 1987, anti-HDV antibodies were detected in 40% of patients with hepatic cirrhosis. Despite the fact that in 2000 their percent was reduced to 11% [14], HDV infection continues to be a huge burden for health care service A long-term study showed that 20% of patients suffering from hepatitis B with delta agent over an average of 4 years developed adverse events associated with hepatic injury. During the same period, only 8.5% of patients with HBV monoinfection developed such events [15]. Initially, cirrhosis was diagnosed in 19.8% of patients from this cohort compared to 7.3% of patients with CHB. HDV was the cause of death of 60% of patients in the 28-year study conducted in Italy [16]. The HDV co-infection is associated with a faster progression to fibrosis and cirrhosis, an earlier onset of hepatic complications and an increase in the likelihood of liver transplantation [17-19]. Liver cirrhosis and cancer developed in patients with co-infections with HBV/HDV 10-15 years earlier, and 5-year mortality of patients with co-infection twice as high as that of those with HBV monoinfection [20]. Chronic HDV infection causes cirrhosis and HCC with an average annual rate of 4% and 2.8%, respectively [16].

On average, 5-10% of HBsAg-positive patients who had underwent an examination at specialized centers in Europe had a positive HDV test result. The number of patients with CHD in the EU is estimated to be 145,000. Taking into account that total EU population comprises 505,665,700 people (in 2013), the estimated prevalence rate of HDV among residents of the EU countries, with due regard to the assumptions (95% confidence interval), is 1.6 and 4.7 per 10,000 people, respectively. The prevalence rate of the disease is below the threshold for assigning the drug an orphan product designation, which is 5 cases per 10,000 people.

The amount of data, allowing to estimate the prevalence rate of HDV in the US, is extremely small. In a recent study that evaluated the highly specific center's database, the prevalence rate of HDV among HBsAg carriers was fixed at 8% [21]. 11% of injecting drug partners in Baltimore had a positive HDV test result; 50% of drug users with chronic HBV infection had a positive HDV test result [22]. On average, 5-10% of HBsAg-positive patients followed up in specialized centers have a positive HDV test result. The total number of patients with

CHD in the US is 63,800 (worst-case scenario). It is below the threshold for assigning the drug an orphan product designation that equals to 200 thousand patients.
Therapeutic options for patients with HDV co-infection are extremely limited. Only interferons feature a certain efficacy in a small percentage of patients, showing of a virology and biochemical response in approximately 25% of cases. Antiviral drugs that are effective in the treatment of HBV are ineffective in the treatment of HDV [18]. Several clinical studies have been conducted recently that studied the role of pegylated interferon alfa in the treatment of CHD. The two largest studies on this indication, HIDIT-1 and HIDIT-2, have shown very moderate long-term virology results. In the clinical study HIDIT-1 involving 91 patients with HDV, the effect of pegylated interferon, with adefovir dipivoxil, a nucleotide analogue, and a combination of these two drugs was compared [23]. At week 48, the negative reaction on HDV RNA was achieved in 23% of patients receiving combination threatment, in 24% of patients receiving pegylated interferon and none of the patients receiving adefovir. The effect continued to last until week 24 of the follow-up period. However, in a further follow-up study, it was found that out of 16 patients who had induced negative reaction of HDV RNA at the end of the treatment period, 9 patients had a positive result of the analysis with a median follow-up of 4.5 years (0.5 to 5.5 years) [24]. In the clinical study HIDIT-2, 120 patients received pegylated interferon alfa in combination with tenofovir disoproxil fumarate or without it for 96 weeks. The prolongation of the period of treatment with interferon for up to 96 weeks and the addition of a tenofovir nucleotide analogue did not lead to an increase in the stable virology response rate: 30% of patients in the combination therapy group and 23% of patients in the monotherapy group had negative HDV RNA test results in 24 weeks after the end of treatment. It is remarkable that 20 patients (16%) have completed no treatment course until week 80. A study with 49 patients who received pegylated interferon alfa-2b showed 33% of the negative reaction of HDV RNA at the end of the treatment period (48 weeks) and 25% at the end of the follow-up period [25].
Thus, there remains an acute unsatisfied medical need for new drugs for the treatment of chronic HDV infection, since 75% of patients with co-infection with HBV / HDV have approximately no therapeutic options.

2.1. Name and Description of the Study Drug

2.1.1. Background information

Myrcludex B (MXB) is a lipopeptide consisting of 47 amino acids, and containing a myristoyl residue in the N-terminal and an amidated C-terminal. All amino acids have an L-form.
Molecular formula C248H355N65O72 (net)
Molecular weight 5398.9 g/mol (average weight, net)
Salt form Acetate salt
Physical form white or grayish-white powder
Appearance of the solution clear and transparent
MXB is a 47-amino-acid N-myristoylated lipopeptide of the HBV-L protein. It prevents the penetration of HBV into hepatocytes by blocking the receptor for HBV and HDV, NTCP/SLC10A1 – a transport protein being in charge of the reabsorption of bile acids in the liver. MXV has shown to be efficient against hepatitis B and D viruses in the *in vitro* and *in vivo* preclinical studies. In a clinical study (HBV infection), a viral load reduction was demonstrated, moreover the optimal response was achieved in a patient cohort who received the drug at a dose of 10 mg once a day. *In vitro* studies demonstrated similar efficacy for both HDV and HBV. In the simulation study on animals with immunodeficiency, both the prevention of *de novo* HDV infection and the suppression of the spread of HBV were demonstrated. In a clinical study (HDV infection), a significant decrease in HDV RNA viremia was demonstrated with the daily dose of 2 mg, and 2 out of 7 patients showed negative reaction. This confirms the pronounced dependence of HDV persistence on the ingress of infection of new hepatocytes, and consequently, a higher sensitivity to entry inhibitors. This may be due to the pathophysiological properties of HDV/HBV co-infection, with a higher degree of immune response and inflammation and a possible direct cytopathic effect of HDV, compared to HBV. In addition, the level of HDV RNA is a unique marker of the determination of response in clinical studies. Negative reaction of HDV RNA is a widely used criterion for evaluating of the results of clinical studies on this indication.
MXB will be provided in sterile bottles with the label claim of 2.0 mg and 5.0 mg of Myrcludex B. Before use, the contents of the vial shall be diluted in 1 ml of sterile water for injection. Containers and caps in use shall be

disposable. MXB is intended for parenteral administration. In the Phase I study, healthy volunteers received the drug as a single intravenous injection in a volume of up to 20 mg. In the Phase Ib/IIa studies, patients with chronic HBV and HDV infection received subcutaneous injections at a dose of up to 10 mg per day for up to 24 weeks. In this case, the drug showed a good safety profile.
MXV within the scope of Phase II of this clinical study will be administered at doses of 2, 5 and 10 mg / day / subcutaneously for 24 weeks together with the administration of tenofovir, with the follow-up for 24 weeks on treatment with tenofovir.
MXV within the scope of Phase III of this clinical study will be administered at the optimal dosage / subcutaneously (the optimal dosage will be determined on the basis of the results of Phase II) for 24 weeks together with the administration of tenofovir, with the follow-up for 24 weeks on treatment with tenofovir.
For more information, see the Clinical Investigation Brochure.

2.2. Summary of Preclinical and Clinical Studies

2.2.1. Preclinical studies

MXB prevents the penetration of HBV into hepatocytes by blocking the main HBV receptor, recently identified as NTCP [26]. MXB acts at the stage after the virus is attached and, possibly, redirects the pathway of HBV entry into the unproductive cellular flow.
The antiviral effect was investigated [36] in studies on the inhibition of HBV and HDV in cell cultures susceptible to HBV and HDV infection: the HepaRG cell line, the primary hepatocytes of Tupaia belangeri and PHH [27, 28]. HBeAg and HBsAg secreted in a cell culture supernatant were measured as markers of infection by ELISA method. The number of infected cells was counted using an immunofluorescence method with the determination of the number of HBcAg-positive cells (HBV) and HDV-Ag-positive cells (HDV). The IC_{50} was 14.5 pm to 9.5 nm, depending on the viral load and cell culture conditions. When concentrations of MXB were up to 50 μm, no *in vitro* toxicity measured by the release of LDH was detected.
The *in vivo* antiviral activity of acetylated HBV peptides similar to MXB were been studied in uPA/RAG-2 mice that had been transplanted with Tupaia belangeri hepatocytes and PHH. Mice were injected with HBV, as well as an active peptide at various concentrations, or a blank peptide. In this model, the systemic use of peptides provided complete prevention of HBV infection at a concentration of 200 μg/kg, the minimum concentration studied [29]. MXB is the product of optimization of the peptides studied in this study. Further, MXB was studied in uPA/SCID mice with transplanted human hepatocytes after the mice had been infected with HBV. Compared with the animals treated with placebo, there was a significant suppression of HBV extension in the liver, measured by the serum level of HBV DNA and HbsAg, as well as by the results of immunohistological analysis [30].
Possible secondary pharmacological effects were studied in a study on a single dosing of the drug to chimpanzee. The chimpanzee is the only pharmacologically animal model (relevant species) that fully conforms to human, because they have a receptor for HBV and they can develop an acute and chronic infection. With the intravenous injection of MXB at a dose of 300 μg/kg, no deviations from clinical or laboratory parameters associated with the drug were detected.
To assess a single dose toxicity, a study was performed on CD® rats (analysis for the maximum tolerated concentration of a single dose). The study included an assessment of the pharmacological safety parameters (Irwin screen). When 12.5 mg MXV/kg body weight were injected intravenously to rats, no signs of toxicity were determined. No animal death cases were reported.
The evaluation of some toxicological parameters (clinical signs, clinical chemical/haematological parameters) was included in the study of pharmacokinetics and secondary pharmacology for a single drug dose delivered to chimpanzees.
A repeated dose toxicity was studied after daily subcutaneous injections to rats (7 days, 4 weeks, 6 months) and dogs (3 months). The studies included an evaluation of cytokine levels (rats, a 4-week study) and pharmacological safety evaluation parameters (a 3-month study on dogs).
In all studies conducted until recently, no signs of an increase in the mortality associated with the study drug, general or local intolerance, impaired body weight and weight gain, food and water intake, hematological and biochemical blood parameters have been determined. Macroscopic analysis and histological evaluation have

shown no signs of changes due to the study drug.

2.2.2. Clinical use of MXB

At the moment, two clinical studies on MXB have been completed, and two more studies are being conducted now:

- Study MYR 101: Phase I study involving healthy volunteers (Germany) – completed.
- Study MYR 201: Phase Ib/IIa clinical study in the presence of HBV (Russia) – completed.
- Study MYR 102: Phase I study on drug interaction involving healthy volunteers (Germany) - ongoing.
- Study MYR 201 (substudy): Phase Ib/IIa study involving patients with CHD (Russia) - ongoing.

The Phase I study (MYR 101) was conducted with the participation of 36 healthy male volunteers. The drug was administered in a dose of 0.3 μg, 3 μg, 10 μg, 100 μg, 800 μg, 3 mg, 5 mg, 10 mg and 20 mg intravenously, and in a dose of 800 μg, 5 mg and 10 mg subcutaneously. The drug in each dose was injected to a cohort of 3 volunteers. For all cohorts and both routes of MXV administration, the drug was well tolerated and did not cause adverse events. After the administration, there were no significant changes in vital signs (blood pressure, heart rate, respiration rate and body temperature), 12-lead ECG and laboratory safety evaluation parameters. A total of 85 AEs were registered in 29 participants. No serious adverse event was registered. Adverse events were evenly distributed between cohorts, none of the system organ classes prevailed. Seventy four adverse events were of mild severity, nine were moderate and only two AEs were severe (grade 3), according to the criteria of CTCAE 4.0 (increased lipase levels, increased amylase levels). Anti-drug antibodies were determined within up to 6 months after administration, all participants had a negative antibody test result.

MXB was well tolerated by all volunteers, there was no evidence of SAEs and dose-limiting toxic reactions. AEs were mostly mild and did not require treatment, wherein no association with Myrcludex B or unexpected non-target effects were detected. No dose dependence of incidence and severity of AE was detected. This corresponds to the results of studies in animals in which Myrcludex B showed highly specific exclusive binding to hepatocytes. Thus, MXV is characterized by a good safety profile even in cohorts having received the drug in high doses.

Myrcludex B showed a clear dose-dependent pharmacokinetic profile. The area under the time-concentration curve in plasma (AUC) increased disproportionately, and the clearance and volume of distribution decreased as the dose increased. The drug bioavailability after subcutaneous injections comprised 88%. The release after subcutaneous injections is best characterized as part of a parallel slow and rapid first-order process where 59% of the bioavailable dose has been rapidly absorbed and the remaining 41% of the dose has been slowly absorbed with a half-life of 1.3 and 5.4 hours, respectively. The dose-response simulation on capacity to bind to the target receptor showed that at a dose of 10 mg, binding to the target was >80% within a minimum of twenty hours in a steady state after subcutaneous injections.

A Phase 1 study on the drug interaction (MYR 102) with the participation of healthy volunteers is being conducted now with the aim to study the dose of MXB, necessary for the saturation of receptors, to effect the PK profile of tenofovir for the treatment of HBV infection.

A 1b/2a phase study involving 48 patients with chronic HBV infection (MYR 201) was completed. Patients with negative HBeAg test results with increased ALT levels and viral load higher than 10,000 copies/mL were randomized to the following cohorts:

Cohort A: 0.5 mg MXB/day s/c/12 weeks + 12 follow-up weeks
Cohort B: 1 mg MXB/day s/c/12 weeks + 12 follow-up weeks
Cohort C: 2 mg MXB/day s/c/12 weeks + 12 follow-up weeks
Cohort D: 0.5 mg Entecavir/day per os/24 weeks
Cohort E 5 mg MXB/day s/c/12 weeks + 12 follow-up weeks.
Cohort F 10 mg MXB/day s/c/24 weeks + 12 follow-up weeks

In this study, safety and tolerability, pharmacokinetic parameters of plasma, immunogenicity and virology response were studied. To evaluate the effectiveness indicators of HBsAg, HBV DNA and ALT were used.

In the course of a 12-week treatment, a dose-related decrease in viral load was indicated. In 6 out of 8 patients (75%) in the cohort that received the drug at a dose of 10 mg, the serum level of HBV DNA was reduced by more than 1 log10, compared to the initial one. Patients in the 10 mg cohort continued treatment for 24 weeks,

maintaining during this time the level of HBV DNA at the levels of HBV DNA achieved by week 12. At a lower dose, no dose dependence on the cohort was registered, for each cohort, a maximum of 25% of patients from the low dose group achieved >1 log10 reduction in the level of HBV DNA at week 12. The normal level of ALT was registered in 50-75% of patients who received Myrcludex B at week 12, regardless of the dose. No effect on HBsAg was noted.

In total, 69 adverse events were registered in the study. In general, in the group treated with Myrcludex B, AEs were predominantly classified as 4 SOC: general disorders and administration site conditions, investigations, skin and subcutaneous tissue disorders, blood and lymphatic system disorders. In the group treated with Entecavir, all AEs belonged to 3 SOC: general disorders and administration site conditions, infections and infestations, respiratory, thoracic and mediastinal disorders. 45 adverse events were considered associated with the treatment (TRAE). In general, AEs associated with treatment were of mild severity (total 41 AEs). Erythema, increased levels of gamma-glutamyltransferase, reticulocytes, dermatitis at the injection site were assigned to moderate adverse events. None of the treatment groups reported AEs classified as severe. 2 AEs were considered serious: withdrawal effect in one patient in the group treated with Myrcludex B 1 mg (Arm B) and one patient in the group treated with Myrcludex B 2 mg (Arm C). There were no patients who stopped participating in the study due to AEs/SAEs. No death cases was registered in the study. The level of bile acids is an important additional pharmacodynamic parameter, since the transporter of bile acids NTPC is the target of MXB. A dose-dependent asymptomatic increase in the level of bile acids, which are substrates of NTCP (such as taurocholate and glycocholate), was detected, and the level of lithocholic acid (not a substrate of NTCP) remained unchanged. Anti-MCH antibodies were found in 58% of patients treated with the drug. No relationship between antibodies formation and pharmacodynamic parameters has been established. An increased level of bile acids, which are an additional pharmacodynamic parameter and indicate the binding of the drug to the target receptor, were determined regardless of the positive result of the antibody test. The virology and biochemical response in patients with a positive and negative antigen test results was similar.

There is an ongoing phase IIa study involving patients with CHD. The study includes 24 patients with chronic hepatitis B with delta agent that is determined by the presence of anti-HDV antibodies in the serum and a positive HBsAg test result within more than 6 months. Patients have been randomized to 3 arms each consisting of 8 patients:

Arm A: Myrcludex B 2 mg once a day for 24 weeks, followed by pegylated interferon alfa, 180 μg/week s/c, for 48 weeks

Arm B: Pegylated interferon alfa 180 μg/week s/c for 48 weeks, during the first 24 weeks extra Myrcludex B 2 mg once a day s/c

Arm C: Pegylated interferon alfa 180 μg/week s/c for 48 weeks

At the present day, there are results of the efficacy evaluation for 24 weeks. Six of the seven and 7/7 patients for whom data were available, reported a decrease in HDV RNA in >1log10 at week 24 during monotherapy with Myrcludex B (A) or combination therapy (B), and this response was observed in 7/7 patients in Arm C. A negative result of HDV RNA test was registered in 2 and 5 patients from Arm A and B and 2 patients from Arm C.

The ALT level decreased at week 24 in 6/7 (A), 4/7 (B) and 2/7 (C) patients. One patient in Arm A had a negative HDV RNA level and a normal ALT level at week 24. In Arm A, there was a tendency towards a decrease in ALT, in comparison with the baseline. It is curious that the median ALT level tended to decrease in the group receiving Myrcludex monotherapy, having decreased from 66 units/L to 40 units/L ($p = 0.06$). In Arms B and C, such a trend has not been established.

Thus, a pronounced anti-viral effect of MXV in relation to HDV when used as monotherapy was shown, as well as the possible additive effect to the action of pegylated interferon against HDV. The use of MXV as monotherapy led to a pronounced decrease in the activity of hepatitis, measured by a decrease in ALT levels. MXV showed a very good safety and tolerability profile in the study, only 4 severe AEs were registered, and there was no increase in toxicity due to pegylated interferon.

Thus, the existing data showed a favorable safety and efficacy profile of MBX and provides a possibility of further clinical use of the drug.

2.3. Information on the Drug for Treatment of the Co-Infection with Hepatitus B virus

According to modern clinical recommendations:

- Recommendations for diagnosis and treatment of adult patients with hepatitis B (2014);
- EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection (2012)

both IF treatment and treatment with nucleoside/nucleotide analogue can be used for the Treatment of Patients with Chronic Hepatitis B with delta agent (CHD).

According to the instructions for medical use (IMU), drugs belonging to both groups of recommended treatment (interferons and nucleoside analogues), have no indication for use "chronic hepatitis B with delta agent", concurrently they have an indication "chronic hepatitis B". The use of the above groups of drugs can be explained by the suppression of hepatitis B virus replication (HBV), i.e. Hepatitis D virus (HDV) is certainly associated with HBV infection, since HDV ribonucleoprotein is packaged in HBsAg.

According to clinical studies performed, the IF treatment of patients with CHD is effective only in a small number of patients (approximately only 25% of cases have virology and biochemical responses). Thus, in a clinical study of HIDIT-2, 120 patients received pegylated interferon alfa in combination with tenofovir disoproxil fumarate or without it for 96 weeks. The prolongation of the period of interferon treatment to 96 weeks and the addition of the tenofovir nucleotide analogue did not lead to an increase in the level of a stable virology response: in 30% of patients in the combination therapy group and in 23% of patients in the monotherapy group, negative results of HDV RNA analysis persisted 24 weeks after the end of treatment. In a study involving 49 patients who received pegylated interferon alpha 2b, a negative PCR result was shown on HDV RNA in 33% of cases at the end of the treatment period (48 weeks) and 25% at the end of the follow-up period [34].

It should also be noted that, according to the study performed, even when HCG patients achieve a long-term virology response, the probability of recurrence remains high [35].

Thus, the effectiveness of IF treatment in treatment of CHD is not high enough that does not allow to attribute it to effective methods of treatment of HGD patients.

According to the Recommendations for diagnosis and treatment of adult patients with hepatitis B (2014), EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection (2012): "The feasibility of prescription of interferons should be determined individually for each patient". In accordance with the inclusion / exclusion criteria described in the MYR 202 Clinical Study Protocol, patients with liver cirrhosis may be included in the study, as well as patients in whom previous interferon therapy ha been ineffective or is currently contraindicated, that excludes the possibility of using interferons, but does not exclude the possibility of using nucleoside/nucleotide analogue as a treatment aimed at suppressing the replication of the hepatitis B virus in the control and study groups. The use of tenifovir also helps to clearly distinguish the effect of Myrcludex B on the infection with delta agent and to obtain evidence of the validity of the use of IP in the treatment of hepatitis B co-infection. Thus, the use of drugs in the control group to treat co-infection with hepatitis B virus is reasonable in ethics and science terms.

Tenofovir (Viread®) is a highly effective HBV polymerase inhibitor approved for the treatment of chronic hepatitis B. Nucleoside / nucleotide analogues are widely used in clinical practice for the treatment of patients with chronic hepatitis B with delta agent. The possibility of their use in this category of patients is regulated by the Guidelines for Diagnosis and Treatment of Adults with Hepatitis B Patients (2014), EASL Clinical Practice Guidelines: Management of chronic hepatitis In virus infection (2012), the use of these drugs is aimed at suppressing the replication of the hepatitis B virus, which plays an important role in the progressive liver damage in the presence of a delta agent. At the same time dosage strengths and dosing schedules of nucleoside / nucleotide analogues do not differ in patients with chronic hepatitis B with and without delta agent.

Tenofovir will be prescribed to all patients involved in the study as a concomitant treatment of infection of hepatitis B virus. The drug will be used in the study in accordance with the instruction for use.

2.4. Administration, Dosage and Duration of the Administration of the Investigational Medical Product

MXB in the first (corresponding to phase II) and in the second (corresponding to phase III) parts of the planned study is assumed to be used as a part of this Protocol.

Phase II of the planned study will evaluate the benefits of 3 doses of MXB before clinical observation in patients with hepatitis CHD with limited therapeutic options. Patients will be randomized to one of the 4 treatment groups in a ratio of 1:1:1:1. Patients with compensated cirrhosis will be stratified to ensure a uniform assignment to each treatment group. If patients have previously received no treatment with a nucleoside/nucleotide analogue, a treatment with a group of nucleotide analogues – tenofovir – will be initiated on the first day of the study. Patients who have previously received tenofovir will continue to receive it at the same dose. Patients who have previously received a different nucleoside / nucleotide analogue will be transferred to tenofovir.

Phase III of the planned study will evaluate the benefits of the optimal dosage strength of MXB chosen according to the results of the analysis of the efficacy and safety parameters of the Phase II before the clinical observation against concomitant chronic hepatitis B treatment with tenofovir in patients with CHD with limited therapeutic options. Patients randomized to one of the 2 treatment groups in a ration 1:1. Patients with compensated cirrhosis will be stratified to ensure a uniform assignment to each treatment group. If patients have previously received no treatment with a nucleoside/nucleotide analogue, a treatment with a group of nucleotide analogues – tenofovir – will be initiated on the first day of the study. Patients who have previously received tenofovir will continue to receive it at the same dose. Patients who have previously received a different nucleoside / nucleotide analogue will be transferred to tenofovir.

Study groups for Phases II and III has been deemed to be adequate control groups, as daily placebo injections for 24 weeks have been found to be near-impossible and ethically unacceptable.

In the Phase 2a study, the effect on HDV RNA, including negative HDV RNA test result, has been observed for 24 weeks. Consequently, the duration of MXB administration in 24 weeks has been deemed sufficient for primary endpoint evaluation. The follow-up period with aim to study the sustainability of responses obtained will comprise 24 weeks.

Phase II and III of this study will not include patients whose ALT is >10 times higher than UGN, creatinine clearance is <60 ml/min, total bilirubin is >34.2 μmol/L, who have decompensated liver disease or carcinoma. Patients with ant-HCV antibodies, but with negative HCV RNA test results at the screening stage are allowed to be enrolled into the study.

Within the scope of phase II of this clinical study, MXB will be administered at doses of 2, 5 and 10 mg / day / subcutaneously for 24 weeks along with the administration of tenofovir, with a 24-week follow-up period on treatment with tenofovir.

A dose of 2 mg is theoretically sufficient to achieve concentrations exceeding IC90 in vitro. In the ongoing Phase 2a study involving patients with chronic Hepatitis B with delta agent, Myrcludex B injected at a dose of 2 mg subcutaneously once a day for 24 weeks, with after or combining treatment with pegylated interferon alpha, showed its efficacy and good tolerability.

In the Phase 2 study involving patients with HBV, a 10 mg dose subcutaneous injections once a day for 24 weeks resulted in the most pronounced effect on HBV DNA. The use of a 10 mg dose was further confirmed by pharmacokinetic modeling, which showed that this dose could result in a minimum of 80% saturation of NTCP within a minimum of 20 hours.

An intermediate dose of 5 mg will also be studied. When using the drug at a dose of 5 mg, you can achieve the target level of saturation of the target within several hours. In the *in vitro* studies, cells that are initially susceptible to HBV/HDV infection also became resistant when the exposure of MXB was limited (15-30 minutes), and maintained their status within at least 24 hours. It can be assumed that if the achievement of the target saturation level is important for increasing the antiviral effect, a dose of 5 mg may be sufficient. In addition, an increase in the level of bile acid concentration in the groups receiving the drug at a dose of 5 mg and 10 mg in the Phase 2a study involving patients with HBV was similar, indicating that the drug in both doses had the same effect on the function of the transporter of bile acid NTCP.

The dose of MXB for Phase III of this clinical study will be determined on the basis of the Phase II results. Within the scope of phase III of this clinical study, MXB will be administered at the optimal dosage / subcutaneously for 24 weeks along with the administration of tenofovir, with a 24-week follow-up period on treatment with tenofovir.

It is assumed that tenofovir, an inhibitor of HBV polymerase, used individually, will have no effect on HDV replication.

The objectives and end points for phases II and III of this study are the same. The main objective of the study is to study the effect of Myrcludex B on the level of HDV RNA in the setting of effective suppression of HBV replication and to study the synergistic effect of two drugs on reducing the HBsAg level.
The primary endpoint of the study is the negative PCR result on HDV RNA or reduction of HDV RNA by ≥2 log_{10} at week 24, compared with the study group, i.e. to show the superiority of MXV in different doses under observation. The negative PCR result on HDV RNA is a standard parameter used in clinical studies and routine practice to monitor the success of treatment in cases of HDV infection. In the analysis of primary variable for the interim analysis during phase II, patients who do not have data at week 24 will be considered as non-responders to therapy. Data on patients with a long-lasting response during the follow-up period with no treatment will be presented separately. No statistical analysis is planned to determine the sustainability of the response. The most important secondary endpoint of the study will be the normalization of ALT, showing a decrease in hepatitis activity, which is important for this patient population.
The analysis of qualitative secondary end points (normalization of ALT and loss of HBsAg/seroconversion) will be carried out using the Fisher's exact test. The analysis of quantitative secondary endpoints (a serum marker for fibrosis, HBsAg and HBV DNA) will be presented in dynamics (actual value and change from baseline). Comparisons between the groups on endpoints will be conducted using a two-tailed Wilcoxon signed-rank test with an adjustment for a significance level of 0.0167. A composite indicator for the control period with no treatment will also be presented for each point. As part of the analysis for the control period with no treatment, statistical testing is not expected to be performed.
The sample size calculation has been performed for Phase II and is based on the following results: the study has sufficient strength to determine a 34% decrease of HDV RNA or negative PCR result on HDV RNA by 2log (304 activity in the study groups) compared to the observation group, taking into account 3% of spontaneous loss of HDV RNA or 2log decrease in connection with the primary treatment. To achieve a significance level of 0.0167 with 80% strength, taking into account multiple comparisons, each group should count 30 patients, given that the study is suggested to study 3 doses of the drug.
No sample size calculation has been performed for Phase III. When the last patient completes a 24-week treatment period as a part of Phase II clinical study, patients from all treatment arms will be analyzed for viral load based on PCR results on HDV RNA (the negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug will be considered as the primary endpoint). Results of the test performed will provide the basis for estimating the number of patients needed to confirm the hypothesis of the statistical superiority of the selected dosage strength of the study drug over the drug of the standard treatment. When calculating the sample size, the correction for a plurality of comparisons (Pocock correction) will be taken into account with due regard to two statistical analyzes (at treatment week 24 of phase II and treatment week 24 of phase III). If a statistically significant conclusion is obtained based on the results of phase II on the statistical superiority of study drug in chosen dosage over the control group with respect to the primary endpoint at the bilateral significance level of 5%, then the recruitment of patients into Phase III of the study will not be performed, and the statistical analysis will be performed as a part of the Interim Report on Phase II and the Final Report on the Clinical Study Results.
To monitor safety and missed dose of the study drug, dose modification and treatment discontinuation, standard methods will be used that comply with the Good Clinical Practice guidelines.

