CLINICAL STUDY PROTOCOL

Study title:	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent
Sponsor:	Hepatera LLC, 12/19 b.1 Verkhnyaya Radischevskaya str., 109240 Moscow, Russia
Protocol Number:	MYR 203
Protocol version and date:	Final version 7.0 dated September 24, 2019

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SIGNATURE PAGE 1 (STUDY SPONSOR)

The Clinical Study as per Protocol: A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent.
The signatories of the document confirm the approval of the Protocol and guarantee that the present study will be conducted in accordance with all the requirements of this Protocol.

Yana Anatolievna Deloveri,
General Manager
Hepatera LLC

Signature _____ Date: _____/_____/_____
Day/month/year

Alexander Alexandrov,
Medical director
Hepatera LLC

Signature _____ Date: _____/_____/_____
Day/month/year

SIGNATURE PAGE 2 (PRINCIPAL INVESTIGATOR)

The Clinical Study as per Protocol: A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent.

I have read all the pages of this clinical study protocol, sponsored and I agree that it contains all the information needed to perform this study. I will conduct the study in accordance with all the requirements of the Protocol, including all data protection guidelines, in accordance with the ICH GCP, the ethical principles of the World Medical Association Declaration of Helsinki and local regulatory requirements.

Clinical Center Name _____
_____

Clinical Center Address _____
_____

Principal Investigator _____
(full name, title) _____

Signature: _____ Date: _____/_____/_____
day/month/year

GENERAL INFORMATION

Study sponsor:	Yana Anatolievna Deloveri, General Manager Hepatera LLC, 12/19 b.1 Verkhnyaya Radischevskaya str., 109240 Moscow, Russia
Central laboratories *(Evaluation of pharmacokinetics, evaluation of immunogenicity, resistance, NTCP polymorphism, virology analysis, HBV, HDV genotyping, safety parameters analysis, liver biopsy study: pathomorphological, immunohistochemical, and also the examination of intrahepatic parameters, alfa-fetoprotein blood test, blood test for TSH and T_4, hematology, blood chemistry, urinalysis):*	The information will be presented in the investigator's/organization's file

All specialists/organizations involved in the study and not mentioned in this section will be listed in a separate list in accordance with the established procedure. The current version of the list will be presented in the main study archive, as well as in the archives of each study center.

List of medical sites where the clinical study No. MYR 203 (including pharmacokinetic study) will be performed:

Clinical Centre 1	State-Financed Health Institution of Moscow Oblast "Moscow Regional Research Clinical Institute n.a. M.F. Vladimirskiy" 129110, Moscow, 61/2 Schepkina str.
Principal Investigator	Pavel Olegovich Bogomolov
Clinical Centre 2	State-Financed Health Institution of the Stavropol Territory "Stavropol Regional Clinical Center of the specialized types of medical care" 355030, Stavropol, 1 Semashko str.
Principal Investigator	Natalia Ioganovna Geyvandova
Clinical Centre 9	State-Financed Health Institution "Specialized Clinical Infectious Diseases Hospital" of the Ministry of Health of the Krasnodar Territory, 350015, Krasnodar, 204 Sedina str.
Principal Investigator	Vladimir Nikolaevich Gorodin
Clinical Centre 12	Federal State-Funded Educational Institution of Higher Vocational Education "South Ural State Medical University" of the Ministry of Health of the Russian Federation 454052, Chelyabinsk, 64 Vorovskogo At the premises of the Clinics of the Federal State-Funded Educational Institution of Higher Vocational Education "South Ural State Medical University" of the Ministry of Health of the Russian Federation 454052, Chelyabinsk, 2 Cherkasskaya str.
Principal Investigator	Olga Igorevna Sagalova
Clinical Centre 17	Medical company "Hepatologist" Ltd. 443063, Samara, 36A Serdobskaya
Principal Investigator	Vyacheslav Gennadievich Morozov
Clinical Centre 18	Federal Budget Institution of Science "Central Research Institute of Epidemiology" of The Federal Service on Customers' Rights Protection and Human Welfare 111123, Russia, Moscow, 3a Novogireevskaya str.
Principal Investigator	Vladimir Petrovich Chulanov
Clinical Centre 19	"Clinic of Modern Medicine HD" Limited Liability Company 121293, Moscow, 2 Victory Square, bld. 1
Principal Investigator	Tatiana Vladimirovna Stepanova

LIST OF ABBREVIATIONS

CTCAE	Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practice
HBV	Hepatits B virus
HDV	Hepatits D virus
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intention-to-treat
MedDRA	The Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NTCP	Sodium taurocholate co-transporting polypeptide
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
BMI	Body Mass Index
CRF	Case report form
NCSD	Non-clinically significant deviations
AR	Adverse reaction
AE	Adverse event
PCR	Polymerase chain reaction
SAE	Serious adverse event
T4	Thyroxine
TSH	Thyroid-stimulating hormone
PK	Pharmacokinetics
ECG	Electrocardiogram

SYNOPSIS

Study title	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent.
Study phase	Phase II
Protocol number	MYR 203
Study drug	Myrcludex B (MXB), lyophilisate for solution for subcutaneous injection, 2 mg/vial, 5 mg/vial. The drug is administered subcutaneously, in the doses of 2 mg, 5 mg or 10 mg every 24±1 hours (once a day for groups B-E) or every 12±1 (twice a day, group F).
Reference Product	Peginterferon alfa-2a (PEG-IFN alfa-2a), solution for subcutaneous injection, 180 mg/0.5 mL (unit-dose syringe/autoinjector) manufactured by F. Hoffmann-La Roche Ltd., Switzerland The drug is administered subcutaneously, once a week at a dose of 180 μg.
Product in combination therapy for group F	Tenofovir disoproxil fumarate (Tenofovir), film-coated tablets, 300 mg, manufactured by Gilead Sciences (Ireland). Should be administered orally, once daily, 300 mg
Study purpose	The purpose of this clinical study is to investigate the efficacy and safety of the monotherapy with Myrcludex B, the combination of Myrcludex B and the peginterferon alfa-2a (PEG-IFN alfa-2a) and in combination with Tenofovir as compared to the monotherapy with peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent.
Study Objectives	*Primary objective:* • To Investigate the efficacy of Myrcludex B in monotherapy in combination with PEG-IFN alfa-2a and with Tenofovir as compared with PEG-IFN alfa-2a monotherapy, based on the achievement of undetectable viral load at the end of follow-up period: 6 months (24 weeks) after the end of treatment. *Secondary objectives:* • To investigate the efficacy of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir as compared with monotherapy with PEG-IFN alfa-2a, based on the secondary efficacy endpoints. • To investigate the safety of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and in combination with Tenofovir compared with PEG-IFN alfa-2a monotherapy. • To investigate the pharmacokinetics of Myrcludex B in monotherapy and when administered in combination with PEG-IFN alfa-2a and in combination with Tenofovir. • To investigate the immunogenicity of Myrcludex B
Planned number of patients	Screened: 123 patients Randomised: 90 patients
Study design and methodology	This study is a multicenter, open-label, randomized, comparative, controlled, parallel-arm phase II study. The study will be performed in Russia. The study objective is to investigate the efficacy and safety of the monotherapy with Myrcludex B and the combination of Myrcludex B and the peginterferon alfa-2a and also Myrcludex B + Tenofovir as compared to the monotherapy with peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent. In the course of the study, it is also planned to investigate the immunogenicity of Myrcludex B and the

	pharmacokinetics of the drug when administered alone and in combination with PEG-IFN alfa-2a and in combination with Tenofovir. It is planned that 123 patients will be screened and 90 of them will be randomized into 6 treatment groups in a 1:1:1:1:1:1 ratio: • Arm A (n=15): PEG-IFN alfa-2a 180 μg during 48 weeks • Arm B (n=15): Myrcludex B 2 mg + PEG-IFN alfa-2a 180 μg during 48 weeks • Arm C (n=15): Myrcludex B 5 mg + PEG-IFN alfa-2a 180 μg during 48 weeks • Arm D (n=15): Myrcludex B 2 mg during 48 weeks. • Arm E (n=15): Myrcludex B 10 mg (10 mg once a day) + PEG-IFN alfa-2a 180 μg during 48 weeks • Arm F (n=15): Myrcludex B 10 mg (5 mg twice a day) + Tenofovir during 48 weeks After the end of the treatment period, there will be a follow-up period of 24 weeks. Patients from group F will continue Tenofovir treatment during follow-up period. It is planned to perform a pharmacokinetic study of Mircludex B during the study: 1. Pharmacokinetic substudy (PK-substudy) 10 patients of groups B and C (20 patients in total) are planned to be enrolled. Blood samples for estimation of drug concentration will be collected at Days 1, 2 and 14, 15 in the following timepoints: • Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection. • Day 2 – in 24:00 (hh:min) after the drug injection. • Day 14 – before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection. • Day 15 – in 24:00 (hh:min) after the drug injection. 2. Pharmacokinetic main study (PK-main study). For a more precise investigation of the possible study drug accumulation in all patients of each Myrcludex B treatment arm, blood sampling points for the pharmacokinetic study are assigned: week 4, 8, 12, 16, 20, 24, 28, 32, 40, 48[1] (in 1hour +/-15 min after the drug injection). For the patients not enrolled into the pharmacokinetic substudy, a sampling point at a randomization visit (in 1hour +/-15 min after the first drug injection) is introduced. 3. Pharmacokinetic study in group F (the second part of the study) 10 patients of group F will take part in the study. Blood samples for estimation of drug concentration will be collected at Days 1, 2 and 14, 15 in the following timepoints: • Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min) after the drug injection. Blood sampling <u>in 12 hours</u> after the first injection should be performed <u>before the second injection</u> of MXB. • Day 2 – in 12:00 (hh:min) after the second injection on Day 1 Blood sampling should be performed <u>before the third injection</u> of Myrcludex B. • Day 14 - before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min)

	after the drug injection. Blood sampling in 12 hours should be performed before next injection of MXB. • Day 15 - in 12:00 (hh:min) after the second injection on Day 14 Blood sampling should be performed before next injection of Myrcludex B. The study plan includes a screening period – maximum 4 weeks, treatment period - 48 weeks, follow-up period - 24 weeks. The total number of visits is 19 (screening visit, 13 visits of the treatment period, 5 visits of the follow-up period). Patients participating in the pharmacokinetic substudy (PK-substudy and pharmacokinetic study in group F) will be hospitalized before the start of study treatment and will stay in the hospital (day-stay or 24-hour) during Days 1, 2, 14, 15. Other visits of pharmacokinetics (PK-main study) will be done outpatiently. Patients not participating in the pharmacokinetic substudy (PK-substudy and pharmacokinetic study in group F) during the whole study period will receive treatment and have scheduled observations outpatiently. The study includes 2 phases: I phase – patients enrollment in groups A – D (Protocol version 1.0, dd. 16.12.2015, Protocol version 1.1, dd. 16.03.2016, Protocol version 2.0, dd. 31.05.2016, Protocol version 3.0, dd. 23.08.2017) II phase - patients enrollment in groups E – F (Protocol version 4.0, dd. 19.01.2018)
Efficacy criteria	*Primary efficacy endpoint:* • Proportion of patients with a negative PCR result of HDV RNA (undetectable HDV RNA level) at week 72 (end of the follow up period) *Secondary efficacy endpoints:* • Proportion of patients with a negative PCR result of HDV RNA (undetectable HDV RNA level) at weeks 24 and 48 • Proportion of patients with HDV RNA response (decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) at weeks 24, 48 and 72 • Proportion of patients with ALT normalization in weeks 24, 48 and 72 • Proportion of patients with combined treatment response (result of HDV RNA negativation and ALT normalization) at weeks 24, 48 and 72 • Proportion of patients with a combined response to therapy ((decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) and normalization of ALT) at weeks 24, 48 and 72 • Proportion of patients with HBsAg response (HBsAg negativation or >1 log10 IU/mL decline) at weeks 24, 48 and 72 • Proportion of patients with HBsAg negativation with the appearance of anti-HBsAg antibodies and without it at weeks 48 and 72 • Proportion of patients with a negative PCR result of HBV DNA at weeks 24, 48 and 72 • The intensity of liver fibrosis based on results of transient elastometry at weeks 48 and 72 • Changes in the results of liver biopsy before and after the treatment As part of the study of efficacy, HBV, HDV genotyping, resistance assay and NTCP polymorphism will be performed additionally.

Safety criteria	• Adverse events, serious adverse events • Physical examination • Ophthalmological examination • Vital signs • 12-lead ECG. • Hematology • Blood chemistry • Total bile acids • Coagulogram • Urinalysis • Blood test for Blood test for TSH, T4
Immunogenicity	Assessment of immunogenicity will be performed in the arms of patients administered the study drug (Arms B - F). Antibodies to Myrcludex B will be assessed during the treatment period (drug injection pre-dose [Day 1], weeks 12, 24, 48) and during follow-up period (4, 12, 24 weeks after the end of treatment).
Pharmacokinetic parameters	The following PK parameters will be assessed using the non-compartmental methods: • C_{max} – maximum concentration • T_{max} – time of maximum concentration • K_{el} – elimination rate constant • $T_{1/2}$ – elimination half-life • CL/F – total clearance • AUC_{0-t} – area under the curve "drug concentration-time" from time 0 to the sampling time (t) of the last sample • $AUC_{0-\infty}$ – area under the curve "drug concentration-time" from time 0 to ∞
Inclusion Criteria	To be included in the study, patients must meet all of the following inclusion criteria: 1. Signed informed consent form. 2. Males and females 18 to 65 years of age (inclusively). 3. Patients with chronic hepatitis B (HBeAg-positive or negative) and HBsAg-positive for at least 6 months prior to Screening. 4. Positive for anti-HDV antibodies for at least 6 months prior to Screening. 5. HDV RNA-positive at Screening. 6. ALT more than or equal 1 x ULN and less than 10 x ULN 7. The patient agrees to use adequate method of contraception during the study, starting from the time of Informed Consent signing and until completion of Follow-up Period.
Exclusion criteria	Patients cannot be enrolled into the study if they meet any of the following criteria: 1. Intolerance or hypersensitivity to the active ingredient or other components of the study drug Myrcludex B. 2. Intolerance or hypersensitivity to interferons alfa, genetically engineered E.coli medications, polyethylene glycol or other components of peginterferon alfa-2a. 3. Previous treatment with Myrcludex B (patients with previous exposure to interferon are eligible). 4. Therapy with antiviral drugs for chronic viral hepatitis B with delta-agent over the previous 6 months. 5. Therapy with anti-tumor agents (including radiotherapy) or immunomodulatory medications (including systemic glucocorticoids)

	over the previous 6 months. 6. The following laboratory test results at Screening: a) Hemoglobin less than 100 g/L b) Leucocytes less than 3000/μL c) Neutrophils less than 1500/μL d) Platelets less than 90000/μL e) Serum creatinine more than 1.5 x ULN. 7. Total bilirubin more than 34.2 μM/L. Patients with higher total bilirubin may be enrolled upon consultation with the study Medical Monitor, if there is clear evidence that the elevated bilirubin is caused by Gilbert's syndrome. 8. Current or previous decompensated liver disease, including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites, and esophageal varices hemorrhage; Child-Pugh score of B/C or more than or equal 6 points. 9. HCV or HIV coinfection (patients with anti-HCV antibodies and no HCV RNA at Screening are eligible). 10. Hepatocellular carcinoma. 11. Signs of drug- or alcohol-induced liver disease or any other medical conditions associated with chronic liver disease (e.g. autoimmune hepatitis, hemochromatosis, thalassemia, alcoholic hepatitis, toxic liver disease). 12. Contraindications for liver biopsy. 13. Concurrent malignancy (current diagnosed or suspected malignancy; risk of a previous malignancy recurrence). 14. Severe decompensated cardiovascular diseases, including unstable and poorly controlled conditions, over 6 months before Screening. 15. History of poorly controlled thyroid conditions or clinically significant signs of thyroid dysfunction at Screening. 16. Previous or current severe renal failure or significant renal dysfunction at Screening. 17. Previous or current chronic pulmonary disease with respiratory distortion at Screening. 18. Previous or current severe retinopathy, significant ophthalmology disorders associated with diabetes mellitus or hypertension. 19. Previous or current severe psychiatric disorders at Screening (e.g. severe depressions, suicidal attempts, severe neuroses or cognitive disorders). 20. Previous or current endocrine disorders (hypoglycemia, hyperglycemia, diabetes mellitus) that are not adequately controlled at Screening. 21. History of visceral organ transplantation. 22. Signs of drug and/or alcohol dependence (80 g of alcohol/day for men and 40 g of alcohol/day for women) within 1 year before Screening. 23. History of immune disorders (e.g. idiopathic thrombocytopenic purpura, lupus erythematosus, sclerodermia, severe psoriasis, rheumatoid arthritis). 24. Need for concomitant use of glucocorticoids or myelotoxic agents. 25. Participation in another clinical study within 30 days prior to enrollment into this study. 26. Pregnant or breast-feeding females. 27. Any other condition that, in the opinion of Investigator, precludes the patient from taking part in this study.

Duration of the study for each patient	The total duration of the patient's participation in the study is up to 76 weeks: • The screening period is up to 4 weeks. • The treatment period is 48 weeks. • The follow-up period is 24 weeks. The total number of visits is 19 (screening visit, 13 visits of the treatment period, 5 visits of the follow-up period).
Blinding procedure	Not applicable. The study is an open-label one.
Randomization	Randomization will be performed in a ratio of 1:1:1:1:1:1 using the IWRS (Interactive Web Response System).
Sample size justification	This clinical study is an exploratory, controlled, parallel-arm study with a control arm and five test arms to demonstrate the differences in monotherapy with the study drug, the combination of the study drug and standard treatment, and combination of the study drug and Tenofovir versus the standard treatment. The study results will be used to select the optimal treatment regimen with Myrcludex B in the next phase. The primary endpoint (negative result of PCR on HDV RNA at week 72) was used to justify the minimum size of treatment arms. The calculation of the sample size was carried out according to the method described in the book by Chow Sh.-Ch., Sample Size Calculations in Clinical Research [Chow Sh.-Ch., Shao J., Wang H., 2008], by means of the Trial Size package for the R programming language. The results of the previous MYR 201 substudy, data at the 24 treatment week were used: in treatment group with study drug (peginterferon alfa-2a 180 μg for 48 weeks), the proportion of participants with negative PCR result of HDV RNA was 29% (2 of 7 participants), in treatment group with combination therapy (Myrcludex B 2 mg + peginterferon alfa-2a 180 μg for 24 weeks, followed by peginterferon alfa-2a 180 μg for 24 weeks), the proportion of participants with a negative PCR result of HDV RNA was 71% (5 of 7 participants). It is expected that 5 tested groups will demonstrate the efficacy comparable to the results of MYR201 substudy. Under such assumptions and a given critical value of the significance level of 0.1, the arm size n = 15 will make it possible to reach the power of a study at the level more than 60%. Considering the exploratory nature of the study, the calculated number of arms can be considered sufficient to obtain conclusions about the optimal dosing schedule to be used in clinical studies of the following phases.
Interim data analysis	The interim analysis will be performed when efficacy and safety data are available after the end of follow up period of participants in the first phase of the clinical study (Arms A-D). Considering the fact that the study is exploratory, there is no provision for adjusting the level of significance due to intermediate analysis. The premature termination of the study based on the results of the interim analysis is not planned.