2.5. Study Compliance with Regulatory Requirements

2.5.1. List of Applicable Standards and Regulatory Requirements

This study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki of the World Medical Association (WMA) (Fortaleza, 2013), the tripartite guideline on Good Clinical Practice (ICH GCP) and the current legislation of the Russian Federation:

1. Federal Law N 61-FZ dd. April 12, 2010 "On Medicine Circulation";
2. National Standard of the Russian Federation GOSTR 52379-2005 "Good Clinical Practice";
3. Order of the Ministry of Health of the Russian Federation No. 200н dd. April 01, 2016 "On Approval of Rules of Good Clinical Practice in the Russian Federation";
4. Resolution of the Government of the Russian Federation N 714 dd. September 13, 2010 "On approval of

Standard Rules of Compulsory Insurance of Life and Health of the Patient Participating in Clinical studies of Medicine" and Resolution No. 393 dd. May 18, 2011 "On Amendments to the Standard Rules of Compulsory Insurance of Life and Health of the Patient Participating in Clinical studies of Medicine";
5. Order of the Ministry of Health of the Russian Federation No. 774n dd. August 31, 2010 "On the Ethics Board";
6. Recommendations for Diagnosis and Treatment of adult Patients with Hepatitis B (2014);
The Investigator and Sponsor must sign the protocol and the study contract. The Investigator should not deviated from the study protocol without the consent of the Sponsor and the approval of the Ethics Committee, unless an immediate elimination of an urgent threat to the patient is required, or when the changes relate only to supplies or administrative aspects.

2.5.2. Clinical Center's Responsibilities

The clinical center shall be responsible for:
- ensuring compliance with the clinical study protocol of clinical research;
- knowledge of and compliance with the GLP and regulatory requirements;
- contacts with the Local Ethics Committee (LEC), providing it with all necessary documents of the study, obtaining written and dated approval of the LEC for conducting the study;
- compliance with the conditions for obtaining, storing and consuming the study drugs;
- following the randomization procedure;
- providing the Sponsor with sufficient and accurate information necessary to obtain reliable results;
- storage of documents of the study for a period of 15 years;
- immediate notification of the Sponsor and the Ethics Committee about all serious and adverse events;
- quality control of the data obtained.

The Investigator is obliged to provide information (for example, data on the work of the center for the previous period), confirming the feasibility of timely recruitment of patients in accordance with the criteria as per protocol. If, after one month from the planned start of the study in the clinical center, no patient is engaged in the study, this center may be closed, about which the Principal Investigator will be notified in writing by the Sponsor.

2.6. Description of the Study Population

The selection of the arm of study is based on the requirements of the Federal Law No. 61-FZ dd. 12.04.2010 "On Medicine Circulation" and GOST R52379-2005 "Good Clinical Practice".
The study will include patients, men and women at the ages from 18 through 65, with chronic HDV infection with positive HDV RNA at the screening stage to confirm the efficacy of treatment with Myrcludex B in this category of patients.
The primary data on the efficacy of Myrcludex B in the treatment of patients with chronic viral hepatitis B with delta agent was obtained in the Phase IIa clinical study. In the Phase Ib / IIa study, treatment with Myrkludex B resulted in reduction of HDV RNA and ALT in patients with HDV infection. Out of 24 subjects in the Phase Ib / IIa, 10 patients had hepatic cirrhosis or had previousle undergone the IF treatment. In this population of patients with the most limited therapeutic options, the possibility of a positive response to Myrcludex B treatment was shown.
Thus, the present study will include patients suffering from chronic hepatitis B with delta agent in whom the prior IF therapy has been ineffective or, in the opinion of the investigating physician, is currently contraindicated (including cases of interferon intolerance in the past medical history), as well as patients with hepatic cirrhosis. Inclusion of such a patient population is justified both ethically and by the previous study results.
Phase II of the planned study will be performed on 120 patients. The number of patients required to be enrolled in phase III will be calculated on the basis of data of the Interim report on the Clinical Study Results performed as a part of phase II.
Patients will be included in the study only if they have signed the informed consent form and meet all the inclusion/exclusion criteria.

2.7. Literary Sources and Data

References to literature sources and data relevant to the study and its justification are given in section 19 at the end of the protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

Primary objective

For Phase II: to investigate the efficacy of MXB in patients with chronic hepatitis B with delta agent and compare the results of MXB treatment in three doses with a comparison group receiving treatment with tenofovir against HBV.

For Phase III: to investigate the efficacy of MXB in patients with chronic hepatitis B with delta agent and compare the results of MXB treatment in the optimal dose with a comparison group receiving treatment with tenofovir against HBV.

Secondary objectives

For Phase II: to study the safety and tolerability, as well as to assess the pharmacokinetic properties (including the effect of MXB on the CYP3A activity) and immunogenicity of MXB in three doses when used in patients with chronic hepatitis B with delta agent.

For Phase II: to study the safety and tolerability, as well as to assess the immunogenicity of MXB in the optimal dose when used in patients with chronic hepatitis B with delta agent.

Primary endpoint for efficacy parameter evaluation for phases II and III:

- The negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.

Secondary endpoints for efficacy parameter evaluation for phases II and III:

- The duration of the effect (no increase) on HDV RNA at week 24 after treatment (study week 48) compared to the results obtained at the end of the treatment period (study week 24).
- The presence of a combined response: the negative PCR result on HDV RNA, or a decrease by ≥2 log and normalization of ALT at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics of ALT activity at treatment week 24 and study week 48 compared to results obtained before the initiation of treatment with the study drug.
- Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) according to the liver biopsy study results or the absence of a fibrosis progression according to the findings of transient elastometry (fibroscan) at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics (no increase) of the serum marker for fibrosis – alpha-2 macroglobulin in the serum at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics of HBsAg (decrease in the quantitative content, disappearance of HBsAg, developent of anti-HBsAg antibodies) at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.
- Decrease in HBV DNA levels at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.

Criteria for safety parameter evaluation for phases II and III:

- Data on adverse events, physical examination, weight measurement, vital signs examination, 12-lead ECG, clinical blood test, coagulation test, blood chemistry, urinalysis, serum bile acid test.
- Antibody response to Myrcludex B.

4. STUDY DESIGN

This study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki of the World Medical Association (WMA) (Fortaleza, 2013); National Standard of the Russian Federation GOSTR 52379-2005 "Good Clinical Practice"; Federal Law N 61-FZ dd. 12.04.2010 "On Medicine Circulation"; Order of the Ministry of Health of the Russian Federation No. 200н dd. April 01, 2016 "On Approval of Rules of Good Clinical Practice in the Russian Federation"; Recommendations for Diagnosis and Treatment of Adult Patients with Hepatitis B (2014); EASL Clinical Practice Guidelines: Management of chronic hepatitis In virus infection (2012); normative standards of regulatory authorities and this study protocol.

4.1. Study Design Description

This study is a randomized, open-labeled, multicenter phase II/III clinical study.

Justification of a two-phase adaptive design. The following features of the study drug (Myrcludex B):

- it is administrated to treat chronic hepatitis B with delta agent - the most severe form of viral hepatitis;
- it has an orphan status in the European Union and the United States;
- there is currently no effective standard treatment for chronic hepatitis B with delta agent;
- it has the ability to simulate a dose / response reaction based on the viral kinetics

determine the availability of the possibility of using a two-phase adaptive design for the planned clinical study, with its assignment to phase II / III.

The possibility of using an adaptive design in clinical studies conducted on small patient populations, such as the population of patients with chronic hepatitis B with delta agent, is also described in the European Medicines Agency (EMA) [GUIDELINE ON CLINICAL STUDIES IN SMALL POPULATIONS. London, 27 July 2006. Doc. Ref. CHMP/EWP/83561/2005].

The methodology for the planned Phase II / III study is based on EMA guidelines [REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL STUDIES PLANNED WITH AN ADAPTIVE DESIGN. London, 18 October 2007. Doc. Ref. CHMP/EWP/2459/02].

Phase II. Taking into account the dropout of patients at the stage of Screening, approximately 200 patients will undergo Screening procedures, and 120 of them will be randomized into 4 treatment arms in the ratio of 1:1:1:1:

Arm A (30 patients): Myrcludex B 2 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy.

Arm B (30 patients): Myrcludex B 5 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy.

Arm C (30 patients): Myrcludex B 10 mg/day/subcutaneously (s/c) for 24 weeks + tenofovir, with the further follow-up period of 24-weeks of continued tenofovir therapy.

Arm D (30 patients): tenofovir treatment for 48 weeks.

The main part of the study includes a Screening period of 28 days (day -28/-1), a pre-treatment periodfor patients, who the pre-treatment period with tenofovir is indicated to, lasting up to 84 days, an baseline randomization visit (day 1) and a 24-week active treatment period and a 24-week follow-up period.

Phase III. The number of patients required to be enrolled in phase III will be calculated on the basis of data of the Interim report performed as a part of phase II. Patients will be randomized to one of 2 treatment groups in the ratio of 1:1.

Group I: Myrcludex B in the optimal dosage /subcutaneously (s/c) for 24 weeks + tenofovir, with the 24-week follow-up on treatment with tenofovir.

Group II: treatment with tenofovir for 48 weeks.

The main part of the study includes a Screening period of 28 days (day -28/-1), a pre-treatment period for patients, who the pre-treatment period with tenofovir is indicated to, lasting up to 84 days, an baseline randomization visit (day 1) and a 24-week study period. The follow-up period will be 24 weeks for all treatment Arms.

The graphical scheme of the clinical study is presented in Figures 1a and 1b.

Figure 1a. Graphical scheme of the Phase II clinical study.

Screening **Visit 01** (Day (-)28/112* - (-)1)	Preexamination of patients, evaluation of compliance with inclusion / non- inclusion criteria	%
	Visit 02* (Day (-)84)	**Period of** pre-treatment period**with tenofovir *** (Day (-)84 - (-)l)
	Off-site visit 03* (Day (-)28)	
	Visit 04* (Day (-)14 - (-)1)	

Randomization visit **Visit 1** (day l)	**Arm** A **Arm** B **Arm** C **Arm** D	MXB 2 mg + tenofovir MXB 5 mg + tenofovir MXB 10 mg + tenofovir tenofovir

Study period (Treatment according to the randomization scheme)	Visit 2 (1 week after randomization visit) Visit 3 (2 weeks after randomization visit) Visit 4 (4 weeks after randomization visit) Visit 5 (8 weeks after randomization visit) Visit 6 (12 weeks after randomization visit) Visit 7 (16 weeks after randomization visit) Visit 8 (20 weeks after randomization visit) Visit 9 (24 weeks after randomization visit) Visit FU1 (25 weeks after randomization visit) Visit FU2 (26 weeks after randomization visit) Visit FU3 (28 weeks after randomization visit) Visit FU4 (36 weeks after randomization visit) Visit FU5 (48 weeks after randomization visit)
Follow-up period (All patients take only tenofovir)	

End of study

** Only for patients who have undergone the* pre-treatment period*with the drug for concomitant hepatitis B infection (Pretreatment period - PreT)*

Figure 2b. Graphical scheme of the Phase III clinical study.

Screening Visit 01 (day (-)28/112*-(-1))	Preexamination of patients, evaluation of compliance with inclusion / non- inclusion criteria

Visit 02* (Day (-)84)	The period of pre-treatment periodwith tenofovir * (Day (-)84 - (-)1)
Off-site visit 03* (Day (-)28)	
Visit 04* (Day (-)14 - (-)1)	

Randomization visit Visit 1 (day 1)	Group I Group II	MXB (optimal dose) + tenofovir tenofovir

Study period (Treatment according to the randomization scheme)	Visit 2 (1 week after randomization visit) Visit 3 (2 weeks after randomization visit) Visit 4 (4 weeks after randomization visit) Visit 5 (8 weeks after randomization visit) Visit 6 (12 weeks after randomization visit) Visit 7 (16 weeks after randomization visit) Visit 8 (20 weeks after randomization visit) Visit 9 (24 weeks after randomization visit)
Follow-up period (All patients take only tenofovir)	Visit FU1 (25 weeks after randomization visit) Visit FU2 (26 weeks after randomization visit) Visit FU3 (28 weeks after randomization visit) Visit FU4 (36 weeks after randomization visit) Visit FU5 (48 weeks after randomization visit)

End of study

** Only for patients who have undergone the* pre-treatment period *with the drug for concomitant hepatitis B infection (Pretreatment period - PreT)*

The study procedures and design of are the same for Phases II and III, are presented in Table 1: Study diagram.

Table 1. Study diagram for Phases II and III.

Procedures	**SCR**	**PreT***			**RV**	**Study period**								**Follow up**					**Early Termination**
Visits	01	02	03	04	1	2	3	4	5	6	7	8	9	FU1	FU2	FU3	FU4	FU5	Study end visit
Day (D)/ Week (W)	D –28/-112* -1	D - 84 ±1D	D - 28 ±1D	D - 14 - 1	D1 ±2D	W1/D8 ±2D	W2/D15 ±2D	W4/D28 ±2D	W8 ±2D	W12 ±2D	W16 ±2D	W20 ±2D	W24 ±2D	FUW1/ W25 ±3D	FUW2/ W26 ±3D	FUW4/ W28 ±3D	FUW12/ W36 ±3D	FUW24/ W48 ±3D	D X
Informed consent	X																		
Demographic data and medical history	X																		
Physical examination	X	X		X*	X					X			X					X	X
Body height	X																		
Body weight	X	X		X*	X					X			X					X	X
Vital signs	X	X		X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X									X			X					X	
Urine pregnancy test [1]	X			X*	X			X	X	X	X	X	X						
Urine drug test (test strip)	X																		
Urine analysis	X				X			X		X			X				X	X	X
Serological analysis	X																		
AFP blood test	X																		
Abdominal ultrasound	X																		
Alcohol-breath test	X				X														
Inclusion/exclusion criteria	X			X*	X														
Liver biopsy study [(2)]/Transient elastometry [(3)]	X												X						
Randomization					X														
Handing the study product for 28 days over					X			X	X	X	X	X							
Handing the nucleotide analogue over- tenofovir		X*			X			X	X	X	X	X	X			X	X		
Evaluation of compliance with the prescribed treatment			X*	X*		X	X	X	X	X	X	X	X						
Issuance and evaluation of patient's diaries					X	X	X	X	X	X	X	X	X						
PK analysis of Mircludex B (for patients from the PK-substudy)[2]					X		X												
PK analysis of MDZ (CYP3A activity) (for patients from the PK-substudy)[3]				X[4]	X		X												
PK analysis (for all study					X			X	X	X	X	X	X						

[2] For Phase II only.

[3] For Phase III only.

[4] If a patient does not need a pre-treatment period with tenofovir, but is involved in the PK-substudy, then the following tests are performed during the visit: registration of AEs; collection of data on the concomitant treatment; physical examination; vital sings (blood pressure, heart rate, temperature, respiratory rate); urine pregnancy test (only for women of childbearing potential).

subjects)																			
HBV/HDV genotype test (frozen samples)		X			X****														
NTCP polymorphism (frozen clot of cells)					X														
Clinical blood test, coagulogram	X	X**		X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (complete panel)	X				X					X			X					X	X
Blood chemistry (abbreviated panel))		X**		X*		X	X	X	X		X	X		X	X	X	X		
Serum total bile acids (in the central laboratory)					X	X	X	X	X	X	X	X	X	X	X			X	X
Serum bile acids (frozen samples)					X	X	X	X	X	X	X	X	X	X	X			X	X
HDV RNA (samples of room temperature)	X																		
HDV RNA (frozen samples)		X*			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA (frozen samples)		X*			X					X			X				X	X	X
HBsAg (frozen samples)		X*			X			X	X	X	X	X	X			X	X	X	X
HBeAg и anti-HBeAg antibodies	X												X***					X***	
HBsAg (nonquantitative determination in a local laboratory	X																		
Immunogenicity(frozen samples)					X					X			X				X	X	
Serum marker for fibrosis (frozen samples)					X								X					X	
Resistance analysis (frozen samples)		X			X****								X						
Adverse events	X	X*	X*	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant drugs*****	X	X*	X*	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* *Only for patients who have undergone the* pre-treatment period *with the drug for concomitant hepatitis B infection (Pretreatment period - PreT)*

** *It shall be performed if more than 14 days have elapsed since the laboratory test was performed at the screening*

*** *Only in patients with positive HBeAg during the screening*

****It shall be performed once at the visit_Pre-T 02 in patients who have been indicated a* pre-treatment period *with tenofovir. If the* pre-treatment period *with tenofovir is not indicated, the analysis shall be performed at the randomization visit only.*

*****Including the previous therapy of hepatitis with interferon medications regardless of treatment prescription*

(1) *Only for women of childbearing potential*

(2) *According to the investigator's decision, it can be replaced with transient elastometry.*

The study includesprocedures that are the same for phases II and III:

- Screening period of 28 days duration (Visit 01);
- Period of pre-treatment periodwith tenofovir for patients who have been indicated the pre-treatment periodwith tenofovir for up to 12 weeks (84 days) (starting from the moment of receiving the results of screening procedures that allow assessing the patient's compliance with inclusion / exclusioncriteria in this clinical study, includes:

– Visit 02 (face-to-face) - prescription of tenofovir to the patient in 84 days before the proposed randomization visit;
– Visit 03 (off-site) - phone call to the patient in 28 days before the proposed randomization visit;
– Visit 04 (face-to-face) up to 14 days before the proposed randomization visit;

- Randomization visit (Visit 1 - day 1);
- Treatment period of 24 weeks (Visits 2-9, performed at week 1, 2, 4, 8, 12, 16, 20 and 24 after the randomization visit, randomization);
- Follow-up period of 24 weeks (Visits FU1-FU5, performed at week 25, 26, 28, 36 and 48 after the randomization visit, respectively).

The screening period (procedures are the same for phases II and III)

During the screening period, at Visit 01 (up to 112 days before the first administration of MXB if there is a pre-treatment periodwith tenofovir; up to 28 days before the first administration of MXB for patients whom pre-treatment periodwith tenofovir has not been presribed) the following examinations will be performed: physical examination, laboratory tests, serological tests (HIV, HCV antibodies), HCV RNA in patients with anti-HCV antibodies, antibodies to HDV, HDV RNA, evaluation of inclusion/exclusion criteria.

During the screening, patients will undergo a liver biopsy study, with the determination of the level of hepatic necroinflammation and fibrosis. An immunohistochemical analysis of HDV RNA-positive cells will be performed. A part of the biopsy material will be frozen to determine intrahepatic parameters. No use of maintenance drugs (for example, to stimulate the growth of platelets) is allowed.

A liver biopsy study may be replaced, by the decision of the investigating physician, with transient elastometry (fibroscan)[5].

If a patient needs the pre-treatment periodwith a nucleotide analogue, the patient will receive tenofovir for the entire period of pre-treatment period (for 84 days of admission).

Period of pre-treatment periodwith tenofovir (procedures are the same for phases II and III)

The period of pre-treatment periodwith tenofovir is introduced in order to enroll patients who have not previously received nucleoside analogues but need them, as well as to achieve the greater homogeneity of a number of patients enrolled in this clinical study. The total duration will be 12 weeks.

The period of pre-treatment periodwith tenofovir includes:

– Visit 02 (face-to-face) - prescription of tenofovir to the patient in 84 days before the proposed randomization visit;
– Visit 03 (off-site) - phone call to the patient in 28 days before the proposed randomization visit, it is performed to assess the compliance with prescribed treatment, to collect information about concomitant drugs, to register AEs;
– Visit 04 (face-to-face) is performed up to 14 days before the proposed randomization visit (physical examination, weight measurement, laboratory tests, estimation of the taken tenofovir, assessment of the compliance with prescribed treatment, re-evaluation of the inclusion / exclusion criteria).

Randomization visit for Phase II

All patients who meet the inclusion / exclusion criteria and who have been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatmentof the course of treatment with the study drug or pre-treated with a nucleotide analogue, tenofovir, as per the protocol will be invited to a

[5] The possibility of such a replacement is due to the fact that it is possible to enroll patients with advanced stages of the disease, herewith, the inclusion of a significant number of patients with hepatic cirrhosis or progressive liver fibrosis is expected. Therefore, a liver biopsy study will not be compulsory and can be replaced, by the decision of the physician, with transient elastometry.

randomization visit: the following examinations will be conducted: physical examination, weight measurement, safety laboratory tests, virology parameters, serum marker for fibrosis, immunogenicity. All evaluations performed during this visit should be qualified as the main parameters for safety monitoring and should not be qualified as the inclusion/exclusion criteria. During the randomization visit, after the completion of all procedures specified in the protocol, patients will be randomized to one of 4 treatment groups and will receive the study drug for the first 28 days of use.

Randomization visit for Phase III

All patients who meet the inclusion / exclusion criteria and who have been treated with nucleoside / nucleotide analogues for at least 12 weeks before the planned start of study treatment with the study drug or pre-treated with tenofovir as per the protocol will be invited to a randomization visit: the following examinations will be conducted: physical examination, weight measurement, safety laboratory tests, virology parameters, serum marker for fibrosis, immunogenicity. All evaluations performed during this visit should be qualified as the main parameters for safety monitoring and should not be qualified as the inclusion/exclusion criteria. During the randomization visit, after the completion of all procedures specified in the protocol, patients will be randomized to one of 2 treatment groups and will receive the study drug for the first 28 days of use.

Treatment period (procedures are the same for phases II and III)

The treatment with the study drug and/or tenofovir will last for 24 weeks, followed by a 24-week follow-up period. The treatment will be conducted in an outpatient setting.

The follow-up period (procedures are the same for phases II and III)

The follow-up period will last for 24 weeks. During this period, patients from all groups will receive treatment with tenofovir.

4.2. Pharmacokinetic Study

4.2.1. Pharmacokinetic Substudy (PK-substudy)

Substudy of the pharmacokinetics of Myrcludex B

Within the scope of Phase II, 10 patients from each Arm: A, B and C (total 30) will participate in the pharmacokinetic substudy. On the eve of the first day of the drug administration (Period I) and on administration day 13 (Period II), the drug administration, the patients will be hospitalized to the appropriate study site for blood sampling for PK study.

For the first period of PK study patients will be hospitalized before start of investigational drug therapy, but after randomization.

The next day in the morning, each patient will have a catheter in the elbow vein installed, through which blood will be sampled (including sampling of the 24-hour point, after which it will be removed). If the catheter is thrombosed and removed a little too soon, Blood sampling should be performed by venipuncture.

The first blood sampling should be performed before the drug is administered 5-10 minutes after the catheter is installed (Point 0).

The drug should be administered under the supervision of a physician investigator.

On the dosage day, blood will be sampled from the median cubital vein through a pre-installed catheter. The catheter will be removed after collecting 14 blood samples (24 hours after dosing).

24 hours after the drug administration, patients will be left to go home.

Patients will return to the clinical center for Period II of the pharmacokinetic study on treatment day 13 (on the eve of Visit 3). The next morning, patients will have an intravenous catheter installed and have the first blood sample collected. Then the patient will inject the drug, after which the blood samples will be collected, according to the bio-sample schedule.

24 hours after the drug administration, patients will be left to go home.

In total, in Periods I and II for the pharmacokinetic study, 14 blood samples will be collected from each patient at each study period according to the following schedule: 0 h (before the investigational drug and MDZ administration), and at 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 6:00, 10:00, 14:00, 24:00 (hh:min) after the administration of Myrcludex B.

In each period, blood samples should be collected at the same time.

The actual PK sampling time will be recorded. Blood samples should be collected in accordance with the

schedule, the following time deviations from the schedule are possible:

Scheduled hour(s) from the moment of the drug administration:	Deviation (absolute value):
From 0 to 6 h	± 5 min
From 10 to 24	± 15 min

All blood samples collected beyond the abovementioned deviations will be recorded as protocol deviations and recorded in the monitor's report, and actual deviations from the sampling schedule will be corrected during pharmacokinetic and statistical calculations.
The procedures of sampling, storage and processing of blood samples are indicated in paragraph 4.7.
When hospitalized, patients must follow the internal regulations of the hospital.
Substudy of the systemic (general) metabolic CYP3A activity
It is also planned to study the P450 (CYP3A) cytochrome activity in 30 patients from Arms A, B and C (10 patients from each group), as a part the pharmacokinetic substudy (PK-substudy).
Performance of this substudy is due to the fact that CYP3A is involved in the metabolism of about 50% of currently registered drugs and is the most common isoenzyme from the cytochrome family with localization in liver and intestines.
To study the metabolic CYP3A activity in patients enrolled in the study, it is planned to use data on the pharmacokinetics of the benzodiazepine derivative, Midazolam (MDZ).
In clinical practice, MDZ is used in patients with sleep disturbance, for premedication and sedation, and as an initial narcosis. In the planned substudy, patients will be injected with MDZ intravenously (iv) in a microdose (10 μg) that is unable to have any therapeutic effect due to the fact that the MDZ microdose is significantly less than the no observed adverse effect level (NOAEL) in humans. [Hohmann N. et al. Midazolam microdose to determine systemic and pre-systemic metabolic CYP3A activity in humans // Br J Clin Pharmacol /2014/79:2/278–285].
The possibility of using MDZ as an agent for studying the systemic metabolic CYP3A activity is regulated by the EMA guidelines [EMA. Guideline on the investigation of drug interactions. 2012, Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf] and FDA [CDER. Guidance for industry drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations. 2012, Available at // http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm292362.pdf].
The introduction of MDZ and its PK study is planned during the following time intervals:
– day (-13) – day (-12) [Visit 04] apart from the injection and PK-study of Myrcludex B;
– day 1 – day 2 [Visit 1] together with the injection and PK-study of Myrcludex B;
– day 14 – day 15 [Visit 3] together with the injection and PK-study of Myrcludex B.
Patient hospitalization will be carried out on the eve of the day of the PK-study. Thus, patients will be hospitalized (including the time of the PK-study:
– on day (-14) – day (-12) [Visit 04, for 3 days];
– on day (-1) – day 2 [Visit 1, for 3 days];
– on day 13 – day 15 [Visit 3, for 3 days].
On the first day of the PK-study (on day (-13), day 1, day 14, respectively) in the morning, each patient will have a catheter in the elbow vein installed, through which blood will be sampled (including sampling of the 24-hour point, after which it will be removed). If the catheter is thrombosed and removed a little too soon, Blood sampling should be performed by venipuncture.
The drug should be administered under the supervision of a physician investigator.
24 hours after the drug administration, patients will be left to go home.

Principles of storage, preparation and terms of administration of MDZ
MDZ will be administered to patients intravenously (IV) in a microdose of 10 μg before injection of Myrcludex B. The drug should be stored at a temperature below 30°C in a dark place.
The MDZ solution preparation will be performed by a pharmacist in accordance with the method described in the laboratory manual for pharmacokinetics substudies.

On day (-13-12), the PK of Midazolam is studied before starting the treatment with Myrcludex B at the following time points: before the injection of MDZ and in 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 (hh:min) after the injection of MDZ.
To study the PK of MDZ on day 1 and day 14, Midazolam is administered prior to the administration of the study drug Myrcludex B, while blood sampling (except for the zero line) is performed after the administration of Myrcludex B. The blood sampling for MDZ analysis: before the administration of MDZ and Myrcludex B and in 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 (hh:min) after the administration of Myrcludex B.
In total, for the pharmacokinetic study of MDZ, 14 blood samples will be collected from each patient at each study period.
In each period, blood samples should be collected at the same time.
The actual PK sampling time will be recorded. Blood samples should be collected in accordance with the schedule, the following time deviations from the schedule are possible:

Scheduled hour(s) from the moment of the administration MDZ:	Deviation (absolute value):
From 0 to 1 h	± 1 min
From 1.5 to 3 h	± 2 min
from 4 to 24 h	± 5 min

All blood samples collected beyond the abovementioned deviations will be recorded as protocol deviations and recorded in the monitor's report, and actual deviations from the sampling schedule will be corrected during pharmacokinetic and statistical calculations.
The procedures of sampling, storage and processing of blood samples are indicated in paragraph 4.7.
When hospitalized, patients must follow the internal regulations of the hospital.

4.2.2. Pharmacokinetic main study (PK-main study)

For a more accurate study of the possible cumulation of the study drug in all patients treated with Myrcludex B, blood sampling points for the pharmacokinetic study are assigned: Week 4, 8, 12, 16, 20, 24 (1 hour +/- 15 minutes after the drug administration). Patients not enrolled in the pharmacokinetic substudy are assigned with a blood sampling point at the randomization visit (1 hour +/- 15 minutes after the drug administration).

4.3. Randomization

To minimize an error, randomization will be done in a stratified manner. Patients should be stratified according to the presence or absence of hepatic cirrhosis. The aim of stratification is to collect a comparable number of patients with cirrhosis in each treatment group. Neither patients nor researchers will go through the blinding procedure relating to the prescribed treatment in this open-labeled study.
Within the scope of Phase II, patients are randomized to Arms A, B, C and D in the ratio of 1: 1:1:1; within the scope of Phase III, patients are randomized to Groups I and II in the ratio of 1:1 using an electronic randomization protocol.
Detailed information will be provided in the randomization plan.

4.4. Study Stages and Procedures

Any deviations from protocol procedures should be recorded in the monitor's report, with notification of the sponsor and CRO. The study procedures and visits are described below. Unscheduled visits can be conducted at the discretion of the investigator, the data on their conduct should be reported in CRFs.
The following possible deviations are acceptable in the schedule of patient visits:
For pretreatment visits ± 1 day;
For the randomization visit ± 1 day,
For the treatment period ± 2 days,
For follow-up period ± 3 days.

4.4.1. Screening Procedures

The Screening procedures are the same for Phases II and III. Compliance of the patient with inclusion criteria and non-compliance with exclusion criteria will be confirmed during the screening period (maximum 112 days before the first day of drug administration in patient subgroups with indications for the treatment therapy with a nucleotide analogue; maximum 28 days before the first day of drug administration in patient subgroups without appropriate indications).

During the screening visit (Visit 01) in an outpatient setting, the following procedures will be performed:

- Providing patients with information on participants and obtaining written informed consent for participation in the study with a signature of the participant and the date of signing;
- Medical history and demographic data;
- Collection information on medications taken, as well as on previous therapy of hepatitis with interferon, regardless of the prescription of treatment;
- Registration of SAEs;
- Physical examination;
- Weight measurement;
- Body height;
- Vital signs (blood pressure, heart rate, temperature, respiratory rate);
- 12-lead ECG;
- Clinical blood test, blood clotting test;
- Blood chemistry (complete panel);
- Serological analysis;
- Urine analysis;
- Abdominal ultrasound;
- Liver biopsy study /transient elastometry (fibroscan);
- AFP blood test;
- HDV RNA (samples at room temperature, central laboratory);
- HBeAg and anti-HBeAg antibodies;
- HBsAg (qualitative determination in a local laboratory);
- Alcohol-breath test;
- Urine drug screen (test strip);
- Urine pregnancy test (only for women of childbearing potential);
- Evaluation of inclusion/exclusion criteria;

Patients who meet all inclusion criteria and do not meet any of exclusion criteria must come to the hospital within 4 weeks after screening for a randomization visit at the study.

Only patients with a positive HDV RNA test result can be included in the study. The patient will be considered to meet the inclusion criterion of "positive HDV RNA test result" only if the result of the HDV RNA test in the central laboratory is positive.

During the screening period, adverse events should be observed in patients. However, all unfavorable medical events (other than serious adverse events) that occurred during the screening period will be recorded as indicators to be included in the medical history of patients.

If there are indications for a pre-treatment period with a nucleotide analogue (the patient have not used any nucleoside/nucleotide analogues or have used any nucleoside/nucleotide analogues for less than 12 weeks before enrollment), the patient is scheduled to Visit 02 of preliminary tenofovir treatment period.

4.4.2. Procedures and evaluations during the period of pre-treatment period with tenofovir

Procedures and evaluations during the period of pre-treatment period with tenofovir are same for Phases II and III.

If the patient has confirmed his/her consent to participate in the study and is in full compliance with the inclusion criteria, but previously the patient have not taken nucleoside/nucleoside analogues or have used nucleoside/nucleoside analogues preparations for less than 12 weeks before enrollemnt, a period of preliminary

treament with tenofovir for up to 84 days should be scheduled before the randomization visit.
Confirmation of compliance of patient subgroup with indications for the pre-treatment period with tenofovir, with the participation in the study will be based on results obtained during Visit 04 (maximum 14 days before the first day of drug administration).
Period of pre-treatment periodwith tenofovir includes:
Visit 02 (face-to-face) – shall be performed in an outpatient setting. The following procedures during the Visit:

- Data on the drugs being taken;
- Collection information on medications taken
- Registration of SAEs;
- Physical examination;
- Weight measurement;
- Vital signs (blood pressure, heart rate, temperature, respiratory rate);
- Clinical blood test, blood clotting test (if the blood has been sampled at screening for more than 14 days);
- Blood chemistry (if the blood has been sampled at screening for more than 14 days);
- HBV/HDV genotype test (frozen samples) shall be performed in patients whom the pre-treatment period with tenofovir has been indicated;
- Resistance analysis (frozen samples) shall be performed in patients whom the pre-treatment periodwith tenofovir has been indicated
- HDV RNA (frozen samples);
- HBV DNA and HBsAg (frozen samples);
- Issuance of tenofovir.

Visit 03 (off-site) – shall be performed by phone call to the patient in 28 days before before the proposed randomization visit. The following procedures will be performed during the Visit:

- Data on the drugs being taken;
- Collection information on medications taken
- Registration of SAEs;
- Evaluation of adherence to prescribed treatment according in patient words.

Visit 04 (face-to-face) shall be performed in an outpatient setting in 14 days before the proposed randomization visit. The following procedures shall be performed during Visit 04:

- Registration of SAEs;
- Collection of data on the concomitant treatment;
- Physical examination;
- Weight measurement;
- Vital signs (blood pressure, heart rate, temperature, respiratory rate);
- Clinical blood test, blood clotting test;
- Blood chemistry (abbreviated panel);
- Urine pregnancy test (only for women of childbearing potential);
- Calculation of the drug taken (tenofovir);
- Evaluation of the compliance with the prescribed treatment;
- Evaluation of inclusion/exclusion criteria.
- For patients participating in the PK-substudy within the scope of Phase II: hospitalization on the eve of blood sampling (day (-14)). Blood sampling should be performed immediately before the administration of MDZ and in 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 the next day** (hh:min) after the administration of MZD (days (- 13) and (-12)).

If a patient does not need preliminary treament with tenofovir, but is enrolled in the PK-substudy, the following should be performed during the visit:

- Registration of SAEs;
- Collection of data on the concomitant treatment;
- Physical examination;

- Weight measurement;
- Vital signs (blood pressure, heart rate, temperature, respiratory rate);
- Urine pregnancy test (only for women of childbearing potential).

The patient should return all used bottles with tenofovir to the clinical center and also bring all the unused bottles for recording the drug intake (after that unused bottles will be returned to the patient for continuation of therapy). The researcher should enter data on compliance with ttreatment to the CRF.
The investigator will re-evaluate the patient's compliance with the inclusion/exclusion criteria and, if the patient meets all inclusion criteria and does not meet any of the exclusion criteria, he appoints the date of Visit 1 for the randomization procedure to be performed.
During the pre-treatment period with a nucleotide analogue adverse events in patients should be monitored (they will be recorded as indicators to be included in a participant's medical history, except for serious adverse events).

4.4.3. Randomization Visit

All patients who meet the inclusion/exclusion criteria will be invited to the Randomization Visit (Visit 1, day 1). During the randomization visit after the completion of the planned procedures, patients will be randomized: at Phase II – to one of four treatment groups, at Phase III – to one of 2 treatment groups.
Treatment and visits will be conducted in an outpatient setting, in the same manner for Phases II and III. As a part of Phase II, only patients participating in the pharmacokinetic sibstudy will be hospitalized on the eve of the visit during which the PK-study will be performed, and will leave the center the next morning 24 hours after the drug administration. Remaining visits during the study will be performed on an outpatient basis.
Subcutaneous injections of the study drug and oral administration of tenofovir will be performed every 24 ± 1 hour after the first drug dose administration. In this case patient can adjust the introduction of the second and subsequent doses of the study drug under a convenient schedule which should be reflected in the patient's diary. Administration of subsequent doses of the drug should be carried out every 24 ± 1 hours from the time set by the schedule.
The following procedures and initial evaluations will be conducted as a part of the randomization visit:

- Registration of AEs;
- Certification of inclusion/exclusion criteria based on the screening test results;
- Randomization;
- Issuance of patient diaries;
- Handing the study drug for 28 days over;
- Handing tenofovir for 28 days over;
- Collection of data on the concomitant treatment;
- Physical examination;
- Weight measurement;
- Vital signs examination;
- Clinical blood test and blood clotting test;
- Blood chemistry (complete panel);
- Serum total bile acids test (central laboratory);
- Serum bile acids test (frozen samples);
- Urine analysis;
- HDV RNA (frozen samples);
- HBV DNA and HBsAg (frozen samples);
- HBV/HDV genotype test (frozen samples) shall be performed in patients whom NO pre-treatment periodwith tenofovir has been indicated;
- Resistance analysis (frozen samples) shall be performed in patients whom NO pre-treatment periodwith tenofovir has been indicated;
- Urine pregnancy test (only for women of childbearing potential);
- Alcohol-breath test;

- Immunogenicity (frozen samples);
- Serum marker for fibrosis (frozen samples);
- NTCP polymorphism (frozen clot of cells);
- For patients participating in the PK substudy within the scope of Phase II **(Pharmacokinetic study of Myrcludex B):** hospitalization on the eve of blood sampling. Blood sampling should be performed immediately before the administration of MXB and MDZ and in 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 the next day** (hh:min) after the administration of Myrcludex B (days 1-2).
- For patients participating in the PK-substudy within the scope of Phase II **(Study of systemic (general) metabolic CYP3A activity):** hospitalization on the eve of blood sampling (day (-1)). Blood sampling should be performed immediately before the administration of MDZ and in 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 the next day** (hh:min) after the administration Myrcludex B (days 1-2).
- Blood sampling for pharmacokinetic main study **(PK-main study)**. For patients not invovled in the pharmacokinetic substudy, a blood sampling point should be scheduled at the randomization visit (1 hour +/- 15 minutes after the administration of Myrcludex B).

A patient receives the study drug, tenofovir and all other materials associated with the study, for the 1-28th day of the study.
The tests conducted as a part of this visit represent the next evaluation in safety monitoring and should not be considered as inclusion/exclusion criteria.

4.4.4. Procedures and Evaluations during the Treatment Period

Procedures and Evaluations during the Treatment Period are same for Phases II and III.
Patients will begin treatment during the randomized visit. Subcutaneous injections of the study drug and oral administration of tenofovir will be performed every 24 ± 1 hour after the first drug dose administration. In this case patient can adjust the introduction of the second and subsequent doses of the study drug under a convenient schedule which should be reflected in the patient's diary. Administration of subsequent doses of the drug should be carried out every 24 ± 1 hours from the time set by the schedule.
Patient visits should occur according to the schedule presented in this section and in the study schedule.
Randomization visit, visit at week 1, 2, 4, 8, 12, 16, 20, 24; FU (follow-up) at week 1, 2, 4, 12, 24.
Week 1/day 8 ± 2 days/Visit 2: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment.

Investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. Patient's diary is classified as the primary documentation.
2 Week 2/day 15 ± 2 days/Visit 3: the following procedures will be performed:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);

- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment.
- For patients participating in the PK-substudy within the scope of Phase II: hospitalization on the eve of day 14. Blood should be sampled immediately before the administration of MXB and MDZ and in 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 the next day** (hh:min) after the administration of Myrcludex B.
- For patients participating in the PK-substudy within the scope of Phase II: hospitalization on the eve of blood sampling (day 13). Blood should be sampled immediately 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 the next day** (hh:min) after the administration of Myrcludex B (days 14-15).

Investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. Patient's diary is classified as the primary documentation.

Week 4/day 28 ± 2 days/Visit 4: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Urine analysis;
- Urine pregnancy test (only for women of childbearing potential);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment;
- Handing the study drug for 28 days over;
- Handing tenofovir over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

Week 8 ± 2 days/Visit 5: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- Urine pregnancy test (only for women of childbearing potential);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);

- Evaluation of compliance with the prescribed treatment;
- Handing the study drug for 28 days over;
- Handing tenofovir over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

Week 12 ± 2 days/Visit 6: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Physical examination;
- Weight measurement;
- Vital signs examination;
- 12-lead ECG;
- Clinical blood test, coagulogram;
- Blood chemistry (complete panel);
- Urine analysis;
- Urine pregnancy test (only for women of childbearing potential);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- Immunogenicity (frozen samples);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment;
- Handing the study drug for 28 days over;
- Handing tenofovir over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

Week 16 ± 2 days/Visit 7: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- Urine pregnancy test (only for women of childbearing potential);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment;
- Handing the study drug for 28 days over;
- Handing tenofovir over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

Week 20 ± 2 days/Visit 8: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Urine pregnancy test (only for women of childbearing potential);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- Collection of data on the concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Evaluation of compliance with the prescribed treatment;
- Handing the study drug for 28 days over;
- Handing tenofovir over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

Week 24 ± 2 days/Visit 9: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Physical examination;
- Weight measurement;
- Vital signs examination;
- 12-lead ECG;
- Clinical blood test,
- Coagulogram;
- Blood chemistry (complete panel);
- Urine analysis;
- Urine pregnancy test (only for women of childbearing potential);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Blood sampling for the pharmacokinetic main study (after 1h ± 15min after administration of Myrcludex B);
- HBeAg and anti-HBeAg antibodies (frozen samples) – only for patients with positive HBeAg results at screening;
- Liver biopsy study/transient elastometry (fibroscan);
- Serum marker for fibrosis (frozen samples);
- Resistance analysis (frozen samples);
- Immunogenicity (frozen samples);
- Collection of data on the concomitant treatment;
- Evaluation of patient diaries;
- Evaluation of compliance with the prescribed treatment;

- Handing tenofovir for 56 days over.

The patient should return the used and unused vials with the study drug, as well as used and unused vials with tenofovir to the clinical center. The investigator must verify records in the patient diary and add data on the compliance with the treatment to the CRF. The patient diary is classified as the primary documentation.

4.4.5. Evaluation after the end of the treatment

At the end of the treatment period, a 24-week follow-up period will start, which procedures are the same for Phases II and III. During the follow-up period, all patients will continue to be treated with tenofovir.

FU week 1 – treatment week 25 ± 3 days/ FU visit 1 (follow-up period): the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- Collection of data on the concomitant treatment.

FU week 2 – treatment week 26 ± 3 days/ FU visit 2: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test, coagulogram;
- Blood chemistry (abbreviated panel);
- Serum total bile acids (central laboratory);
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- Collection of data on the concomitant treatment.

FU week 4 – treatment week 28 ± 3 days/ FU visit 3: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test,
- Coagulogram;
- Blood chemistry (abbreviated panel);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Collection of data on the concomitant treatment;
- Handing tenofovir for 56 days over.

All patients should return packaging of used tenofovir to the clinical center.

FU week 12 – treatment week 36 ± 3 days/ FU visit 4: the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Vital signs examination;
- Clinical blood test;

- Coagulogram;
- Blood chemistry (abbreviated panel);
- Urine analysis;
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Immunogenicity (frozen samples);
- Collection of data on the concomitant treatment;
- Handing tenofovir for 56 days over.

All patients should return packaging of used tenofovir to the clinical center.

24 FU week 24 – treatment week 48 ± 3 days/ FU visit 5 (study termination visit) the following procedures will be performed in an outpatient setting:

- Registration of AEs;
- Physical examination;
- Weight measurement;
- 12-lead ECG;
- Vital signs examination;
- Clinical blood test,
- Coagulogram;
- Blood chemistry (complete panel);
- Serum total bile acids (in the central laboratory);
- Serum bile acids (frozen samples);
- Urine analysis;
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- HBeAg and anti-HBeAg antibodies - only in patients with positive HBeAg resulta at screening;
- Immunogenicity (frozen samples);
- Serum marker for fibrosis (frozen samples);
- Collection of data on the concomitant treatment.

All patients should return packaging of used and unused tenofovir to the clinical center.
Upon completion of the visit procedures, the patient is considered to have completed his/her participation in the study, according to the protocol.

4.5. Premature Drop-out from the Study, Dose Interruption, Dose Correction

If a study subject stops injecting MXV, for example, due to the development of an adverse event (AE), every effort should be made to ensure that the subject continues to participate in the study and to continue to perform all study procedures and observation, including administration of tenofovir. If it is not possible or unacceptable for the study subject or investigator, the subject may discontinue participation in the study.
Before withdrawing subjects from the groups receiving MXV at a dose of 5 mg or 10 mg from the study, the investigator may consider the possibility of tapering the drug dose: dose should be tapered from 10 mg and 5 mg to 5 mg and 2 mg per day. At the same time, monitoring of AEs should be carried out. If in the opinion of the investigator it is possible to continue treatment in a dose of 2 mg, the subject should continue treatment with the prescribed dose and undergo all the necessary study procedures and follow-up.
If, in the opinion of the investigator, a subject is indicated an interruption of treatment with MXB or a nucleoside/nucleotide analogue, this should be discussed with the sponsor’s medical monitor.
If a subject from one of the groups treated with MXB discontinues the administration of tenofovir but continues treatment with MXB, he/she must continue to participate in the study. If a subject in the study group discontinues the administration of tenofovir, efforts should be made to continue his/her participation in the study.

Participants dropped out of the study should undergo a visit at the end of treatment, including the following evaluations, within 14 days after discontinuation of the administration of the study drug:
During the final visit, the following procedures will be carried out in an outpatient setting:

- Registration of AEs;
- Physical examination;
- Weight measurement;
- Vital signs examination;
- Clinical blood test;
- Coagulogram;
- Clinical blood chemistry (full panel);
- Serum total bile acids;
- Serum bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Urine analysis;
- Collection of data on the concomitant treatment.

4.6. Treatment of the Activation of an Inflammatory Process

If the activation of the hepatic inflammatory process occurred during the treatment period (during Phase II or III) in the absence of signs of depression of liver function (increase in bilirubin level is ≥34.2 mg/dL, INR is ≥1.7), the treatment should be continued in connection with a careful monitoring of liver function. The possibility of holding unscheduled visits to monitor patients and evaluate laboratory parameters should be discussed with the sponsor's medical monitor.
In case of impaired liver function, the treatment with MXB should be discontinued, and treatment with the nucleotide analogue should be continued. At the investigator's discretion, the patient can be transferred to another registered drug for HBV treatment.

4.7. Detailed Description of the Study Procedures

This section provides a general description of the evaluations conducted as a part of phases II and II of the study. A more detailed description will be provided in the laboratory guide.

Patient demographics and medical history

During the screening period, the following demographics should be recorded:

- Date of birth,
- Gender,
- Race.

Data on the history of the disease under study, other underlying diseases and previous diseases (at the investigator's discretion), information about the previous treatment with interferon medications that the patient receives for the treatment of hepatitis, regardless of the prescription of treatment should also be recorded in the CRF. Information on any concomitant treatment / therapy should be collected from the time of screening.

Vital signs

The respiration rate, blood pressure, heart rate and body temperature will be measured regularly during the study. The schedule of the above mentioned measured tests is presented in the study design. The measurement data should be recorded in the CRF.

Physical examination

A complete physical examination of the subjects will be conducted as a part of the study. Its results should be recorded in the CRF.

Body height and weight
The measurement of body height and weight should be carried out within the time limits as per the study schedule. The measurement results should also be recorded in the CRF.

Urine pregnancy test
Urine pregnancy test will be conducted in women of childbearing age. The test will be performed at the clinical center using test strips.

Drug screening (urine test strips)
Urine test strips will be used to detect traces of methadone, benzodiazepines, cocaine, amphetamines, cannabinoids, opiates, barbiturates, tricyclic antidepressants.

Alcohol-breath test
Alcohol-breath test will be determined using an alcohol breathalyzer.

Abdominal ultrasound
During the screening period, an ultrasound of the abdominal cavity will be performed. Particular attention should be paid to the evaluation of the liver structure. All disturbances are subject to be registered the CRF in the present disease section.

Serum alpha-fetoprotein screening
A serum alpha-fetoprotein screening will be performed for all patients during the screening stage. The screening should be performed in the central laboratory to exclude hepatocellular carcinoma.

Liver biopsy study and transient elastometry
During the screening stage and the visit at the end of treatment, patients will undergo a liver biopsy study, with the determination of the level of hepatic necroinflammation and fibrosis. An immunohistochemical analysis of HDV RNA-positive cells will be performed. A part of the biopsy material will be frozen to determine intrahepatic parameters. No use of maintenance drugs (for example, to stimulate the growth of platelets) is allowed. A liver biopsy study may be replaced, by the decision of the investigating physician, with transient elastometry (fibroscan).
Transient elastometry and biopsy procedures can be performed directly at the clinical site or (if not possible) in an authorized medical organization that has the proper equipment and staff qualification.

Laboratory blood tests for safety evaluation
Laboratory blood tests for safety evaluation will be performed during the study in accordance with the study design in the central laboratory. If there is any laboratory abnormality and confirmation of deviations' clinical significance, the investigator should fill in the adverse event registration form in the CRF.
Clinical laboratory tests that should be performed during the study are listed below:

Clinical blood test, including blood coagulation parameters
(should be performed in the central laboratory)
- White blood cell differential count (relative count): neutrophils, eosinophils, basophils, monocytes, lymphocytes;
- White blood cell differential count (absolute count): neutrophils, eosinophils, basophils, monocytes, lymphocytes;
- RBC;
- WBC;
- Hematocrit;
- Hemoglobin;

- PLT;
- Reticulocytes;
- Prothrombin time;
- Activated partial thromboplastin time.

Blood chemistry
(should be performed in the central laboratory)
Blood chemistry – **complete panel:**
- Sodium;
- Potassium;
- Chloride;
- C-reactive protein;
- Total protein;
- Albumin;
- Total bilirubin;
- Direct (unconjugated) bilirubin;
- Total cholesterol;
- Creatinine;
- Blood urea;
- Glucose;
- Gamma-glutamyltransferase;
- Alanine aminotransferase;
- Alkaline phosphatase;
- Aspartate aminotransferase;
- Lipase;
- P-amylase;
- Phosphate;

Blood chemistry – **abbreviated panel:**
- Albumin;
- Total bilirubin;
- Direct bilirubin;
- Creatinine;
- Gamma-glutamyltransferase;
- Alanine aminotransferase;
- Aspartate aminotransferase;
- Phosphate.

Serum bile acids
Total bile acids will be tested in the central laboratory. Sampling will be performed in accordance with the methodology instructions on laboratory work and stored at -20°C until being sent to the central laboratory.
Individual bile acids will be tested in the central laboratory in Germany, serum total bile acids – in the central laboratory in the Russian Federation.

Serological analysis
- Anti-HIV antibodies;
- Anti-HCV antibodies;
- Anti-HDV antibodies;
- Non-quantitative HBsAg test to evaluate patient eligibility for participation in the study;
- Non-quantitative HBeAg test;

- Anti-HBeAg antibodies.

The above mentioned serological analysis should be performed at the local laboratory of the clinical center, unless otherwise agreed with the Sponsor. If anti-HCV antibodies are detected, the HCV RNA test should be performed. If the HCV RNA test results are negative, the patient may be enrolled in the study.

Urine analysis for safety parameter evaluation

The urine analysis will be performed in accordance with the study design. The results should be reported in the CRF.

The following parameters will be evaluated:

- pH;
- Specific gravity;
- Protein;
- Glucose;
- Bilirubin;
- Urobilinogen;
- Ketones;
- RBC;
- WBC;
- Nitrites.

The urine analysis will be performed at the local laboratory of the clinical center.

Laboratory tests performed according to the requirements of the Protocol in local laboratories of clinical centers will be performed using standard methods adopted in the clinical center laboratories.

Laboratory tests performed in the central laboratories will be performed using the following methods:

Virology tests

The virology parameters will be evaluated as a part of the study: HDV RNA, HBsAg and HBV DNA. Blood samples from veins will be collected at specified time points.

The following parameters will be evaluated:

- HDV RNA using the quantitative PCR;
- HBsAg level using the quantitative ELISA;
- HBV DNA using the quantitative PCR;
- HBV genotype test – using the sequencing method, once as a part of the study during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated;
- HDV genotype test – using the sequencing method, once as a part of the study during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated;
- Test on the development of resistance – using the sequencing method, one sample at the initiation of the study, one – at the end of the study. The first blood sample should be collected for analysis during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated. The second one – in all patients according to the procedure schedule.

Analysis will be performed in the central virology laboratory.

The blood samples will be collected in sterile, sealed-off disposable plastic K2-EDTA Vacutainer® tubes. All collected samples of plasma /serum are stored in the clinical center at -20°C before sending and then sent to the central laboratory in a validated thermal container at -20°C or -80°C (more details about the sampling, bio-sample storage and transportation conditions are described in the laboratory manual)

The Blood plasma samples for analysis for the presence of HDV RNA at the screening stage are stored and transported to the central laboratory at room temperature.

Determination of antibodies to HBsAg will be performed at the end of the study in a central virology laboratory using appropriate back-up samples (for HBsAg determination) in patients with negative result of quantitative

HBsAg determination at Week 24 and Week 48 of active treatment. The samples are not to be taken separately for this analysis.

NTCP polymorphism
NTCP polymorphism will be evaluated once during the study (baseline) in the central laboratory, using the sequencing method.

Serum marker for fibrosis
Serum marker for fibrosis, alpha-2-macroglobulin, will be evaluated at the beginning of the study, at the end of the treatment period and at the end of the follow-up period in the central laboratory, using ELISA.

Immunogenicity
The detection of anti-Myrcludex B antibodies will be performed only in patient groups treated with Myrcludex B, using ELISA.

Pharmacokinetic parameters of plasma (as a part of Phase II)
The blood samples will be collected in sterile, hermetically sealed disposable plastic Li-Heparin Vacutainer® tubes. The minimum volume of the blood sample, which is necessary for analytical purposes for the pharmacokinetic substudy (PK-substudy) of Myrcludex B and MDZ, comprises 4 ml, and for the pharmacokinetic main study (PK-main study) of Myrcludex B comprises 4 ml.
Blood sampling for studying the pharmacokinetics of Myrcludex B and MDZ is carried out in different tubes. The amount of blood sampled to study the concentration of Myrcludex B (as a part of the PK-substudy) in plasma will be no more than 112 ml, and to study the concentration of MDZ – 168 ml.
The pre-printed labels will be pasted onto the tubes.
Procedures for blood sample processing and storing in the clinical center, as well as transportation of blood samples to study the pharmacokinetics of Myrcludex B (PK-main study and PK-substudy), as well as to study the systemic (general) metabolic CYP3A activity (MDZ pharmacokinetics study) will be identical.
Immediately after sampling, tubes with blood samples should be carefully turned upside down for 4-6 times (to avoid the clotting reaction).
In the laboratory, the samples will be centrifuged at 4°C for at least 10-15 minutes at a centrifugal force of 2800-3000g. The resulting supernatant will be transferred into polypropylene plastic tubes (two tubes per sample, at least 1.0 ml of plasma should be placed in each tube) and frozen in a vertical position in the freezer. The samples should be stored in the freezer at a constant temperature control of ≤-20°C, until they are sent to the bioanalytical laboratory.
If plasma and blood corpuscles are noted to have mixed during plasma separation process, the tubes should be re-centrifuged so that a maximum amount of intact plasma could be obtained from each sample.
Acceptable time for handling each individual tube, i.e. time between blood sampling and placement the sample in the centrifuge, should not exceed 20 minutes, the time between centrifugation and placement of the sample in the freezer should not exceed 90 minutes. It is necessary to make every effort to minimize the time interval from the moment of blood sampling to the moment of freezing of plasma samples. The site staff should record any deviations from this requirement in the case of each sample.
Tubes should be of room temperature and labeled appropriately. The labelling should represent the time point of the blood sampling, the protocol number, the study period, the serial number of the tube for the given point, the patient's randomization number.
The frozen samples will be transported in a special container with a sufficient amount of dry ice to ensure the preservation of freezing during transportation. The frozen samples contained in Aliquots 1 will be sent to the central laboratory. Aliquot 2 (reserve aliquot) will be sent to the central laboratory only if necessary.
Determination of Myrcludex B and MZD plasma level will be performed using validated technique of HPLC-MS/MS. Quantitative concentration determination will be carried out in the central laboratory.
For each of the doses studied, for which sufficient information can be obtained on the basis of the plasma concentration assessment, an evaluation of the pharmacokinetic parameters will be performed. More detailed

information will be provided in the statistical analysis plan.
The total amount of blood sampled throughout the study will be about 648 ml. If a 12-week pre-treatment period with tenofovir is prescribed, the volume of the blood sampled will increase by approximately 30 mL. In patients involved in the study if pharmacokinetics of the Myrcludex B and the systemic (total) metabolic CYP3A activity, the volume of the blood sampled will increase by approximately 280 ml.
Clinical events and clinically significant laboratory abnormalities grade 3 and 4 will be classified according to National Cancer Institute (NCI) Common Toxicity Criteria (NCI Common Terminology Criteria for Adverse Events, version 4.0. In case of inability to analyze the collected sample (hemolysis, transport damage, etc.), additional blood volume will be required for re-analyzes.
If there is a need to conduct re-analyzes or safety monitoring of investigational therapy, additional visits can be scheduled. After the unscheduled visit, the next monitoring visit is to be carried out in accordance with previously approved plan and protocol.
To determine Myrcludex B effects or physiological effect of increased level of bile acids on the metabolism or inflammation, blood samples collected in the study can be analyzed for parameters that characterize carbohydrate and lipid metabolism and also play a role in the development of vascular diseases.