Table 1 Flow Chart

Procedures	**SCR**	**Treatment period**													**Follow-up period**				
Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/EOT**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5/EOF**
Week (W)	**W-4 -1**	**W 0**	**W 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W1 6**	**W2 0**	**W2 4**	**W2 8**	**W3 2**	**W4 0**	**W48**	**EOT+ W2**	**EOT+ W4**	**EOT+ W8**	**EOT+ W12**	**EOT+ W24**
Day	**–28 - 1**	**1**	**8± 2**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	**113 ±2**	**141 ±2**	**169 ±2**	**197 ±2**	**225 ±2**	**281 ±2**	**337+2**	**351±3**	**365±3**	**393±3**	**421±3**	**505±3**
Informed consent	X																		
Demography, medical history	X																		
Physical examination	X						X			X				X					X
Body height, weight, BMI[1]	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	X
Urine pregnancy test	X									X				X					
Urine drug screening	X																		
Alcohol-breath test	X																		
Alpha-fetoprotein blood test	X																		
Blood test for HIV (HIV antibodies)	X																		
Blood test for Hepatitis C (anti-HCV antibodies, HCV RNA)[2]	X																		
Inclusion/Exclusion criteria	X																		
Randomization[3]	X	X																	
Anti-HDV antibodies	X																		
HBeAg, anti-HBeAg antibodies[4]	X									X				X					X
HBsAg quantification	X[5]																		

[1] Body height, weight, BMI are measured at screening; only weight is evaluated in the course of the study.
[2] Evaluation of HCV RNA is performed only if there is a positive result of anti-HCV antibodies.
[3] Randomization should be performed after confirmation of patient`s eligibility according to inclusion/exclusion criteria within Day-3 – Day -1 of the study
[4] In the course of the study, a re-evaluation of HBeAg, anti-HBeAg antibodies is performed only in patients with positive results in screening.
[5] Local laboratory, to confirm participation in the study

Procedures	**SCR**	**Treatment period**													**Follow-up period**				
Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/EOT**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5/EOF**
Week (W)	**W-4 -1**	**W 0**	**W 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W1 6**	**W2 0**	**W2 4**	**W2 8**	**W3 2**	**W4 0**	**W48**	**EOT+ W2**	**EOT+ W4**	**EOT+ W8**	**EOT+ W12**	**EOT+ W24**
Day	**–28 - 1**	**1**	**8± 2**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	**113 ±2**	**141 ±2**	**169 ±2**	**197 ±2**	**225 ±2**	**281 ±2**	**337+2**	**351±3**	**365±3**	**393±3**	**421±3**	**505±3**
Anti-HBsAg antibodies	X[6]													X[7]					X[8]
HDV RNA[9]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA (quantification)		X		X	X		X			X		X		X				X	X
HBsAg (quantification)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulogram	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood bile acids		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood test for TSH, T4	X						X			X				X					
Urinalysis	X	X			X	X	X	X	X	X	X	X	X	X					X
ECG	X						X			X				X					X
Abdominal ultrasound	X													X					X
Transient elastometry (Fibroscan)	X													X					X
Liver biopsy	X													X[10]					X[11]
Evaluation of immunogenicity		X					X			X				X		X		X	X
HBV, HDV genotyping		X																	
NTCP polymorphism (frozen blood clot)		X																	

[6] Local laboratory, to confirm participation in the study
[7] At the end of the study, the determination of anti-HBsAg antibodies will be performed in a central virology laboratory using the appropriate archival samples (for the HBsAg determination) in those patients for whom a negative result of the HBsAg quantification was obtained at Week 48.
[8] At the end of the study, the determination of anti-HBsAg antibodies will be performed in a central virology laboratory using appropriate archival samples (for HBsAg determination) in those patients for whom a negative result of the HBsAg quantification was obtained at Week 72.
[9] At screening – a blood sample at room temperature, later – frozen blood samples.
[10] It shall be performed within ± 7 days from the date of the visit, only for groups D and F
[11] Should be performed only for groups A, B, C, E within ± 7 days from the date of the visit

Procedures	**SCR**	**Treatment period**												**Follow-up period**				
Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/EOT**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5/EOF**
Week (W)	**W-4 -1**	**W 0**	**W 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W1 6**	**W2 0**	**W2 4**	**W2 8**	**W3 2**	**W4 0**	**W48**	**EOT+ W2**	**EOT+ W4**	**EOT+ W8**	**EOT+ W12**	**EOT+ W24**
Day	**–28 - 1**	**1**	**8± 2**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	**113 ±2**	**141 ±2**	**169 ±2**	**197 ±2**	**225 ±2**	**281 ±2**	**337+2**	**351±3**	**365±3**	**393±3**	**421±3**	**505±3**
Resistance assay (frozen samples)		X												X[12]					
Drug dispensing		X			X	X	X	X	X	X	X	X	X	T[13]	T	T	T	T	
Filling the patient diary in		X	X	X	X	X	X	X	X	X	X	X	X	X	T[14]	T	T	T	T
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic main study (PK-main study, for patients in arms B - F)		X			X	X	X	X	X	X	X	X	X	X[15]					
Pharmacokinetic substudy (PK-substudy), for 10 patients from group B and 10 patients from group C		Days 1, 2, 14, 15 (hospitalization to the study center)[16]																	
Pharmacokinetic study for group F		Days 1, 2, 14, 15 (hospitalization to the study center)[16]																	
Ophthalmological examination[17]	X	*If there are any indications for the examination*																	

[12] In case of a patient's drop out of the study before the end of the treatment period, a resistance analysis is performed during the Premature Dropout Visit.
[13] "T" means Tenofovir dispensing during follow-up period
[14] "T" means filling the data into Patient's diary regarding Tenofovir in the follow-up period
[15] Only for patients from groups E - F
[16] Patients from groups B, C and F participated in the PK sub-study are not allowed to deviate in the schedule of visits in Day 1 and 2. Sample collection for PK analysis should be performed before and after the first injection of Myrcludex B. The second part of PK sub-study could be performed within ±1 day (Days 15 – 16)
[17] Ophthalmological examination during screening is performed for patients with mild and moderate retinopathy in history to evaluate baseline ocular changes.

Procedures	SCR	Treatment period													Follow-up period				
Visits		1	2	3	4	5	6	7	8	9	10	11	12	13/EOT	FU1	FU2	FU3	FU4	FU5/EOF
Week (W)	W-4 -1	W 0	W 1	W 2	W 4	W 8	W 12	W16	W20	W24	W28	W32	W40	W48	EOT+ W2	EOT+ W4	EOT+ W8	EOT+ W12	EOT+ W24
Day	–28 - 1	1	8± 2	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±2	197 ±2	225 ±2	281 ±2	337+2	351±3	365±3	393±3	421±3	505±3

SCR: screening; W: week; FU: follow up; EOT: End of treatment; EOF: End of follow up, BMI: body mass index, EKG: electrocardiography, TSH: thyroid-stimulating hormone, T4: thyroxine

1 INTRODUCTION

1.1 Chronic viral hepatitis B with delta agent

Chronic viral hepatitis B with Delta Agent (ICD-10: B 18.0) is an inflammatory liver disease induced by hepatitis D virus that requires HBsAg replication. Hepatitis D virus (HDV) is a hepatotropic virus with a small RNA genome, which also contains HDV antigen. HDV is necessarily associated with infection with the hepatitis B virus (HBV), since HDV ribonucleoprotein is packaged in HBsAg. The HDV genome is a single-stranded RNA with 1680 bases that is historically homogeneous with viroids or with RNA satellite viruses affecting plants [20]. HDag (hepatitis delta virus antigen) consists of 2 isoforms - a small 24 kD protein required for replication, and a larger 27 kD protein needed to form a virion [23]. There are eight genotypes of HDV, where genotype-1 is the most widespread in the world and in Europe [18].

Hepatitis D virus is a highly pathogenic virus inducing acute and chronic hepatic injury. Although cases of the benign disease have been described [19], a progressive hepatic disorder leading to compensated or decompensated cirrhosis usually develops in patients with chronic viral hepatitis B with delta-agent. There is evidence in the literature that unlike HBV, HDV can lead to direct cytotoxicity, which can lead to an acceleration of the fibrosis process [3, 14]. Although the immune system plays an important role in the eradication of infected hepatocytes; the level of HDV viremia has no direct relationship with histological changes [29]. There are no histological signs that make it possible to distinguish chronic viral hepatitis B with delta agent from other forms of viral hepatitis. The biopsy materials taken from patients with chronic viral hepatitis B with delta-agent have no signs of portal and periportal inflammation, fragmentary necrosis, often accompanied by fibrosis and cirrhosis. There are pronounced intralobular mononuclear cell infiltration and degenerative changes of hepatocytes [23]. The clinical events of chronic viral hepatitis B with delta-agent can be acute or fulminant, a chronic infection can lead to asymptomatic carriage and progress to chronic liver disease rapidly.

Chronic viral hepatitis B with delta-agent develops in 70-90% of patients with viral hepatitis B with HDV superinfection. The hepatic injury associated with HDV has a more progressive course, compared to chronic hepatitis B, and can lead to cirrhosis in 10-15% of patients in a period of 2 years [28]. Chronic viral hepatitis B with delta-agent is the most severe form of viral hepatitis in humans [25], accompanied by progression of hepatic injury, development of cirrhosis and decompensation [21, 25].

In a study performed with a cohort of patients who had been observed for a long time in a specialized center, it was shown a clear trend to decrease survival in HBeAg-negative patients with HDV compared to patients with HBV-monoinfection [16]. In HDV endemic regions, liver disease is a serious medical problem. A study, performed in Italy in 1987, found the presence of anti-HDV antibodies in 40% of patients with cirrhosis. Despite the fact that in 2000 their portion has reduced to 11% [6], HDV infection still represents a significant public health problem. In a long-term study, it was shown that 20% of patients with chronic viral hepatitis B with delta-agent develop an adverse event associated with liver injury within on an average of 4 years. During the same period, only 8.5% of patients with HBV monoinfection develop such events [17]. Initially, cirrhosis was diagnosed in 19.8% of patients from this cohort versus 7.3% of patients with chronic hepatitis B. HDV caused the death of 60% of patients participated in the 28-year study performed in Italy [22]. Co-infection with HDV is associated with a faster progression to fibrosis and cirrhosis, an earlier onset of hepatic complications and an increased probability of liver transplantation [2, 11]. Liver cirrhosis and cancer develop 10-15 years earlier in patients with co-infections with HBV/HDV, and a 5-year mortality of patients with co-infection is twice as high as that of patients with monoinfection with HBV [4]. Chronic HDV infection causes cirrhosis and hepatocellular carcinoma with an average annual rate of 4% and 2.8%, respectively [22].

On average, 5-10% of HBsAg-positive patients undergoing screening in specialized centers in Europe have a positive HDV test result. The number of patients with chronic viral hepatitis B with delta-agent in the EU is estimated to be 145,000 people. Given the total population of the EU is 505,665,700 people (2013), the estimated prevalence rate of HDV among residents of the EU countries, under the given assumptions (95% confidence interval), is 1.6 and 4.7 per 10,000 people, respectively. The prevalence of the disease is below the threshold for assigning the drug the orphan product designation, which is 5 cases per 10,000 people.

Data on the prevalence of HDV in the United States are very limited. In a recent study that evaluated the highly specific center's database, the prevalence rate of HDV among HBsAg carriers was fixed at 8% [8]. 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 [13]. 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 chronic viral hepatitis B with delta-agent in the US is 63,800 people (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 [1, 15]. Antiviral drugs that are effective in the treatment of HBV are ineffective in the treatment of HDV [11].

Efficacy and safety of peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent
The role of pegylated interferon alfa-2a in the treatment of chronic viral hepatitis B with delta-agent was studied in two recently performed studies HIDIT-1 and HIDIT-2.
Study HIDIT-1 [27]
This was a randomized, controlled study on the efficacy and safety of a 48-week treatment with peginterferon alfa-2a 180 μg weekly + adefovir 10 mg daily (PA) versus monotherapy with peginterferon alfa-2a + placebo (P) and adefovir + placebo (A). A total of 90 patients (n=31 [pa], n=29 [P], n=30 [A]) participated in the study. Upon the end of treatment, a follow-up period of 24 weeks followed. The efficacy evaluation criteria included clearance of HDV RNA, ALT normalization, decline in HBsAg level.
Based on the results of the study, the primary endpoint –ALT normalization and negative PCR result of HDV RNA at week 48 – was achieved in 2 (7%, ITT) patients receiving peginterferon alfa-2a + adefovir, and 2 (7%, ITT) patients receiving monotherapy with peginterferon alfa-2a; the primary endpoint was not achieved in the patient arm receiving monotherapy with adefovir. At week 48, a negative PCR result of HDV RNA was observed in 7 (7/31, 23%) patients of the first arm (PA), 7 (7/29, 24%) patients of the second arm (P) and in none patient of the third arm (A) ($p = 0.006$ for the comparison of PA and A groups, $p = 0.004$ for the comparison of P and A arms).
The efficacy of treatment with peginterferon alfa-2a persisted for a 24-week follow-up period: at week 72, a negative PCR result of HDV RNA was observed in 8 (26%) patients of the peginterferon alfa-2a + adefovir (PA) arm, 9 (31%) patients in the peginterferon alfa-2a (P) arm and none of the adefovir arm (A).
When evaluating the peginterferon alfa-2a (with and without adefovir) in the combined arm, the proportion of patients with a negative PCR result of HDV RNA was 23% (14/60) at the end of treatment (week 48), 28% (17/60) at the end of the follow-up period (week 72).
A HBsAg decline by more than 1 log10 IU/mL at week 48 compared to baseline was observed in 10 patients of the peginterferon alfa-2a + adefovir (PA) arm, 2 patients in the peginterferon alfa-2a (P) arm, and none patient of the adefovir arm (A) ($p <0.001$ for the comparison of PA and A groups, $p = 0.01$ for the comparison of PA and P arms).
The ALT normalization at week 48 was achieved in the following treatment arms: in 10 (10/31, 32%) patients of the peginterferon alfa-2a + adefovir (PA) group, 8 (8/29, 28%) patients of the peginterferon alfa-2a (P) arm and 2 (2/30, 7%) patients of the adefovir arm (A). At week 72, the ALT normalization was observed in 11 (35%) patients of the first arm (PA), 13 (45%) patients of the second arm (P) and 3 (10%) patients of the third arm (A).
Based on the results of the treatment safety evaluation, 318 adverse events were registered in 66 (73%) patients. The most common adverse events were recorded in the peginterferon alfa-2a treatment arms. All registered adverse events corresponded with the safety profile of peginterferon alfa-2a and adefovir.
Study HIDIT-1, follow-up period [12]
A retrospective-prospective study was performed to collect further data on the treatment efficacy in patients participating in the HIDIT-1 study. Data were available for 58 (58/77, 75%) patients, the median of the follow-up period was 4.5 years (0.5-5.5), the median number of visits was 3 visits per patient.
Patients who received monotherapy with adefovir have more often received further treatment with peginterferon alfa-2a (48% vs. 19%, p=0.02). HBsAg negativation before the end of the prolonged follow-up period was observed in 6 patients who received peginterferon alfa-2a.
Among patients who received peginterferon alfa-2a during the HIDIT-1 study and had a negative PCR result of HDV RNA at study week 72, 16 patients were enrolled into the follow-up period. Of these, 9 patients showed a positive PCR result of HDV RNA at least once, 7 patients showed a positive result at their last visit. Clinical endpoints (fatal outcome due to liver disease, liver transplantation, liver decompensation, hepatocellular carcinoma) were observed in 3 (8%) patients who received peginterferon alfa-2a, and in 3 (14%) patients who received adefovir; the average annual level was 2.5% (4.9% in patients with cirrhosis).

In these patients, a strain of the virus detected before treatment was confirmed by the sequencing method.
HIDIT-2 study [26]
This study was a randomized, controlled study a study on the efficacy and safety of a 96-week treatment with peginterferon alfa-2a 180 μg weekly + placebo (P) versus treatment with peginterferon alfa-2a 180 μg. A total of 120 patients were enrolled into the study. Upon the end of treatment, a follow-up period of 5 years was designated. To date, the interim results of this study are available after the first 24 weeks of follow-up.
Based on the results of the study, the primary endpoint –negative PCR result of HDV RNA at week 96 – was achieved in 47% of patients in the peginterferon alfa-2a + Tenofovir (PT) arm and in 33% in the peginterferon alfa-2a (P) arm, p=0.10 (ITT analysis). The results of the per protocol analysis (n=99) were as follows: 54% of responders on HDV RNA in the first arm (PT) and 41% of respondents in the second arm (P), p=0.19.
After completion of the first 24 weeks of follow-up (study week 120), the proportion of patients with negative PCR result of HDV RNA decreased, and was 30% in the peginterferon alfa-2a + Tenofovir arm, 23% in the peginterferon alfa-2a arm (ITT, p=0.34).
Twenty (20) patients did not complete a minimum of 80 treatment weeks, 9 patients in the peginterferon alfa-2a arm, and 9 patients in the peginterferon alfa-2a + Tenofovir arm. 976 adverse events (AEs) were registered during the analyzed period, 515 – in the peginterferon alfa-2a arm, 461 – in the peginterferon alfa-2a + Tenofovir arm. Of these, 65 AEs met the criteria of a serious AE: 30 SAEs in the peginterferon alfa-2a arm (31% of patients), 22 of which were regarded as unrelated to the study treatment; 35 patients – in the peginterferon alfa-2a + Tenofovir arm (34% of patients), of these, 24 – unrelated to the study treatment. Two fatal outcomes were recorded in the study, 1 per each treatment arm, both of which were probably associated with the injection of peginterferon alfa-2a. The cause of death included the mitral valve rupture, pneumonia and sepsis developed in another patient 6 months after the end of treatment.
Based on the results of the interim analysis of the HIDIT-2 study, the following preliminary conclusions were made:

- 96-week treatment with peginterferon alfa-2a + Tenofovir may be performed, but this modality is associated with a high incidence of SAE development.
- Compared to the monotherapy with peginterferon alfa-2a, combined treatment showed higher values of the response of PCR on HDV RNA during treatment, but a comparable effect to reduce HBsAg levels.
- More than one-third of patients experienced recurrence of HDV RNA, despite a long-lasting treatment.
- A 96-week treatment with peginterferon alfa-2a did not result in an increase in the proportion of patients with a negative PCR result of HDV RNA after the end of treatment (compared to the 48-week treatment in the HIDIT-1 study).
- For HDV-infected patients, the development of alternative treatment approaches is required at the earliest.

Thus, by now, there is no therapy with proven efficacy and favorable safety profile for patients with chronic viral hepatitis B with delta-agent, which makes it extremely important to develop new drugs aimed at treating this pathological condition.

1.2 Study drug Myrcludex B

1.2.1 General Information

Myrcludex B (MXB) is a polypeptide chain consisting of 47 amino acids. The N-terminus of this polypeptide chain is represented by the fatty acid (myristoyl residue) and the C-terminus – by the amide arm. All the amino acids that make up the above mentioned polypeptide chain are represented by the L-configuration.

Molecular formula:	$C_{248}H_{355}N_{65}O_{72}$ (net)
Molecular weight:	5398.9 g/mol (average weight, net)
Salt form, in which the active substance is presented in the drug composition:	Salt of acetic acid (acetate)
Physical form:	White or off-white powder
Appearance of the prepared solution:	Transparent and clear

Myrcludex B prevents the penetration of Hepatitis B virus (HBV) into hepatocytes by binding and inactivating the recently described NTCP receptor (Na+-taurocholate cotransporting polypeptide), which participates in the mechanism of HBV penetration into the cell. This receptor is represented mainly in the liver, the function of the molecule is to transport bile acids (salts) from blood to hepatocytes. Myrcludex B

presumably produces an effect at the stage after the interaction of the virus with the cellular receptor and prevents the fusion of the virus and cell membranes, thus preventing the penetration of the genetic material of the virus into the hepatocyte.
To date, a wide program of preclinical studies of the drug and phases I and II clinical studies have been performed demonstrating the favorable safety profile of Myrcludex B and the potential efficacy of the drug in the treatment of chronic viral hepatitis B and chronic viral hepatitis B with delta-agent.

1.2.2 Preclinical Study Results

Preclinical Pharmacology

Antiviral activity of the drug was evaluated in experimental studies using cell cultures susceptible to infection with hepatitis B virus (in the culture of HepaRG cells; liver cell culture of Tupaia belangeri tree shrews, and also in human liver cells culture), the virus replication was inhibited by various agents. HBeAg and HBsAg were determined as markers of infection in cell culture supernatants using the ELISA (enzyme immunoassay) method. The number of infected cells was determined by the HBcAg-specific immunofluorescence. At the same time, the value of the IC50 index ranged from 14.5 pM to 9.5 nM, depending on the virus titer, as well as on the conditions in which the cell culture was incubated. *In vitro*, the use of Myrcludex B in a wide dosage range (up to 50 μM) was not accompanied by toxic effects, which were evaluated by the intensity of LDH release by the destroyed hepatic cells.
In vivo, the antiviral activity of acylated peptides derived from hepatitis B virus, close in their structure to Myrcludex B, was studied in uPA/RAG-2 mice with immunodeficiency, which hepatocyte cell cultures of Tupaia belangeri tree shrews and human, sensitive to hepatitis B virus, were transplanted. The laboratory mice were infected with the hepatitis B virus, then they were given active peptide (in different concentrations) or a control peptide that did not have any pharmacological activity. In this experimental model, the systemic injection of the active peptide at the lowest concentration of all studied in this study (200 μg/kg) completely prevented the development of hepatitis B in experimental animals.
The properties of Myrcludex B were studied in a population of experimental uPA/SCID mice previously infected with the hepatitis B virus, which further, human hepatocytes were transplanted. In this case, a much less pronounced prevalence of hepatitis B viruses in liver tissue was found (compared to the experimental animals in the control group that received placebo), which was confirmed by laboratory methods for determining the concentration of HBV DNA and HBsAg antigen in the blood serum, as well as the results of immunohistological study.
The presence of additional pharmacological effects of the drug was studied in a study with chimpanzees under single-dosing conditions. Chimpanzees are a suitable biological model, since specific receptors to the hepatitis B virus are expressed in their bodies only, and it is also possible to model acute or chronic viral hepatitis B. The intravenous injection of Myrcludex B at a dose of 300 μg/kg was not accompanied by any clinically significant effects or changes in laboratory parameters that could be attributed solely to the injection of the study drug.

Preclinical pharmacokinetics

The HPLC-MS/MS method was developed and validated to analyze the drug content in plasma samples of dogs and humans. The method was applied in accordance with the GLP recommendations for the assessment of toxicokinetic properties of this drug. The evaluation of the pharmacokinetic properties of the drug was performed in the following studies: investigation of the pharmacokinetic parameters of the drug after a single injection to rats; investigation of the toxic properties of the drug in 4- and 26-week-old rats; in a 12-week study in dogs; additional studies in mice, rats, dogs and long-tailed macaques, with the injection of the isotopically labeled drug.
The drug concentration in the liver tissue was further determined by the HPLC-MS/MS method during the following studies: investigation of the pharmacokinetic parameters of the drug after a single administration to rats; a 26-week study in rats and a 12-week study in dogs.
Furthermore, the isotopically labeled Myrcludex B was indicated to the experimental animals, and after the injection its concentration in samples of various biological fluids and tissues was recorded by determining the content of radioactive components in the organs of experimental animals subjected to autopsy or by scintigraphic imaging methods. It is most critical, that pharmacokinetic parameters of the drug were analyzed in serum samples and samples of the hepatic tissue of chimpanzees, which the drug was administered

intravenously.
In a 26-week study in rats that received the drug subcutaneously, plasma samples were collected on the Day 1, 85, 177 and 183 of the study. The systemic exposure to the study drug when administered in three different doses was dose-dependent, which was confirmed by an almost proportional increase in the values of the area under the curve (AUC). When the drug was administered to males at a dose of 2.5 mg/kg/day, the C_{max} values in 2 or 4 hours were 768.68 ng/mL, 3686.20 ng/mL and 3972.13 ng/mL at Day 1, 85, 177 of the study, respectively. After dosing, the drug concentration in the plasma gradually decreased; while the value of the drug half-life indicator ranged within the following limits: on the follow-up day 1 - from 1.08 to 2.04 h; on the follow-up day 85 - from 1.33 to 7.05 h; on the follow-up day 177 - from 1.31 to 6.90 h.
A 12-week study on dogs analyzed blood samples collected on the follow-up day 1 and 91. The results of the investigation of drug concentrations, as well as the values of the area under the curve (AUC), showed a dose-dependent nature of the systemic exposure to the drug. This was confirmed by the nearly proportional increase in the values of the area under the curve (AUC). When the drug was administered to males at a dose of 2.5 mg/kg/day, the C_{max} values in 2-3 hours were 2544 ng/mL and 5234 ng/mL at Day 1 and 91 of the study, respectively. In females, the C_{max} values were 2095 ng/mL and 3198 ng/mL on the study day 1 and 91, respectively. The half-life values ranged within the following limits: on the follow-up day 1 - from 2.2 to 2.8 h; on the follow-up day 91 - from 2.7 to 5.4 h. An increase in the values of the above indicators, which characterize the level of the systemic exposure to the drug, may indicate the ability of the latter to accumulate in the body.
In studies in mice, rats, and dogs, which the isotopically labeled Myrcludex B was indicated, this drug was found to be distributed into the liver tissue relatively quickly and almost uniformly. In this case, the values of such indicators as the maximum drug concentration in the liver tissue, as well as the drug half-life from liver the tissue, were significantly higher than the values of the same indicators calculated for blood plasma.
In the experimental chimpanzees, it was possible to perform a detailed analysis of the pharmacokinetic parameters of the drug with the subsequent prediction of their values in the human body. Apparent volume of distribution of the drug (VD), consists of components unabsorbed (3.18 L/70 kg) and absorbed (10.0 L/70 kg) by peripheral tissues. It is estimated that the plasma clearance of the drug shall be 2.2 L/h/70 kg. It is assumed that the drug half-life from blood plasma depends on the degree of saturation of the peripheral tissues with the drug (on the volume of distribution of the component absorbed by the peripheral tissues), and decreases with an increase in its dosage intended for single use (the value of this index varies within 4.31-1.19 h). The maximum hepatic binding ability to the study drug (B_{max}) is 2551 ng/g of liver tissue. The process of the drug binding to the hepatic tissue was characterized by the following value of the equilibrium dissociation constant - 0.85 ng/mL (plasma). However, the half-life value for the "hepatic tissue-drug" complex is 12.5 hours.

Preclinical Toxicology
The acute toxicity study assessed the drug toxicity when the drug was used once in the experimental CD® rats. Therewith, some parameters characterizing the drug safety were evaluated in this study (including the Irwin test for assessing neuro-psychic reactions in rodents). In the experimental rats, the intravenous injection of Myrcludex B at a dose of 12.5 mg/kg was not accompanied by any toxic reaction. No fatal outcomes were also recorded among the experimental animals.
An investigation of some toxicological parameters (clinical symptoms, hematology and biochemistry) was performed during the study of pharmacological and pharmacokinetic properties of the drug administered to chimpanzee in a single dose.
In the study of chronic toxicity, the drug was administered to rats (for 7 days, 4 weeks or 6 months) and dogs (for 3 months) on a daily basis as a subcutaneous injection. A 4-week study in rats and a 3-month study in dogs included the assessment of blood cytokine levels.
No deaths, cases of local or system drug intolerance, changes in the body weight of the experimental animals and in the rates of its gain, in the amounts of food and liquid consumed by the experimental animals, in the values of hematological and biochemical indices were recorded in all the above mentioned studies. A macro or microscopic examination detected no pathological changes that could be related to the study drug.

1.2.3 Clinical Study Results
Four clinical studies of Myrcludex B have been completed to date:

- MYR 101: phase I study with healthy volunteers (performed in Germany);
- MYR 102: phase I study (drug interaction) with healthy volunteers (performed in Germany);
- MYR 201: phase Ib/IIa study, the drug injection to patients with chronic hepatitis B (performed in Russia);
- MYR 201 substudy (supportive study): Pilot, phase Ib/IIa study, injection of Myrcludex B and peginterferon alfa-2a in patients with chronic viral hepatitis B with delta agent (performed in Russia),

The following clinical study is ongoing:

- MYR 202: phase II/III study with Myrcludex B and Tenofovir in patients with chronic viral hepatitis B with delta-agent (ongoing in Russia and Germany).

Phase I clinical study (MYR 101) was performed with the participation of 36 healthy male volunteers. Volunteers received the study drug in the following doses: 0.3 μg, 3 μg, 10 μg, 100 μg, 800 μg, 3 mg, 5 mg, 10 mg and 20 mg with intravenous injection, and 800 μg, 5 mg and 10 mg with subcutaneous injection. The study evaluated the pharmacokinetics, safety, and tolerability of Myrcludex B. In general, 85 adverse events (AEs) were registered in 29 study subjects, none of the AEs met the criteria for serious AE. Based on the results of severity assessment, 74 AEs were assigned to mild AEs, 9 AEs were moderate, 2 AEs were severe (increased lipase, increased amylase) according to the CTCAE 4.0 criteria. Antibodies to the study drug were evaluated before the expiration of 6 months after the drug exposure, the test results were negative in all study subjects.
A good tolerability of the drug was noted when it was used in healthy volunteers, there were no serious adverse events or dose-limiting toxicity. The adverse events were mostly mild, they resolved independently. The incidence and severity of adverse events were not dose-dependent.
The following AEs were regarded as possibly related to the drug: excessive sweating (in one volunteer in a cohort that received 3 μg i.v.), headache (in one volunteer from each cohort that received 10 μg and 5 mg that AEs resolved without consequences within 24 hours).
The following changes in laboratory parameters were regarded as AEs, possibly related to the drug: reduced hemoglobin, reduced hematocrit (in one volunteer in a cohort that received 3 μg, mild, resolved without consequences within 24 hours); increased bilirubin (in one volunteer in a cohort that received 3 μg, mild, returned to normal within 7 days); transient increase in lipase level (one volunteer in each of the cohorts that received 3 μg, 0.8 mg subcutaneously and in two of the cohort that received 5 mg, from mild to severe, returned to normal within ≤ 3 days).
The pharmacokinetics of Myrcludex B was dose-dependent, the area under the curve (AUC) concentration-time increased disproportionately, while clearance and volume of distribution decreased when the dose increased. The drug bioavailability after subcutaneous injection was assessed to be 88%.

Phase I clinical study (MYR 102) was performed with participation of healthy volunteers. The study objective was to assess potential drug interaction between Myrcludex B and Tenofovir.
12 healthy volunteers were administered monotherapy of Tenofovir 245 mg during 5 days, followed up combination with Myrcludex 10 mg during 6 days.
Concentration of Tenofovir, Myrcludex B and bile acids were measured in plasma samples. Also participants were administered midazolam 30 μg for assessment of influence anti-viral drugs for activity of CYP3A.
Co-administration of Tenofovir with Myrcludex B was well tolerated and revealed no clinically relevant change in Tenofovir pharmacokinetics and activity of CYP3A.

Phase Ib/IIa clinical study (MYR 201) was performed in 48 patients with HBeAg-negative chronic viral hepatitis B of mild to moderate activity (HBV DNA ≥ 10,000 copies/mL, and ALT ≥ 1.5 ULN and ≤ 6 ULN). Patients were randomized to 6 treatment arms.
Arm A (n=8): Myrcludex B 0.5 mg/day/s/c/12 weeks + 12 weeks of follow-up
Arm B (n = 8): Myrcludex B 1 mg/day/s/c/12 weeks + 12 weeks of follow-up
Arm C (n = 8): Myrcludex B 2 mg/day/s/c/12 weeks + 12 weeks of follow-up
Arm D (n=8): Entecavir 0.5 mg/day/orally/24 weeks
Arm E (n=8): Myrcludex B 5 mg/day/s/c/12 weeks + 12 weeks of follow-up
Arm F (n=8): Myrcludex B 10 mg/day/s/c/24 weeks + 12 weeks of follow-up
The efficacy, safety, pharmacokinetics and immunogenicity of the drug Myrcludex B were investigated in

the study. The efficacy criteria included the evaluation of HBsAg, HBV DNA and ALT levels before, during treatment and during the follow-up period.

When evaluating the HBV DNA response, defined as a > 1 log IU/mL decline in HBV DNA by or its negativation, among the Myrcludex B treatment arms at week 12, the largest proportion of responders was observed in the patient arm receiving the drug at a dose of 10 mg (6/8, 75% of patients). In the remaining study drug arms, the proportion of responders was: 2/8 (25%) patients in the Myrcludex B 0.5 mg and 2 mg arms, 1/8 (12.5%) patient in the Myrcludex B 5 mg arm. In the Myrcludex B 1 mg arm, none of the patients reached the HBV DNA level corresponding to the response criteria. In the joint Myrcludex B arm, the proportion of responders was 11/40 (27.5%). Patients receiving the drug at a dose of 10 mg continued the treatment to 24 weeks, the proportion of responders at the end of treatment remained the same (6/8, 75%).

Based on the study findings, no significant effect of Myrcludex B on the dynamics of HBsAg level was found. At week 12, the change in the level of HBsAg compared to the baseline was: 0.10 log IU/mL in the 0.5 mg dose arm; 0.16 log IU/mL in the 1 mg arm; 0.04 log IU/mL in the 2 mg arm; -0.01 log IU/mL - in the 5 mg arm; 0.13 log IU/mL - in the 10 mg arm. At week 24, the change in the HBsAg level was 0.10 log IU/mL in the Myrcludex B 10 mg arm. However, a small number of patients in each treatment arm should be noted, since the study was a pilot and an exploratory one.

When assessing the biochemical response, defined as the normalization of ALT levels, among the Myrcludex B treatment arm, the proportion of responders at week 12 was: 3/7 (42.9%) patients in the 0.5 mg dose arm, 4/7 (57.1%) - in the 1 mg arm, 4/8 (50%) - in the 2 mg arm, 2/4 50%) - in the 5 mg arm, 4/6 (66.7%) - in the 10 mg arm. At week 24, the proportion of responders was 3/6 (50%) in the Myrcludex B 10 mg treatment arm. The biochemical response was assessed only in patients with abnormal baseline ALT levels.

A total of 69 AEs were registered during the study, of which 45 AEs were associated with the study drug Myrcludex B:

- Myrcludex B 0.5 mg arm: 14 AEs were registered in 4 (4/8, 50%) patients - increased blood amylase (1 AE), increased body temperature (1 AE), increased lipase (1 AE), weight gain (1 AE), eosinophilia (2 AEs), erythema (2 AEs), hyperhidrosis (1 AE), psoriasis (1 AE), xeroderma (1 AE), drowsiness (1 AE), respiratory infection (1 AE), hematuria (1 AE).
- Myrcludex B 1 mg arm: 4 AEs were registered in 4 (4/8, 50%) patients - drug withdrawal syndrome (1 AE), injection site reaction (1 AE), increased blood bilirubin (1 AE), ventricular ectopic beats (1 AE).
- Myrcludex B 2 mg arm: 4 AEs were registered in 3 (3/8, 37.5%) patients - increased blood creatinine (1 AE), a furuncle (1 AE), drowsiness (1 AE), drug withdrawal syndrome (1 AE).
- Myrcludex B 5 mg arm: 10 AEs were registered in 4 (4/8, 50%) patients - injection site reaction (4 AEs), increased GGT (1 AE), increased reticulocytes (1 AE), leukopenia (1 AE), right bundle branch block (1 AE), ventricular arrhythmia (1 AE), hypersensitivity (1 AE).
- Myrcludex B 10 mg arm: 13 AEs were registered in 5 (5/8, 62.5%) patients- dermatitis at the injection site (5 AEs), injection site reaction (1 AE), increased blood creatinine (1 AE), eosinophilia (2 AEs), rash (1 AE), respiratory infection (1 AE), diarrhea (1 AE), nasopharyngitis (1 AE).

Most AEs (41 AEs) were mild. Moderate AEs included: erythema, increased GGT, reticulocyte, dermatitis at the injection site (a total of 4 AEs). No severe AEs were recorded.

Two AEs were considered as serious AEs: the drug withdrawal syndrome in one patient from the Myrcludex 1 mg arm, and in one patient from the Myrcludex 2 mg arm. Both cases of serious AEs were recorded at a follow-up visit after the end of treatment, and were considered as mild ones directly associated with the study drug. One of these cases was regarded as a suspected unexpected serious adverse drug reaction, information about which was sent to the regulatory authorities as part of expedited reporting. There were no prematurely withdrawn patients due to the development of AEs/SAEs during this study. No fatal outcomes were also registered.