Patient diary
At randomization period patients will be given diaries in which they will make the following entries during the the study drug treatment period:

- Adverse events, especially reactions at the injection site,
- Day and time of administration of each dose of the study drug and the nucleotide analogue.

Copies of completed diary pages will be stored in the sourse documentation.

4.8. Study Completion, Suspension or Termination and Withdrawal of a Center or a Patient

4.8.1. Study completion as per protocol

Study completion as protocol provides for the patient to undergo all the protocol procedures described in Section 4.4. of the Protocol.
The study completion date as per protocol should be the date of the last visit or the last planned procedure provided for in Section 4.4. of the Protocol. The study completion date as a whole should be the date of the last visit of the last patient enrolled in the study.
The sponsor reserves the right to suspend or terminate the study at any time for certain reasons, which include (but are not limited to) safety issues, ethical issues and serious non-compliance with the agreed requirements and conditions. If the study is suspended or terminated in connection with safety issues, the Sponsor will promptly notify the contracting research organization (CRO), investigators, as well as the IEC and regulatory authorities about the study suspension/termination, specifying the reasons for such a measure.

4.8.2. Study Suspension or Termination

The Investigator and Sponsor reserve the right to terminate the study at any time. If necessary, the procedures will be agreed upon after consultation with both parties. If the study is terminated prematurely or suspended, the Sponsor shall promptly notify Investigators/organizations and authorized bodies of the termination or suspension, as well as indicate the reasons for the termination or suspension. The Sponsor or the Investigator/organization (in accordance with regulatory requirements) should also immediately inform LEC about it, including the reasons for the study termination or suspension. At the time of study termination, the Sponsor and the Investigator will assure the compliance with provisions for the best protection of patient interests.
The main reasons for the suspension or premature termination of the study include the occurrence of serious or unlabeled adverse reactions in the majority of patients during the first study days, non-compliance with the rules for the conduction of the study, the inability to conduct the study in accordance with the protocol.
Possible reasons for terminate the Sponsor's study may include an increase in the risk to the health or life of patients, significant violations in the conduct of the study, etc. If the study is terminated by the Sponsor, the sponsoring company should notify the CRO, investigators, as well as the IEC and regulatory authorities

(Ministry of Health of the Russian Federation). The Sponsor is authorized to terminate the study at any time.
The Investigator has the right to terminate the study in case of an increased risk to the health and/or life of patients. In this case, the Investigator should inform the CRO/Sponsor and local ethics committee.
The Ministry of Health of the Russian Federation can temporarily or completely terminate the study if, in its opinion, the conditions contained in the application are not met, or the regulatory body has the data that challenge the safety of patients or the scientific justification of the study at its disposal.
If for any reason the study is prematurely discontinued or suspended, the Investigator should immediately inform the patients enrolled in the study hereof and provide them with appropriate treatment and supervision.
If for any reason the study is prematurely discontinued or suspended, the Investigator should immediately inform the patients enrolled in the study hereof and provide them with appropriate treatment and supervision.

4.8.3. Premature termination of a center's participation in the study

The clinical center may be prematurely closed or its work may be suspended if it is revealed that the investigational team of the center significantly violates the requirements of the GCP, protocol and/or regulatory authorities, contractual obligations or cannot provide for an adequate study management.

4.8.4. Premature termination of a patient's participation in the study

Data on the patients who have been enrolled in the study and have completed the study not in accordance with the protocol, i.e. have been dropped out of the study, should be recorded in the Final visit section in the CRF, where the reason why the patient has been dropped out of the study should mandatorily be indicated in detail. The reasons can include:

- The case when the Investigator has made a decision that a patient should be dropped out in the very interests of the patient;
- Incorrect inclusion;
- Serious protocol deviation, protocol violation;
- Serious adverse event, including death (with the indication of the date of death);
- Any adverse event;
- The patient receives/requires supportive treatment, which may affect the study results;
- Positive pregnancy test results (for women);
- Failure to appear at the visit and loss of communication of the patient;
- Refusal or lack of discipline of the patient

4.9. List of Data Registered Directly in the CRF

The source data is all information contained in original medical records and their certified copies, describing the results of clinical observations, surveys and other activities, allowing to recreate the course of clinical study and evaluate it. The source data is kept in the primary documentation (original texts or their certified copies).
All source data, including information on AEs, will be recorded in the primary documentation (out-patient medical record, past medical history) at first, and then it will be transferred to the CRFs. The CRF will not contain data that are not displayed in the primary documents, except for cases when the data is available in the form of original printouts or can be directly entered into the system according to the monitoring manual.
The study monitor will be verify the completed CRFs via the source data. All deviations and errors will be corrected by the Investigator and reported in the monitor's report.

5. PATIENT SELECTION AND DROP-OUT

This study will include patients with chronic hepatitis B with delta agent and a detectable level of HDV RNA replication.

5.1. Inclusion Criteria

The inclusion criteria are the same for phases II and III.

To be suitable for participation in the study, participants must meet *all* the inclusion criteria listed below.

1. Age from 18 through 65 years at the time of granting of a written informed consent for the participation in the study.
2. Presence of HBsAg in serum within at least 6 months before the screening period.
3. Anti-HDV antibodies in serum within at least 6 months.
4. Positive PCR on HDV RNA in serum during screening.
5. Patients with hepatic cirrhosis, regardless of prior treatment with interferons.
6. Patients without hepatic cirrhosis in whom prior IF treatment was ineffective or, in the opinion of the investigator, is currently contraindicated (including cases of interferon intolerance in the past medical history)[6].
7. Alanine aminotransferase index is >1 UNL, but less than 10 UNL.
8. Prior treatment with nucleotide / nucleoside analogues for at least 12 weeks prior to the planned start of study treatment with the study drug or patient's consent to take tenofovir for at least 12 weeks before the planned start of study treatment.
9. Negative urine pregnancy test in female subjects of childbearing age:
10. Inclusion criteria for women:

- Menopause within at least 2 years, or
- Surgical sterilization (complete hysterectomy or bilateral oophorectomy, or ligation of both fallopian tubes, staples, or other method of sterilization), or
- No heterosexual contactsduring the study period, or
- Consent to use a highly effective contraceptive method (a double barrier method or a combination of a barrier method with a hormonal or intrauterine contraceptive) during the study period and within 3 months after the last dose of the study drug.

11. Men must agree to use a highly effective contraceptive method (double barrier methods or a combination of a barrier method and a hormonal or intrauterine contraceptive used by a female partner) and not be a sperm donor during the study period and within three months after the last dose of the study drug.

5.2. Exclusion Criteria

The exclusion criteria are the same for phases II and III.

Participants who meet *any* of the following exclusion criteria can not participate in the study.

1. The Child Pugh score should be B-C or above 6 points;
2. The co-infection with hepatitis C virus (HCV) or HIV. Patients with the presence of anti-HCV antibodies in the presence of negative HCV RNA at the stage of screening are considered acceptable to participate in the study;
3. Creatinine clearance is <60 ml/min;
4. Total bilirubin is> 34.2 μmol / L. Patients with an increased total bilirubin level may be included in the study after consulting with the Medical Research Monitor if it is clearly established that such an increase is an evidence of Gilbert's syndrome.
5. Malignant tumors in any organ system, including hepatocellular carcinoma, in the past or current history.
6. Systemic connective-tissue diseases.

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[6] Inclusion of patients who have previously undergone IF treatment in the study is possible not earlier than 30 days after the last administration of interferon.

7. Chronic heart failure of functional classes III-IV according to NYHA (New York Heart Association) classification.
8. Patients with uncontrolled arterial hypertension (BP> 150/100 mm Hg affected by the administration of antihypertensive drugs) during previous 3 months before the initiation of the clinical phase.
9. Patients with past or unstable concomitant diseases, or clinical conditions that prevent the inclusion of this patient in the study.
10. Patients with mental disorders or social circumstances that interfere with the requirements of the protocol.
11. Decompensated liver disease in the current or previous history, including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding esophageal varices;
12. WBC count is <3000 cells/mm^3;
13. Neutrophil count is <1500 cells/mm^3;
14. Platelet count is <60,000 cells/mm^3;
15. A patient takes illegal psychiatric drugs at the time of screening;
16. Treatment with Interferon within 30 days before screening;
17. Transplantation of a solid organ in the past history;
18. Patients who abuse alcohol now or have abused d it for 6 months before the enrollment;
19. A history of a disease requiring regular use of systemic corticosteroids;
20. Pregnant and lactating women;
21. Participation in other clinical studies within 30 days before screening;
22. Patients who have received Myrcludex B as a part of previous studies.

5.3. Criteria for Premature Withdrawal of Patients from the Study

5.3.1. Withdrawal criteria

The withdrawal criteria are the same for phases II and III.
The study subjects are entitled at any time and for any reason to discontinue participating in the study without explaining the reasons. Nevertheless, the Investigator must make every effort to obtain complete information on the reasons for the patient's refusal and to report them in the source data and the CRF.
The patients can be withdrawn from the study in a number of the following cases:
1. The Investigator has made a decision that a patient should be dropped out in the very interests of the patient;
2. The Investigator's decision to withdraw the patient from the study due to a serious protocol deviation/protocol violation;
3. Intercurrent disease or progression of the underlying disease, which in the investigator's opinion, will significantly affect the evaluation of the clinical status of the patient.
4. The need to use illegal drugs.
5. Unacceptable toxicity, according to the definition given in the protocol section on toxic reactions, or a reaction that, in the investigator's opinion, makes it impossible to continue the study procedures or does not meet the subject's needs.
6. The subject declares about the desire to drop out the study for any reason.
7. The subject does not adhere to the appointments (unsatisfactory compliance). It is defined as missing the dose of the study drug for 3 consecutive days or 4 missed doses of the drug for 28 days.
8. Pregnancy occurred during the study.
9. Termination of participation in the study at the request of the sponsor, regulatory agency or ERB / IEC.
10. Loss of communication with the patient.

The protocol violations listed below may be the cause, but do not necessarily lead to the withdrawal of the patient from the study. The decision in this case should be made by the Sponsor, both individually and in coordination with the investigators:

- Failure to inform the Sponsor in due time about the development of AEs in patients (in case there is a documented fact that the investigator has received information about development of AEs in the patient);
- Development of a concomitant disease or condition that leads to difficulties in carrying out any mandatory study procedure, that, in the opinion of the investigator, can have a significant impact on the objectivity of the results in assessing the patient's condition;

- The need to take other medicines other than the study drug that do not have a significant effect on the study results.
- Other study protocol violations, which, in the opinion of the Investigator or Sponsor, are not significant.

The patient can be withdrawn at any stage of the study without any further delay.
If there is a serious illness or intolerance to the study drug, the Investigator will make a decision to withdraw the subject from the study. Patients who have been withdrawn from the study due to a serious intercurrent disease or for safety reasons will be treated in accordance with established medical practice and will be monitored prior to resolution or stabilization of their condition. In this case, the Investigator will notify the Sponsor in advance and provide for the sufficient medical justification for his decision.
In addition, patients will be deemed to be dropped out of the study if they are lost for the follow-up, i.e., if the patient has discontinued participation without notifying the Investigator.
Since the excessive number of patients withdrawn from the study may result in the impossibility of interpreting the data obtain, it is necessary to avoid an excessive withdrawal of patients.

5.3.2. Data on the patients dropped out

The Investigator will be responsible for recording the reason(s) of any withdrawal from the study after the randomization, as well as for filling all the necessary detailed information in the CRF and completing the "Final visit" section in the CRF, where the reason why the patient has dropped out of the study must be recorded in detail. If the reason the subject withdrawal is AE, it is necessary to record the main specific event or laboratory test in the CRF, and the Investigator should make every effort to record the outcome of the AE in a clear way.
The Investigator transfers the following data on patients dropped out the study to the Sponsor and study monitor within 24 hours, including information on the reason for the premature discontinuation of the patient's participation in the study:

- investigational error;
- adverse events;
- serious adverse events;
- pregnancy;
- protocol violations;
- a patient's desire to withdraw from the study;
- due to the absence of the patient and loss of communication with him;
- other reasons (should be specified).

5.3.3. Subject substitution

Replacement of study participants in this study is not applicable.

5.3.4. Follow-up of patients dropped out

If there is any SAE, the patient should be monitored before the resolution of the SAE or it's transition to a chronic condition, by phone calls with an interview for complaints and anamnesis, as well as during visits that are not part of the study design but are necessary from the point of view of the patient safety.
If, in the opinion of the attending physician, AE, which is not a serious one, requires a patient follow-up, this observation can also be performed by phone calls and visits, with an interview for complaints and anamnesis.
If a SAE that has a probable connection with the drug administration as assessed by the investigating physician has developed, the observation and necessary treatment should be made regardless of the development period of the SAE; monitoring of the patient should also be carried out before the resolution of the SAE.
If the dropout has occurred due to other reasons, the follow-up will not be carried out.

6. PATIENT TREATMENT

6.1. Myrcludex B

6.1.1. Dosage form

Myrcludex B is manufactured in the form of a lyophilized powder for injection. The drug is supplied in sterile vials, the contents of which are diluted before use with 1 ml of water for injection.

Composition:

Active ingredient: Myrcludex B acetate, 2.0 mg/vial, 5.0 mg/vial.

Excipients: water for injection (WFI), sodium carbonate, sodium bicarbonate, mannitol, hydrochloric acid and sodium hydroxide are used to dissolve the drug substance before aseptic filling and lyophilization. The excipients of pharmaceutical grade are used.

Physical form: white or grayish-white powder

Appearance of the solution: clear and transparent.

6.1.2. Container Closure System

The study drug Myrcludex B will be administered in the form of a lyophilized powder for injection 2.0 mg/vial and 5.0 mg/vial.

Primary packaging

Container: 2 R injection vial, colorless glass, EF Hydrolytic class I

Closure: Lyophilization rubber stopper for 2R vials, E.P. Type I (diameter 13 mm)

Secondary packaging

Closure: 13 mm bordered cap, aluminum with plastic disc

Disposable containers and closures are used. Vials and lyophilization rubber stoppers are sterilized, all materials are tested before use.

6.1.3. Drug Handling and Storage

In the research center, the drug should be stored at -20±5 °C in the dark place.

It is allowed to store the drug at + 5°C at home (in the refrigerator).

The cold chain tolerance is acceptable (storage at room temperature within up to 3 days).

After reconstitution of the contents of the vial with water for injection, the drug remains stable for 120 minutes at room temperature.

6.2. Dose and Administration of Myrcludex B

The site staff will teach patients the procedure of subcutaneous injections of the drug. Separately, patients will be provided with training materials.

Phase II

Arm A: 2 mg Myrcludex B once a day s/c

During the treatment period, at each visit patients randomized to Arm A will be provided with sets of study drug for use for 28 days containing:

30 vials of 2.0 mg MXB

30 vials with sterile water for injection (minimum 2 mL)

30 disposable syringes

Patients will be instructed on the procedure for a dilution of a 2 mg Myrcludex B vial with 1 ml of WFI and self-administration of the contents of one 2 mg vial once a day. Dilution should be performed immediately before injection. The diluted solution remains stable for 2 hours.

Arm B: 5 mg Myrcludex B once a day s/c

During the treatment period, at each visit patients randomized to Arm B will be provided with sets of study drug for use for 28 days containing:

30 vials of 5.0 mg MXB

30 vials with sterile water for injection (minimum 2 ml)

30 disposable syringes

Patients will be instructed on the procedure for a dilution of a 5 mg Myrcludex B vial with 1 ml of WFI and self-administration of the contents of one 5 mg vial once a day. Dilution should be performed immediately before injection. The diluted solution remains stable for 2 hours.

Arm C: 10 mg Myrcludex B once a day s/c
During the treatment period, at each visit patients randomized to Arm C will be provided with sets of study drug for use for 28 days containing:
60 vials of 5.0 mg MXB
30 vials with sterile water for injection (minimum 5 ml)
60 disposable syringes
Patients will be instructed on the procedure for a dilution of a 5 mg Myrcludex B vial with 1 ml of WFI and self-administration of the contents of one 5 mg vial twice a day. Injections should be performed at a 1-30-minute interval.
Dilution should be performed immediately before injection. The diluted solution remains stable for 2 hours
Dose adjustment
No dose adjustment in Arm A is allowed.
In case of any toxicity in Arms B and C, a dose adjustment is acceptable. For more information, refer to **paragraph 4.5. "Premature Drop-out from the Study, Dose Interruption, Dose Correction".**
Missing a dose
If a dose is missed, the following algorithm should be followed:
If the patient recalled the missed dose no later than 4 hours after the time prescribed during the randomization visit, the dose should be injected. The next day, the scheduled dose should be injected at the time prescribed. If it has passed more than 4 hours after the scheduled time, the dose should not be injected, it should be considered missed, and the next day the next dose should be injected at the time prescribed.
The data on missing the dose should be registered in the patient diary and in the CFR. The patient should inform the investigator about the missed dose by a phone call.
Phase III
Group I: optimal dosage (in mg) Myrcludex B per day s / c
During the treatment period, at each visit patients randomized to Group I will be provided with sets of study drug for use for 28 days containing:
30 vials of MXB in optimal dosage (in mg)
30 vials with sterile water for injection
30 disposable syringes
Patients will be instructed on the procedure for a dilution of a vial with Myrcludex B with WFI and self-administration of the contents of one vial once a day. Dilution should be performed immediately before injection. The diluted solution remains stable for 2 hours
Dose adjustment
No dose adjustment in Group I is allowed.
Missing a dose
If a dose is missed, the following algorithm should be followed:
If the patient recalled the missed dose no later than 4 hours after the time prescribed during the randomization visit, the dose should be injected. The next day, the scheduled dose should be injected at the time prescribed. If it has passed more than 4 hours after the scheduled time, the dose should not be injected, it should be considered missed, and the next day the next dose should be injected at the time prescribed.
The data on missing the dose should be registered in the patient diary and in the CFR. The patient should inform the investigator about the missed dose by phone.

6.3. Previous and Concomitant Medication

Patients treated with nucleoside/nucleotide analogs for HBV treatment should be transferred to entecavir or tenofovir at the beginning of the study (randomization visit).
Tenofovir (VIREAD®) for the study will be studied by Gilead Science (Ireland) in the form of film-coated tablets, 245 mg of tenofovir disoproxil, that is equivalent to 300 mg of tenofovir dizoproxil fumarate, in the vial N30. Packaging of the drug will be marked in accordance with the requirements of Russian legislation by the Heidelberg University Hospital, Germany (see the example of label below). VIREAD® (245 mg of tenofovir dizoproxil, that is equivalent to 300 mg of tenofovir dizoproxil fumarate), film-coated tablets.
Trademark: (VIREAD®)

Registration numbers:
EU/1/01/200/001
EU/1/01/200/002
INN: tenofovir dizoproxil (fumarate)
Chemical name: 9-[(R)-2-[[bis[[(isopropyl carbonyl)oxy]methyl]phosphine]methoxy]propyl] adenine fumarate
Manufacturer:
– dosage form and packaging: Patheon Inc., Canada;
– final quality control and marketing authorisation holder: Gilead Sciences (Ireland)
– product labeling and release certificate – Heidelberg University Hospital, Germany.
The drug label, developed in accordance with Art. 13.3 of Directive 2001/20/EC, FZ-61, 2010, as well as Annex 13 "Production of medicines for clinical studies" of the Good Manufacturing Practices (GMP), 2007, for the study, Heidelberg University Hospital, Germany, will be specified as a manufacturer, as the institution that conducts the final stage of the drug release.
Label for tenofovir (example):

For clinical studies only! Hepatera **Study No. MYR202** **Biread** (245 mg of tenofovir dizoproxil, that is equivalent to 300 mg of tenofovir dizoproxil fumarate), 30 film-coated tablets **Batch No.** MYR202/2015KW **Expiry date:** 06.12.2019 **Randomized patient No.:**_____ **Full name of the Investigator/Center No.**_____ Date of the drug issue «__»_____20__ ***Visit No.:*** ☐	***Administration route:*** oral, with food, with a small amount of water. Tablets cannot be chewed or broken. Store in the dry and dark place not above 30°C. Keep out of reach of children. Return empty packaging or unused drug. **Sponsor**: Hepatera LLC, 109240, Moscow, Verkhnyaya Radishchevskaya Street, 12/19, bldg. 1, Tel. +7 (495) 726-52-53 **Manufacturer:** 69120 Heidelberg, Germany, Heidelberg University Hospital, Neuerheimer-Feld-Strasse, 670

Marketing authorization holder: Gilead Sciences, Ireland
Dosage form
Film-coated tablets, 245 mg (tenofovir disoproxil)
Composition
Each film-coated tablet contains:
Active ingredient: tenofovir disoproxil, 245 mg, that is equivalent to 300 mg of tenofovir dizoproxil fumarate;
Excipients:
Tablet core: pregelatinized starch, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, magnesium stearate;
Coat: glycerol triacetate (E1518), indigo carmine aluminum lake (E132), hypromellose (E464), lactose monohydrate, titanium dioxide (E171).
Description
Almond shaped tablets coated with a light blue film coat, 16.8 mm*10.3 mm, engraved with "GILEAD" and "4331" on one side, and "300" on the other side.
Presentation
Film-coated tablets 245 mg of tenofovir disoproxil. 30 tablets per a high density polyethylene vial with a child-proof cap with an embedded moisture absorber (silica gel).
Storage conditions
Do not store above 30°C. Store in the dry, dark place.
Keep out of the reach of children.

Shelf life
5 years.
Do not use after the expiry date printed on the package.

6.4. Excluded medication

- Systemic glucocorticosteroids
- Illegal psychotropic drugs, drugs and psychoactive drugs.
- The use of immunomodulators and antiviral drugs, in addition tenofovir, should be discussed with the medical monitor.

6.5. Methods of Monitoring Patient Compliance

During the screening and at the time of randomization, patients undergo laboratory and instrumental examinations, confirming their compliance or incompliance with inclusion/exclusion criteria. Female patients are additionally tested for pregnancy.
Also during the study, at each visit, a collection of data on the concomitant treatment, an assessment of treatment regimen adherence and an assessment of the presence of AEs are performed. These procedures additionally provide for the confirmation of study inclusion and exclusion criteria and assessment of patient compliance with the research procedures.

7. EFFICACY EVALUATION

7.1. Efficacy Criteria

Efficacy parameter evaluation criteria are the same for Phases II and III.

Primary endpoint

- The negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.

The reduction in the viral load recorded by the level of HDV RNA (decrease HDV RNA by ≥ 2log10) at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug, is the primary endpoint in the planned study.

Due to the fact that Myrcludex B does not directly affect the level of HDV viral replication, but prevents the penetration of HBV into hepatocytes, by blocking the HBV and HDV NTCP / SLC10A1 receptor, thereby stopping the spread of the virus into the liver, a decrease of HDV RNA by ≥ $2\log_{10}$ may be indicative of the reduction of the number of infected cells by a factor of 100 (this information is needed to evaluate the duration of Myrcludex B treatment required for complete virus elimination in a particular patient, depending on the dynamics of the decrease in viral load) only.

Due to the fact that the level of HDV RNA at the time of inclusion into the study may be low, the patients who have achieved the virus elimination during the study may not meet the criterion of :HDV RNA reduction by ≥ $2\log_{10}$", herewith, the virus elimination is considered as a positive event. Thus, it becomes necessary to supplement the formulation of the main endpoint with information about the negative PCR result on HDV RNA.

Secondary endpoints

- The duration of the effect (no increase) on HDV RNA at week 24 after treatment (study week 48) compared to the results obtained at the end of the treatment period (study week 24).
- The presence of a combined response: the negative PCR result on HDV RNA, or a decrease by ≥2 log and normalization of ALT at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics of ALT activity at treatment week 24 and study week 48 compared to results obtained before the initiation of treatment with the study drug.
- Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) according to the liver biopsy study results or the absence of a fibrosis progression according to the findings of transient elastometry (fibroscan) at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics (no increase) of the serum marker for fibrosis – alpha-2 macroglobulin in the serum at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.
- Dynamics of HBsAg (decrease in the quantitative content, disappearance of HBsAg, development of anti-HBsAg antibodies) at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.
- Decrease in HBV DNA levels at treatment week 24 and study week 48 compared to the results obtained before the initiation of treatment with the study drug.

7.2. Efficacy Parameter Evaluation Methods and Terms

Efficacy parameter evaluation methods and terms are the same for Phases II и III.

According to the requirements of the protocol, the results obtained at the randomization visit (Visit 1) is considered to be the source data for determining the therapeutic efficacy of MXB. To evaluate the endpoint on the basis of the liver biopsy study results, the results obtained on Visit 01 of the Screening is considered to be the source data for determining the therapeutic efficacy of MXB.

The efficiency parameter evaluation will be performed according to the following schedule:

- The negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 (Visit 9) compared to the results obtained before the initiation of treatment with the study drug (Visit 1) will be evaluated using virology analysis by PCR.

- The duration of the effect (no increase) on HDV RNA at week 24 after treatment (FU5 Visit: study week 48) compared to the results obtained at the end of the treatment period (Visit 9: study week 24) will be evaluated using virology analysis by PCR.
- The presence of a combined response: the negative PCR on HDV RNA, or a decrease by ≥2 log and normalization of ALT at treatment week 24 (Visit 9) compared to the results obtained before the initiation of treatment with the study drug (Visit 1) will be evaluated using virology analysis by PCR.
- Dynamics of ALT activity at treatment week 24 (Visit 9) and study week 48 (FU5 Visit) compared to results obtained before the initiation of treatment with the study drug (Visit 1) will be evaluated on the basis of results obtained from the blood chemistry.
- Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) at treatment week 24 (Visit 9) compared to results obtained before the initiation of treatment with the study drug (Visit 01) or the absence of a fibrosis progression at treatment week 24 compared to the results obtained before the initiation of treatment with the study drug (Visit 01) will be evaluated on the basis of the results of liver biopsy study/transient elastometry (fibroscan).
- Dynamics (no increase) of the serum marker for fibrosis – alpha-2 macroglobulin in the serum using ELISA at treatment week 24 (Visit 9) and study week 48 (FU5 Visit) compared to the results obtained before the initiation of treatment with the study drug (Visit 1).
- Dynamics of HBsAg (decrease in the quantitative content, disappearance of HBsAg, development of anti-HBsAg antibodies) at treatment week 24 (Visit 9) and study week 48 (FU5 Visit) compared to the results obtained before the initiation of treatment with the study drug (Visit 1) will be evaluated using virology analysis by the quantitative ELISA.
- Decrease in HBV DNA levels at treatment week 24 (Visit 9) and study week 48 (FU5 Visit) compared to the results obtained before the initiation of treatment with the study drug (Visit 1) will be evaluated on the basis of results obtained in virology analysis by the quantitative PCR.

8. SAFETY EVALUATION

8.1. Safety parameter evaluation criteria

Safety parameter evaluation criteria are the same for Phases II and III

The safety parameter evaluation criteria include:

- Data on adverse events, physical examination, weight measurement, vital signs examination, 12-lead ECG, clinical blood test, coagulation test, blood chemistry, urinalysis, serum bile acid test.
- Antibody response to Myrcludex B.

8.2. Adverse Events

The study subjects will be carefully monitored for the adverse events (AEs) by interviews, physical examination and analyzing laboratory and instrumental indicators from the moment of the first dose of the study drug will be used (Randomization visit). All unfavorable medical events which occurred prior to the first dose of the study drug administration will be recorded as indicators to be included in patients' medical history with the exception of serious adverse events. Monitoring will be carried out in accordance with the "procedure schedule". Adverse events will be classified and registered in the CRF. The classification will include the following parameters: severity, stage, intensity, the presence of a causal relationship with the study drug, the outcome, the actions taken and the countermeasures. The classification will be performed by a responsible investigator in accordance with the definitions given below.