The data for the immunogenicity assessment were available in the Myrcludex B 0.5 mg, Myrcludex B 5 mg and Myrcludex B 10 mg treatment arm. The result was evaluated as positive when the antibody titer increased twice at treatment weeks 1, 4 or 12. Based on the assessment results, 14/24 (58.3%) patients had a positive result: 4/8 (50%) in the Myrcludex 0.5 mg B arm and 5/8 (62.5%) in each of the Myrcludex B 5 mg and 10 mg arms. There were no differences in the level of virologic and biochemical response, pharmacodynamic parameters of the drug in patients with positive and negative immunogenicity evaluation results.

In general, the MYR 201 study demonstrated potential antiviral activity and a favorable safety profile of the

drug Myrcludex B in the studied range of doses.

Phase Ib/IIa clinical study MYR 201(supportive study).

This study is a randomized, open-label study on the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity of the drug Myrcludex B when administered to patients with chronic viral hepatitis B with delta-agent. 48 patients were randomized into the study with HBeAg-negative chronic viral hepatitis B and HDV coinfection of mild to moderate activity (HBV DNA ≥ 10,000 copies/mL, and ALT ≥ 1.5 ULN and ≤ 6 ULN). Treatment arms included:

Arm A (n=8): Myrcludex B 2 mg during 24 weeks, followed by peginterferon alfa-2a 180 μg during 48 weeks

Arm B (n=8): Myrcludex B 2 mg + peginterferon alfa-2a 180 μg during 24 weeks, followed by peginterferon alfa-2a 180 μg during 24 weeks

Arm C (n=8): peginterferon alfa-2a 180 μg during 48 weeks

Interim results of MYR201 study (brief description below) formed the basis of MYR203 clinical study.

Interim efficacy results, 24 treatment weeks

Based on the evaluation of the HDV RNA response, defined as a > 1 log 10 decline in HDV RNA by or its negativation, the number of responders after 24 treatment weeks was 6 patients in arm A (6/7), 7 patients in arm B (7/7), 7 patients in arm C (7/7).

A negative PCR result of HDV RNA was observed in 2 patients of arm A (2/7), 5 patients of arm B (5/7) and 2 patients of arm C (2/7).

A decrease in ALT level was observed in 6 patients of arm A (6/7), 4 patients of arm B (4/7), and 3 patients of arm C, week 12 (3/7). A tendency to decrease in the median ALT in the Myrcludex B monotherapy arm from 66 U/L to 40 U/L (p = 0.06) was noted. Such tendency was not noted in the treatment arms B and C.

One patient - from arm A -had both a negative PCR result of HDV RNA and ALT normalization at treatment week 24.

The obtained results suggest a significant potential efficacy of Myrcludex B in the treatment of chronic viral hepatitis B with delta-agent that was used as the basis for the development and planning of the MYR 203 clinical study specified in this protocol.

Interim safety results, 24 treatment weeks

No serious adverse events were recorded during the study. One patient, according to the decision of the physician investigator, discontinued the treatment prematurely due to the development of an AE - a patient of arm B, who had eczema, according to the investigator's assessment, associated with the use of peginterferon alfa-2a.

The Myrcludex-related AEs included single cases of hematological disorders (leucopenia, neutropenia, thrombocytopenia and eosinophilia). Related to PEG IFN-alpha 2a were leucopenia, neutropenia, thrombocytopenia, anemia, ALT, AST, GGT, bilirubin increased, APTT prolonged, influenza-like illness, fatigue, pyrexia, dizziness, irritability and rash.

Summary results of MYR201 sub study

The main efficacy results (absolute number of responders for each of investigated parameters) are shown on Figure 1. There were the following responders criteria in the Study protocol: HbsAg response - HBsAg decline of at least 0.5 log IU/mL or HBsAg negativation; HBV DNA response - reduction of HBV DNA by >1 log IU/mL or negativation; HDV RNA response - reduction of HDV RNA by >1 log IU/mL or negativation; ALT response – ALT normalization.

There were not a lot of HbsAg responders during 24 weeks of treatment with Myrcludex B in groups A and B compared with group C, however there were substantial proportion of HBV DNA responders. Herewith the majority of HBV DNA responders (week 12) were shown in the group of combination of Myrcludex B and PEG IFN-alpha 2a.

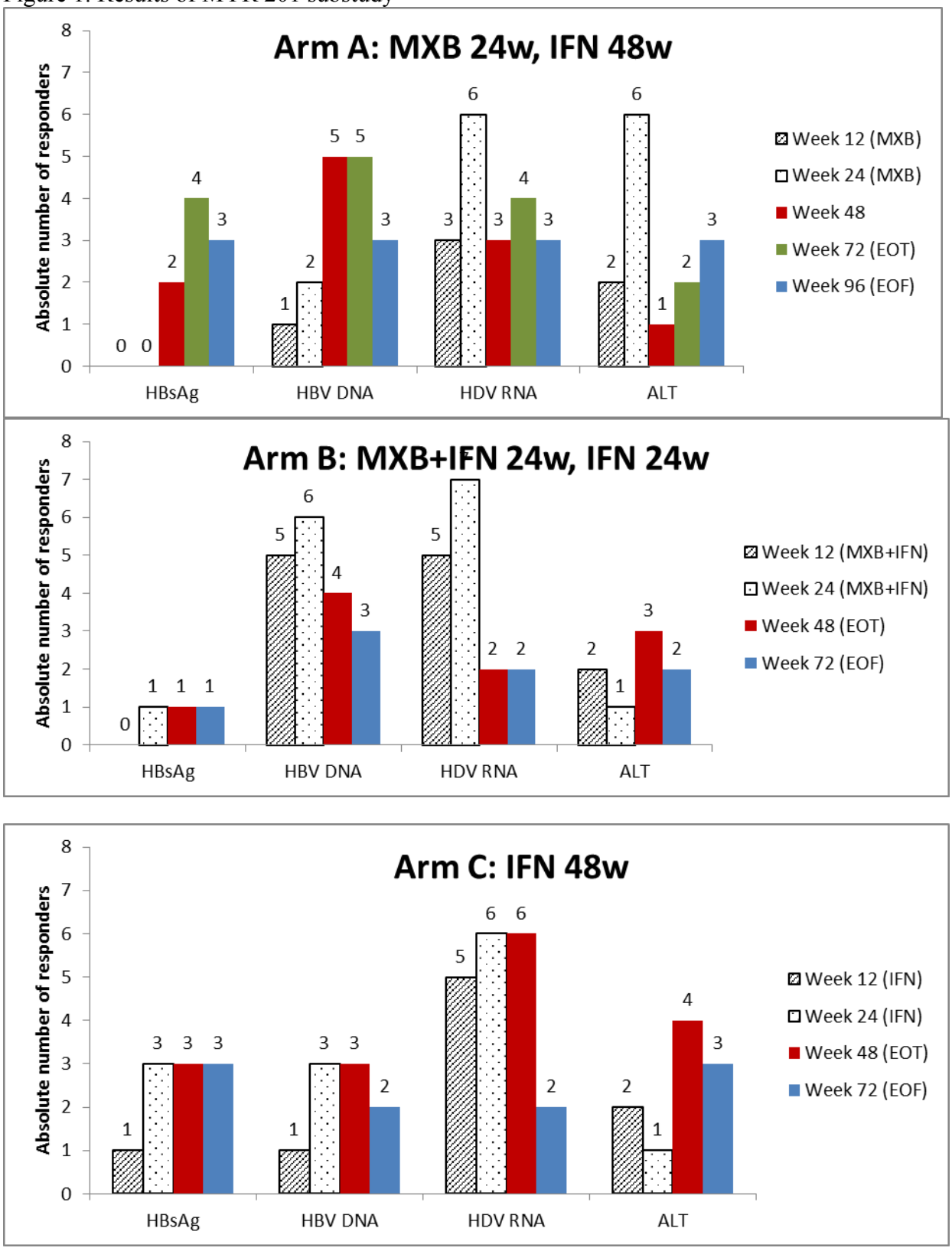
The combination treatment of Myrcludex B plus PEG IFN alfa-2a during 24 weeks demonstrated the highest HDV RNA responder’s rate. HDV RNA became negative in 5 of 8 patients while only 2 of 7 patients treated with Myrcludex B (Arm A) and PEG IFN alfa-2a (Arm C). After the treatment of Myrcludex B there was an obvious decrease in the number of HDV RNA responders in Arm A and Arm B.

24-week monotherapy with Myrcludex B (Arm A) showed the highest rate of ALT responders, however further switching to PEG IFN alfa-2a led to the decrease of ALT response. No considerable difference was observed between Arm B and Arm C

Study results suggest that Myrcludex B in combination and in monotherapy regimen is very perspective for the treatment of hepatitis B with delta agent.

For more detailed information about the study drug Myrcludex B, the results of preclinical and clinical studies refer to the Investigator's Brochure.

Figure 1. Results of MYR 201 substudy



MXB: Myrcludex B, IFN: Peginterferon alfa-2a, EOT: End of treatment, EOF: End of follow up
Note: For HBsAg, HBV DNA, ALT, the absolute number of responders in presented for FAS population, for HDV RNA data – among the patients with measurable HDV RNA at baseline.

The main results of the safety assessment are shown in Table 2. In general, Myrcludex B demonstrated a favorable safety profile both when prescribed in monotherapy and as part of combination therapy with Peginterferon alfa-2a.

Table 2. MYR 201 substudy: Brief Summary of Adverse Events (Safety Set)

SOC, PT *(MedDRA 18.1)*	**Arm A** **MXB 24w, IFN 48 w (N=8)**	**Arm B** **MXB+IFN 24w, IFN 24w (N=8)**	**Arm C** **IFN 48w (N=8)**
Number of reported AEs	**85**	**59**	**82**
Number of patients reporting at least one AE, n (%)	**8 (100.0)**	**8 (100.0)**	**8 (100.0)**
AEs by SOC, n (%)/c			
Blood and lymphatic system disorders	8 (100.0)/57	8 (100.0)/40	7 (87.5)/58
Investigations	7 (87.5)/19	4 (50.0)/14	3 (37.5)/15
General disorders and administration site conditions	5 (62.5)/8	4 (50.0)/4	4 (50.0)/8
Nervous system disorders	1 (12.5)/1	0 (0.0)/0	1 (12.5)/1
Skin and subcutaneous tissue disorders	0 (0.0)/0	1 (12.5)/1	0 (0.0)/0
AEs by severity, n (%)/c			
Mild	8 (100.0)/55	7 (87.5)/33	8 (100.0)/49
Moderate	8 (100.0)/25	7 (87.5)/24	6 (75.0)/28
Severe	2 (25.0)/5	1 (12.5)/2	2 (25.0)/5
AEs by relatedness to study medication, n(%)/c			
AEs judged to be related to Myrcludex B	3 (37.5)/4	1 (12.5)/1	N/A
AEs judged to be related to PEG IFN alfa-2a	8 (100.0)/76	8 (100.0)/56	8 (100.0)/82
Number of patients who died or experienced SAE, n (%)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Number of patients who withdrew from the study due to AE, n (%)	**0 (0.0)**	**1 (12.5)**	**0 (0.0)**

n: number of patients, c: number of events
AE: adverse event; PT: preferred term; SOC: system organ class; IFN: Peginterferon alfa-2a; MXB: Myrcludex B

1.3 Study Justification

1.3.1 Overall Study Design and Plan

This study is a multicenter, open-label, randomized, comparative, parallel-arm phase II study.
The study objective is to investigate the efficacy and safety of the monotherapy with Myrcludex B and the combination of Myrcludex B and the peginterferon alfa-2a and Tenofovir as compared to the monotherapy with peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent.
Previously performed preclinical studies of Myrcludex B make it possible to consider Myrcludex B as a promising drug for treatment of chronic viral hepatitis B with delta-agent. In addition, the results of the MYR 201 substudy (refer to Section 1.2.3) suggest that both monotherapy with Myrcludex B and combination treatment with Myrcludex B in combination with peginterferon alfa-2a make it possible to achieve a better response than monotherapy with interferon.
In the second phase of this study, it is also planned to investigate the efficacy and safety of the combination therapy of Mircludex B with Tenofovir from the nucleoside / nucleotide analog group. Tenofovir disoproxil

fumarate (Tenofovir) is a highly effective inhibitor of HBV polymerase, approved for the treatment of chronic hepatitis B. Nucleoside / nucleotide analogues can be 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 Adult Hepatitis B Patients (Ministry of Health of the Russian Federation, 2014), EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection (European Association for the Study of Liver Disease, 2017). The use of these drugs is aimed at suppressing the replication of the hepatitis B virus, which plays an important role in the progressive lesion of the liver in the presence of a delta agent.

This study MYR 203 is an exploratory one, and is aimed at determination of efficacy and safety parameters of Myrcludex B used in monotherapy, for the selection of the optimal dose of parameters B as part of a combination treatment with a peginterferon alfa-2a and Tenofovir for the treatment of chronic viral hepatitis B with delta-agent. Patients will be randomly assigned to one of six treatment arm:

- Arm A (n=15) - monotherapy with peginterferon alfa-2a 180 μg during 48 weeks,
- Arm B (n = 15) - combination treatment with Myrcludex B 2 mg and peginterferon alfa-2a 180 μg during 48 weeks,
- Arm C (n = 15) - combination treatment with Myrcludex B 5 mg and peginterferon alfa-2a 180 μg during 48 weeks,
- Arm D (n = 15) - monotherapy with Myrcludex B 2 mg during 48 weeks.
- Arm E (n=15) – combination treatment with Myrcludex B 10 mg (10 mg once a day) and peginterferon alfa-2a 180 μg during 48 weeks.
- Arm F (n=15) - combination treatment with Myrcludex B 10 mg (5 mg twice a day) and Tenofovir during 48 weeks.

After the end of the treatment period, a 24-week follow-up period will follow to assess the stability of the viral response. Patients from group F will continue Tenofovir treatment during follow-up period. In other treatment arms there will no treatment.

Peginterferon alfa-2a has been chosen as a reference product, since it is currently a type of drug treatment of chronic viral hepatitis B with delta agent, that shows the most efficient and acceptable safety profile. The efficacy and safety of the peginterferon alfa-2a in the treatment of chronic viral hepatitis B with delta-agent has been demonstrated in recent studies with a long period of treatment and follow-up (HIDIT-1, HIDIT-2, refer to Section 1.1).

The main efficacy criterion in this study (primary endpoint) is the proportion of patients with negative PCR result of HDV RNA (undetectable level of HDV RNA) at week 72 (end of follow-up period). The evaluation of the proportion of patients with a stable virologic response after a long (6 months) period without treatment is considered one of the most reliable criteria for evaluating the effectiveness of treatment of chronic viral hepatitis B with delta-agent and is widely used in similar clinical studies and routine clinical practice.

Additional efficacy criteria include evaluation of the dynamics of ALT, HBsAg, HBV DNA, the severity of fibrosis in the liver tissue, both after the end of treatment, and after the end of the 6-month follow-up period. Before and after the treatment all patients should be performed liver biopsy for histological and virological tests. HBV, HDV genotyping, resistance and polymorphisms NTCP is also planned as a part of the examination of efficacy. The listed criteria for assessing the treatment efficacy meet the requirements of guidelines for the study of drugs for the treatment of chronic viral hepatitis [5].

Criteria for the safety evaluation of the treatment being studied include the collection of data on adverse events, physical examination, ophthalmological examination, evaluation of vital signs, electrocardiography, standard laboratory tests (hematology, coagulogram, biochemistry, urinalysis), determination of common bile acids, as well as the estimation of TSH and T4 levels. This list of parameters appears to be complete for the evaluation of the safety profile of the treatment as a part of the study, and takes into account the safety data of Myrcludex B and peginterferon alfa-2a and Tenofovir obtained so far.

The study also plans to study the immunogenicity of the drug Myrcludex B (arms B - F,) and the pharmacokinetics of the drug in the monotherapy and in the combined therapy with Myrcludex B + peginterferon alfa-2a and Myrcludex B + Tenofovir. The level of antibodies to the study drug Myrcludex B will be determined before, during, and after the end of treatment. The pharmacokinetic substudy will enroll 20 patients (10 patients from arms B and C), in pharmacokinetic of second phase – 10 patients from arm F who, during the study, will be hospitalized (day-stay or 24-hour hospital) for blood sampling for the investigation of the pharmacokinetic parameters of the study drug after single and multiple dosing as part of

a combination therapy. The selection of time points for the pharmacokinetic evaluation is based on the accumulated data of preclinical and clinical studies of the pharmacokinetics of Myrcludex B. In addition, for a more exact investigation of the possible cumulation of the study drug, blood sampling is planned for all patients receiving Myrcludex B (the main study, PK main study).

1.3.2 Study population

The study plans to randomize 90 male and female patients aged 18 through 65 years of age with chronic viral hepatitis B with delta-agent. Taking into account the possible drop-out during the randomization period, 123 patients are planned to be screened for the study.
The study selection criteria suggest the enrollment of patients with a positive result of HDV RNA, anti-HDV antibodies, HBeAg-positive or negative chronic hepatitis B, ALT level ≥ 1 ULN and <10 ULN, and with no co-infection with the hepatitis C virus or HIV. Antiretroviral therapy must be completed at least in six months before screening, and the prior interferon therapy is allowed (interferon therapy must be completed at least in 6 months before screening).
The study population is of representative nature, maximally close to clinical practice in the studied therapeutic area.

1.3.3 Justification of the administration route, dose, dosage regimen and treatment duration

The test drug Myrcludex B will be administered in doses of 2 mg, 5 mg or 10 mg in the form of subcutaneous injections, which should be performed daily, every 24±1 hours (once a day for groups B – E) or 12+1 hours (twice a day, group F). The administration route, the dosage regimen, the study dose selection are based on the results of previously performed studies of Myrcludex B, which demonstrated a favorable efficacy and safety profile of the drug use (refer to Section 1.2.3).
The peginterferon alfa-2a will be administered at a dose of 180 μg in the form of subcutaneous injections, which should be administered subcutaneously, once a week. The administration route and the dosage regimen comply with the Instruction for medical use.
Tenofovir will be taken internally, 300 mg (1 tablet), once a day, daily. Dosage regimen corresponds to the instruction for medical use.
The main treatment duration in all study arms will be 48 weeks, which corresponds to the recommendations for the investigation of drugs for the treatment of chronic viral hepatitis and the standards of routine clinical practice. Patients in group F will follow Tenofovir treatment during follow-up phase.

1.3.4 Brief description of known and potential risks and benefits for study subjects

According to previous studies and considering that chronic viral hepatitis B with delta-agent is difficult to treat with modern available drugs of different pharmacological groups, it is quickly reactivated and can lead to severe liver injury, but also, therapy being investigated may be useful for the patient. With that, patients will be under close medical control for a long time and will undergo examinations, including laboratory and instrumental procedures, which will enable them to obtain complete information about their health status during the entire period of participation in this clinical study.
In the course of the study, side effects that are characteristic of Myrcludex B, Tenofovir and peginterferon alfa-2a may be registered, as well as side effects not identified earlier may be identified.
The procedures and examinations performed as a part of this protocol are routine in clinical practice. However, during the collection of blood samples from patients and performing biopsy procedure, discomfort or painful sensations, which resolve rapidly, may appear. In rare cases, biopsy procedure could be accompanied with such adverse events: accidental puncture of another organ (bowel, lung, gallbladder, kidneys), contamination of abdomen, bleeding.
If patients develop adverse events, appropriate corrective therapy will be prescribed. If there is any health damage caused by the clinical study, the patient will be provided with the necessary medical care and compensated for the expenses in accordance with the insurance procedure.

1.4 Regulatory documents

This study will be performed in accordance with the protocol, ICH GCP requirements, the provisions of the World Medical Association Declaration of Helsinki, and the relevant regulatory requirements of the Russian Federation listed below.

1. Federal Law N 61-FZ dd. April 12, 2010 “On Medicine Circulation”.
2. Federal Law No. 323-FZ dd. November 21, 2011 "On the fundamentals of protection of the public health in the Russian Federation".
3. Order of the Ministry of Health of the Russian Federation No. 200n dd. 01.04.2016 "On Approval of Rules of Good Clinical Practice"
4. National Standard of the Russian Federation GOST R 52379-2005 “Good Clinical Practice”
5. Guidelines for the drug expertise (FSBI "Scientific Center for Expertise of Means of Medical Application", 2013).
6. Guidelines for clinical studies of drugs (FSBI "Scientific Center for Expertise of Means of Medical Application", 2012).

2 OBJECTIVES AND ENDPOINTS OF THE STUDY

2.1 Study objective

The objective of this clinical study is to investigate the efficacy and safety of Myrcludex B used in monotherapy and the combination of Myrcludex B with peginterferon alfa-2a (PEG-IFN alfa-2a) and with Tenofovir as compared to the monotherapy with peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent.

2.2 Study objectives

Primary objectives:

To investigate the efficacy of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir compared to monotherapy with PEG-IFN alfa-2a, based on the achievement of undetectable viral load at the end of the follow-up period (6 months after the end of treatment).

Secondary objectives:

- To investigate the efficacy of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir as compared with monotherapy with PEG-IFN alfa-2a, based on the secondary efficacy endpoints.
- To investigate the safety of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir compared with PEG-IFN alfa-2a monotherapy.
- To investigate the pharmacokinetics of Myrcludex B when administered in combination with PEG-IFN alfa-2a and with Tenofovir.
- To investigate the immunogenicity of Myrcludex B

2.3 Study Endpoints

Primary efficacy endpoint:

- Proportion of patients with a negative PCR result of HDV RNA (undetectable level of HDV RNA) at week 72 (end of the follow up period)

Secondary efficacy endpoints:

- Proportion of patients with a negative PCR result of HDV RNA (undetectable level of HDV RNA) at weeks 24 and 48.
- Proportion of patients with HDV RNA response (decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) at weeks 24, 48 and 72
- Proportion of patients with ALT normalization at weeks 24, 48 and 72.
- Proportion of patients with combined treatment response (negative PCR result of HDV RNA and ALT normalization) at weeks 24, 48 and 72.
- Proportion of patients with a combined response to therapy ((decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) and normalization of ALT) at weeks 24, 48 and 72
- Proportion of patients with HBsAg response HBsAg negativation or >1 log10 IU/mL decline) at weeks 24, 48 and 72.
- Proportion of patients with the HBsAg negativation with the appearance of anti-HBsAg antibodies and without it at weeks 48 and 72.
- Proportion of patients with a negative PCR result of HBV DNA at weeks 24, 48 and 72.
- The intensity of liver fibrosis based on results of transient elastometry of liver at weeks 48 and 72
- Changes in the results of liver biopsy before and after the treatment

As part of the study of efficacy, HBV, HDV genotyping, resistance assay and study of NTCP polymorphism will be performed additionally.

Safety criteria:

- Adverse events, serious adverse events
- Physical examination
- Ophthalmological examination
- Vital signs
- 12-lead ECG
- Hematology

- Blood chemistry
- Total bile acids
- Coagulogram
- Urinalysis
- Blood test for TSH, T4

Evaluation of immunogenicity:

- The level of antibodies to Myrcludex B (arms B - F)

2.4 Investigated pharmacokinetic parameters

The following pharmacokinetic parameters will be evaluated using non-compartmental analysis:

- C_{max} – maximum concentration
- T_{max} – time of maximum concentration
- K_{el} – elimination rate constant
- $T_{1/2}$ – elimination half-life
- CL/F – total clearance
- AUC_{0-t} – area under the curve "drug concentration-time" from time 0 to the sampling time (t) of the last sample
- $AUC_{0-\infty}$ – area under the curve "drug concentration-time" from time 0 to ∞

3 STUDY DESIGN AND PLAN

3.1 Study design and plan

This study is a multicenter, open-label, randomized, comparative, parallel-arm phase II study
The study will be performed in the Russian Federation.
The study objective is to investigate the efficacy and safety of the monotherapy with Myrcludex B and the combination of Myrcludex B with peginterferon alfa-2a and with Tenofovir as compared to the monotherapy with peginterferon alfa-2a in patients with chronic viral hepatitis B with delta-agent. In the course of the study, it is also planned to investigate the immunogenicity of Myrcludex B and the pharmacokinetics of the drug when administered in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir.
It is planned that 123 patients will be screened and 90 of them will be randomized into 6 treatment arms in a 1:1:1:1:1:1 ratio:

- Arm A (n=15): PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm B (n=15): Myrcludex B 2 mg + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm C (n=15): Myrcludex B 5 mg + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm D (n=15): Myrcludex B 2 mg during 48 weeks
- Arm E (n=15): Myrcludex B 10 mg (10 mg once a day) + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm F (n=15): Myrcludex B 10 mg (5 mg twice a day) + Tenofovir during 48 weeks

After the end of treatment period, there will be a follow-up period of 24 weeks. Patients from group F will continue Tenofovir treatment during follow-up period.
The study includes 2 phases:
I phase – patients enrollment in groups A – D (Protocol version 1.0, dd. 16.12.2015, Protocol version 1.1, dd. 16.03.2016, Protocol version 2.0, dd. 31.05.2016, Protocol version 3.0, dd. 23.08.2017)
II phase - patients enrollment in groups E – F (Protocol version 4.0, dd. 19.01.2018)
An additional pharmacokinetic study (PK substudy) is planned to be performed as a part of the I phase of the study, in which 10 patients randomized to each of treatment arms B and C (20 patients in total) will be enrolled. During II phase of the study patients from group F (the first 10 randomized patients) will take part in the pharmacokinetic study. Blood samples for the assessment of the drug concentration will be collected at the following time points: Days 1, 2, 14, 15.
For a more precise investigation of the possible study drug accumulation in all patients of each Myrcludex B treatment arm (PK main study), blood sampling points for the pharmacokinetic study are assigned: week 4, 8, 12, 16, 20, 24, 28, 32, 40, 48 (in 1hour +/-15 min after the drug administration) (week 48 only for patients from groups E – F). For the patients not participating in the pharmacokinetic substudy, a blood sampling point at a randomization visit (in 1hour +/-15 min after the drug injection) is assigned.
The study plan includes a screening period – up to 4 weeks, treatment period - 48 weeks, follow-up period - 24 weeks. Study scheme is presented on Figure 2. The flow chart is presented in Table 1.
The total duration of the patient's participation in the study is up to 76 weeks.
The total number of visits is 19 (screening visit, 13 visits of the treatment period, and 5 visits of the follow-up period).
Patients enrolled into the pharmacokinetic substudy (PK substudy) and pharmacokinetic study for group F will be taken to hospital (day-stay of 24-hour) on the day before the start of treatment and will stay in the hospital during the blood sampling period to assess the pharmacokinetics (Days 1, 2, 14, 15).
Throughout the entire study, patients not enrolled into these pharmacokinetic substudies will undergo treatment and planned examinations on an outpatient basis.

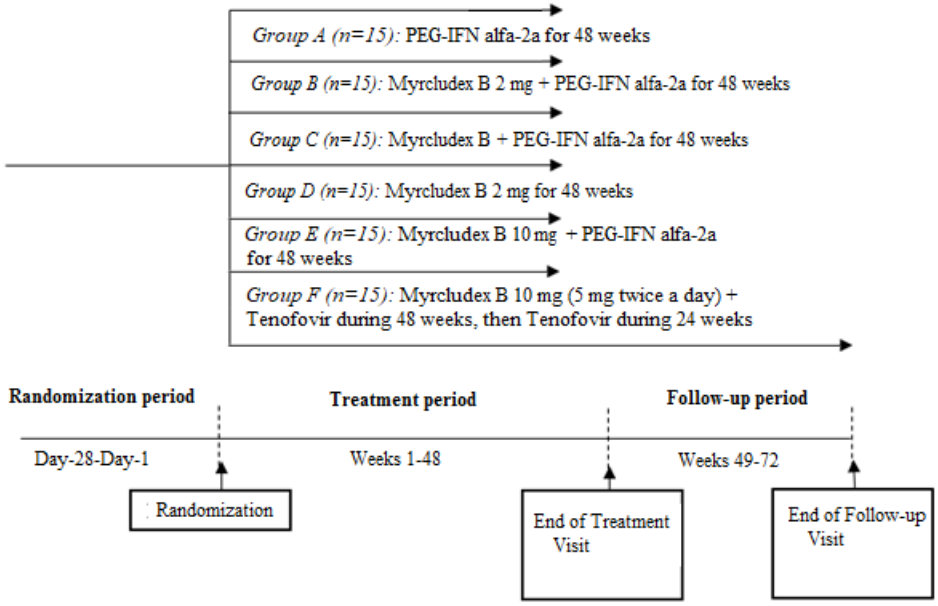


Figure 2 Study scheme

3.2 Randomization

Randomization will be performed in a ratio of 1:1:1:1:1:1 using the IWRS (Interactive Web Response System). The separate randomization list will be created for both phases of the study.

Randomization must be implement only after approval study Sponsor based of signed by Investigator "Form for assessing inclusion/non-inclusion criteria" and scans of listed in the form documents, confirming patient's compliance with the eligibility criteria (in blind form). No later than 3 days before scheduled randomizing date, this form must be shipped to monitor of the center and study sponsor to receive signed randomization approval.

3.3 Blinding procedure

Not applicable. The study is an open-label one.

3.4 Schedule of study procedures and stages

3.4.1 Informed consent

All procedures provided for in this clinical study protocol will be performed only after the patient has signed a written form of informed consent to participate in the study.

Each participant in the study will be provided with appropriate and reliable information on the study objectives and methods, risks and difficulties associated with the participation in the study, and other aspects of this study. If a patient agrees to participate in the study, he/she signs and dates a written informed consent form in 2 copies. The investigator also signs and dates the informed consent form, certifying that the consent was received and that the patient had the opportunity to ask questions of interest and received full answers to them. The patient will be given one original informed consent form, and the other original will be deposited at the study center along with other study documentation.

3.4.2 Screening period (Day-28 – Day-1)

The screening procedures will be carried out during the Days-28 – 1. Screening period may be less than 28 days (not less than 3 days) subject to receipt all required for randomization results of procedures/analyzes during the screening period. A detailed description of the procedures and a list of data recorded in the patient CRFs are provided in Section 6.

- Collection of demographics and medical history data
- Collection of data on previous and concomitant treatment
- Physical examination
- Ophthalmological examination (for patients with a history of mild and moderate retinopathy to

evaluate baseline ocular changes)
- Measurement of body height, weight, calculation of BMI
- Evaluation of vital signs
- Urine pregnancy test (for women with reproductive potential)
- Urine drug screening
- Alcohol-breath test
- Anti-HDV antibodies *(local laboratory)*
- Alpha-fetoprotein test *(central laboratory)*
- Blood test for HIV (HIV antibodies) *(local laboratory)*
- Blood test for Hepatitis C (anti-HCV antibodies, HCV RNA (if the test is positive for anti-HCV antibody) *(local laboratory)*
- Blood test for TSH, T4 *(central laboratory)*
- HDV RNA tests *(room temperature samples, central laboratory) (qualitative and quantitative)*
- HBeAg, anti-HBeAg antibody tests *(local laboratory)*
- HBsAg, anti-HBsAg antibody tests *(local laboratory)*
- Urinalysis *(central laboratory)*
- 12-lead ECG
- Abdominal ultrasound
- Fibroscan (transient elastometry of liver)
- Liver biopsy
- Hematology*(central laboratory)*
- Biochemistry *(central laboratory)*
- Coagulogram *(central laboratory)*.

Once the screening criteria are confirmed, patients will be randomized in one of the treatment arms. Randomization should be performed on Day -3 – Day-1 of the study.
Patients from groups B, C, F participating in the pharmacokinetic study will be hospitalized to the clinical center for sample collection on Days 1-2 of the study.
The patients not enrolled into the pharmacokinetic substudy start treatment and planned examinations and procedures on an outpatient basis.

3.4.3 Treatment period (Week 1 – Week 48)

The treatment period is 48 weeks. 13 visits to the study center are planned during this period. A detailed description of the procedures and a list of data recorded in the patient CRFs are provided in Section 6.

Visit 1/Week 0/Day 1

Randomization must be implemented after the approval of patient's conformity to selection criteria for the study in interval from Day 3-Day 1 of the investigation. The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory. The results of laboratory studies on Visit 1/Day 1 will be used as baseline data for the efficacy and safety evaluation.
The sequence of the procedures should be in accordance with the list below.
- Urinalysis (central laboratory)
- Evaluation of vital signs
- HDV RNA blood test
- HBV DNA, HBsAg tests (quantification)
- Hematology
- Coagulogram
- Blood chemistry
- Blood bile acids
- Blood sampling to estimate immunogenicity
- Blood sampling for HBV, HDV genotyping
- Resistance assay
- Examination of NTCP polymorphism

- Issuance of patient diaries, instructions on how to fill it
- Dispensing the study drug/ PEG-IFN alfa-2a/Tenofovir and accompanying materials over, instruction on how to conduct the self-injection
- Injection of the first dose of the Myrcludex B (groups B- F)/ PEG-IFN alfa-2a (group A – C, E)/Tenofovir (group F)
- Blood sampling for the pharmacokinetic main study in 1 hour ±15 min after the first injection of Myrcludex B (groups B – F)
- Filling the patient diary in
- Collection of data on adverse events
- Collection of data on concomitant treatment

Procedures for patients participating in the PK-substudy (10 patients from groups B, C, F)
The following procedures will be performed under the conditions of the inpatient hospitalization (all blood samples will be analyzed in the central laboratory):

Day 1
• Urinalysis (central laboratory)
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling to estimate immunogenicity
• Blood sampling for HBV, HDV genotyping
• Resistance
• NTCP polymorphisms
• Issuance of patient diaries, instructions on how to fill it
• Instructions on the self-injection of the drug
• Blood sampling before the start of the treatment
• Injection of the first dose of the Myrcludex B (groups B, C, F)/ PEG-IFN alfa-2a (groups B, C)/Tenofovir (group F)
• Blood sampling for PK study
Groups B and C: Blood sampling after the injection of the first dose of Myrcludex B: in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection.
Group F: Blood sampling after the injection of the first dose of Myrcludex B: in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min) after the drug injection

Blood sampling in 12 hours after the first dose should be performed before the second injection of MXB.

• Injection of the second dose of the Study drug (for group F only)
• Filling the patient diary in
• Collection of data on adverse events, Evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Day 2
The following procedures will be performed in hospital (day-stay or 24-hour):
- Blood sampling for PK study

Groups B and C: Blood sampling 24 hours after the injection of Myrcludex B (before injection of the second dose in Day 2)
Group F: Blood sampling in 12 hours after the second injection of Myrcludex B in Day 1 (before injection of third dose on Day 2)
- Injection of the second (groups B and C)/third (group F) dose of Myrcludex B
- Tenofovir intake (group F)

• Filling the patient diary in
• Handing the study drug/reference product/Tenofovir and accompanying materials over for the self-injection of drugs by the patients at home
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Further procedures are performed on an outpatient basis until the next hospitalization as per the study protocol.

Visit 2/Week 1/Day 8 ± 2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Evaluation of vital signs
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Return of used packages of the study drug/reference product
• Evaluation of the patient diary, registration of data in the patient CRFs
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 3/Week 2/Day 15 + 2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification) (central laboratory)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Return of used packages of the study drug/reference product
• Evaluation of the patient diary, registration of data in the patient CRFs
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Procedures for patients participating in the PK-substudy (10 patients from group B, C and F)

The following procedures will be performed under the conditions of the inpatient hospitalization (all blood samples will be analyzed in the central laboratory):

Day 14
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification) (central laboratory)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Return of used packages of the study drug/reference product
• Evaluation of the patient diary, registration of data in the patient CRFs
• Blood sampling before the injection of Myrcludex BInjection of Myrcludex B (groups B, C and F)/ PEG-IFN alfa-2a (groups B, C)/Tenofovir (group F) according to treatment scheme
• Blood sampling for PK study

Groups B and C: Blood sampling after the injection of Myrcludex B: in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00,

4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection.
• *Group F:* Blood sampling after injection of Myrcludex B in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min) after the drug injection

Blood sampling in 12 hours after injection should be performed before the second injection of MXB on Day 14.
• Second injection of study drug on Day 14 (only for group F)
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Day 15
The following procedures will be performed in hospital (day-stay or 24-hour):
- Blood sampling for PK study

Groups B and C: Blood sampling 24 hours after the injection of Myrcludex B (before injection on Day 15)
Group F: Blood sampling in 12 hours after the second injection of Myrcludex B in Day 14 (before the first injection on Day 2)
- Injection of Myrcludex B (groups B, C, F)
- Tenofovir intake (group F) in the investigational site or at home according to treatment scheme
- Filling the patient diary in
- Collection of data on adverse events, evaluation of the Myrcludex B injection site
- Collection of data on concomitant treatment

Further visits and procedures are performed on an outpatient basis.