In order to identify adverse events in this study assessment of deviations in patients health will be performed (based on the results of physical examination, laboratory and instrumental research methods) from the data obtained at Screening and at the period before the first dose of study drug administration and the accepted reference values. After receiving the necessary information, the investigating physician will classify the patient condition as "norm", "non clinically significant abnormalities" or "clinically significant abnormalities". If the observed abnormalities have been considered by investigators as clinically significant and have not been previously recorded, or if there is a deterioration in the patient condition as compared to the findings obtained during Screening or before the first dose of study drug administration, the observed abnormalities will be classified as adverse events (AEs) and correlated with the severity level according to CT CAE.

If the observed abnormalities have been recorded during Screening or before the first dose of study drug administration and there is no negative dynamics, the observed abnormalities will be classified as non clinically significant abnormalities (NCSA).

The Protocol provides for the registration of all AEs that will occur in the patient after the first dose of study drug administration and before completing his/her participation in the study. An adverse event is understood as "any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment" (National Standard of the Russian Federation "Good Clinical Practice" GOST R52379).

An AE can be any adverse symptom (including laboratory abnormality), a complaint or a disease whose time of occurrence does not exclude a causal relationship with the use of the study drug, regardless of the presence or absence of such a link.

All clinically significant laboratory, instrumental and physiological *abnormalities* and / or deviations from data obtained after study drug administration will be recorded by the investigating physician in the AE registration form, if the detected deviation falls under the definition of an AE, thereafter, the investigating physician must give a medical assessment of the deviations observed. Investigator should register AEs, otherwise, the observed abnormality will be treated as a non clinically significant abnormality (NCSA).

8.2.1. Definitions

The protocol adopted the following definitions (quotes from the ICH E2A Cclinical Safety Data Management: Terminology and Standards for Rapid Reporting guideline, as well as from GOST R 52379-2005 are given in italics).

Adverse event:

"Any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment" (National Standard of the Russian Federation "Good Clinical Practice" GOST R52379-2005)

AEs include:

- New symptom/medical condition,
- New diagnosis,
- Changed laboratory parameters,
- Concomitant diseases and accidents,
- Deterioration of medical conditions/diseases that existed before the beginning of the clinical study,
- Recurrence of the disease,
- Increased rate of occurrence and intensity of episodic worsening disease.

The disease or symptom already existing in the patient will be considered as an adverse event only if there are an unfavorable change of their intensity, rate of occurrence or qualitative changes. The responsible investigator will register such changes as adverse events.

Surgical procedures are not AEs, but are measures taken to treat diseases requiring a surgery. A condition requiring a surgery can be considered as an AE. Planned hospitalization, surgery, or conditions that have led to the need for these measures are not AEs if the condition that has led to the need for hospitalization/surgery has existed before the subject's enrollment into the study.

All AEs (including SAE) will be recorded in the CRF.

Adverse events will be categorized as "non-serious" or "serious" ones (see below)

Adverse drug reaction:

"All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."

Severity

"A serious adverse event or reaction (SAE) is any untoward medical occurrence that at any dose of a medicinal product matches any of the following definitions:

- *results in death,;*
- *is life-threatening;*
- *requires inpatient hospitalization or prolongation of existing hospitalization;*
- *results in persistent or significant disability/incapacity,*
- *is a congenital anomaly/birth defect."*

In addition, adverse events or reactions that, in the responsible investigator's opinion, are **significant from a medical or scientific point of view** will also be classified as "serious" ones.

Serious adverse events that occur after the termination of participation in the study will NOT be recorded except for cases when, in the investigator's opinion, the event could be caused by the study drug or any protocol procedure:

- Death is the outcome of an adverse event, not the event itself. Fatal cases reported due to the "progression of the disease" in the absence of other information will imply that the death occurred due to the progression of the disease, the treatment of which is the target of the drug.
- All fatal cases, regardless of their cause or association with the study drug, should be recorded for study subjects within 30 days from the administration of the last dose of the study drug or no later than days from the last evaluation in the study, whichever comes first.
- "Regardless of dose" does not imply that the subject received the study drug at the time of occurrence of the adverse event. The drug could be administered as part of a treatment period, the treatment could be temporarily suspended until the occurrence of the SAE, but it could affect the occurrence of an adverse event.
- "Life-threatening" means that the subject did not have an immediate death risk due to an adverse event. This category does not include adverse events that could lead to death if they were more severe.
- Sequelae that occurred during hospitalization are AEs. If the sequelae leads to prolongation of hospitalization, then it is classified as a SAE.
- "Hospitalization" means the official admission of a patient to a hospital on medical indication within any period of time. This category does not necessarily include hospitalization for more than a day. This category

does not include cases of admission and care provided in an intensive care unit.

- The investigator should attempt to diagnose an adverse event based on signs, symptoms and/or other clinical data. In such cases, the diagnosis, rather than individual signs/symptoms, should be recorded as an AE or a SAE.

Expectedness:

"An adverse reaction, the nature and severity of which is not consistent with the applicable product information (i.e., the Investigator's Brochure)".

8.2.2. Suspected unexpected serious adverse reaction (SUSAR (SUSAR)

Suspected Unexpected Serious Adverse Reaction

Serious adverse events as expected, i.e. (possibly) associated with the study drug, and the "unexpected", are classified as the suspected unexpected serious adverse reactions (SUSARs).

If the investigator who first reported on the SAE considers the causal relationship of the SAE with the study drug at least as "unlikely" and the SAE is the "unexpected" one, this SAE should be classified as SUSAR.

All SUSARs are subject to expedited communication. Reports should be submitted to the responsible ethics committee and the relevant regulatory authorities (detailed information is provided in the "Safety Guide").

8.2.3. Follow-up period and recordkeeping

In this study, adverse events will be registered from the date of the administration of the first dose of the study drug (visit on the first day of the study) until the last visit of follow-up. All adverse medical events that occurred prior to the first administration of the study drug will be recorded as indicators to be included in the medical history of the subject.

During each study visit, the responsible investigator will interview subjects about the adverse events. If necessary, the AEs and SAEs will be registered in the electronic CRF and in paper forms of SAE registration in accordance with the principles stated above.

All subjects with AEs, whether associated with the study drug or not, will be monitored by the responsible investigator in order to determine the outcome. The clinical course of AEs will be monitored until complete resolution or stabilization of the condition.

8.2.4. Adverse event characteristics

All adverse events will be classified according to the following characteristics:

Intensity/severity

The severity of AE in the study will be assigned in accordance with the Common Toxicity Criteria (NCI Common Terminology Criteria for Adverse Events, Version 4.0, available at http://ctep.cancer.gov)

- **Mild:** presence of signs and symptoms, on the other hand easily tolerable and not affecting daily activity ones. Symptoms do not require treatment or medical evaluation, signs and symptoms are temporary,
- **Moderate:** Adverse events lead to inconvenience or anxiety for the subject and can affect the performance of daily activities, but are usually reversed with simple therapeutic measures. Moderate adverse events can have an impact on body functions to a certain extent,
- **Severe:** Adverse events that cause a subject to interrupt daily activities and usually require systemic drug therapy or other treatment. They usually lead to disablement.

For serious adverse events, there are also possible degrees: **Life-threatening** and **Death**.

The seriousness criterion, not the intensity (severity) of AEs and adverse drug reactions will be used as a guide to determine obligations about regulatory authority reporting.

Causal relationship with the study drug

The investigator is responsible for the evaluation of the relationship between AEs and the study drug. The investigator must determine whether there is a reasonable probability that the study drug has caused or contributed to the development of AEs. The evaluation of causal relationship based on a clinical evaluation is often based on the following criteria:

- Temporal relationship between the onset of AEs and the administration of the study drug;
- The likely biological mechanism by means of which the study drug could cause AE;
- Other possible etiology of AEs;
- Previous reports of similar AEs associated with the study drug or with other drugs of a similar class and
- Recurrence of AE after reinitiation of treatment or resolution after discontinuation of treatment, if applicable.

The following terms are used to evaluate the relationship between the event and the study drug:

- **Associated** – there is an anticipated probability that an AE can be associated with the study drug;
- **Non-associated** – there is no anticipated probability that an AE is associated with the study drug.

If the event is assessed as "non-associated" with the study drug, an alternative etiology, a diagnosis or justification for the development of an adverse event should be identified.

Outcome

The outcome of the AE will be classified as follows:

- **Complete resolution**: All signs and symptoms of the AE at the time of the last interview disappear, leaving no consequences,
- **In the process of resolution/recovery:** The intensity of signs and symptoms is reduced, their clinical character has changed before the last interview according to the scenario typical for the resolution,
- **No resolution/no recovery:** The signs and symptoms of the AE have remained almost unchanged since the last interview,
- **Resolution/recovery with sequelae:** The actual signs and symptoms of the AE have disappeared, but has had sequelae associated with AEs**,**
- **Fatal outcome:** The AE has led to death. If a patient has several adverse events, the outcome "death" is assigned only to the AE that has led to death,
- **Unknown:** The outcome is unknown or unlikely and the information can not be added or confirmed.

Acts Relating to the Study Drug

Acts relating to the study drug must be assigned to one of the following categories:

- **Dose is not changed:** the dose of the study drug is not changed,
- **Dose is reduced:** reduction of the dose of the study drug,
- **The drug treatment is temporarily suspended:** Temporary suspension of the treatment with the study drug**,**
- **Dechallenge:** Complete discontinuation of the treatment with the study drug,
- **Not applicable:** The issue is irrelevant (due to the death of the subject or a single use of the drug, excluding the possibility of dose modification).

Countermeasures:

The term "countermeasures" refers to special actions taken to treat or alleviate a condition when there are adverse events in order to avoid their sequelae. The following categories have been accepted:

- **Absent:** measures have not been taken,
- **Treatment with the medicinal product:** newly prescribed drug or a dose modification of the study drug,
- **Other:** Other countermeasures, such as surgery**.**

8.2.5. Investigator's reports about serious adverse events

The investigator submits a report about all SAEs to the sponsor within 24 hours after the SAE has occurred by sending the SAE form via Fax or email:

Fax: +7 495 726-52-53

E-mail: pharmacovigilance@ammaxwell.ru

Before sending the SAR form, the sponsor's monitor should be informed about that by phone.

The initial report should be as complete as possible and include information on the present disease and the event, as well as an evaluation of the causal relationship between the adverse event and the study drug.

Detailed information about the report on the SAE and the SAE form, including instructions for its completion, are provided in the "Safety Guide".

8.2.6. Emergency notification

SUSAR should be reported to the ethics committee and to the relevant regulatory authorities within the time limits specified by the regulatory documents, i.e. they are subject to emergency notification.

Investigators involved in this study should report an authorized member of the safety department about all SAEs as quickly as possible, but no later than 24 hours after the presence of the relevant information. The report should be sent by fax as the completed SAE form.

The sponsor's designated employee should make the emergency notification. A more detailed description of the

procedures related to pharmacovigilance in this study is presented in the "Safety Guide".

8.2.7. Pregnancy

If a female subject becomes pregnant, discontinue the treatment with the study drug immediately.

Pregnancy is not an adverse event as such, except cases when there are reasons to believe that the study drug led to a decrease in the effectiveness of contraceptives. Congenital abnormalities and developmental disorders in patient children are classified as serious adverse events. Medical abortion and other serious complications of pregnancy (including spontaneous abortion) are classified as serious adverse events. Artificial abortion in the absence of complications is not considered an adverse event.

All cases of pregnancy (including pregnancy of partners of male patients) should be duly recorded during the clinical study. At the time of pregnancy confirmation, the investigator should submit the report to the pharmacovigilance department staff of the sponsor. The sponsor should also be informed about the outcome of pregnancy. Pregnancy in female patients and partners of male patients is subject to registration, from the first day of administration of the study drug to the completion of the final procedures of the study.

Pregnancy outcome (spontaneous abortion, artificial abortion, the birth of a healthy child or child with congenital anomalies or malformations) should be recorded even if the subject(s) has not terminated the clinical study.

8.2.8. After-treatment reporting requirements

All deaths occurred throughout the study period and within 30 days since the last injection of the drug dose, regardless of the cause or association with the study drug, should be recorded.

8.3. Laboratory Abnormalities and Other Deviations Classified as Adverse Events and Serious Adverse Events

In order to identify adverse events in this study assessment of deviations in patients health will be performed (based on the results of physical examination, laboratory and instrumental research methods) from the data obtained at Screening and at the period before the first dose of study drug administration and the accepted reference values. After receiving the necessary information, the investigating physician will classify the patient condition as "norm", "non clinically significant abnormalities" or "clinically significant abnormalities". If the observed abnormalities have been considered by investigators as clinically significant and have not been previously recorded, or if there is a deterioration in the patient condition as compared to the findings obtained during Screening or before the first dose of study drug administration, the observed abnormalities will be classified as adverse events (AEs) and correlated with the severity level according to CT CAE. If a laboratory abnormality is a part of the syndrome, this syndrome or diagnosis should be identified.

The severity of AEs must be indicated in accordance with the common toxicity criteria (CTC AE, NCI Common Terminology Criteria for Adverse Events, version 4.0, available at http://ctep.cancer.gov). Particular attention should be paid to reactions at the injection site and to dermatitis, as they are expected reactions in the treatment with MXB.

As for adverse events accompanied by a laboratory abnormality, the clinical severity score of the adverse event against the background of the underlying disease should be evaluated, wherein the evaluation may differ from evaluation of the severity of the laboratory abnormality itself.

As for the possible nephrotoxicity developed during administration of the nucleotide analogue product Viread® (tenofovir), adverse events should be recorded if the creatinine clearance is <50 mg/dL – 0.48 mmol/L (two independent calculations) or serum phosphate is > 0.5 mg/dL in two separate evaluations. In this case, the administration of tenofovir should be discontinued, and renal function evaluation should be performed weekly. Further patient treatment should be discussed with the medical monitor of the study.

The increase of bile acid levels against the background of the use of Myrcludex B is directly related to the mechanism the drug effect – blocking NTCP receptor on the liver cells, which functions as a reverse transport of bile acids from the bloodstream to the liver. Therefore, an isolated increase in bile acid level in the absence of clinical significance should not be classified as an AE. If the investigator considers the increase to be clinically significant or it will be associated with the occurrence of clinical symptoms, this increase should be recorded as an AE.

If the observed abnormalities have been recorded during Screening or before the first dose of study drug administration and there is no negative dynamics, the observed abnormalities will be classified as non clinically

significant abnormalities (NCSA).
All observed abnormalities, regardless of whether attributed to AEs or NCSAs, will be analyzed when reporting clinical study results.

8.4. Managing Toxic Reactions

- Clinically significant 3 to 4 Grade laboratory abnormalities should be verified by duplicate analyzes within three calendar days from the moment of result generation before the treatment with the study drug is terminated, if such a delay does not meet the requirements of good medical practice (central laboratory).
- Clinical events and clinically significant laboratory abnormalities will be classified according to National Cancer Institute (NCI) Common Toxicity Criteria (NCI Common Terminology Criteria for Adverse Events, version 4.0, are available at http://ctep.cancer.gov)
- When the treatment with the study drug is reinitiated after an adverse event has been resolved, the study drug will be administered in full or in a modified dose, as agreed with the medical monitor.
- Recurrence of a clinical or clinically significant 3 to 4 Grade laboratory abnormality, after the reinitiation of treatment following its suspension, requires the complete discontinuation of treatment with the study drug.
- Any questions regarding the managing toxic reactions should be directed to the medical monitor.

The classification of skin adverse events, possible to occur with the use of the study drug, is given in the table 2.

Table 2 Classification of Skin Adverse Events, Associated with the Study drug Injections

Parameter	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)
Skin Reaction/ Rash/ Dermatitis	Hyperemia, skin itch	Diffuse maculopapular rash OR dry peeling skin	Vesiculation OR moist peeling skin OR ulceration	ANY OF THE STATED BELOW: mucous membrane lesions, suspicion of Stevens-Johnson syndrome, erythema multiforme, necrosis requiring surgical treatment, exfoliative dermatitis
Local reactions	Hyperemia	Induration <10 mm OR inflammation OR phlebitis	Induration ≥10 mm OR ulceration	Cutaneous necrosis

8.4.1. Grade 1 to 2 laboratory abnormalities

- Continuation of treatment with the study drug at the discretion of the investigator.

8.4.2. Laboratory abnormality or Grade 3 clinical event

- If a clinically significant laboratory abnormality or a Grade 3 clinical event develops, the treatment with the study drug can be continued if this event was found not to be associated with the study drug.
- If there is a Grade 3 clinical event or a clinically significant laboratory abnormality confirmed by a duplicate analysis, considered to be associated with the study drug, the treatment should be discontinued until the toxic reaction is reduced to Grade 2 and below.
- If, after the reinitiation of the treatment with the study drug, toxicity returns to Grade 3 and above and its aggravation is found to be associated with the study drug, the treatment should be completely discontinued, and subjects should be treated according to the local practice accepted in the institution. Recurrence of adverse events considered not to be associated with the study drug does not require the irrevocable termination of treatment with the study drug.

8.4.3. Laboratory abnormality or Grade 4 clinical event

- If a clinically significant laboratory abnormality or a Grade 4 clinical event develops, the treatment with the study drug should be discontinued and subjects should be treated according to the local practice accepted in the institution. The subjects should be monitored in accordance with clinical indications before resolution to baseline values. A clinically significant Grade 4 laboratory abnormality, not confirmed by duplicate analyzes, should be adjusted in accordance with the algorithm for a new degree of toxicity.
- If there is a clinically insignificant Grade 4 laboratory abnormality (for example, a Grade 4 QC deviation after intense physical activity or an increase in the nonfasting triglyceride level or in the triglyceride level not subject to medical correction) or a Grade 4 clinical event, considered not associated with the study drug,

treatment with the drug can be continued without interruption.

8.5. Risks for Women of Childbearing Age and Risks during Pregnancy

No evaluations of the risks associated with MXB treatment during pregnancy was not performed. Studies in animals have not shown the presence of direct or indirect adverse events of MXB on pregnancy. For more information, see the latest version of the Investigator's Brochure. Women of childbearing age and women whose menopause occurred less than 2 years before should use barrier methods of contraception in combination with other methods of contraception (for example, oral or other hormonal contraceptives) during the period of participation in the study and within 3 months after administration of the last dose of the study drug. Sexually active male subjects should use barrier methods of contraception during the same period of time upon contact with partners of childbearing age, or they should keep themselves from heterosexual contacts.

The subjects should be aware of the need to stop taking all the drugs and **immediately** inform the investigator about pregnancy during the study.

The investigator must inform the sponsor about all cases of pregnancy no later than 24 hours from the time he has learnt about pregnancy. The investigator should inform the subject about the possible effects of the previous intake of the study drug on the fetus and about the need to inform the clinical center about the outcome of pregnancy.

Pregnancy complications, as well as the planned termination of pregnancy on medical indications should be reported as an AE or a SAE.

Spontaneous abortion is always considered as SAE, it should be reported in accordance with the requirements set out in the section on serious adverse events. In addition, any SAE that has occurred as an adverse event of pregnancy after the study should be reported to the sponsor.

In addition, all cases of pregnancy that occurred during the study should be reported on the CRF "Report on pregnancy". Monitoring of the study subject should be performed until the end of pregnancy. The outcome of pregnancy should be reported to the sponsor using the CRF "Pregnancy outcome" page (including, if applicable, the section "Complicated outcome of pregnancy"). If the termination of pregnancy occurs at the time after the study termination, the sponsor should be informed about the outcome directly. The cases of pregnancy that occurred after the study subject has stopped to take the study drug, do not require monitoring.

9. STATISTICS

9.1. Documentation of Statistical Methods

9.1.1. General principles

The statistical analysis will be carried out under supervision of the responsible biostatistician in accordance with the requirements of the National Standard of the Russian Federation "Good Clinical Practice" and other applicable requirements and laws.

Before the statistical analysis is carried out, data from different centers will be combined into a common data set.

If the assumptions made in the preliminary planning of the study prove to be erroneous, the analysis methods will be changed for a more appropriate analysis to be carried out. If the change in the statistical analysis is significant and affects the study results or their interpretation, an amendment to this study protocol will be issued in advance.

Statistical analysis is scheduled to be carried out using IBM SPSS Statistics software (IBM Corporation, Armonk, New York, USA), SAS software (Statistical Analysis Software, SAS Institute Inc. Cary, NC, USA), or another commercial product with validated algorithms for statistical method implementation and with relevant documentation.

9.1.2. Demographic and baseline characteristics

The descriptive statistics will be used to describe baseline demographic parameters and characteristics for the analysis population in general and for treatment subgroups. The arithmetic mean (with a 95% confidence interval for the mean), the standard deviation, the median, 25- and 75-percentiles will be calculated for interval variables. The frequency rates, rates of the categories and the confidence intervals for rates(95% confidence intervals according to the Clopper-Pearson method) will be calculated for nominal variables.

9.1.3. Efficacy analysis methods

Primary efficacy analysis for Phase II and III will be based on the following efficacy endpoint:

- The negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the data obtained before the initiation of treatment with the study drug.

This endpoint will be analyzed in modified Intent-to-Treat Set (mITT), which includes all randomized subjects who started study treatment (Myrcludex B or Tenofovir) in study period after randomization. Additionally these data will be analyzed in the Per Protocol (PP) set that includes subjects with available Week 24 efficacy results (see below for PP set definition).

In Phase II, treatment arms will be compared using the Wald test for Superiority by Margin of 5%; 95% Clopper-Pearson confidence interval will also be calculated for treatment response rates (for each treatment arm). Each experimental treatment arm (Myrcludex B) will be compared to the control arm receiving tenofovir alone. Each Myrcludex B treatment arm will be compared to the control arm separately (Arm A vs Arm D, Arm B vs Arm D, Arm C vs Arm D). Hypotheses will be tested sequentially, using Bonferroni-Holm method. Null hypotheses will be defined for each prior test, and appropriate p-values will be calculated (based on data obtained in the study). After that, null hypotheses will be rejected in descending order of respective p-values for critical values of type I error (α), calculated as $\alpha/(k - i + 1)$, where k is the number of planned comparisons and i is the sequential number of the comparison [31].

In Phase III, the hypothesis of statistical superiority will be tested with the help of the two-sided Fisher exact test for the primary efficiency index.

Qualitative secondary endpoints (ALT normalization and disappearance of HBsAg/ seroconversion) will be analyzed using the Fisher's exact test. Quantitative secondary endpoints (serum fibrosis marker, HBsAg and HBV DNA) will be presented as absolute values and changes from baseline. To compare treatment arms on the basis of endpoints, two-sided Wilcoxon rank sum test will be employed with adjustment at the significance level of 0.0167. If the assumptions necessary for carrying out parametric approach are not violated (will be verified using graphical methods), parametric analogues of the above methods will be used: analysis of variance ANOVA/ analysis of covariance ANCOVA, the paired Student's t-test for dependent samples.

9.1.4. Safety analysis methods

MXB safety (Phase II and III) will be analyzed for the following evaluation parameters:

The main safety evaluation parameter:

- The incidence of adverse events associated with the administration of the study drug, estimated from Visit 1 to the end of study visit (EOS visit)

Secondary safety evaluation parameters:

– Type and severity of AEs associated with the administration of the study drug, estimated from Visit 1 to the final visit.

– Rate of occurrence, type and severity of any other AEs, as well as evaluation of physical examination findings, vital signs, 12-lead ECG, clinical blood test, coagulation test, blood chemistry, urine analysis, serum bile acid test, antibody response to Myrcludex B.

These evaluation parameters will be analyzed in the safety population (refer to paragraph 9.7).

The AE associated with the administration the study drug is defined as any AE started after administration the study drug or before administration the study drug, but the severity of which has increased after the administration, that has any connection with the study drug, with the exception of "not associated". The severity of AEs will be presented in the number of subjects with different severity of AEs (mild, moderate and severe).

The AEs, including serious adverse events, will be classified according to the latest version of the Medical Dictionary for Regulatory Activity Terminology (MedDRA) available at the time the database freeze. Further analysis of AEs and SAEs will include the calculation of the number of AEs, the number of subjects with AEs, the number of AEs associated with the study drug, the number of AEs requiring discontinuation of therapy, the number of WAE.

The rate of occurrence and severity of all AEs and AEs associated with the study drug will be presented for all system organ classes (SOC MedDRA). SAE will also be presented in the form of descriptions (narratives).

Numerical safety data will be presented as summary tables of descriptive statistics for each treatment arms. Descriptive statistics will be provided for each numerical safety endpoint. Vital sign and laboratory data as well as change from baseline will be summarized (where applicable) by visit of assessment and by treatment group. In addition, shifts in laboratory parameters will be presented by treatment group.

The safety data sheets will also be included in the final analysis.

9.2. Scheduled Number of Subjects

For Phase II. This study is scheduled as a comparative parallel group clinical study with three groups of the study drug (of a dosage strength of 2 mg, 5 mg and 10 mg) and one comparison group (all three comparisons will be conducted as independent ones) to study the hypothesis of superiority of the study drug with the reference drug.

The basic variable of the study is the response rate, defined as decrease in the level of HDV RNA by at least 2 $\log_{10}$ (assay) or lack of HDV RNA (in 24 weeks after the initiation of treatment). It is a frequency index.

In accordance with the study aim and objectives, the null hypothesis (H_0) will be formulated as follows:

H_0: $\varepsilon \leq \delta$

and an alternative hypothesis (H_a) will be as follows

H_a: $\varepsilon > \delta$

where ε – an expected difference between the response rates in the treatment group with the study drug and the reference drug, δ – a limit of clinically significant differences (superiority limit).

Given the study design, type and nature of the basic variable (parallel group comparative study), the size of each group can be estimated by the formula:

$$n_1 = \kappa n_2$$
$$n_2 = \frac{(z_\alpha + z_\beta)^2}{(\epsilon - \delta)^2}\left[\frac{p_1(1-p_1)}{\kappa} + p_2(1-p_2)\right]$$

where: z_α and z_β — corresponding values of the z-function for the planned values of I and II type error; p_1 and p_2 – a response rate in the treatment and control groups respectively; ε — estimated differences between groups with respect to the basic variable of the study; k — coefficient when number of subjects in groups is unequal (in this study k=1); n_1 and n_2 – scheduled number of subjects in the main and control groups, respectively.

Thus, the sample size was calculated on the basis of the following parameters:

1. Critical significance level for the null hypothesis testing α = 0.0167 (using the Bonferroni amendment).
2. The power of the study is not less than 0.8 (80%), the probability of II type error (β), thus, will not

exceed 0.2.

3. The superiority limit (clinical significance of differences) δ will be taken as 5%;

4. The estimated difference between groups in the basic variable of the study will be at least 34.0%. The performed phase 1b/2a clinical study in patients with CHD showed efficacy in the monotherapy group in 57% of patients after 24 treatment weeks, with the lower limit of the confidence interval in~ 37%.

5. The estimated response rate in the control group does not exceed 3% (when there was no treatment, as well as when patients with hepatitis delta were prescribed nucleoside/nucleotide analogues registered for the treatment of CHD, the investigators observed no positive dynamics; for example, the HIDIT-1 study in 90 patients with CHD did not show an effect on HDV RNA when monotherapy with a nucleotide analog adefovir was prescribed). It is assumed that there may be a spontaneous decrease in the HDV RNA level by $2\log_{10}$ in no more than 3% cases.

The sample size was calculated as follows:

$$n1 = n2 = \frac{(2.13 + 0.84)^2 * (0.37 * (1 - 0.37) + 0.03 * (1 - 0.03))}{(0.34 - 0.05)^2} = \frac{8.8209 * 0.2622}{0.0841} \approx 28$$

Thus, to test the hypothesis of the superiority of the study drug (each dosage group should be tested separately) against the control group, it is necessary to include at least 28 subjects in each group in the efficacy analysis. Assuming the drop-out is no more than 5% subjects in each study group, each group arm should be at least 30 subjects.

For Phase III. When the last patient completes a 24-week treatment period as a part of Phase II clinical study, patients from all treatment arms will be analyzed for viral load based on PCR data on HDV RNA (the negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the data obtained before the initiation of treatment with the study drug will be considered as the primary endpoint). Results of the test performed will provide the basis for estimating the number of patients needed to confirm the hypothesis of the statistical superiority of the selected dosage strength of the study drug over the drug of the standard treatment. When calculating the sample size, the correction for a plurality of comparisons (Pocock correction) will be taken into account with due regard to two statistical analyzes (at treatment week 24 of phase II and treatment week 24 of phase III).

If a statistically significant conclusion is obtained based on the results of phase II on the statistical superiority of study drug in chosen dosage over the control group with respect to the primary endpoint at the bilateral significance level of 5%, then the recruitment of patients into Phase III of the study will not be performed, and the statistical analysis will be performed as a part of the Interim Report on Phase II and the Final Report on the Clinical Study Results.

9.3. Applicable Significance Level

In Phase II, for testing the main variable of the study, the significance level will be a one-sided one (a superiority test is planned). Non-inferiority test will be performed in series, according to the Bonferroni-Holm method. This method allows you to monitor the FWER (Familywise error rate) for a family of null hypotheses. In the course of the planned comparisons, the type I error probability will not exceed 0.05, and the significance levels for each successive comparison will be calculated individually according to the Bonferroni-Holm method (see above).