Visit 4/Week 4/Day 29±2
The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F; injection in the investigational site)
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product/Tenofovir and study materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 5/Week 8/Day 57±2
The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBsAg test (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)

• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 6/Week 12/Day 85±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Physical examination
• Measurement of the body weight
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Blood test for TSH, T4
• Blood sampling to estimate immunogenicity
• Electrocardiography
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product/Tenofovir and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 7/Week 16/Day 113±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBsAg test (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product/Tenofovir and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 8/Week 20/Day 141±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs

• HDV RNA blood test
• HBsAg test (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference/Tenofovir product and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 9/Week 24/Day 169±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Urine pregnancy test (for women with reproductive potential)
• Physical examination
• Measurement of the body weight
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)
• HBeAg, anti-HBeAg antibody tests (*only in patients with positive results at screening*)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Blood test for TSH, T4
• Blood sampling to estimate immunogenicity
• Electrocardiography
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product/Tenofovir and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 10/Week 28/Day 197±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBsAg test (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy (in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)

• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference/Tenofovir product and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 11/Week 32/Day 225±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference/Tenofovir product and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 12/Week 40/Day 281±2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Evaluation of vital signs
• HDV RNA blood test
• HBsAg test (quantification)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Blood sampling for the pharmacokinetic substudy in 1h±15min after the injection of Myrcludex B (groups B – F, injection at the investigational site)
• Return of used packages of the study drug/reference product/Tenofovir
• Evaluation of the patient diary, registration of data in the patient CRFs
• Dispensing the study drug/reference product/Tenofovir and accompanying materials
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

Visit 13 (End of treatment visit, EOT visit)/Week 48/Day 337+2

The following procedures are performed during the visit. All blood samples will be analyzed in the central laboratory.
• Urinalysis *(central laboratory)*
• Urine pregnancy test (for women with reproductive potential)
• Physical examination
• Measurement of the body weight
• Evaluation of vital signs
• HDV RNA blood test
• HBV DNA, HBsAg tests (quantification)

• HBeAg, anti-HBeAg antibody tests (only in patients with positive results at screening)
• Hematology
• Coagulogram
• Blood chemistry
• Blood bile acids
• Resistance assay
• Blood test for TSH, T4
• Blood sampling to estimate immunogenicity
• Groups E and F: blood sampling for PK main study in 1 hour ± 15 min after Myrcludex injection (injection at the investigational site)
• Electrocardiography
• Abdominal ultrasound
• Fibroscan (transient elastometry of liver)
• Liver biopsy for patients from groups D and F (allowable time for liver biopsy: ± 7 days from the date of the end of treatment visit)
• Return of used and unused packages of the study drug/reference product/Tenofovir
• Tenofovir dispensing for follow-up period (group F)
• Evaluation of the patient diary, registration of data in the patient CRFs
• Collection of data on adverse events, evaluation of the Myrcludex B injection site
• Collection of data on concomitant treatment

3.4.4 Follow-up period (Week 49 –Week 72)

The duration of the follow-up period is 24 weeks. 5 visits to the study center are planned during this period.
1) Follow-up visit 1/Week 50(EOT+2 weeks)/Day 351±3
2) Follow-up visit 2/Week 52(EOT+4 weeks)/Day 365±3
3) Follow-up visit 3/Week 56(EOT+8 weeks)/Day 393±3
4) Follow-up visit 4/Week 60(EOT+12 weeks)/Day 421±3
5) Follow-up visit 5 (End of treatment visit)/Week 72 /
(EOT+24 weeks)/Day 505±3

Procedures during the **Follow-up visits 1-4** (all blood samples will be analyzed in the central laboratory):
- Evaluation of vital signs
- HDV RNA blood test
- HBsAg test (quantification)
- Hematology
- Coagulogram
- Blood chemistry
- Blood bile acids
- Collection of data on adverse events
- Collection of data on concomitant treatment
- Return of used and unused packages of Tenofovir (Week 52, 56, 60)
- Evaluation of the patient diary, registration of data in the patient CRFs
- Dispensing of Tenofovir for FUP period (Week52, 56, 60)

In addition, blood sampling to assess immunogenicity will be performed at **Follow-up visits 2 (Week 52) and 4 (Week 60)**. The HBV DNA test will be performed at **Follow-up Visit 4 (Week 60)**.

Procedures during the **Follow-up visit 5/End of treatment** (all blood samples will be analyzed in the central laboratory):
- Urinalysis *(central laboratory)*
- Physical examination
- Measurement of the body weight
- Evaluation of vital signs
- HDV RNA blood test
- HBV DNA, HBsAg tests (quantification) (central laboratory)
- HBeAg, anti-HBeAg antibody tests (*only in patients with positive results at screening*)

- Hematology
- Coagulogram
- Blood chemistry
- Blood bile acids
- Blood sampling to estimate immunogenicity
- Electrocardiography
- Abdominal ultrasound
- Fibroscan (transient elastometry of liver)
- Liver biopsy for patients from groups A - C and E (allowable time for liver biopsy: ± 7 days from the date of the end of treatment visit)
- Collection of data on adverse events
- Collection of data on concomitant treatment
- Return of used and unused packages of Tenofovir

Evaluation of the patient diary, registration of data in the patient CRFs

3.5 Acceptable window periods for planned visits and procedures

Acceptable days for window periods for visits are presented in Table 1. During the treatment period, window of ± 2 days are allowed for visits 2-12, +2-day window is allowed for the end of treatment visit, a ±3-day window is allowed for all visits during the follow-up period.

For patients in Arms B, C and F participating in the pharmacokinetic substudy, there is no time window for Day 1 and 2, blood sampling for assessment of pharmacokinetics of Myrcludex B should be performed before and after the first dose of Myrcludex B. The second part of the PK study may be performed within time window + 1 Day (Day 15 – 16 of the study). Directly during the visits the following window periods for blood sampling to evaluate pharmacokinetics are allowed:

- in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00 (hh:min) after the injection of Myrcludex B – a window of ±5 minutes,
- in 6:00, 8:00, 10:00, 12:00, 14:00, 24:00 (hh:min) after the injection of Myrcludex B – a window of ±10 minutes.

Blood sampling for PK main study for all patients from Myrcludex B groups on weeks, 4, 8, 12, 16, 20, 24, 28, 32, 40, 48 should be performed in accordance with time window indicated in Table 1. Blood sampling during the visit should be performed in 1 hour after injection of Murcludex B, allowed deviation is ± 15 min.

3.6 Limitations of the study

Limitations on concomitant treatment

For information on the limitations of concomitant treatment, refer to Section 5.4.

During the clinical study, the patient consumption of alcohol should not exceed 20 g/day.

Method of birth control during the study

All women of childbearing potential and men who have a partner of childbearing potential must, upon signing informed consent, agree to the adhere to the adequate contraceptive methods during the study from the date of signing the informed consent and to the end of the follow-up period.

Requirements for registration and reporting of cases of pregnancy are presented in Section 7.8.

Women of no childbearing potential meet one of the following criteria:

- women in the postmenopausal period, which is defined as the absence of menstruation for 24 consecutive months, for no alternative medical reason,
- women who have been sterilized (for example, a bilateral tube ligation for more than one menstrual cycle before the enrollment; hysterectomy or bilateral oophorectomy).

The following are considered to be appropriate methods of birth control:

1. Complete sexual abstinence [periodic sexual abstinence (e.g., calendar, symptomatic methods) is not an adequate method of contraception].
2. Male sterilization (with documented confirmation of the absence of spermatozoa in the ejaculate after a performed vasectomy).

3. Intrauterine device or intrauterine system.
4. Hormonal birth control method: oral, injectable hormonal contraceptives or implants. Women using hormonal birth control methods should apply a certain method for at least 4 weeks/1 menstrual cycle before initiating the treatment, and should continue using the same birth control method throughout the study and until the end of the follow-up period.
5. Condom plus spermicide (foam/gel/film/cream/suppository).
6. Occlusal cap (diaphragm, cervical or vaulted caps) plus spermicide (foam/gel/film/cream/suppository).
7. Double barrier method: condom and occlusive cap (diaphragm, cervical or vaulted caps) plus spermicide (foam/gel/film/cream/suppository).

4 PATIENT SELECTION AND DROP-OUT

4.1 Patient selection

The study plans to randomize 90 male and female patients aged 18 through 65 years with chronic viral hepatitis B with delta-agent (ICD-10: B 18.0). Taking into account the possible drop-out during the randomization period, 123 patients are planned to be screened for the study.

According to inclusion criteria only patents with positive results of HDV RNA (qualitative and quantitative), presence of HDV antibodies, with chronic hepatitis B (HBeAg positive or negative), ALT ≥ 1 ULN but < 10 ULN and absence of co-infection of HCV and HIV should be included in the study. Antiviral therapy should be stopped at least in 6 months before the screening. Interferon therapy is allowed (should be stopped at least 6 months before screening).

4.2 Inclusion Criteria

To be included in the study, patients must meet all of the following inclusion criteria:

1. Signed informed consent form.
2. Male and female patients aged from 18 through 65 years.
3. Patients with chronic hepatitis B (HBeAg positive or negative) and presence of HBsAg for at least 6 months prior to screening.
4. Positive results on anti-HDV antibodies for at least 6 months prior to screening.
5. Positive result of HDV RNA during screening.
6. ALT ≥ 1 ULN but < 10 ULN.
7. Patient agrees to use adequate methods of contraception during the study from the time of signing the informed consent and until the follow-up period is completed.

4.3 Exclusion criteria

Patients cannot be enrolled into the study if they meet any of the following criteria:

1. Intolerance, hypersensitivity to the active ingredient and other components of Myrcludex B.
2. Intolerance, hypersensitivity to alpha interferons, genetically engineered drugs obtained with E.coli, to polyethylene glycol or other components of peginterferon alfa-2a
3. A history of therapy with Myrcludex B. (Patients who were treated with interferon drugs are allowed to be included in the study
4. Antiviral therapy to treat chronic viral hepatitis B with delta-agent during the previous 6 months.
5. Anticancer therapy (including radiation therapy) or immunomodulatory therapy (including systemic glucocorticoids) during the previous 6 months.
6. Results of laboratory tests performed at screening:
    a. Hemoglobin < 100 g/L
    b. Leucocytes <3000/μL
    c. Neutrophils <1500/μL
    d. Platelets <90 000/μL
    e. Serum creatinine >1.5 ULN
7. Total bilirubin >34.2 μmol/L. Patients with a higher level of total bilirubin may be enrolled into the study after consultation with the Medical Monitor of the study, if it has been clearly established that such an increase is a manifestation of Gilbert's syndrome.
8. Decompensated liver disease in the current or past medical history, including blood-clotting disorder, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminemia, ascites and bleeding esophageal varices; B/C class or Child-Pugh-Score ≥6
9. Co-infection with the hepatitis C or HIV. (Patients with presence of anti-HCV antibodies at screening but absence of HCV RNA are allowed to participate in the study)
10. Hepatocellular carcinoma
11. Signs of medication or alcohol-induced liver impairment or other medical conditions associated with chronic liver disease (for example, autoimmune hepatitis, hemochromatosis, thalassemia, alcoholic hepatitis, toxic hepatitis).
12. Contraindications to liver biopsy.
13. Concomitant oncological diseases (active or suspected cancer; risk of recurring oncological disease,

observed in the past medical history).
14. Decompensated severe cardiovascular disorders, including those unstable and poorly controlled during the previous 6 months prior to screening.
15. History of poorly controlled thyroid disease or clinically significant manifestations of thyroid dysfunction at screening.
16. History or evidence at the screening of severe renal insufficiency or significant renal function disorders.
17. History or evidence at screening of chronic pulmonary diseases with functional limitation.
18. History or evidence at screening of severe retinopathy, severe ophthalmological disorders due to diabetes mellitus or idiopathic hypertension.
19. History or evidence at screening of significant psychiatric disorders (e.g., severe depression, suicidal attempts, severe neurosis or cognitive disorders.
20. Endocrine disorders (hypoglycemia, hyperglycemia, diabetes mellitus), which cannot be adequately corrected, in the past medical history or at screening.
21. History of organ transplantation.
22. Evidence of drug and/or alcohol abuse (80 g of alcohol/day for men and 40 g of alcohol/day for women) within 1 year prior to screening.
23. History of immunologically mediated diseases (e.g., idiopathic thrombocytopenic purpura, lupus erythematosus, scleroderma, severe psoriasis, rheumatoid arthritis).
24. The need for concomitant treatment with glucocorticoids, drugs with myelotoxic effect.
25. Participation in another clinical study within 30 days before enrollment into this study.
26. Pregnancy and lactation.
27. Any other condition that, in the opinion of the investigator, makes the patient unsuitable for this study.

4.4 Enrollment of patients who are unable to give informed consent to participate in the study

This study does not intend to enroll patients who are unable to give informed consent for their participation.

4.5 Exclusion criteria

In accordance with the principles of the World Medical Association Declaration of Helsinki and other relevant regulations, a patient is entitled to withdraw from the study at any time and for any reason that should not in any way affect the quality of medical care provided to him in the future.
In addition, patients may be withdrawn from the study/study treatment for the following reasons:

- Development of intolerable adverse events
- Changes in the patient's health that, in the opinion of the investigator or sponsor, prevent the patient to continue his participation in the study or to continue the treatment under the study
- Violation of the study protocol requirements
- Inability to contact the patient
- Pregnancy of the female patient participating in the study

If a patient prematurely discontinues the treatment as per the clinical study protocol, and there is no reason preventing further monitoring of the patient's health, the investigator must notify the sponsoring company thereof as soon as possible. Upon the decision of the sponsoring company, the patient may be invited to visit the study center for scheduled visits, even if the treatment was discontinued prematurely, and provided that the patient has not withdrawn his/her consent to participate in the clinical study.
If a patient discontinues the participation in the study prematurely, the investigator should notify the sponsoring company thereof within a short time. The date of the patient's discontinuation of the participation in the study and the reason for the patient's drop-out must be recorded in the patient's CRF, as well as in the patient's medical history.
Patients prematurely withdrawn during the treatment period should complete procedures of Visit 13/Week 48.
Patients prematurely withdrawn during the follow-up period should complete the Follow-up visit procedure/week 72.
The need to perform transient elastometry of liver (Fibroscan) and liver biopsy at the prematurely withdrawal visit should be discussed with the sponsoring company.
There is no substitution for the patients withdrawn from the study. This is with the exception of patients who

underwent screening procedures and who meet the inclusion criteria, but who for some reason dropped out of the study before randomization and start of the study treatment.

4.6 Premature Termination of the Study

The sponsoring company reserves the right to terminate the study at any time for medical and/or administrative reasons. The operating revision of new medical data and information on the treatment safety, performed together with the investigator is a standard practice. As a result of this revision, it may be decided to discontinue the study before all patients complete their participation.

In case of premature termination of the study, regardless of the reason for this decision, the investigator should immediately notify all patients and provide them with appropriate follow-up and further treatment. The sponsoring company will notify the investigator, regulatory authorities and the Institutional Review Board/Independent Ethics Committee in writing of the termination of the study, specifying the reasons for the decision.

In case of the premature termination of the study, the investigator should, if possible, conduct the procedures and examinations described in Section 4.5 to all the patients who have not completed their participation in the study by that time.

5 TREATMENTS

5.1 General Information

5.1.1 Drug Myrcludex B

The study drug Myrcludex B is manufactured as sterile vials with lyophilized powder. The content of the vial is to be reconstituted in 1 mL water for injections

Name:	Myrcludex B (MXB)
Chemical name:	Myristoyl-Gly-Thr-Asn-Leu-Ser-Val-Pro-Asn-Pro-Leu-Gly-Phe-Phe-Pro-Asp-His-Gln-Leu-Asp-Pro-Ala-Phe-Gly-Ala-Asn-Ser-Asn-Asn-Pro-Asp-Trp-Asp-Phe-Asn-Pro-Asn-Lys-Asp-His-Trp-Pro-Glu-Ala-Asn-Lys-Val-Gly-NH2, salt of acetic acid (acetate)
Dosage form:	Lyophilized powder for solution for subcutaneous injection
Formula:	*Active pharmaceutical ingredient:* Myrcludex-B acetate, 2.0 mg/vial, 5.0 mg/vial. *Excipients:* sodium carbonate, sodium hydrogen carbonate, mannitol, hydrochloric acid and sodium hydroxide are used as excipients for dissolution and lyophilization of the drug
Description:	White to off-white powder
Appearance of the prepared solution:	Transparent and clear
Administration route:	Subcutaneous
Originator:	Hepatera LLC, Russia
Manufacturers:	Baccinex SA, Rue de la Source 3, 2822 Kuru, Switzerland LYOcontract GmbH, Pulverwiese 1, 38871 Ilsenburg, Germany (5.0 mg/vial)

5.1.2 Peginterferon alfa-2a (PEG-IFN alfa-2a)

Brand name:	Pegasys®
Dosage form:	Solution for subcutaneous injection
Formula:	*Active pharmaceutical ingredient:* peginterferon alfa-2a (40 kDa)-180 μg/0.5 mL. *Excipients:* sodium chloride, benzyl alcohol, sodium acetate trihydrate, ice acetic acid, polysorbate 80, 10% sodium acetate, 10% acetic acid, water for injection.
Description:	Transparent clear to light yellow solution
Administration route:	Subcutaneous
Marketing authorization holder:	F. Hoffmann-La Roche Ltd., Switzerland

5.1.3 Tenofovir

Trademark:	VIREAD®
Pharmaceutical form:	Film-coated tablets
Ingredients:	*Active ingredient:* Tenofovir disoproxil, 245 mg that is equivalent to 300 mg of Tenofovir disoproxil fumarate. *Excipients:* *Tablet core:* pregelatinized starch, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, magnesium stearate; *Coat:* glycerol triacetate, indigo carmine aluminum lake, hypromellose, lactose monohydrate, titanium dioxide.
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

Administration route:	Per os
Marketing authorization holder:	Gilead Sciences International, Ireland

5.2 Packaging, labeling, storage conditions and drug accountability

Packaging
Drug Myrcludex B
2R vials for injection, colorless glass, European Pharmacopoeia, hydrolytic class I, capped with rubber stopper, European Pharmacopoeia, type I (diameter 13 mm), and aluminum lid, diameter 13 mm, with a plastic disc.
The vial is for single use.

Peginterferon alfa-2a
Presentation and packaging comply with the Instructions for medical use of the registered medicinal product Pegasys®.

Tenofovir
Presentation and packaging comply with the Instructions for medical use of the registered medicinal product Viread®.

Labeling
The drug labeling is performed in accordance with local regulatory requirements for the clinical studies of drugs. The label states "For clinical studies."

Storage conditions
The authorized employee or pharmacy technician of the study center should monitor the temperature regime of drug storage, and record the temperature in a special log. If any deviation from the prescribed temperature regime is detected, an authorized employee or pharmacy technician of the study center should immediately notify the clinical study monitor thereof.

Drug Myrcludex B
In the study center, **the vials with the drug Myrcludex B should be stored in a dark place at minus 20 ± 5°C**.
At the patient's home, the vials with the drug should be stored in the refrigerator, at 2-8°C.
The authorized employee or pharmacy technician of the study center should instruct the patient in detail about the Myrcludex B transportation and storage conditions. The patient should immediately notify the site staff of any deviations in the drug storage conditions.
Temporary storage of the drug at room temperature up to 25°C for not more than three days is allowed.
The prepared drug solution remains stable for 2 hours at room temperature.

Peginterferon alfa-2a
The storage conditions must comply with the Instruction for medical use of the registered medicinal product.
The authorized employee or pharmacist of the investigational site should instruct the patient in detail about the peginterferon alfa-2a transportation and storage conditions at home. The patient should immediately notify the site staff of any deviations in the drug storage conditions.
Tenofovir
The storage condition must comply with the Instruction for medicinal use of the registered medicinal product.
The authorized employee or pharmacist of the Investigational site should instruct the patient in detail about the Tenofovir transportation and storage conditions at home. The patient should immediately notify the site staff of any deviations in the drug storage conditions.

Drug Accountability
For the drug accountability, special forms for entering relevant information will be sent to the study center. After the completion of the study, the authorized employee of the study center must provide originals of completed forms for recording the receipt and return of the study drug/reference product/Tenofovir together with unused and used drug packages.
The investigator is responsible for the drugs to be used for patients in this clinical study only; to be stored in a safe place, access to which is provided for the authorized site staff only; drug accountability is documented according to the established procedure.
Requirements for self-injections performed by patients at home are described in Section 5.3.56, Tenofovir use in Section 5.3.7.

5.3 Administration route, dose, dosage regimen

5.3.1 Myrcludex B

The study drug Myrcludex B should be injected subcutaneously daily, once a day, every 24±1 hour (once daily for groups B- E) and 12±1 hour (twice a day for group F). Application rules:

1. Patient should establish the consent time for daily injection of study drug in the first days of treatment and then should follow the estimated schedule of injection during all period of the study.
2. For patients from group F: First injection should be performed from 6:00 a.m. till 11:59 a.m. (hh:min), the second injection – from 18:00 p.m. to 23:59 p.m. (hh:min).
3. The interval between injections should be 24±1 hours for groups B-E and 12±1 hours for group F. The exact time for the next injection should be calculated from the previous injection with possible deviation ±1 hour.

Actions in case of deviations from schedule of injection are described in Section 5.3.1.2.

The duration of therapy is 48 weeks. Totally patient should receive 337-339 injections of Myrcludex B (groups B-E) or 674-678 injections (group F) of Myrcludex B during the study, the last injection should be performed at the Investigation site on Visit 13 (End of treatment, EOT) / week 48 / Day 337+2).

Depending on the dose of the study drug, injections of Myrcludex B should be performed as follows:

Myrcludex B dose	Drug form, Necessary quantity of vials	Volume of solution of study drug necessary for injection
2 mg/per day	2,0 mg/vial 1 vial	1 ml
5 mg/per day	5,0 mg/vial 1 vial	1 ml
10 mg/per day (10 mg once daily)	5,0 mg/vial 2 vials	2 ml Should be injected by two separate injection for 1 ml
10 mg/per day (5 mg twice daily)	*Each injection:* 5,0 mg/vial 1 vial	*Each injection:* 1 ml

The contents of the vial (2.0 mg/vial, 5.0 mg/vial) should be dissolved in 1 mL of water for injection. The prepared drug solution remains stable for 2 hours at room temperature.
Injection sites: outer surface of the shoulder, anterolateral surface of the thigh, anterolateral surface of the abdominal wall with well-developed subcutaneous fat. During the treatment period, the injection sites may be changed.
Patients will make self-injections of Myrcludex B, except for the visits on the days of blood sampling for pharmacokinetic evaluation of Myrcludex B. The rules for preparing and performing self-injections are described below in Section 5.3.6.

5.3.1.1 Doses, dosage regimen
Patients randomized to arms B-F, will be treated with the study drug Myrcludex B at doses of 2 mg/day, 5 mg/day or 10 mg/day:

- Arm B (n=15): Myrcludex B 2 mg + PEG-IFN alfa-2a 180 μg during 48 weeks
- Arm C (n=15): Myrcludex B 5 mg + PEG-IFN alfa-2a 180 μg during 48 weeks
- Arm D (n=15): monotherapy with Myrcludex B 2 mg during 48 weeks
- Arm E (n=15): Myrcludex B 10 mg (once a day) + PEG IFN alfa-2a 180 μg during 48 weeks
- Arm F (n=15): Myrcludex B 10 mg (5 mg twice a day) and Tenofovir 300 mg during 48 weeks

Sequence and localization of the subcutaneous injection sites on the days of co-prescribing of drugs Myrcludex B and peginterferon alfa-2a: injection(s) of Myrcludex B should be done at first and after that peginterferon alfa-2a. Subcutaneous injections of Myrcludex B and peginterferon alfa-2a should be performed in different anatomical regions.

5.3.1.2 Measures to be taken when the dose of the study drug Myrcludex B is missed
If the injection is not performed at the scheduled time (i.e. after 25 hours [24+1] hours from the previous injection in Arms B-E and 13 hours [12+1] hours from previous injection in arm F), but can be performed within 4 hours after the scheduled injection (i.e. not more than 28 hours [24+4] in Arms B-E and 16 hours [12+4] hours in Arm F), it is necessary to perform the injection and specify the exact time of drug injection in the appropriate section of the Patient Diary. Further treatment is not carried out from the time of this dosing with a deviation, but according to the previously planned administration schedule, i.e., relative to a previous time set up by the schedule.
If the injection cannot be performed within 4 hours after the planned injection, the drug is not injected, the dose is missed. Further treatment is provided according to the previously planned and administration schedule, i.e., relative to previous time on schedule. No injection of the missed and planned dose is allowed!
If injection was done incorrectly with interval more than 4 hours from previous one (i.e. the interval between the two injections was more than 28 hours in arms B-E and 16 hours in arm F), than further treatment should also be carried out according to previously planned administration schedule, i.e. relative to previous time set

up by the schedule.
All cases of deviation from the schedule of injection should be reported in the Patient Diary and the patient's case report form. The patient should be instructed on measures in case of the missing the dose.

5.3.1.3 Adjustment of the dose of Myrcludex B
Dose adjustment can be performed only in arms C, E, F, which receive treatment with Myrcludex B at a dose of 5 mg or 10 mg. The dose correction in arms B and D receiving the drug at a dose of 2 mg is not performed.
If a patient receiving Myrcludex B at a dose of 5 mg or 10 mg develops the study drug related adverse event, which is not resolved or stabilized during the subsequent follow-up to a state that, in the opinion of the investigator, is acceptable, then can be made a decision to reduce the dose of Myrcludex B up to one level (from 5 mg to 2 mg or from 10 mg to 5 mg) in accordance with the following provisions:
1. The dose reduction of Myrcludex B is performed after receiving a written confirmation by the sponsoring company.
2. The treatment duration, the schedule of planned visits and the list of necessary examinations is not changed after the reducing of the dose and is performed in accordance with the flow chart presented in Table 1.
3. If during the subsequent treatment period, the patient develops intolerable adverse events/toxic reactions, or the patient's health, in the opinion of the investigator or the sponsoring company, does not allow continuing the treatment with the study drug, the treatment should be discontinued.

Grade 3 and 4 toxic reactions
- If a clinically significant laboratory abnormality or a Grade 3 clinical event under CTCAE develops (refer to Section 7.4.1), the treatment with the study drug can be continued if this event was found not to be related to the study drug.
- If a Grade 3 adverse event (clinical event or a clinically significant laboratory abnormality), considered to be related to the study drug, develops, the treatment should be discontinued until the toxic reaction is reduced to Grade 2 and below.
- If, after the renewal 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 with the study drug should be completely discontinued. Recurrence of adverse events considered not to be related to the study drug does not require the discontinuation of the treatment.
- If a clinically significant laboratory abnormality or a Grade 4 clinical event under CTCAE, considered to be related to the study drug, develops, the treatment with the study drug should be completely discontinued. A Grade 4 clinically significant laboratory abnormality, not confirmed by repeated analyzes, should be adjusted in accordance with the algorithm for a new toxicity grade.
- If a Grade 4 clinically insignificant laboratory abnormality is found (for example, increased triglyceride level when blood is sampled not under fasting condition or subject to medical correction) or Grade 4 clinical events, which are evaluated as not related to the study drug, treatment can be continued without interruption.

5.3.2 Peginterferon alfa-2a (PEG-IFN alfa-2a)
Peginterferon alfa-2a should be injected subcutaneously, in the area of the anterior abdominal wall or in the thigh area, once a week. The drug must be injected in different sites every time. The treatment lasts 48 weeks. Totally, Patients should receive 48 injections of drug during the treatment (arms A-C, E).
Preparation and performance of injections must comply with the requirements of the Instruction for medical use of the registered drug Pegasys®.
Patients will make self-injections of peginterferon alfa-2a, except for the visits on the days of pharmacokinetic evaluation of Myrcludex B for patients in arms B and C (10 patients in each arm). Patients of arms B and C enrolled into the additional pharmacokinetic substudy should receive injections of peginterferon alfa-2a at the study center on Days 1 and 14. However, injections PEG-IFN alfa- 2a for other treatment arms may be performed in investigational site, if it is necessary.
The rules for preparing and performing self-injections are described below in Section 5.3.6.

5.3.2.1 Doses and dosage regimen
The drug peginterferon alfa-2a will be injected at a dose of 180 μg:

- Arm A (n=15): PEG-IFN alfa-2a 180 μg during 48 weeks
- Arm B (n=15): Myrcludex B 2 mg + PEG-IFN alfa-2a 180 μg during 48 weeks
- Arm C (n=15): Myrcludex B 5 mg + PEG-IFN alfa-2a 180 μg during 48 weeks
- Arm E(n=15): Myrcludex B 10 mg (once a day) + PEG-IFN alfa-2a 180 μg during 48 weeks

Sequence and localization of the subcutaneous injection sites on the days of co-prescribing of drugs Myrcludex B and PEG-IFN alfa 2a: *injection(s) of Myrcludex B should be done at first and after that* peginterferon alfa-2a. Subcutaneous injections of Myrcludex B and peginterferon alfa-2a should be performed in different anatomical regions.

5.3.2.2 Adjustment of the dose of peginterferon alfa-2a
Dose adjustment instructions are provided according to the Instruction for medical use.

General disorders
If dose adjustment is required due to moderate and severe clinical or laboratory reactions, it is usually sufficient to reduce the dose of the drug to 135 μg. However, in some cases, it is necessary to reduce the dose to 90 μg or 45 μg. When adverse reactions are resolved, it may be possible to consider increasing the drug dose up to the initial dose (additional information is provided in the sections "Special instructions" and "Side effect" in the Instruction for medical use).

Hematologic disorders
Dose reduction is recommended when the neutrophil count decreases less than 750 cells/μL. Treatment of patients with an absolute neutrophil count of less than 500 cells/μL, should be discontinued until this value exceeds 1,000 cells/μL. The drug injection should be reinitiated at a dose of 90 μg under periodic control of the neutrophil count (the control period is determined by the doctor in each case individually).
The dose reduction to 90 μg is recommended when the platelet count decreases less than 50,000 cells/μL. The drug should be discontinued in patients with a platelet count of less than 25,000 cells/μL.

Neuropsychiatric disorders
In accordance with the Instruction for medical use of Pegasys®, severe adverse reactions of the central nervous system (CNS) were observed in some patients, both during the drug treatment and within 6 months after the discontinuation of treatment. In particular: depression, suicidal trials, and attempted suicides. In the treatment with alpha interferons, there were other CNS side effects, including aggressive behavior, sometimes against other people (e.g., homicidal ideation), confused mental state, mental disorders. Patients should be closely monitored to identify signs and symptoms of mental disorders. If such symptoms develop, the patient should be carefully monitored, and a psychiatrist should be appointed if necessary. If symptoms of mental disorders persist or worsen, or if suicidal trials are identified, treatment with Pegasus® should be discontinued.

Endocrine system disorders
When alpha interferons, including Pegasys® were used, thyroid dysfunction or worsening of previous thyroid diseases were observed. If there are clinical symptoms of possible thyroid dysfunction and/or clinically significant abnormalities based on the results of the TSH and T4 tests performed during the study, a decision to adjust the dose and/or the duration of the drug treatment may be made.
As with other interferon therapy, hypoglycemia, hyperglycemia, and diabetes mellitus were observed with the injection of Pegasys®. In the case of the development of such conditions, which cannot be adequately corrected, the drug treatment should be discontinued.

Cardiovascular system
If cardiovascular status worsens during the study, the drug treatment should be suspended or discontinued.

Autoimmune diseases

Autoantibodies and autoimmune diseases are described to develop during treatment with alpha interferons. If necessary, treatment of patients with signs or symptoms similar to those of autoimmune diseases should be discontinued.
There are reports of cases of Vogt-Koyanagi-Harada syndrome in patients with chronic hepatitis C treated with interferons. If the Vogt-Koyanagi-Harada syndrome is suspected, the drug treatment should be discontinued.
Fever and infections
Although fever may be associated with the flu-like syndrome often related to interferon therapy, other causes of persistent fever (severe bacterial, viral and fungal infections, in particular) should be excluded, especially in patients with neutropenia. When interferon alfa, including Pegasys®, were used, severe infections (bacterial, viral, fungal) were reported. When these conditions develop, the drug treatment should be discontinued.

Ophthalmic changes
As with other interferon treatment, when treated with Pegasys®, retinopathy was rarely noted, including retinal hemorrhage, cotton wool spots, swelling of the optic nerve, optic neuritis and thrombosis of retinal arteries and veins. If there are any complaints of the worsening of visual acuity or narrowing of the visual fields, an ophthalmological examination should be performed immediately. If an ophthalmic disease occurs or deteriorates, the treatment should be discontinued.

Changes in the respiratory system
As with other interferon treatment, when treated with Pegasys®, respiratory adverse reactions were observed, including shortness of breath, pulmonary infiltrates, pneumonia and pneumonitis. If there are persistent (persistent) infiltrates or infiltrates of unknown origin or if there is a respiratory failure, the treatment should be discontinued.

Skin disorders
The use of alpha interferons was associated with aggravation or induction of psoriasis and sarcoidosis. In case of the disease development or aggravation, the drug withdrawal should be considered.

5.3.2.3 Rules for dose adjustment, delayed injection and dose delay
If the acceptable safety profile of the treatment is preserved, no missed drug dose or delayed injection is allowed. These recommendations are stipulated by the risk of re-activation of resistant strains of the virus in presence of a decrease in the blood drug concentration, which may prevent the development of a stable treatment response.
If, in the opinion of the physician investigator, the patient is required to skip the dose or delay the injection of the drug, these cases should be discussed with the study's sponsoring company. First of all, it is recommended to consider the possibility of dose adjustment (temporarily or permanently), and only then a dose will be skipped or delayed.
The dose adjustment of peginterferon alfa-2a must be performed in accordance with the following rules:

Initial dose	180 μg
1st level of dose reduction (75%)	135 μg
2nd level of dose reduction (50%)	90 μg
3rd level of dose reduction (25%)	45 μg

After the reduction, the dose may be adjusted upward to an acceptable level, subject to the following conditions:

- The medical event that led to the dose correction has resolved or improved.
- If the patient received 4 or more consecutive reduced drug doses or a total of 6 reduced doses, no upward adjustment should be made.

If the delay of the planned dose is necessary, further treatment should be performed in accordance with the following recommendations:

Dose delayed 1-2 days: The following doses are assigned according to the originally planned schedule of injection (e.g., if the drug is injected every Monday, due to the need for delayed injection, the next injection is performed on Wednesday, the next injection

should be performed on Monday, according to the schedule)

Dose delayed 3-5 days: The following doses are assigned every 5 or 6 days before the renew of the initial schedule (e.g., if the drug is administered every Monday, the delayed injection is performed on Saturday, the following injections must be performed on Thursday, then on Tuesday, then on Monday [until the original schedule is renewed])

Dose delayed 6 days: The weekly dose is missed, the following doses are assigned according to the originally planned schedule of injection (e.g., if the drug is administered every Monday, the delayed injection is performed on Sunday, the nearest planned injection is missed [Monday], the next injection is performed next Monday)

Dose delayed ≥7 days: The treatment is reinitiated at the required time, if necessary, injections can be performed at intervals of every 5 or 6 days, until the original schedule is renewed.

If the patient has not received 4 or more sequential drug doses (for medical or any other reasons), further treatment with the peginterferon alfa-2a drug should be discussed with the study's sponsoring company.

5.3.3 Tenofovir

Tenofovir should be administered orally, once daily, 300 mg. Duration of the treatment is 72 weeks.
Patients will take the drug on their own at home. Mode of application, rules of dosing regimen must comply with Instructions for medical use of the registered medicinal product Viread®.

5.3.4 Dose adjustment of Myrcludex B and peginterferon alfa-2a with increased ALT and AST activity

With a progressive or clinically significant increase in ALT activity, the dose of peginterferon alfa-2a should be reduced. The dose adjustment of Myrcludex B should be discussed with the sponsoring company. The patient's condition should be followed under careful medical supervision; additional examinations and visits to the study center may be prescribed, if necessary.
If, despite the treatment correction, the ALT activity continues to increase or, if this increase is accompanied by an increase in the direct bilirubin concentration, the drug treatment should be discontinued.

5.3.5 Missing one or more drug doses in connection with the development of adverse events

If, in the opinion of the investigator, the patient needs to miss one or more doses of Myrcludex B and/or peginterferon alfa-2a and/or Tenofovir due to the development of adverse events, these cases should be discussed with the study's sponsoring company in an expedited fashion.
If a patient randomized to a combination treatment arm requires the suspension/discontinuation of treatment with one of the drugs, these cases should be discussed with the study's sponsoring company in an expedited fashion. If the patient's health state allows to continue his/her participation in this clinical study, treatment will be continued as a monotherapy in accordance with the planned dosage regimen.