If Phase II results require the inclusion of additional patients in Phase III, when calculating the sample size, the correction for a plurality of comparisons (Pocock correction) will be taken into account with due regard to two statistical analyzes (at treatment week 24 of phase II and treatment week 24 of phase III).

9.4. Study Termination Criteria

Interim and final data analysis as a part of Phase II

When the last patient completes a 24-week treatment course as a part of Phase II clinical study, patients from all treatment arms will be analyzed for viral load based on PCR data on HDV RNA (the negative PCR result on

HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the data obtained before the initiation of treatment with the study drug will be considered as the primary endpoint). The results of this study will be used to draw up the Interim report on the results of the Phase II clinical study, herewith, all patients will continue to be treated with tenofovir. During the Interim analysis, the recruitment of new patients into the clinical study will be suspended.

Based on the data from the Phase II Interim Report, the optimal (based on efficacy and safety analysis) dosage for the second part of the clinical study (corresponding to phase III) will be selected, and the required number of patients to be enrolled in Phase III will be calculated. When calculating the sample size, the correction for a plurality of comparisons (Pocock correction) will be taken into account with due regard to two statistical analyzes (at treatment week 24 of phase II and treatment week 24 of phase III). The results of the Phase II Interim analysis will be submitted to the Ministry of Health of the Russian Federation.

If a statistically significant conclusion is obtained based on the results of phase II on the statistical superiority of study drug in chosen dosage over the control group with respect to the primary endpoint at the bilateral significance level of 5%, then the recruitment of patients into Phase III of the study will not be performed, and the statistical analysis will be performed as a part of the Interim Report on Phase II and the Final Report on the Clinical Study Results.

When the last patient completes the follow-up period of the first part of the clinical study, the data on the treatment studied will be analyzed in all patients who have completed the 48-week treatment course in phase II, the Final Report on the Results of the Phase II Clinical Study will be drawn up and submitted to the regulatory authorities.

Interim and final data analysis as a part of Phase III

When the last patient completes a 24-week treatment course as a part of Phase II clinical study, patients from all treatment arms will be analyzed for viral load based on PCR data on HDV RNA which results will be used to draw up the Interim report on the results of the Phase III clinical study, herewith, all patients will continue to be treated with tenofovir. The negative PCR result on HDV RNA or a decrease by ≥2 log at treatment week 24 compared to the data obtained before the initiation of treatment with the study drug will be considered as the primary endpoint. The results of the Interim Report on the Results of the Phase III Clinical Study will be submitted to the regulatory authorities with the aim of the study drug marketing authorization.

When the last patient completes the follow-up period of the first part of the clinical study, the data on the treatment studied will be analyzed in all patients who have completed the 48-week treatment period, the Final Report on the Clinical Study Results will be drawn up and submitted to the regulatory authorities.

9.5. Procedures for Accounting Missing Data not to be Analyzed

If there are any missing, not to be analyzed and spurious data, the randomness of such data will be evaluated. An analysis of the stability of the results obtained and the conclusions drawn from them will be made. During interim analysis after the last patient will complete 24-week therapy within Phase II of the clinical trial for the primary efficacy parameter, if there is no HDV RNA data at the 24-week Visit, the patient will be considered as non-responder to therapy. The procedure for restoring missing values will be described in more detail in the Statistical Analysis Plan.

9.6. Procedures for Reporting Any Deviations from the Original Statistical Plan

Detailed information about the statistical analysis will be presented in the statistical analysis plan. The statistical analysis plan will be consummated before the database freeze. All deviations from the final version of the statistical analysis plan will be justified in the final study report.

9.7. Selection of participant for the statistical analysis

The statistical analysis will include the following populations:

Safety Set: all subjects who received at least one dose of the study medication in Myrcludex B groups or Tenofovir in group of observation after randomisation.

Full set of data for efficacy analysis (Modified Intent-to-Treat Set (mITT): all randomized subjects who received at least one dose of the study medication in Myrcludex B groups or who was randomized in observation group and received Tenofovir after randomisation.

Per Protocol Set (PP): subjects from full set of data for efficacy analysis who completed 24-week treatment period without major protocol deviations and with efficacy results for 24-week time point.

10. DIRECT ACCESS TO SOURSE DATA/DOCUMENTS

10.1. Access and Verification of Source Data and Records

All the information contained in the original records and certified copies of the clinical data, observations and other activities in the study, and which is necessary for the reconstruction and evaluation of the study, is the source data. The investigator permit study-related monitoring, audit(s), IEC review, and regulatory inspections, as well as to provide direct access to source data/records and study documents.

Direct access to source data and documentation should be provided to the Sponsor's clinical research associate and its authorized representatives (CROs), the Sponsor/CRO auditor, the regulatory inspector, ethical reviewers, the insurance company representatives.

10.2. Access to Additional Information

Upon request, the Investigator provides the Sponsor with additional data regarding the study, or copies of the related source records, after proper processing of the data to achieve anonymity of the participant's data. This is important when case report form are filled in illegible, or if there are errors in data recorded. In special cases or when requested by governmental organizations, it is also necessary to have access to the full study records, provided that the patient's confidentiality complies with applicable regulations.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Periodic Monitoring

Monitoring is the process of supervision of the progress of a clinical study, designed to ensure that it is conducted, documented and information about it is transmitted to the appropriate authorities in accordance with the Protocol and the rules. The Sponsor appoints the person conducting the monitoring. The monitor is the main link between the Sponsor and the Investigator. The monitor, in accordance with the requirements of the Sponsor, must ensure the proper conduct and documentation of the study

The CRO and the Sponsor will carry out monitoring in the center before, during and after the study. The monitor will check that the study is being conducted, the data is recorded and presented in accordance with the protocol, SOP, GRP and applicable regulatory requirements. The monitor will check the accuracy and integrity of the data entered in the CRF, the primary documentation, and other records related to the study, compared to each other.

The Principal Investigator provides quality control of the study, and quality inspection is performed by monitoring visits, the terms of which are determined by the Sponsor.

The Sponsor representative or specially designated person will monitor the study to ensure that:

- data is true, accurate and complete;
- safety and rights of the study subjects are protected;
- the study is conducted in accordance with the currently approved protocol version and any other study agreements, ICH GCP, and all applicable regulations.

The monitor, in accordance with the requirements of the Sponsor, must ensure the proper conduct and documentation of the study. With that in mind, the monitor performs the following actions:

- Verifies the correspondence of the Investigator's qualifications and resources, as well as the sufficiency of available human and material resources, including laboratories, equipment and personnel, for the safe and appropriate conduct of the study, at the beginning and throughout the study
- Verifies that storage period and conditions of the IMP are acceptable and the amount is sufficient until the end of the study
- Verifies that the IMP is received only by those patients whom it is prescribed, and at the doses established by the protocol;
- Verifies that patients are provided with the necessary instructions for the correct use of the investigational products, for their handling, storing, and returning them;
- Verifies that the receipt, application and return of the products in the clinical center are properly monitored and documented;
- Verifies that the Investigator complies with the approved protocol and all approved amendments to it, if any.
- Verifies that the written informed consent of each patient has been received before conduct of the study.

- Ensures that the Investigator has an up-to-date version of the Investigator's Brochure, all other documents and materials required to conduct the study in an appropriate manner and in accordance with regulatory requirements.
- Ensures that the Investigator and his staff involved in the study are sufficiently informed about the study.
- Verifies that the Investigator and his staff involved in the study exercise the study-related duties in accordance with the protocol and all other written agreements between the Sponsor and the Investigator/Center and do not transfer their functions to unauthorized persons.
- Verifies that the Investigator complies with the enrollment criteria when patients are included in the study.
- Reports the enrollment rate.
- Verifies the accuracy, integrity and timeliness of data registration in primary and other documents related to the study, as well as the procedure for their entry.
- Verifies the accuracy and integrity of the data in the CRFs, the primary documents and other records related to the study by comparing them with each other.
- Informs the Investigator about any errors made in the CRFs, omissions and illegible records. The monitor should ensure that appropriate corrections, additions or deletions are made, dated, explained (if necessary) and signed by the Investigator himself or by a member of the research team authorized to sign changes for him in the CRFs. These powers must be documented.
- Verifies the compliance with the deadlines for reporting adverse events identified by GCP, protocol, IEC, Sponsor and regulatory requirements.
- Verifies that the Investigator maintains the basic documents.
- Informs the Investigator about deviations from the protocol, SOP, GCP and regulatory requirements, as well as takes the necessary actions to prevent the recurrence of such deviations.

The monitor will periodically contact the Investigator and perform visits to analyze all the source data/records relevant to the study, verify compliance with the protocol, and the integrity, validity and accuracy of all records in the CRFs in comparison with the source data. The Investigator will cooperate with the monitor in order to eliminate all identified discrepancies.

The Monitor will submit a written report to the Sponsor after each visit to the clinical center and/or contact with the investigators in accordance with standard operating procedures (SOPs).

In this study, it is planned that monitoring visits will take place before the initiation of the study (preliminary visit and initial visit) and during the study (routine visits every 4-6 weeks and final visit). The first routine visit will be scheduled within 2 weeks after the first patient is randomized in the center.

11.2. Audit and Inspection

The Sponsor provides for such a quality control system that will guarantee the conduct of this clinical study in accordance with the study protocol, the principles of the GCP and the current requirements of the legislation of the Russian Federation.

If a situation arises that requires an on-site inspection during the study, the Sponsor initiates an audit conducted by its representatives or independent auditors. Comments and conclusions of the audit should be documented. The objective of the audit is a comprehensive and independent verification of the activities and documentation related to the study performed to confirm the compliance with this activity, as well as with procedures for data collecting, analyzing and reporting, with the Sponsor's standard operating procedures, with the Good Clinical Practice principles and regulatory requirements.

Inspection is the actions of the authorized body for the official verification of documents, premises, quality assurance measures, as well as all other materials that, in the opinion of the authorized body, are related to the conduct of a clinical study and that may be on a clinical site.

After the audit is completed, a report should be prepared, which must be available to the Sponsor provided that the confidentiality is respected.

In order to ensure compliance with the ICH GCP and all applicable regulations, at any time during or after the end of the study, the Sponsor or regulation authorities may conduct an audit or inspection to control the quality of the records of the medical center. In the case of an audit or inspection, the Ivestigator (as well as the institution) must agree to provide the auditor(s) and/or inspector(s) with the immediate access to all study-

relevant documents and to appoint them and the center staff time to discuss the results or issues.
The Investigator will ensure that all source data and records relevant to the study are accessible to a qualified auditor authorized by the Sponsor or to inspectors from regulators after due notice. The main objectives of audits and inspections are to confirm that the rights and well-being of the patients involved in the study are protected, and that all data relevant to the evaluation of the study drug have been processed and reports on them have been submitted in accordance with the GCP and applicable regulatory requirements.

12. LEGAL AND ETHICAL ISSUES IN STUDY MANAGEMENT

12.1. General requirements

The participation of patients in the study is voluntary. The patient has the right to reject participation in the study at its any stage.

The study should be carried out in accordance with ethical principles set forth in the Declaration of Helsinki of the WMA (adopted at the 18th WMA General Assembly in Helsinki in June 1964, the latest edition was adopted at the 64th WMA General Assembly in Fortaleza, in October 2013).

Ethical standards for clinical studies are regulated by the relevant documents: Art. 21 of the Constitution of the Russian Federation, Federal Law No. 61-FZ dd. 12.04.2010 "On Medicine Circulation", National Standard of the Russian Federation GOSTR 52379-2005 "Good Clinical Practice", Principles of Good Clinical Practice in the Russian Federation (approved by Order of the Ministry of Health N 200н dd. April 04, 2016).

The Investigators involved in the clinical study prior to the initiation of the study should provide the Sponsor with signed and dated summaries that contain the description of clinical practice, data on professional and scientific activities.

12.2. Ethical Conduct of the Study

The approval of the study by an independent ethical committee and the patient's signature on the informed consent are the guarantees of compliance with ethical standards during the study.

Each patient will be informed that a study monitor, a quality assurance department auditor or a health inspector, in accordance with applicable regulatory requirements, can review his/her personal data, including the study-related ones.

12.3. Council on Ethics and Local Ethics Committee

Ethical review of clinical study of drugs is carried out by the Council on Ethics of the Ministry of Health and the Local Ethics Committee (LEK). The Council on Ethics and LEC are intended to protect the rights, safety and well-being of all study subjects. The Council on Ethics and LEC should evaluate the conformity of the Investigator's qualifications to the proposed study on the basis of his curriculum vitae. Prior to the initiation of the study, the approval of the protocol, the informed consent form and any other document handed over the patient, should be obtained from the LEC of those institutions where the clinical study will be conducted. The findings of the Council on Ethics and LEC must be dated, signed and issued in writing. Clinical study can be initiated only after obtaining the approval of the relevant Council on Ethics and the local EC.

The Investigator, the head of the medical institution or other responsible person must submit the required documentation to the local ethics committee for consideration in time. Documents submitted to the local ethics committee may vary in different institutions, but must necessarily include the final version of the clinical study protocol, information for patient and informed consent, the Investigator's Brochure with information about the study drug.

A list of all members of the Council on Ethics who have conducted consultations or participated in voting, as well as of the Council President(s), will be included in the study report.

12.4. Regulatory Approval

An approval to conduct the clinical study is issued by the Ministry of Health of the Russian Federation (MoH of the RF) subsequent to the results of the expert review of documents required to obtain an approval to conduct the clinical study, and ethical review conducted in accordance with the procedure established by Article 20 of Federal Law No. 61-FZ dd. April 12, 2010 "On Medicine Circulation".

In accordance with the current legislation, the clinical study protocol and other necessary documents will be submitted to the Ministry of Health of the Russian Federation for obtaining an approval to conduct the study. Clinical study can be initiated only after the approval from the Ministry of Health of the Russian Federation has been obtained. The approval for all documents and for the study should be obtained before the patient undergoes any study procedures, including screening tests for acceptability appraisal.

12.5. Periodic Informing of the Independent Ethics Committee

In accordance with federal law No. 61-FZ "On Medicine Circulation" and GCP principles, the IEC and the competent regulatory authorities should be informed of all suspected unexpected serious adverse drug reactions (SUSAR) occurred during the study. Both institutions should be informed of changes in the risk/benefit ratio or

about a significant new health and safety risk of the subjects.
The IEC and regulatory authorities should be informed of the end of the study. Not later than one year after the end of the clinical phase of the study, they should be provided with generalized data on the study results.

12.6. Notification to Regulatory Authorities

Local regulatory authorities responsible for each investigator must receive information before initiation, during and at the end of the study in accordance with the applicable law.

12.7. Information for the Patient and Informed Consent Form

Prior to the initiation of the study, the Investigator will receive a voluntary signed and dated informed consent from each patient after properly explaining the aims, methods, potential benefits, possible risks and all other aspects of the study that may influence the patient's decision to participate in the study, and the patient will get acquainted with a patient information leaflet that includes information for the patient and an informed consent form. The informed consent form must be signed and dated by the patient prior to undergoing any study-related procedures, including screening tests for acceptability appraisal.
The Investigator will explain that patients have the full right to refuse to participate in the study or to withdraw their consent at any time, without any consequences for their further treatment and without explaining the reasons.
The consent should be signed by both the patient (or his legal representative) and the Investigator in duplicate. One copy is given to the patient or his legal representative, and the other remains with the Investigator.
The signed informed consent form must be stored in the clinical center and be available for inspection by the study monitor or by the auditors upon request. All information on the process of obtaining of the informed consent must be reflected in the primary documentation.
Each patient will be informed that a study monitor, a quality assurance department auditor or a health inspector, in accordance with applicable regulatory requirements, can review his/her personal data, including the study-related ones.

13. DATA MANAGEMENT AND RECORDKEEPING

13.1. Clinical Study Documents

The sponsor company submits the following basic documents and materials to the clinical center:

- Study protocol (and amendments thereto, if any);
- Investigator's Brochure;
- CRF;
- Information for patients with the informed consent form;
- Scales, questionnaires, enquirers (if any);
- Investigator File (Study Documentation Log);
- The study drug;
- Agreement;
- Approval of regulatory bodies and the Ethics Committee;
- Documents required for submission to the local ethics committee.

The Investigator provides the Sponsor with the following basic documents before the study begins:

- Referral letter to the local ethics committee;
- Signed confidentiality agreement;
- Signed investigator agreement with the terms of the protocol;
- Protocol approval by the local ethics committee members;
- List of the local ethics committee members;
- Recently compiled scientific Curriculum Vitae of all investigators and co-investigators (signed and dated);
- Laboratory norms with the signature and date of the designated employee from the laboratory (using a local laboratory);
- Medical/laboratory equipment certificates (at the request of the Sponsor).

The Investigator must store the documentation related to the clinical study (primary documentation, copies of CRFs and the Investigator File) for 15 years after the end of the study.

13.2. Presentation (Delivery) of Study Documents and Materials

The Sponsor should provide the Investigator with the investigational product, the Clinical Study Protocol, the Investigator's Brochure, the CRFs and other documents, materials and equipment (where applicable) required for the study.

The Investigator must provide the Sponsor with a signed clinical study agreement, a signed confidentiality and non-disclosure agreement, a copy of the local EC approval, a list of LEC members, signed and currently dated Curriculum Vitae of the principal investigator and research team, and other documents (where applicable).

All deliveries to the center and withdrawal of study materials from the center will be documented using the Study Material Transfer/Return Forms.

13.3. Primary Documentation

The presence of primary documentation in the clinical center is necessary to confirm the existence of subjects and to confirm the truth of the information collected. Primary documentation includes original documents that are relevant to the study, treatment, anamnesis and description of the patient's condition. For example, such documents include the past medical history and extracts (printouts) with laboratory study results.

The primary medical documentation should include the following information:

- Demographic data;
- Information on inclusion and exclusion criteria;
- Evidence of participation in the study, indicating the study number and the patient number;
- Date and time of all visits;
- Historical and physical examination data;
- Adverse events;
- Prior therapy and concomitant treatment;
- Examination results;
- Laboratory test results;

- Information on the administration of the study drug.

The reason for the premature dropout (when applicable).

13.4. Data Collection: Case Report Forms (CRFs)

All the data obtained, including the study results, will be recorded for each patient in the electronic CRF (eCRF). For patients prematurely withdrawn from the study for any reason, all necessary documentation should be filled out completely with the indication of a reason for the early withdrawal.

The Principal Investigator or an authorized Co-investigator will fill in eCRFs for each patient enrolled and endorse them by their electronic signature.

Case Report Forms are used to complete several task:

- provide for data collection in accordance with the Protocol;
- ensure the compliance with the requirements of the control and permission system authorities for information collecting;
- contribute toward efficient and complete data processing, analysis and reporting on results;
- contribute toward the exchange of safety data among the project team and other organization units.

The data collected during the study at the clinical center should be complete and accurately represent what has happened to each subject.

The monitor should verify the information recorded in eCRFs for compliance with the primary documentation, which will allow confirming the absence of discrepancies in various documents during data registration. If the monitor reveals inconsistencies, necessary changes will be made in the eCRF. If any discrepancies are revealed, the monitor should discuss this issue with the investigator to ensure timely introduction of appropriate alterations in the eCRF.

The monitor must follow up the completeness and accuracy of the eCFR completion. The monitor does not have the right to alter the eCRF in his own hand.

The Investigator or other person authorized to fill eCRFs out must fill in eCRFs with data during or immediately after each visit in accordance with the source documents.

13.5. Data Processing and Introduction of Amendments to eCRFs

Data processing will be coordinated by the Sponsor. All information for each patient that is registered in accordance with the protocol must be timely entered in CRFs, which design is developed in accordance with this protocol.

In order to ensure the most efficient data collection and transmission, the investigator or the authorized clinical center employee should record the information in eCRFs as soon as possible immediately after the patient's visit. The access to CRFs, all primary documentation should be available for verification by the monitor.

The Sponsor or his representative will verify eCRFs during data processing. If any inconsistencies and/or errors that could affect the analysis and interpretation of results are found during data processing, data refinement requests will be sent to the clinical center (data discrepancy resolution forms). The investigator must reply to them in accordance with the established procedure.

13.6. Confidentiality of Patient Data

The personal medical information of the patient obtained during the study is considered confidential and can not be disclosed to third parties. This information can be communicated to the attending physician of the patient or other health care provider responsible for the health of the patient after the submission of the patient's consent.

An identification number will be assigned to each patient, this number will be used instead of the patient's name to preserve patient confidentiality during the transfer of information about adverse events or other data related to the ongoing study.

Complete identification information about each patient will be stored only by the investigator who must provide it at the request of the auditor, insurance company or competent authorities. This information should be stored taking into account its confidential nature. With that in mind, the Clinical Center will fill out and keep the Patient Identification Log, which contains information about the patient (name, date of birth, medical record number in the institution, etc.) and the randomization code assigned to it. The identification Log or its copy will not be transferred to the Sponsor/CRO and will be kept in the archive of the clinical center after the end of the study. This Log will ensure the identification of coded information about the study subject with his/her individual data and medical record.

All persons involved in the study process must ensure the maintenance of patient's confidentiality, not allowing the use of any information that can identify the patient (for example, his name or address).

13.7. Investigator File (Study Documentation Log)

The Investigator must keep all records to ensure full documentation of the study progress, in accordance with Good Clinical Practice standards. The Investigator must store all necessary study documentation for 15 years, unless otherwise required by the Sponsor; the Investigator must take measures to prevent the accidental or premature destruction of this document.

The Investigator must maintain a confidential patient identification code list, which provides a unique link between the primary records which indicate the name, and the anonymous data of CRFs for the Sponsor. The Investigator must arrange for the storage of this confidential code for at least 15 years after the study completion or termination.

No study documents can be destroyed without a prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to transfer the study documentation to another party, or to transport it to another location, the Sponsor must be notified of this.

The Study Documentation Log includes the following documents that are mandatory for detailed examination:

- Investigator's Brochure;
- Clinical Study Protocol;
- Information for the study subject and informed consent form;
- Clinical Study Reports;
- Case report form of the subject (CFR)
- Responsibility assignment matrix;
- Patient Identification Log;
- IMU log/IMU issue log;
- Screening and randomization log.

13.8. Data Archiving

Electronic copies of the CRFs and the primary documentation relevant to the study, the subject identification list and the informed consent form should be stored by the investigator for 15 years. In case of the Investigator's moving, retirement or other changes related to the archiving of the documentation during the mentioned time (15 years), the Sponsor should be notified of who will be responsible for storing the CRFs and other study documentation. An inventory of the stored data will be stored by the Investigator, a copy will be provided to the Sponsor.

The Clinical Study Protocol and Protocol Amendments, all editions of the Investigator's Brochure, the CRFs, copies of regulatory permits, all correspondence and reports relevant to the study, as well as other documents relevant to the study will be stored by the Sponsor or his authorized representative for 15 years.

14. FINANCING AND INSURANCE

The Sponsor will fund the study management and performance.

The financial aspects of the study will be documented in the form of an agreement between the Sponsor and the clinical center.

If the patient follows the investigator's instructions and if a harm is inflicted on his/her health as a result of the drug administration or procedures performed in accordance with the study design, the Sponsor will pay for all medical treatment costs. No other compensation from the Sponsor is forthcoming, except for compensation for travel expenses of patients (if applicable).

In accordance with Article 44 of the Federal Law "On Medicine Circulation" No. 61-FZ dd. 12.04.2010 prior to the beginning of the study, a procedure for the insurance of patient health and civil liability of persons conducting clinical studies should be carried out. If a harm associated with a clinical study is inflicted on patient health, the Insurance Company through which the Sponsor has concluded an insurance contract undertakes to reimburse all costs for the necessary medical examination and treatment that will be required as a direct result of the study drug and/or medical procedures performed in accordance with the Study protocol.

The Sponsor of the clinical study is Hepatera LLC, Russia. The Sponsor takes over the responsibility for insuring each study subject in accordance with the requirements for conducting clinical studies in the Russian Federation. The Sponsor effected a life insurance policy for patients participating in the study of drugs intended

for medical use, in accordance with the current legislation of the Russian Federation, with an insurance company: IPJSC INGOSSTRAKH, Russia, 127994, Moscow, Lesnaya str., 41, Office of Claims Settlement and Property and Casualty Insurance.
Tel./Fax: 8 (495) 641-41-01, 725-73-25, 234-36-00.
All discussions (if any) will be subject to the terms of the local insurance policy signed by the Sponsor and the Insurance Company.

15. PUBLICATION AND STUDY RESULT USAGE

Information regarding the study drug and/or the conditions for conducting this study or the study results, as well as unpublished scientific data on the investigational product, is considered confidential and is the property of the Sponsor. This information can only be transferred to the authorities that approve the study, or to those parties that participate in the study on a confidentiality basis. The investigator must use this information only for the purpose of carrying out this study, unless otherwise provided by a separate written permission of the Sponsor.

The Investigator agrees that the Sponsor can use the information obtained during the clinical study for publication and, thus, make it available to other investigators or regulatory authorities.

The results of this study can be published or presented at scientific conferences. Publication or presentation of the study results by the Investigator is possible only after obtaining approval from the Sponsor. In this case, the Investigator must provide the Sponsor with all scripts and abstracts of the planned publication for getting an approval prior to submission to the editorial board or scientific expert advice. This will allow the Sponsor to protect the information that is its property and to supplement the report with comments based on information that may not yet be available to the Investigator.

In accordance with publishing practice standards, the Sponsor is usually in favor of the publication of multicenter study results from cover to cover, and not as data from individual clinical centers. Any publication of the study results in which the Sponsor's expert took a part greater than just standard monitoring should be regarded as a co-publication of the Investigator and this person.

Before presentation of the results (written or oral), the material of the clinical study should be submitted for consideration and approval by Hepatera LLC. The authorship of materials for an oral report or article should be established as agreed by the Sponsor and the Investigator.

16. FINAL REPORT

The final study report should be written after the database freeze and data has been statistically proceeded when the study is completed in accordance with the protocol.

No matter whether the study has been completed as per protocol or terminated prematurely, the Sponsor will ensure that a clinical study report is compiled and submitted to regulatory authorities and the IEC in accordance with the ICH guidelines on "Structure and content of clinical study reports". In some cases, abbreviated reports may be acceptable.

The final report on the clinical study results should contain (but not be limited to) the following information:

- Synopsis;
- List of abbreviations;
- Ethical aspects of the study management;
- Investigators and the administrative structure of the study;
- Introduction;
- Objectives of the Study;
- Plan and design of the study;
- Names of medicinal products-objects of the study and names of manufacturers;
- Numbers of a series of medicinal products-objects of the study, data on their shelf life;
- Demographic and anthropometric patient data;
- Patient screening;
- Route of administration of the study drugs and their doses;
- Patient randomization schedule;
- Protocol amendments;
- Efficacy and safety evaluation criteria;
- Information on the safety and tolerability of the study drugs, adverse reactions/events, including AE lists for each patient;
- Final estimates of the parameters analyzed in this test, both for the study drug and for the reference

product, including arithmetic means, standard deviations;

- ANOVA results, the values of the corresponding coefficients of variation;
- Evaluation criteria and results of statistical analysis of relevant parameters together with comparisons of the study drug with the reference product;
- Data on patients who were discharged or were dropped out the study;
- Data on protocol deviations and the original statistical plan;
- Discussion and conclusions.

The report should clearly state the conclusion about the efficacy and safety of investigational medicinal product. Conclusions and recommendations should be consistent with the results obtained.

The final report should be sent to the Sponsor for approval. The final report, as well as other study documents, is confidential information that can not be disclosed by investigators without the relevant permission of the Sponsor. The report will be prepared in accordance with regulatory requirements.

17. CONFIDENTIALITY

The information contained in this document is the property of the Sponsor, and its transfer to the third parties is permitted with the written permission of the Sponsor only. Only the Investigator(s) and staff of the clinical center(s) participating in the study, members of the independent ethics committee(s) and employees of the health administrations authorized to monitor the study are entitled to familiarize with this information. The information on the study, in the amount necessary for making a decision to grant consent for participation, is given to patients whom the Investigator plans to enroll in the study.

18. PROTOCOL AMENDMENTS AND/OR PROTOCOL REVIEW

Any protocol amendment will be agreed to between the Investigator and the Sponsor before it is accepted valid. Any changes in the study that occurred after the protocol has been approved should be registered as additions or amendments to the protocol and/or an updated version of the protocol. Depending on the nature of the amendment, approval or notification of the Council on Ethics and regulatory authorities will be required. Ethical approval will be required for any protocol amendment that may affect the patient safety, the scope/design of the study, cause any increase in the dosage or duration of administration of the study drug, an increase in the number of patients treated, the addition of a new analysis/procedure or the exclusion of analysis designed to monitor safety. Amendments may go into effect only after being approved by the Sponsor, the Investigator and, if necessary, the Council on Ethics and regulatory authorities, unless there is an immediate threat to the life or health of patients enrolled in the clinical study, or when the protocol amendment(s) refer to administrative aspects or supply matters only.

19. REFERENCES

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PCG Clinical Services

Statistical Analysis Plan

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Table of contents

1 Abbreviations 6

2 Introduction 8

3 Study objectives 8

3.1 Primary objective 8

3.1.1 Primary variables 8

3.2 Secondary objectives 8

3.2.1 Secondary efficacy variables 8

3.2.2 Safety variables 8

3.2.3 Pharmacokinetic variables 9

4 Study design 10

5 Study population 10

5.1 Sample size 11

6 Assessments 11

6.1 Demographics and medical history assessments 11

6.2 Efficacy assessments 11

6.2.1 Histological findings 11

6.3 Pharmacokinetic assessments 12

6.3.1 Main study 12

6.3.2 Pharmacokinetic sub-study 12

6.4 Safety assessments 13

6.4.1 Adverse events 13

7 Method of analysis 13

7.1 General 13

7.1.1 Presentation of results 13

7.1.2 Baseline 14

7.1.3 Analysis relative day 14

7.1.4 Analysis visit 14

7.1.5 Handling of missing data and non-quantifiable values 14

7.1.6 Interim analyses 15

7.1.7 Multiplicity 15

7.1.8 Subgroups 15

7.2 Analysis sets 16

7.2.1 Modified intention-to-treat analysis set 16

7.2.2 Per-protocol analysis set 16

7.2.3 Safety analysis set 16

7.2.4 Pharmacokinetic analysis sets 16

7.3 Disposition of subjects 16

7.4 Protocol deviations 17

7.5 Demographics and baseline characteristics 17

7.6 Medical history and concurrent diseases 17

7.7 Prior and concomitant medication 18
7.8 Efficacy evaluation 18
7.8.1 Primary efficacy variable: HDV RNA response 19
7.8.2 Change from baseline in HDV RNA levels 19
7.8.3 Durability of HDV RNA response 20
7.8.4 Combined response 20
7.8.5 Change from baseline in ALAT 20
7.8.6 Change in fibrosis marker 20
7.8.7 Change in hepatitis B surface antigen 20
7.8.8 Change from baseline in HBV DNA 21
7.8.9 Improvement of the histological findings 21
7.8.10 Other efficacy variables 22
7.9 Pharmacokinetic evaluation – main study 22
7.10 Pharmacokinetic evaluation – sub-study 22
7.10.1 Plasma concentrations 22
7.10.2 Pharmacokinetic parameters 23
7.10.3 Dose proportionality 23
7.10.4 Multiple dosing versus single dose 23
7.10.5 PK data for midazolam for investigation of the metabolic activity of CYP3A 24
7.11 Safety evaluation 24
7.11.1 Extent of exposure 24
7.11.2 Adverse Events 24
7.11.3 Laboratory 25
7.11.4 Urine pregnancy test 25
7.11.5 Physical examination 25
7.11.6 Vital signs 26
7.11.7 Electrocardiogram 26
7.11.8 Immunogenicity 26
7.12 Other analyses 26
7.13 Changes to planned analysis 26
7.13.1 HDV RNA levels 26
7.13.2 Combined response 26
7.13.3 Development of antibodies to HBsAg 26
8 Derived variables 26
8.1 General 26
8.1.1 Change from baseline 26
8.1.2 Durations 26
8.2 Disposition of subjects 26
8.3 Demographics and baseline characteristics 27
8.3.1 Age 27
8.3.2 Body mass index 27
8.4 Efficacy variables 27
8.4.1 HDV RNA response (primary efficacy variable) 27

8.4.2 Durability of HDV RNA response 27
8.4.3 Combined response 27
8.4.4 Histological findings 27
8.5 Safety variables 27
8.5.1 Exposure 27
8.5.2 Physical examination 28
8.5.3 Immunogenicity 28
8.6 Pharmacokinetic variables 28
8.6.1 Accumulation ratio 28
8.6.2 AUC ratio 28
8.6.3 Dose-normalisation 28
9 References 28
10 Signoff 29
Appendix A: Schedule of assessments 30

1 Abbreviations

Abbreviation	*Explanation*
1-OHMDL	1-hydroxymidazolam
ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
ASAT	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [classification system]
AUC	Area under the curve
BLQ	Below the limit of quantification
BMI	Body mass index
cccDNA	Cyclic covalently closed deoxyribonucleic acid
CHD	Chronic hepatitis D
CI	Confidence interval
CV%	Coefficient of variation, expressed as a percentage
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FU	Follow-up
GGT	Gamma glutamyl transferase
HAI	Histological activity index
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDV	Hepatitis delta (D) virus
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LLOQ	Lower limit of quantification
LS	Least squares
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat analysis set
MMRM	Mixed-effects model for repeated measures
MXB	Myrcludex B
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample
NTCP	Sodium-taurocholate co-transporting polypeptide

PK	Pharmacokinetic
PPAS	Per-protocol analysis set
RNA	Ribonucleic acid
SAP	Statistical analysis plan
ULOQ	Upper limit of quantification
WHO	World Health Organisation

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Study Protocol and includes a more technical and detailed elaboration of the principal features of the proposed statistical analysis and presentations, and the way in which anticipated analysis problems will be handled.

This SAP is mainly based on the German protocol version 3.0 (2017-12-25), and partly on the Russian protocol version 7.0 (2017-09-28).

If the SAP suggests changes to the principal features stated in the protocol, these should also be documented in a protocol amendment. Otherwise, it will suffice to record the changes in the SAP.

3 Study objectives

3.1 Primary objective

The primary objective is to investigate the efficacy of Myrcludex B (MXB) and to compare three doses of MXB versus observation on background therapy with tenofovir in hepatitis delta patients.

3.1.1 Primary variables

The primary efficacy variable is hepatitis delta (D) virus (HDV) RNA response, defined as HDV RNA negativation or a decrease in HDV NRA by at least 2 $\log_{10}$ from baseline to Week 24.

3.2 Secondary objectives

The secondary objective is to investigate further efficacy parameters as well as safety and tolerability, as well as to assess pharmacokinetics (PK) and immunogenicity, of three doses of MXB in hepatitis delta patients.

3.2.1 Secondary efficacy variables

The secondary efficacy variables are:

- Change from baseline in HDV RNA levels at Week 24 and Week 48.
- Durability of HDV RNA response to 24 weeks post treatment (from Week 24 to Week 48).
- Combined response: HDV RNA response and normal alanine aminotransferase (ALAT), at Week 24 and Week 48.
- Change from baseline in ALAT at Week 24 and Week 48.
- Lack of fibrosis progression based on transient elastometry (Fibroscan) at Week 24 compared to baseline. [German protocol]
- Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 and Week 48 compared to baseline.
- Changes in hepatitis B surface antigen (HBsAg) (decreased level, disappearance of HBsAg, antibodies to HBsAg) at Week 24 and Week 48 compared to baseline.
- Change from baseline in hepatitis B virus (HBV) DNA levels at Week 24 and Week 48.
- Improvement of the histological findings (reduction of necroinflammation, absence of fibrosis progression, etc.) according to the liver biopsy study results or the absence of a fibrosis progression according to the findings of transient elastometry (Fibroscan) at Week 24 compared to baseline. [Russian protocol]

3.2.2 Safety variables

The safety variables are:

- Adverse events.
- Physical examination.
- Vital signs.
- 12-lead electrocardiogram (ECG).
- Laboratory parameters (haematology, coagulation panel, blood chemistry, urinalysis, blood bile acid levels).
- Development of anti-Myrcludex B antibodies.

3.2.3 Pharmacokinetic variables

Plasma concentrations (main study):

- Myrcludex B

Plasma concentrations (PK sub-study):

- Myrcludex B
- Midazolam and its main metabolite, 1-hydroxymidazolam (1-OHMDL).

PK parameters for Myrcludex B (PK sub-study):

- C_{av}: average concentration during dosing interval $\tau = 24h$ (for subperiod II).
- C_{min}: minimum concentration during dosing interval $\tau = 24h$.
- C_{max}: maximum concentration during dosing interval $\tau = 24h$.
- T_{max}: time to reach maximum concentration.
- PTF: peak to trough fluctuation within a dosing interval (for subperiod II).
- PTS: peak to trough swing – the degree of fluctuation over a dosing interval (for subperiod II).
- λ_z (k_{el}): terminal elimination rate constant.
- $T_{1/2}$: terminal elimination half-life.
- CL/F: total body clearance
- V_z/F: apparent volume of distribution based on terminal phase.
- AUC_{0-24}: area under the plasma concentration curve from drug administration (time zero) to the end of dosing interval $\tau = 24h$ (for subperiod II).
- AUC_{0-t}: area under the plasma concentration curve from drug administration to the last measurable concentration
- $AUC_{0-\infty}$: area under the plasma concentration curve from drug administration to infinity.

PK parameters for midazolam (MDZ) and 1-OHMDL (PK sub-study):

- AUC_{0-t}: area under the plasma concentration curve from drug administration to the last measurable concentration
- $AUC_{0-\infty}$: area under the plasma concentration curve from drug administration to infinity.
- C_{max}: maximum concentration during dosing interval $\tau = 24h$.
- T_{max}: time to reach maximum concentration.
- λ_z (k_{el}): terminal elimination rate constant.
- $T_{1/2}$: terminal elimination half-life.
- CL: total body clearance.
- V_{ss}: volume of distribution at steady-state.
- The $AUC_{0-\infty}$ ratio of 1-hydroxymidazolam/midazolam.

4 Study design

This is a randomised, open-label, multicentre phase II clinical study.

The main part of the study includes:

- Screening period of 28 days (visit 01).
- Tenofovir pre-treatment period, for subjects requiring preliminary therapy with tenofovir for up to 12 weeks (84 days), starting from the moment that screening results allowing assessment of inclusion and exclusion criteria become available. This period includes the following visits:
  - visit 02 (site visit) – start of tenofovir treatment 84 days before planned randomisation visit
  - visit 03 (telephone contact) – telephone call to the subject 28 days before planned randomisation visit
  - visit 04 (site visit) – up to 14 days before the planned randomisation visit.
- Randomisation visit (visit 1, day 1).
- Treatment period of up to 24 weeks (visits 2–9 at weeks 1, 2, 4, 8, 12, 16, 20 and 24 after the randomisation visit).
- Follow-up (FU) period of 24 weeks for all treatment arms (visits FU1–FU5 at weeks 25, 26, 28, 36 and 48 after the randomisation visit).

Pre-treatment is required for subjects who have not received nucleotide/nucleoside analogues for at least 12 weeks prior to enrolment.

At the randomisation visit, subjects will be randomly assigned to one of the four treatment arms:

A. Myrcludex B 2 mg/day subcutaneously and tenofovir for 24 weeks + follow-up period of 24-weeks of continued tenofovir therapy.
B. Myrcludex B 5 mg/day subcutaneously and tenofovir for 24 weeks + follow-up period of 24-weeks of continued tenofovir therapy.
C. Myrcludex B 10 mg/day subcutaneously and tenofovir for 24 weeks + follow-up period of 24-weeks of continued tenofovir therapy.
D. Tenofovir treatment for 48 weeks.

The randomisation will be stratified by presence of cirrhosis, and allocation will be done according to a ratio of 1:1:1:1.

A sub-study on pharmacokinetics will be performed, including 30 subjects from the 3 MXB treatment arms (10 subjects per arm). In this sub-study. In addition to evaluation of the pharmacokinetic profile for Myrcludex B, PK data for midazolam, a benzodiazepine derivative, and its main metabolite will be used to investigate the metabolic activity of cytochrome P450 (CYP3A).

5 Study population

The study population consists of male and female subjects aged 18–65 years old with chronic HDV infection and positive HDV RNA results at screening, who failed previous interferon therapy or for whom, in the opinion of the investigator, such therapy is contraindicated (including history of interferon intolerance), as well as cirrhotic subjects. Only subjects who sign the informed consent form and who meet all eligibility criteria will be enrolled into the study.

Up to 200 subjects will be screened for inclusion into the study, and 120 subjects (up to 30 of which in Germany) will be randomised.

5.1 Sample size

The previous phase Ib/IIa clinical study in subjects with chronic hepatitis D (CHD) showed efficacy in the monotherapy group in 57 % of subjects after 24 treatment weeks, with a lower limit of the confidence interval (CI) of approximately 37 %.

It is believed that spontaneous decrease in the HDV RNA level by 2 $\log_{10}$ occurs in no more than 3 % of cases (in the absence of treatment and with nucleoside/nucleotide analogue therapy approved for hepatitis B in subjects with CHD, no response was observed; *e.g.* study HIDIT-1 in 90 subjects with CHD showed no effect on HDV RNA with monotherapy with adefovir, a nucleotide analogue).

Using a two-sided test with a power of 80 %, a significance level of $\alpha = 0.05/3 \approx 0.0167$ (using Bonferroni correction to adjust for multiple testing; the 3 active treatment groups will be tested separately against the control group), and a superiority limit (test margin) of 5 %, a sample size of 28 subjects per group will be sufficient to detect a 34 % increase in response compared to the control group, assuming a response rate of 3 % for the control group.

The sample size for each treatment arm was calculated according to the following formula:

$$n = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2}{(p_1 - p_0 - \delta)^2}(p_1(1-p_1) + p_0(1-p_0)),$$

where z_x is the value of the normal distribution quantile function, α is the type I error, β is the type II error ($1-\beta$ is the power), p_1 and p_0 are the response rates in the test group and the control group, respectively, and δ is the superiority limit (clinically significant difference in proportions).

Assuming a drop-out rate of 5 %, a total number of 30 subjects per treatment arm will be needed.

6 Assessments

This section gives a brief summary of a selection of the assessments in the study; see the study protocol for more details on all assessments.

A schedule of assessments for the study is presented in Appendix A: Schedule of assessments.

6.1 Demographics and medical history assessments

Date of birth

6.2 Efficacy assessments

6.2.1 Histological findings

The histological activity index (HAI), also known as the Knodell score, is an additive score calculated as the sum of the semi-quantitative scores for four individual features: periportal and/or bridging necrosis, hepatocyte degeneration and/or focal necrosis, portal inflammation, and fibrosis. In clinical trials, the first three categories are often totalled to give a necro-inflammatory score (0–18), while the fibrosis score (0–4) is reported separately.

The Knodell fibrosis score stages fibrosis in a 5-tier system (with stage 2 eliminated to overstate the difference between mild and severe disease):

0. No fibrosis
1. Fibrous portal expansion
3. Bridging fibrosis

4. Cirrhosis.

The Ishak fibrosis score is part of the Ishak score, a modified form of the HAI, and has 7 stages:

0. No fibrosis
1. Fibrous expansion of some portal areas, with or without short fibrous septa
2. Fibrous expansion of most portal areas, with or without short fibrous septa
3. Fibrous expansion of most portal areas with occasional portal to portal bridging
4. Fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central)
5. Marked bridging (portal–portal and/or portal–central) with occasional nodules (incomplete cirrhosis)
6. Cirrhosis, probable or definite

The METAVIR scoring system is used to assess the extent of inflammation and fibrosis by histopathological evaluation in a liver biopsy. It comprises two scores, the fibrosis stage representing the amount of fibrosis or scarring, and the activity grade indicating the degree of inflammation.

Fibrosis stage:

- F0: No fibrosis
- F1: Portal fibrosis without septa
- F2: Portal fibrosis with few septa
- F3: Numerous septa without cirrhosis
- F4: Cirrhosis

Activity grade:

- A0: No activity
- A1: Mild activity
- A2: Moderate activity
- A3: Severe activity

6.3 Pharmacokinetic assessments

6.3.1 Main study

In the main study, blood samples for PK analysis are collected at the randomisation visit and then every 4th week during the treatment period, at 1 hour ± 15 minutes after administration of Myrcludex B.

6.3.2 Pharmacokinetic sub-study

The PK sub-study comprises two subperiods during the treatment period: subperiod I (Day 1–2), and subperiod II (Day 14–15). For the PK evaluation for MDZ, samples will also be collected during the pre-treatment period (at Day -13 – -12)

Midazolam will be administered before Myrcludex B, and PK blood sampling (except pre-dose) will be done after MXB dosing.

PK samples are collected pre-dose and at 5, 15 and 30 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 10, 14 and 24 hours after dosing, with allowed windows of ±5 minutes up to 6h and ±15 minutes thereafter for the MXB samples, and allowed windows of ±1 minute up to 1h, ±2 minutes up to 3h and ±3 minutes thereafter for the MDZ samples. Blood samples should be drawn at the same time in each period.

In the pre-treatment period, the planned sampling times are the same as in the subperiods, but in relation to the administration of MDZ (since MXB is not administered during the pre-treatment period).

6.4 Safety assessments

6.4.1 Adverse events

In this study, adverse events will be recorded from the first dose of the study medication to the last visit of the follow-up period. All adverse medical events present before the first administration of the study medication (including the screening period) will be reported as part of subject's medical history.

Already present diseases and symptoms will be considered as adverse events only if their severity or rate worsens, or they change in nature. The responsible investigator will document such changes as adverse events.

7 Method of analysis

7.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline for Statistical Principles for Clinical Trials (1), using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

7.1.1 Presentation of results

All results will be presented by treatment group, in total across all three MXB groups (regardless of dose), and in total (all 4 groups), unless stated otherwise.

Continuous data will be summarised using descriptive statistics, and the following parameters will be reported:

- number of subjects with evaluable observations and missing observations, respectively
- arithmetic mean and standard deviation
- confidence interval for the mean
- median
- first and third quartiles
- minimum and maximum.

Categorical data will be presented using absolute frequency and percentage and Clopper–Pearson exact confidence intervals for binomial proportions. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be the total number of subjects in the applicable analysis set, including subjects with missing data. For variables with missing values, the number and percentage of subjects with missing values will be presented.

Significance tests will be two-sided and performed at the 5 % significance level, unless stated otherwise. When reporting the results of significance tests, p-values will be presented.

All confidence intervals presented will be two-sided with a nominal confidence level of 95 %, unless stated otherwise.

Data will be presented using an appropriate number of decimal places, to ensure that undue precision is not implied (*e.g.* the number of decimals should not exceed the accuracy of the measuring instrument). Raw data will be presented with the same number of decimals as collected, and derived data with an appropriate number of decimals based on general practice, mathematical rationale or scientific rationale.

Minimum and maximum values will be presented with the same number of decimals as the analysed variable and the other descriptive statistics will be presented with one decimal more. Percentages and

proportions will be presented with one decimal. Odds ratios and hazard ratios will be presented with 3 decimals, and small and large values will be presented as '<0.001' and '>999.999' respectively. Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as '<.0001'.

Mock tables and graphs are presented in the Data Display Plan (DDP), which is a supplementary document to this analysis plan. Individual subject data listings will be presented according to the ICH E3 guideline for Structure and Content of Clinical Study Reports (2), unless stated otherwise.

7.1.2 Baseline

Unless stated otherwise, the baseline value for a parameter is defined as the last non-missing value before the first dose of the study treatment.

7.1.3 Analysis relative day

The analysis relative day for an assessment/value is defined as the time in days from the date of randomisation to the date of the assessment. The date of randomisation is considered as day 1, and earlier dates will correspond to a negative day.

7.1.4 Analysis visit

An analysis visit is defined as a categorical variable used to classify values within an analysis variable into temporal or conceptual groups used for analyses.

The study visits as defined in the case report form (CRF) will be used as analysis visits.

In general, data from unscheduled visits will be presented in data listings only and not included in analysis or summary tables. An exception to this is data used to confirm eligibility in association with screening or randomisation where the last assessment will be considered in summaries of screening data.

7.1.5 Handling of missing data and non-quantifiable values

In general, no imputations of missing data will be performed, and the analyses will be performed on the observed cases, unless stated otherwise. In analyses using a mixed-effects model for repeated measures (MMRM), missing values are handled by means of built-in maximum-likelihood based methods in the SAS procedure used for the analysis, under the 'missing at random' assumption.

For all response parameters, the missing equals failure (MEF) approach will be used for the main analysis (*i.e.*, subjects with missing data will be considered as non-responders).

Data listings will include the observed values. For derived variables, values based on imputed data can be presented in listings.

7.1.5.1 Virology

For the virology results, the following rules will be applied:

- Values below the limit of detection will be collected in the database as zero values.
- Values reported as '<x' (below the lower limit of quantification, LLOQ), will be imputed as half the LLOQ value.
- 'Non-measurable' data will be considered as missing data.
- Values reported as '>x' (above the upper limit of quantification, ULOQ), will be imputed as the ULOQ value.
- For the log-10 transformed data, missing values due to untransformed values of zero will be imputed as zero.

7.1.5.2 Pharmacokinetics

Concentration data identified with 'NOS' (no sample), 'NOR' (no valid result), 'NOA (not analysed), or 'NOP' (no peak detectable) will be ignored and not replaced by zero at any time point.

For descriptive statistics, values reported as below the limit of quantification (BLQ) will be imputed as half the LLOQ value. The lower limit of quantification is 1 ng/mL for Myrcludex B, 0.093 pg/mL for midazolam, and 0.255 pg/mL for the midazolam metabolite (1-OHMDL).

In the non-compartmental analysis, concentration data identified with 'NOS', 'NOR', 'NOA', and 'NOP' will not be considered. Pre-dose BLQ values and BLQ values in the lag phase (MXB, 1-OHMDL) will be set to LLOQ/2. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored and set to missing. For $AUC_{0-\tau}$ estimation, all BLQ values in the terminal phase will be set to LLOQ/2.

Every effort will be made to include all concentration data in the analysis. If not possible, a case to case decision is required whether the value should be excluded from the analysis.

If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed and associated with an appropriate flag.

If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will be used for this time point instead.

Pharmacokinetic parameters which cannot be determined will be identified by 'not calculated' (NC).

7.1.5.3 Safety laboratory test results

For safety laboratory parameters, the following rules will be applied:

- Values reported as '<x' (below the LLOQ), will be imputed as half the LLOQ value.
- Values reported as '>x' (above the ULOQ), will be imputed as the ULOQ value.

7.1.6 Interim analyses

An interim safety analysis was performed when 10 subjects of each arm had completed 28 days of treatment. Based on the results of the analysis, it was decided that cirrhotic subjects could be included in the study.

When all randomised subjects had completed the 24-week treatment period, an interim analysis on efficacy and safety of the study treatment was performed and documented in an interim study report.

7.1.7 Multiplicity

Correction for multiple testing will be done by sequential testing of hypotheses using the Bonferroni–Holm method. This will be done for all hypothesis testing of efficacy variables, and adjusted p-values will be presented in addition to the raw unadjusted p-values.

7.1.8 Subgroups

The following subgroups will be defined:

1. Subjects with cirrhosis at baseline.
2. Subjects with no cirrhosis at baseline.
3. Subjects with normal ALAT levels at baseline.
4. Subjects with abnormal ALAT levels at baseline.
5. Subjects who attended at least one follow-up visit.

6. Subjects who tested positive for hepatitis B envelope antigen (HBeAg) at screening.

7.2 Analysis sets

The decision on the classification of subjects to each analysis set will be taken at the clean file meeting and documented in the clean file report together with the reasons for excluding subjects from the analysis sets.

7.2.1 Modified intention-to-treat analysis set

The modified intention-to-treat (mITT) analysis set is defined as all randomised subjects who received at least one dose of the study treatment.

Analysis on the full analysis set will be based on the planned treatment (*i.e.* subjects will be analysed 'as randomised').

7.2.2 Per-protocol analysis set

The per-protocol analysis set (PPAS) is defined as the subset of subjects in the mITT analysis set who completed the 24 week treatment period with efficacy results for Week 24 and for whom no major protocol deviations were reported. When determining if a subject has evaluable data for the primary efficacy variable, HDV RNA assessments from study weeks 24 to 26 (day 166–185, taking visit windows of ±2 and ±3 days, for visits 9 and FU2 respectively, into account) will be considered as valid.

Exclusion of subjects from the per-protocol analysis set was decided upon at the data review meeting before the final analysis of the treatment period. In addition, subjects with violation of any inclusion and/or exclusion criterion will be excluded from the PPAS. Cases where subjects took regularly prescribed tenofovir instead of study tenofovir during the study will not be considered as a reason for exclusion from the PPAS. All other reasons, which were used in the interim analysis, will still be used for exclusion from the PPAS in the final analysis.

Analysis on the per-protocol analysis set will be based on the actual treatment (*i.e.* subjects will be analysed 'as treated').

7.2.3 Safety analysis set

The safety analysis set is defined as all subjects who received at least one dose of the study treatment.

Analysis on the safety analysis set will be based on the actual treatment ('as treated').

7.2.4 Pharmacokinetic analysis sets

The pharmacokinetics concentration analysis set (PKCAS) is defined as the subset of all subjects in the safety analysis set who have at least one measured concentration.

The pharmacokinetics analysis set (PKAS) is defined as the subset of all subjects in the PKCAS who are included in the PK sub-study and have at least 1 estimated PK parameter and no major protocol violations relevant to the evaluation of pharmacokinetics.

Analysis on the PK analysis sets will be based on the actual treatment ('as treated').

7.3 Disposition of subjects

The following will be presented:

- Number of screened subjects, in total.
- Number of screening failures, in total.
- Number of randomised subjects, by treatment group and in total.

Based on the number of randomised subjects, the following will also be presented, by treatment group and in total:

- Number and percentage of subjects who did not receive any dose of study treatment.
- Number and percentage of subjects who received at least one dose of study treatment.
- Number and percentage of subjects who completed the treatment period.
- Number and percentage of subjects who completed the study.
- Number and percentage of subjects who withdrew prematurely from the study.
- Number and percentage of subjects in each of the analysis sets.

In addition, a frequency table on the primary reason for premature withdrawal from the study will be presented by treatment group and in total. Percentages for this table will be based on the number of prematurely withdrawn subjects.

The number of subjects attending each study visit will also be summarised.

The tables on the disposition of subjects will be presented in total as well as per country and study site.

7.4 Protocol deviations

The number and percentage of randomised subjects with at least one protocol deviation, in total and per deviation category will be presented.

7.5 Demographics and baseline characteristics

The following parameters will be summarised descriptively on the safety analysis set:

- Demographics: Age, age groups ('<65 years' and '≥65 years'), sex, and race.
- Baseline anthropometrics: height, body weight, body mass index (BMI) and BMI categories ('<30 kg/m²' and '≥30 kg/m²').
- Baseline data (collected at screening and/or randomisation visit):
  - Urine drug test (positive/negative): amphetamine, barbiturates, benzodiazepine, cannabinoids, cocaine, methadone, opiate, and tricyclic antidepressants.
  - HDV RNA (positive/negative)
  - Serology test: HBeAg and anti-HBeAg antibodies, HBsAg, hepatitis C virus (HCV) RNA and HCV antibodies, HDV antibodies, and human immunodeficiency virus (HIV) antibodies.
  - Creatinine clearance [mL/min].
  - Serum alpha fetoprotein (AFP) test [IU/mL]
  - Abdominal ultrasound (normal/abnormal).
  - Substance abuse: Alcohol breath test (positive/negative), subject status (alcohol: drinker, ex-drinker, non-drinker; drugs: current user, ex-user, non-user; nicotine: current user, ex-user, non-user).
  - sodium-taurocholate co-transporting polypeptide (NTCP) polymorphism.

7.6 Medical history and concurrent diseases

Medical history and concurrent diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by system organ class and preferred term, on the safety analysis set.

For each system organ class and preferred term, the number and percentage of subjects with at least one condition in that system organ class or preferred term will be presented. Medical history and concurrent diseases will be presented in separate tables, based on the safety analysis set.

Medical history is defined as events stopped prior to baseline. Concurrent diseases are defined as events reported as ongoing and events stopped at or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the events:

	Imputed start date	*Imputed end date*
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify the event based on the reported and/or imputed start and end dates, the event will be considered as concurrent. In data listings, the dates will be presented as reported.

7.7 Prior and concomitant medication

Medications will be coded according to the World Health Organisation (WHO) Drug Dictionary and summarised by therapeutic subgroup (ATC level 2) and preferred name, on the safety analysis set.

For each therapeutic subgroup and preferred name, the number and percentage of subjects who used at least one medication of that therapeutic subgroup or preferred name will be presented. Separate tables will be presented for prior medications, concomitant medications during the treatment period, and concomitant medications started during the follow-up period.

Midazolam will be presented separately only (with no distinction between prior and concomitant use).

If a reported medication cannot be coded, it will be presented as 'non-appropriated'.