5.3.6 Rules for preparation and performance of self-injections Myrcludex B + Peginterferon alfa 2a

For the patient's self-injections at home, Myrcludex B and/or peginterferon alfa-2a will be handed over in an amount sufficient for the 28(+2)-day treatment, at visits 11 and 12 (weeks 32 and 40) in an amount sufficient for the 56(+2)-day treatment. Together with the package of the drug, the patient is provided with the required amount of sterile injection water, injection syringes and other related materials for the subcutaneous injections.
Before the beginning of treatment, patients will receive a Patient Diary with Instructions on preparing and performing injections of Myrcludex B and/or peginterferon alfa-2a. Patients should personally record the injection of the drug on a daily basis, the date of receipt of drugs for continuing therapy and the number of packs received, complaints and any health status deviations during the study treatment period. Data on the treatment with Myrcludex B and/or peginterferon alfa-2a should be transferred from the Patient Diary to the appropriate form of the CRF.
During each visit to the study center, the patient should demonstrate the filled Patient Diary, and return used and unused vials/packages of the drug (except for visits days 8 and 15, vials/packages these days are not returned). The physician investigator must record the following information in the Patient Diary: date of the diary review, name and the signature of the physician investigator, the number of vials/packs of the drug returned by the patient. Copies of the filled pages of the Patient Diary will be archived in the study center.

In advance, the investigator should train the patient how to perform self-injections at home, and document in the source documentation that following information has been provided to the patient:

- the drug(s) storage conditions at the patient's home;
- rules for the preparing and performing the drug(s) injections;
- the patient's actions in the event of deviations from the treatment regimen;
- rules for filling the Patient Diary in;
- rules for storage and return of used and unused vials/packs of the drug(s) to the study center.

If necessary, the patient can visit the study center for additional training and performing self-injections under the supervision of medical personnel at the beginning of treatment

5.3.7 Rules of Tenofovir self-taking

For the patient's self-taking of Tenofovir at home the drug will be issued in a quantity sufficient for treatment during 28(+2) days, on visits of weeks 32 and 40 - in a quantity sufficient to treatment during 56(+2) days, on visit of the week 48 – in a quantity sufficient to treatment during 14(+2) days, on visit of the week 50 – in a quantity sufficient to treatment during 14(+3) days, on visits of the weeks 52 and 56 – in a quantity sufficient to treatment during 28(+3) days, on visit of the week 60 – 84(+3) days. On visit of the week 48 drug dispensing is permitted in a quantity sufficient to treatment during 28(+3) days, In that case there will be no drug dispensing on the week 50.

Before the beginning of treatment, patients will receive a Patient Diary with Instructions of drug use. Patients should personally record the information about drug use on a daily basis, the date of receipt of the drug to continue treatment and the number of received packs, complaints and any health status deviations during the study treatment period. Data on the treatment with Tenofovir should be transferred from the patient diary to the appropriate form of the CRF.

During each visit to the study center the patient should demonstrate the filled Patient Diary and return used vials/packages of the drug (except for visits days 8 and 15 on the week 50, vials/packages these days are not returned). The physician investigator should record the following information in the Patient Diary: date of the diary review, name and the signature of the physician investigator, the number of vials/packs of the drug returned by the patient. Copies of the filled pages of the Patient Diary will be archived in the study center.

5.4 Concomitant treatment

Authorized concomitant treatment

During the study period, the concomitant treatment is allowed to correct the patient condition due to the effect of Myrcludex B and/or peginterferon alfa-2a and/or Tenofovir.

Prohibited concomitant treatment

- Other study drugs
- Other antiretroviral therapy (drugs intended for treatment of common cold are allowed)
- Antineoplastic drugs
- Myelotoxic drugs
- Systemic glucocorticoids (except for substitution therapy), radiation therapy, other immunomodulatory treatment (drugs intended for treatment of common cold are allowed and Haematopoiesis -stimulating agents are allowed during interferon therapy only).

In case of concomitant treatment with paracetamol, the daily dose should not exceed 4 g.

During the clinical study, the patient consumption of alcohol should not exceed 20 g/day.

For patients participating in the pharmacokinetic study (patients of arms B, C, F), the use of concomitant treatment during Days 1-15 is allowed only upon the decision of the investigator, provided there are no signs of the drug effect on the pharmacokinetics of the drug Myrcludex B.

6 STUDY PROCEDURES

6.1 Collection of data on demographic and other baseline characteristics

6.1.1 Demographic data

The following demographic data will be recorded during the screening period:

- Date of birth
- Gender
- Race
- Data on bad health habits: smoking, drinking and drug use, drug abuse

6.1.2 Medical history

Detailed medical history data will be collected, including information on all present illnesses and all significant (in the opinion of the investigator) past diseases during the screening.

Information on all the past and present pathologies at the time of the screening visit or those developed between the signing of the informed consent form and the start of treatment are recorded in the case report form in the section "Medical history". At least the following data must be registered in the CRFs: diagnosis/symptom, degree of severity of the disease according to CTCAE, start date, end date, information if the disease is resolved. If the patient has past or concomitant ophthalmic diseases, an ophthalmological examination may be required, as described in Section 6.3.2.

The aggravation of the present illness or any untoward change in the patient's health after the administration of the first dose of the study drug/reference product considered by the investigator as clinically significant should be recorded as an adverse event.

6.1.3 Collection of data on previous and concomitant treatment

Information on the treatment of the underlying disease and other comorbidities, including drug and non-medicinal methods of treatment (for previous 6 months), should be recorded in the case report form. Data on any concomitant treatment performed after the patient has been included in the study are also recorded in CRFs.

Information on prohibited and permitted concomitant treatment is provided in Section 5.4.

6.1.4 Measurement of the body height, weight

During the screening period, the patient's body height (cm), weight (kg) and body mass index (BMI) will be measured. Repeated measurements of body weight will be performed during the study in accordance with the flow chart presented in Table 1.

6.1.5 Urine pregnancy test

The urine pregnancy test will be performed for women of childbearing potential during the screening and during the treatment period (Table 1). The analysis will be performed at the study center using test strips.

6.1.6 Urine drug screening

Urine drug screening will be performed during the screening period using test strips to analyze the urinary methadone, benzodiazepines, cocaine, amphetamines, marijuana, opiates, barbiturates, tricyclic antidepressants.

6.1.7 Alcohol-breath test

The alcohol-breath test will be performed during the screening period using an electronic device.

6.1.8 Alpha-fetoprotein blood test

To exclude hepatocellular carcinoma all patients will be tested for serum alpha-fetoprotein during the screening period.

6.1.9 Serologic assay

- Anti-HIV antibodies;
- Anti-HCV antibodies;

- Anti-HDV antibodies;
- Non-quantitative HBsAg analysis to assess the acceptability of the patient to participate in the study;
- Non-quantitative HBeAg analysis;
- Anti-HBsAG antibodies,
- Anti-HBeAG antibodies.

The above tests should be performed at the local laboratory of the study center, unless otherwise indicated. If any anti-HCV antibodies are found, an analysis on RNA HCV should be performed. If the results of HCV RNA analysis are negative, the patient can be enrolled into the study.

6.2 Efficacy evaluation

The study will evaluate the virology parameters: HDV RNA, HBsAg and HBV DNA. Venous blood samples will be collected at specified time points.

The following parameters will be evaluated:

- HDV RNA by a quantitative PCR method;
- HBsAg level by a quantitative EIA method
- HBV DNA by a quantitative PCR method;
- At the end-of-treatment and follow-up visits: anti-HBsAg antibodies, only in patients with undetectable quantitative HBsAg

No separate sample will be collected for this analysis. At the end of the study, the determination of anti-HBsAg antibodies will be performed at a central virology laboratory using appropriate archival samples (for HBsAg determination) in those patients for whom a negative result of the HBsAg quantification was obtained at Visits 48 and 72.

The blood samples will be collected in sterile, hermetically sealed disposable plastic K2-EDTA Vacutainer® tubes. All collected samples of plasma are stored at -20°C before being sent to a central laboratory in a validated thermal container at a temperature -20° C ± 5°C.

Both qualitative and quantitative HDV RNA blood test may be performed at screening. Plasma samples for HDV RNA analysis at the screening stage are stored until shipping at -20°C, then sent to the central laboratory at room temperature (transport at +2+8°C is also allowed). When samples are transported to the central laboratory on the day of blood sampling, the samples are not frozen.

6.2.1 Fibroscan

To assess fibrosis, transient elastometry of the liver (Fibroscan) will be performed during the screening period, at the end of treatment period (Week 48, End of treatment) and at the end of follow-up period (Week 72, End of follow up). All study patients undergo the transient elastometry. Liver biopsy is not exclusive of transient elastometry.

The procedure of the transient elastometry of liver can be performed directly at the study center, or, if it is impossible, in authorized medical institution, which have a proper equipment and qualification staff.

6.2.2 Liver biopsy

Liver biopsy will be performed during screening period, then for arms D and F – at the end of treatment (week 48, End of treatment), for all other arms – at the end of follow up period (week 72, End of follow up). The second biopsy can be performed within ±7 days after the end-of-treatment visit /follow up period. Repeated liver biopsy is necessary to determine the effect of treatment on the degree of fibrosis and necroinflammation, as well as the correlation of the possible negativation or decline of HDV RNA and cccDNA with viral load and HBsAg dynamics. Loss of cccDNA is the most important endpoint of HBV/HBV infection treatment.

Liver tissue samples should be divided into 3 parts, one part is fixed in the Allprotect Tissue Reagent reagent (Qiagen) and frozen at -20°C, the second part is fixed to get paraffin sections, and the third is fixed in formalin solution for the production of histological slides.

Detailed information on the liver biopsy procedure will be described in the laboratory manual.

The biopsy procedure can be performed directly at the study center as part of the study, or, if it is impossible, in authorized medical institution, which have a proper equipment and qualification staff.

6.2.3 Abdominal ultrasound

Abdominal ultrasound will be performed during the screening period, at the end of treatment period (Week 48, End of treatment) and at the end of follow-up period (Week 72, End of follow up). The procedure will be performed locally, the evaluations should be performed by the same employee of the study center.

6.2.4 HBV and HDV genotyping, resistance assay and analysis of NTCP polymorphism

HBV and HDV genotyping

Blood sample will be taken to perform genotyping of hepatitis B viruses (HBV) and D (HDV) at a randomization visit on Day 1. Blood samples will be frozen and sent to the central laboratory. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

Resistance assay

One blood sample will be taken for a resistance assay at a randomization visit on Day 1, and another one will be taken at visit 13 (end of treatment visit) on Week 48 / Day 337+2. Blood samples will be frozen and sent to the central laboratory. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual. Resistance assay on the Week 48 (or visit of premature drop-out) will be performed only in those patients who have a viral load following the result of virological study.

NTCP polymorphism

NTCP polymorphism will be evaluated once during the study (initially) in the central laboratory, using the sequencing method. Blood sample received by resistance assay on visit 1 in a Day 1 will be used for investigation.

6.3 Safety Evaluation

The safety parameters under the evaluation include:

- Adverse events, serious adverse events (for the detailed description refer to Section 7)
- Physical examination
- Ophthalmological examination
- Vital signs
- 12-lead ECG.
- Hematology
- Blood chemistry
- Coagulogram
- Urinalysis
- Total bile acids
- Blood test for TSH, T4

To identify the adverse events in this study, an evaluation of the patient health abnormalities will be made (based on physical examination findings, results of laboratory and instrumental study methods) from the data obtained during the Screening, from other Visits of the planned study and accepted reference values.

After receiving the necessary information, the investigator will classify the patient's condition as "norm", "clinically insignificant deviations" or "clinically significant deviations". If the observed deviations were not previously recorded and, according to the investigator's assessment, are clinically significant, or the patient's condition will worsen compared to the data obtained during the Screening, the observed deviations will be classified as adverse events (AEs) and identified under the severity as per CTCAE.

6.3.1 Physical examination

A general physical examination will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.

The following patient's organ systems will be evaluated during the physical examination:

- General condition
- Skin, hair and nails
- Ears, nose and throat
- Endocrine system
- Cardiovascular system
- Respiratory system
- Gastrointestinal tract
- Kidneys and urinary system

- Reproductive system
- Musculoskeletal system
- Nervous system
- Visual system
- Lymphatic system

All new clinically significant abnormalities or results obtained at the screening, including clinically significant cases of deterioration in the physical examination findings, should be recorded as adverse events and monitored in a proper way.

6.3.2 Ophthalmological examination

In case of interferon treatment retinopathy was rarely noted, including retinal hemorrhage, cotton wool spots, swelling of the optic nerve, optic neuritis and thrombosis of retinal arteries and veins. In view of possible development of these adverse events, an ophthalmological examination of patients with mild and moderately retinopathy will be performed during the screening period in order to assess the baseline ocular changes. If necessary, an ophthalmological examination can be performed in patients with other concomitant visual organ disorders. During the study, an ophthalmological examination should be performed in patients with complaints of impaired visual acuity, narrowing of the visual fields or worsening of the symptoms of the concomitant ocular disease observed at the screening.

6.3.3 Evaluation of vital signs

A vital signs examination will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.

The following vital signs will be measured in the sitting position after the patient is at rest for 5 minutes:

- Systolic arterial pressure (in mm Hg)
- Diastolic arterial pressure (in mm Hg)
- Heart rate (in beats per minute)
- Body temperature (in °C)

During the study, blood pressure measurement of each patient should be performed using the same measuring instrument, on the same arm. The heart rate is determined at the radial artery for 30 seconds, then the calculation of the number of beats per minute is performed. The body temperature is measured in the axillary (retromuscular) region.

All new clinically significant abnormalities or results obtained at the screening should be recorded as adverse events and monitored in a proper way.

6.3.4 Electrocardiography

A standard 12-lead electrocardiographic study will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.

The tracking of the rhythm in corresponding leads should contain estimable data of at least three cardiac cycles.

6.3.5 Hematology

Hematology will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.

Hematology will be performed in the central laboratory.

Investigators must perform the evaluation of the clinical significance of all laboratory abnormalities. Clinically significant hematology abnormalities, found after the first injection of the study drug/reference product, should be recorded as adverse events.

The following indicators will be evaluated:

- Hematocrit
- Hemoglobin
- Red blood cells
- Reticulocytes
- Platelets

- Leucocytes
- WBC differential (neutrophils, eosinophils, monocytes, basophils, lymphocytes)
- Erythrocyte sedimentation rate (ESR)

6.3.6 Blood chemistry

Blood chemistry will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.
During the screening, the blood chemistry will be performed in the central laboratory.
Investigators must perform the evaluation of the clinical significance of all laboratory abnormalities. Clinically significant blood chemistry abnormalities, found after the first injection of the study drug/reference product, should be recorded as adverse events.
The following indicators will be evaluated:

- Total protein
- Albumins
- ALT
- AST
- GGT
- LDH
- p-amylase
- Alkaline phosphatase
- Lipase
- Triglycerides
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Creatinine
- Urea
- Glucose
- Potassium
- Sodium
- Calcium
- Chlorides
- Phosphates
- C-reactive protein

6.3.7 Coagulogram

Coagulogram will be evaluated during the screening, treatment and follow-up period according to the flow chart presented in Table 1.
During the screening, the coagulogram will be performed in the central laboratory.
The following indicators will be evaluated:

- Activated partial thromboplastin time [aPTT]:
- Prothrombin time

Investigators must perform the evaluation of the clinical significance of all laboratory abnormalities. Clinically significant abnormalities, found after the first injection of the study drug/reference product, should be recorded as adverse events.

6.3.8 Urinalysis

Urinalysis will be performed in the central laboratory. Sampling will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1.
Investigators must perform the evaluation of the clinical significance of all laboratory abnormalities. Clinically significant abnormalities, found after the first injection of the study drug/reference product, should be recorded as adverse events.
The following indicators will be evaluated:

- pH
- Specific gravity
- Protein
- Glucose
- Bilirubin
- Urobilinogen
- Ketones
- Red blood cells
- White blood cells
- Nitrites

If any infection is suspected, the urine culture will be performed. If more than trace amounts of blood or protein are detected in the sample, a microscopic urine analysis for blood or protein will be performed. Urine culture and microscopy will be performed in the local laboratory of the study center using standard methods.

6.3.9 Total bile acids

A total bile acids test will be performed during the screening, treatment and follow-up period according to the flow chart presented in Table 1. Blood samples will be frozen and sent to the central laboratory for an analysis. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

6.3.10 Blood test for TSH, T4

When alpha interferons were used, thyroid dysfunction or worsening of previous thyroid diseases were observed. In view of possible development of these adverse events, this study will assess TSH and T4 levels at the screening and during the treatment according to the flow chart presented in Table 1. Blood samples will be sent to the central laboratory for analysis. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

6.4 Pharmacokinetics Evaluation

6.4.1. Pharmacokinetic substudy (PK-substudy)

An additional pharmacokinetic study (PK substudy) is planned to be performed as a part of the study, in which 20 patients randomized to each of treatment groups B and C (a total of 20 patients) will be enrolled.
Blood samples for the assessment of the drug concentration will be collected at the following time points:
Days 1-2, 14-15:

- Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection.
- Day 2 – in 24:00 (hh:min) after the drug injection.
- Day 14 – before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection.
- Day 15 – in 24:00 (hh:min) after the drug injection.

For patients in arms B and C participating in the pharmacokinetic study, there are no window periods for visits on Days 1 and 2, blood sampling for evaluation the pharmacokinetics of Myrcludex B must be performed before and after the first dose. Directly during the visits the following window periods for blood sampling to evaluate pharmacokinetics are allowed:

- in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00 (hh:min) after the injection of Myrcludex B – a window of ±5 minutes,
- in 6:00, 8:00, 10:00, 12:00, 14:00, 24:00 (hh:min) after the injection of Myrcludex B – a window of ±10 minutes.

Patients participating into the pharmacokinetic substudy (PK-substudy) will be hospitalized (in day-stay or 24-hour hospital) before the start of study treatment and will stay in the hospital during Days 1, 2, 14, 15. Other visits of pharmacokinetics (PK-main study) will be done outpatiently.
Blood samples will be frozen and sent to the central laboratory for analysis by the means of the validated analytical method. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

6.4.2. Pharmacokinetic main study (PK-main study).
For a more precise investigation of the possible study drug accumulation in all patients of each Myrcludex B treatment arm, blood sampling points for the pharmacokinetic study are assigned: week 4, 8, 12, 16, 20, 24, 28, 32, 40, 48 (Week 48 only in arms E-F) in 1hour ±15 min after the drug administration. For the patients not participating in the additional pharmacokinetic studies, a blood sampling point at a randomization visit on a Day 1 (in 1 hour ±15 min after the first drug injection) is assigned.
6.4.3. Pharmacokinetic study in Arm F (the second part of the study). The first 10 patients randomized in Arm F will participate in the study. Blood samples for assessment of drug concentration will be collected on days 1, 2 and 14, 15 at the following time points:

- Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min) after the drug injection.

Blood sampling in 12 hours after the first injection must be performed before the second drug injection MXB.

- Day 2 – in 12:00 (hh:min) after the second drug injection on Day 1.

Blood sampling must be performed before the third drug injection MXB.

- Day 14 – before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, (hh:min) after the drug injection.

Blood sampling in 12 hours after the first injection must be performed before the next drug injection MXB on Day 14.

- Day 15 – in 12:00 (hh:min) after