Prior medication is defined as medication stopped prior to baseline. Concomitant medication during the treatment period is defined as ongoing medication or medication stopped on or after baseline, with a start date before the end of the treatment period. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the medication:

	Imputed start date	*Imputed end date*
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify a medication based on the reported and/or imputed start and end dates, the medication will be considered as concomitant during the treatment period. In data listings, the reported dates will be presented.

7.8 Efficacy evaluation

All analyses of efficacy variables will be performed on both the mITT analysis set (main analysis) and the per-protocol analysis set (supportive analysis).

In addition to the statistical hypothesis testing described in the subsections below, all efficacy variables will be summarised descriptively, on both the mITT analysis set and the per-protocol analysis set. For continuous variables, both the actual values at each visit as well as the change from baseline will be summarised. All descriptive presentations of efficacy data will be done for all subjects as well as for the subgroups based on presence of cirrhosis at baseline.

Whereas the hypothesis testing will be performed only for the timepoints specified in section 3, descriptive presentations will be based on data from all analysis visits at which the variable can be evaluated.

Assumptions for statistical models will be evaluated using graphical methods.

7.8.1 Primary efficacy variable: HDV RNA response

For each of the three MXB treatment groups (arms A–C), a null hypothesis of no clinically significant difference in proportion of responders compared to the control group (tenofovir only; arm D), at Week 24, will be tested using the one-sided Wald test for superiority, at a one-sided overall significance level of 0.05 adjusted for multiple testing according to Bonferroni–Holm, with the superiority limit (test margin) set to 5%:

$$H_0: p_A - p_D \leq \delta, \quad H_A: p_A - p_D > \delta$$
$$H_0: p_B - p_D \leq \delta, \quad H_A: p_B - p_D > \delta$$
$$H_0: p_C - p_D \leq \delta, \quad H_A: p_C - p_D > \delta$$

where p_X is the proportion of responders in treatment group X, and δ is the superiority limit.

As supportive analysis, Fisher's exact test will be used to test a null hypothesis of no difference in proportions against a two-sided alternative hypothesis. Separate tests will be performed for each of the three MXB treatment groups against the control group, at Week 24.

For each of the three MXB treatment groups, the difference in proportions of responders compared to the control group will be presented together with the corresponding confidence interval.

7.8.2 Change from baseline in HDV RNA levels

A null hypothesis of no difference between the MDX treatment groups and the control group in the change from baseline in HDV RNA levels will be tested against a two-sided alternative hypothesis using a mixed-effects model for repeated measures. Assessments from all post-baseline analysis visits up to Week 48 will be considered for the dependent variable, and tests will be performed at Weeks 24 and Week 48. The model will include baseline HDV RNA as a fixed covariate; treatment group, analysis visit, the interaction between treatment group and analysis visit, and presence of cirrhosis (the stratification factor) will be included as fixed factors. An appropriate covariance structure will be selected (unstructured, Toeplitz, auto-regressive and compound symmetry structures will be considered, and the selection will be based on the Akaike information criterion, AIC), and the Kenward–Rogers approximation will be used to estimate the denominator degrees-of-freedom and adjust standard errors.

Adjusted least square (LS) means and corresponding 95 % confidence intervals for the change from baseline for each of the treatment groups and the pairwise differences between the MXB treatment groups and the control group (on the log-10 scale, as well as anti-log transformed into geometric means and geometric mean ratios) will be presented together with the p-values corresponding to the tests of difference.

If the assumptions for the MMRM are not-fulfilled, a non-parametric analysis will be performed instead, using two-sided van Elteren tests (stratified Wilcoxon rank sum tests) adjusted for the stratification factor. Separate pairwise comparisons of the MDX treatment groups against the control group will be made at each of Week 24 and Week 48. The p-values from the tests will be presented.

All analyses on HDV RNA levels will be based on log-10 transformed data. Descriptive statistics will be presented for non-transformed data as well. Descriptive statistics for the follow-up visits will include the change from Week 24 as well.

Data will also be presented graphically, in line charts displaying the mean log-transformed HDV RNA levels over time.

7.8.3 Durability of HDV RNA response

Fisher's exact test will be used to test a null hypothesis of no difference in proportions of subjects with HDV RNA response at both Week 24 and Week 48 against a two-sided alternative hypothesis. Separate tests will be performed for each of the three MXB treatment groups against the control group.

7.8.4 Combined response

Fisher's exact test will be used to test a null hypothesis of no difference in proportions against a two-sided alternative hypothesis. Separate tests will be performed for each of the three MXB treatment groups against the control group, at Week 24 and Week 48.

This analysis, and presentation of descriptive statistics, will be repeated for the subgroups of subjects with normal/abnormal baseline ALAT values.

7.8.5 Change from baseline in ALAT

The change from baseline to Week 24 and Week 48 in ALAT levels will be analysed in the same way as the change from baseline in HDV RNA, using MMRM or van Elteren tests.

Fisher's exact test will be used to test a null hypothesis of no difference in proportions (of subjects with normal ALAT values) against a two-sided alternative hypothesis. Separate tests will be performed for each of the three MXB treatment groups against the control group, at Week 24 and Week 48.

The descriptive presentation will include summary statistics on the ALAT levels and change from baseline, as well as change from Week 24, the number and percentage of subjects with normal ALAT levels, and shift tables on the shift from baseline, and the shift from Week 24 in normal/abnormal status of ALAT.

Data will also be presented graphically, in line charts displaying the mean ALAT levels over time.

7.8.6 Change in fibrosis marker

The change from baseline to Week 24 and Week 48 in fibrosis marker (alpha-2-macroglobulin) will be analysed in the same way as the change from baseline in HDV RNA, using MMRM or van Elteren tests.

Descriptive presentation will include summary statistics on percentage change from baseline as well.

Data will also be presented graphically, in line charts displaying the mean alpha-2-macroglobulin levels over time.

7.8.7 Change in hepatitis B surface antigen

The change from baseline to Week 24 and Week 48 in HBsAg will be analysed in the same way as the change from baseline in HDV RNA, using MMRM or van Elteren tests.

Fisher's exact test will be used to test a null hypothesis of no difference in proportions (of subjects with a decrease by at least 1 on the log-10 scale or disappearance [value is zero]) against a two-sided alternative hypothesis. Separate tests will be performed for each of the three MXB treatment groups against the control group, at Week 24 and Week 48.

The number and percentage of subjects with a decrease by at least 1 on the log-10 scale or disappearance will be presented.

All analyses on HBsAg levels will be based on log-10 transformed data. Summary statistics will be presented for non-transformed data as well.

Data will also be presented graphically, in line charts displaying the mean log-transformed HBsAg levels over time.

7.8.8 Change from baseline in HBV DNA

The change from baseline to Week 24 and Week 48 in HBV DNA will be analysed in the same way as the change from baseline in HDV RNA, using MMRM or van Elteren tests.

All analyses on HBV DNA levels will be based on log-10 transformed data. Descriptive statistics will be presented for non-transformed data as well.

Data will also be presented graphically, in line charts displaying the mean log-transformed HBV DNA levels over time.

7.8.9 Improvement of the histological findings

Summary statistics on liver stiffness (as measured in kPa using transient elastometry) will be presented for baseline and Week 24, as well as for the change from baseline. In addition, the number and percentage of subjects with lack of progression in fibrosis (no increase in liver stiffness) and with progression will be presented, in total and by baseline value categories ('<12', '12–20', and '>20').

The number and percentage of subjects with an improvement (decrease) or worsening (increase) of at least 1 point will be presented for the following parameters:

- Fibrosis:
  - Ishak fibrosis score
  - Knodell fibrosis score
  - METAVIR fibrosis stage
- Histological activity stage:
  - Histological activity index
  - METAVIR activity grade

Descriptive statistics for the following molecular analysis and gene expression parameters will be presented based on log-10 transformed data as well as non-transformed data, including the change from baseline for the transformed data:

- Molecular analysis:
  - relative expression level of HDV RNA
  - HBV RNA (S region) [copies/cell]
  - HBV RNA relative expression level (S region)
  - relative expression level of total HBV RNA (X region)
  - relative expression level of HBV pregenomic RNA
  - HBV DNA (S region) [copies/cell]
  - total HBV DNA (X region) [copies/cell]
  - HBV cccDNA [copies/cell]
- Molecular analysis using immunofluorescence staining:
  - HDAg, % of positive hepatocytes
- Gene expression:
  - relative expression level of NTCP
  - relative expression level of CYP7A1
  - relative expression level of CXCL10
  - relative expression level of ISG15

The following parameters of molecular analysis and gene expression will be reported in listings only:

- Molecular analysis: DNA content [ng/µl], RNA content [ng/µl], HDV RNA [CT], HDV RNA [copies/cell], HBV RNA (S region) [CT], total HBV RNA (X region) [CT], total HBV RNA (X region) [copies/cell], HBV pregenomic RNA [CT], HBV pregenomic RNA [copies/cell], HBV DNA (S region) [copies], total HBV DNA (X region) [copies], beta globin [copies], cccDNA [copies], housekeeping gene GAPDH [CT].
- Gene expression: CXCL10 [CT], CYP7A1 [CT], GAPDH [CT], mean of GAPDH and RPL30 [CT], ISG15 [CT], NTCP [CT], rpl30 [CT].

7.8.10 Other efficacy variables

HBV and HDV genotyping, and resistance testing data will be presented descriptively by visit.

7.9 Pharmacokinetic evaluation – main study

All analyses and summaries of PK data for the main study will be based on the PK concentrations analysis set.

Summary statistics (including the geometric mean, and the arithmetic and geometric coefficients of variation [CV%]) on the Myrcludex B plasma concentrations will be presented by visit. Data will also be presented graphically, in line charts where the mean plasma concentration is plotted against time.

Additionally, for each arm, the attainment of steady state will be analysed exploratorily using linear mixed effect models. The log-transformed concentration values will be used as dependent variable and the model will include subject as a random factor and week of dosing as a fixed categorical effect. The following contrasts will be tested sequentially:

- Week 20 vs Week 24
- Week 16 vs Week 24
- Week 12 vs Week 24
- Week 8 vs Week 24
- Week 4 vs Week 24
- Randomisation vs Week 24.

Geometric mean ratios for each comparison against week 24 will be presented together with 90% confidence intervals, as well as the p-value.

All main study PK analyses and summaries will be based on the PK concentrations analysis set.

7.10 Pharmacokinetic evaluation – sub-study

In the PK sub-study, all analyses and summaries will be based on the PK concentrations analysis set (concentrations) or the PK analysis set (PK parameters).

7.10.1 Plasma concentrations

Summary statistics, including the geometric mean and arithmetic and geometric CV%, on plasma concentrations (MXB, MDZ, 1-OHMDL) will be presented by visit and timepoint.

Plasma concentrations will be presented graphically against time in line charts, both individual curves for each subject and mean profiles for each treatment group. In the graphs for individual subjects, the actual sampling times will be used, whereas the mean profile graphs will be based on the planned sampling times. Mean profiles will be plotted using both linear and semi-logarithmic scales.

Summaries of plasma concentrations will be based on the PK concentrations analysis set.

7.10.2 Pharmacokinetic parameters

Summary statistics, including the arithmetic CV%, on PK parameters for MXB will be presented. For concentration and area under the curve parameters, the geometric mean and CV% will be presented as well.

7.10.3 Dose proportionality

Dose proportionality for MXB will be evaluated separately after single dose (subperiod I) and multiple dosing (subperiod II) for each arm.

The proportionality relationship between AUC (AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$) and $C_{\max}$ parameters and daily dose is described as a power function $y = ax^b$, where a is a constant, x is the daily dose, and b is a proportionality constant. The power model assumes a linear relationship between natural log-transformed pharmacokinetic exposure parameter and natural log-transformed dose. The dose proportionality will be assessed from the 90 % confidence interval for the b, where b equal to 1 indicates the dose proportionality. The proportionality constant and its corresponding confidence interval will be compared with the modified acceptance range.

According to the Smith criteria, dose proportionality is declared when the 90 % CI for b lies completely within the critical region defined as

$$\left(1 + \frac{ln(\theta_L)}{ln(R)};\quad 1 + \frac{ln(\theta_H)}{ln(R)}\right),$$

where R is the ratio of the highest to lowest administered doses, and $\theta_L = 0.8$ and $\theta_H = 1.25$ are the lower and upper critical limits of the ratio of dose-normalised mean values for highest dose relative to lowest dose.

If dose proportionality is not declared for any of the PK parameters based on the Smith criteria, the 90 % CI for b would be compared to a less stringent critical region based on $\theta_L = 0.5$ and $\theta_H = 2.0$ (Hummel criteria).

Additional analysis will be performed to test dose-normalised AUC parameters and $C_{\max}$ using an analysis of variance (ANOVA) model on log-transformed exposure measures between arms. Point estimates and 90 % CI of geometric mean ratios between arms (anti-log transformed LS mean differences from the model) will be presented and judged by bioequivalence acceptance criteria of 80–125 %. Dose proportionality will be concluded if all 90 % CIs fall within 80–125 %.

AUC parameters and $C_{\max}$ will also be presented graphically in scatterplots, where the PK parameter value will be plotted against the daily dose.

7.10.4 Multiple dosing versus single dose

To determine whether multiple-dose pharmacokinetic behaviour of Myrcludex B (with concomitant MDZ administration) is predicted by single-dose pharmacokinetics, the AUC_{0-24} and $C_{\max}$ accumulation ratios will be calculated (on the log-scale and back-transformed for reporting) and compared to 100 %. The geometric mean will be presented together with the corresponding 90 % CI.

In addition, summary statistics on the changes from subperiod I to subperiod II in $T_{\max}$, $T_{1/2}$, CL/F, and V_z/F will be presented. Data will also be presented graphically, in scatterplots where the subperiod II values are plotted against subperiod I values.

7.10.5 PK data for midazolam for investigation of the metabolic activity of CYP3A

The effect of Myrcludex B on the natural log-transformed $C_{\max}$, $AUC_{0-\infty}$, and AUC_{0-t} of midazolam and its main metabolite (1-hydroxymidazolam) will be analysed by treatment arm using ANOVA models. Comparisons will be made for each of the two subperiods versus the pre-treatment period.

Adjusted least square means and corresponding 95 % confidence intervals for the change from baseline for each of the treatment groups and the pairwise differences between the subperiods versus the pre-treatment period will be anti-log transformed (into geometric means and geometric mean ratios) and presented together with the p-values corresponding to the tests of difference.

In addition, summary statistics on the changes from the pre-treatment period in in $T_{\max}$, $T_{1/2}$, CL, V_{ss} and the $AUC_{0-\infty}$ ratio of 1-hydroxymidazolam/midazolam will be presented. Data will also be presented graphically, in scatterplots by subperiod, where the subperiod values are plotted against pre-treatment values.

7.11 Safety evaluation

All evaluations of safety data will be performed on the safety analysis set.

7.11.1 Extent of exposure

Exposure to Myrcludex B will be presented for each of the three MXB treatment groups, separately and in total. Summary statistics on the treatment duration, cumulative dose, dose intensity and compliance will be presented, as well as the number and percentage of subjects with at least one injection interruption.

Exposure to tenofovir will be presented for each of the treatment groups, and in total across the three MXB treatment groups. Summary statistics on the duration of exposure will be presented.

7.11.2 Adverse Events

Adverse events will be coded according to MedDRA.

Only treatment-emergent adverse events will be summarised in tables. Pre-treatment serious adverse events will be presented in listings only.

A treatment-emergent adverse event is defined as an event with a time of onset after administration of the first dose of study medication, and a pre-treatment event is defined as an event starting before the first dose. Events starting on the date of the first dose for which the onset time is not known will be considered as treatment-emergent (*i.e.,* the time of onset will be imputed as 23:59).

An overview of all adverse events will be presented, including the number and percentage of subjects with at least one, and the total number, of the following:

- Adverse events
- Serious adverse events
- Adverse events, broken down by severity
- Adverse events, broken down by causality assessment
- Adverse events leading to withdrawal of the study treatment
- Fatal adverse events

The incidence of adverse will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of adverse events as well as the number and percentage of subjects with at least one adverse event within that system organ class or preferred term will be presented. Serious adverse events will be summarised in the same way.

In the same way, the incidence of adverse events broken down by causality assessment, adverse events broken down by severity, and related adverse events broken down by severity will be presented by system organ class and preferred term. Serious adverse events will be summarised in the same way.

All presentations described above will be repeated for the following subsets of adverse events:

- Adverse events started during the treatment period.
- Adverse events started after the end of treatment period, for the subgroup of subjects who attended at least one follow-up visit.

There will also be tables on the most frequently reported adverse events, on system organ class level and on preferred term level. The decision on the frequency cut-off for these tables will be taken during the analysis of the adverse events data, in consultation with the author of the clinical study report, and could be influenced by factors such as the overall number of adverse events, study design, and the nature of the indication. The frequency cut-off should be mentioned in a table note.

7.11.3 Laboratory

For the purpose of summary tables on laboratory test results, any value reported as below the lower limit of quantification or as undetectable will be considered as missing, and any value reported as above the upper limit of quantification will be considered as being equal to the upper limit. In data listings, reported values will be presented.

Summary statistics on the test results and change from baseline, and shift tables on the categorisation of values in relation to the normal range, will be presented by visit for the following parameters:

- **Haematology:** leukocytes [10^9/L] with absolute [10^9/L] and relative [%] differentials: basophils, eosinophils, lymphocytes, monocytes, neutrophils; erythrocytes [10^12/L], haematocrit [%], haemoglobin [g/dL], platelets [10^9/L], reticulocytes [‰]; coagulation panel: prothrombin time [sec], activated partial thromboplastin time [sec].
- **Blood chemistry:** chloride [mmol/L], C-reactive protein [mg/L], albumin [g/L], alkaline phosphatase [U/L], alanine aminotransferase (ALAT) [U/L], aspartate aminotransferase (ASAT) [U/L], creatinine [umol/L], direct (unconjugated) bilirubin [umol/L], phosphate [mmol/L], gamma glutamyl transferase (GGT) [U/L], glucose [mmol/L], lipase [U/L], pancreatic amylase [U/L], potassium [mmol/L], sodium [mmol/L], total bilirubin [umol/L], total cholesterol [mmol/L], total protein [g/L], urea [mmol/L].
- **Blood bile acids:** total bile acids [umol/L].

Urinalysis data will be presented in listings only.

7.11.4 Urine pregnancy test

Urine pregnancy test results (positive/negative) will be presented by visit for female subjects of childbearing potential. The number and percentage of female subjects of childbearing potential will also be presented.

7.11.5 Physical examination

Physical examination data will be summarised by visit for each of the examined body systems (abdomen, general appearance, hair/eyes/ear/nose/throat, heart, lungs, lymph nodes, musculoskeletal, neurological, skin, thyroid, and vascular) as the number and percentage of subjects with normal/ abnormal findings. The shift from baseline will also be presented.

7.11.6 Vital signs

Summary statistics on vital sign parameters (respiration rate, blood pressure, heart rate, and body temperature), body weight and BMI will be presented by visit. For post-baseline visits, the change from baseline will also be summarised.

7.11.7 Electrocardiogram

A frequency table on the overall ECG evaluation (assessment of normality) will be presented by visit. For post-baseline visits, the shift from baseline will also be presented.

7.11.8 Immunogenicity

Summary statistics on the anti-MXB antibodies concentration values and change from baseline will be presented by visit for the three experimental treatment groups. The number and percentage of positive subjects will also be presented.

7.12 Other analyses

Frequency tables, including confidence intervals, on HBeAg laboratory results will be presented by visit, for the subgroup of subjects in the safety analysis set who were HBeAg-positive at screening.

7.13 Changes to planned analysis

7.13.1 HDV RNA levels

Change from baseline in HDV RNA levels at Week 24 and Week 48 was added as a secondary efficacy endpoint.

7.13.2 Combined response

In addition to the analysis at Week 24, as stated in the protocol, it was decided to perform analysis of this secondary endpoint at Week 48 as well.

7.13.3 Development of antibodies to HBsAg

There were no subjects with HBsAg loss, and thus it will not be necessary to analyse anti-HBsAg.

8 Derived variables

8.1 General

8.1.1 Change from baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value.

Percentage change from baseline will be computed as 100 times the change from baseline divided by the baseline value.

8.1.2 Durations

In general, the duration of a time period will be computed as the time in days from the start date to the end date plus 1 day. The duration in weeks is derived by division by 7 days/week.

8.2 Disposition of subjects

A screening failure is defined as a screened but not randomised subject.

8.3 Demographics and baseline characteristics

8.3.1 Age

Age will be computed as the integer part of the time in years between the date of birth and the date the written informed consent was signed, using the SAS function `yrdif()` with the basis parameter set to 'age'. For subjects for whom only the year of birth is collected, age will be computed as the difference between the year the informed consent was signed and the year of birth.

8.3.2 Body mass index

BMI will be computed as the body weight in kg divided by the squared height in metres.

8.4 Efficacy variables

8.4.1 HDV RNA response (primary efficacy variable)

HDV RNA response is defined as HDV negativation (*i.e.,* HDV RNA level of zero) or a decrease by at least 2 (*i.e.,* change from baseline is less than or equal to -2) in log-10 transformed HDV RNA level.

8.4.2 Durability of HDV RNA response

Durability of HDV RNA response is defined as sustained meeting of the response criterion. A categorical variable indicating 'No response', 'Response at Week 24 only' or 'Response at weeks 24 and 48' will be derived.

8.4.3 Combined response

Combined response is defined as fulfilment of both of the following two conditions simultaneously:

- Response, as defined in section 8.4.1.
- Normalisation of ALAT (i.e., ALAT value is within the normal range).

8.4.4 Histological findings

The change from baseline will be categorised as improvement (decrease of at least 1 point), no change or worsening (increase of at least 1 point) for each of the following parameters: HAI, Knodell fibrosis score, Ishak fibrosis score, METAVIR fibrosis stage and METAVIR activity grade.

8.5 Safety variables

8.5.1 Exposure

The Myrcludex B treatment duration (in weeks) will be computed based on the dates of the first and last injections.

The cumulative dose of MXB (in mg) will be computed as the sum of all injected doses of MXB.

The MXB dose intensity (in mg/week) will be computed as the cumulative dose of MXB divided by the duration of exposure to MXB.

Compliance with MXB treatment (in %) will be computed as the ratio of the cumulative dose of MXB to the planned total dose of MXB (planned daily dose multiplied by 24×7 days) multiplied by 100.

The duration of exposure to tenofovir (in weeks) will be computed based on the first date of drug dispensation and the last date of drug return. If the date of last drug return has not been reported, the duration will be considered as missing.

The durations will be computed according to section 8.1.2.

8.5.2 Physical examination

The analysis parameters will be dichotomous variables categorising the examination results as 'Normal' or 'Abnormal' (findings not reported as normal). For examinations reported as not done, the analysis value will be missing.

8.5.3 Immunogenicity

A subject will be considered as positive at a post-baseline visit if there was an at least twofold increase in the concentration of antibodies compared to baseline (*i.e.*, if the ratio to baseline was at least 2).

8.6 Pharmacokinetic variables

8.6.1 Accumulation ratio

The AUC accumulation ratio will be computed as AUC_{0-24} value for subperiod II divided by the AUC_{0-24} value for subperiod I.

The $C_{\max}$ accumulation ratio will be computed analogously.

8.6.2 AUC ratio

The $AUC_{0-\infty}$ ratio of 1-hydroxymidazolam/midazolam will be computed as the $AUC_{0-\infty}$ value for 1-OHMDL divided by the $AUC_{0-\infty}$ value for MDZ.

8.6.3 Dose-normalisation

A dose-normalised parameter is defined as a parameter divided by the daily dose.

9 References

1. **ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials E9. February 1998.**

2. ICH Harmonised Tripartite Guideline for Structure and Content of Clinical Trial Reports E3. November 1995.

3. Clinical Study Protocol MYR 202, country-specific version 3.0 (Germany), 2017-12-25.

4. Clinical Study Protocol MYR 202, version 7.0, 2017-09-28.

10 Signoff

We have read this SAP for the MYR 202 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

Klaus Junge, External Biostatistician

SIGNATURE AND DATE

PCG Clinical Services SAP Author: Fredrik Thunarf, Senior Biostatistician

SIGNATURE AND DATE

Appendix A: Schedule of assessments

Table 1. Schedule of assessments (excluding the pre-treatment period)

	Screen.	Rand.	Treatment period								Follow-up period				
Visit	01	1	2	3	4	5	6	7	8	9	FU1	FU2	FU3	FU4	FU5
Week			W1	W2	W4	W8	W12	W16	W20	W24	W25	W26	W28	W36	W48
Study day[1]	– -1	1	8	15	28	56	84	112	140	168	175	182	196	252	336
Efficacy assessments															
HDV RNA		X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg		X			X	X	X	X	X	X			X	X	X
HBV DNA		X					X			X				X	X
Serum marker for fibrosis		X								X					X
Liver biopsy[2]	X									X					
Transient elastometry	X									X					
HBV/HDV genotyping		X													
Resistance testing		X								X					
Pharmacokinetics															
PK sampling, main study[3]		X			X	X	X	X	X	X					
PK sampling, sub-study[4]		X		X											
Safety assessments															
Haematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[5]	X	X	(X)	(X)	(X)	(X)	X	(X)	(X)	X	(X)	(X)	(X)	(X)	X
Serum total bile acids		X	X	X	X	X	X	X	X	X	X	X			X
Serum bile acids		X	X	X	X	X	X	X	X	X	X	X			X

[1] Visit windows of ±2 days apply for the treatment period. For Germany, the window is ±2 days for follow-up visits 1, 2 and 5, and ±5 days for follow-up visits 3–4, whereas windows of ±3 days apply to all follow-up visits for Russia.
[2] Can be replaced with transient elastometry, by investigator's decision.
[3] Sampling will be done at 1 hour post-dose.
[4] PK sampling is done at Day 1 and 14, pre-dose and at timepoints 0:05, 0:15, 0:30, 1:00, 1:30, 2:00, 2:30, 4:00, 6:00, 10:00, 14:00, 24:00 after dosing
[5] At visits indicated by '(X)', only the abbreviated blood chemistry panel (albumin, total bilirubin, creatinine, GGT, ALAT, ASAT, phosphate, lipase and pancreatic amylase) is analysed.

	Screen.	Rand.	Treatment period								Follow-up period				
Visit	01	1	2	3	4	5	6	7	8	9	FU1	FU2	FU3	FU4	FU5
Week			W1	W2	W4	W8	W12	W16	W20	W24	W25	W26	W28	W36	W48
Study day[1]	– -1	1	8	15	28	56	84	112	140	168	175	182	196	252	336
Urine analysis	X	X			X		X			X				X	X
Urine pregnancy test[6]	X	X			X	X	X	X	X	X					
Physical examination	X	X					X			X					X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and body weight[7]	X	X					X			X					X
12-lead ECG	X						X			X					X
Immunogenicity		X					X			X				X	X
Other assessments															
HBeAg, anti-HBeAg antibodies[8]	X									(X)					(X)

Table 2. Schedule of assessments (pre-treatment period)

Visit	02	03	04
Study day	-84	-28	-14– -1
Efficacy assessments			
HDV RNA, HBsAg, HBV DNA	X		
HBV/HDV genotyping	X		
Resistance testing	X		
Pharmacokinetics			
PK sampling, sub-study[9]			X
Safety assessments			
Haematology, coagulation	X		X
Blood chemistry[10]	X		X

[6] Only for women of child-bearing potential.
[7] Height is collected at screening only.
[8] Assessments at Week 24 and Follow-up visit 5 only for subjects who were HBeAg-positive at screening.
[9] PK sampling is done at Day -13, pre-dose and at timepoints 0:05, 0:15, 0:30, 1:00, 1:30, 2:00, 2:30, 4:00, 6:00, 10:00, 14:00, 24:00 after dosing.
[10] Only the abbreviated blood chemistry panel (albumin, total bilirubin, creatinine, GGT, ALAT, ASAT, phosphate, lipase and pancreatic amylase) is analysed during the pre-treatment phase.

Visit	**02**	**03**	**04**
Study day	-84	-28	-14– -1
Urine pregnancy test			X
Physical examination	X		X
Vital signs and body weight	X		X

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.

Patient No.: _____
Patient's initials: _____

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.

Patient No.: _____
Patient’s initials: _____

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.

Patient No.: _____
Patient's initials: _____

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.

Patient No.: _____
Patient’s initials: _____

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.

Patient No.: _____
Patient's initials: _____

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.

Patient No.: _____
Patient's initials: _____

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;

Patient No.: _____
Patient's initials: _____

- 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.

Patient No.: _____
Patient's initials: _____

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.

Patient No.: _____
Patient's initials: _____

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-

Patient No.: _____
Patient's initials: _____

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.: _____
Patient's initials: _____

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.

Patient No.: _____
Patient’s initials: _____

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.

Patient No.: _____
Patient's initials: _____

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.

Patient No.: _____
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: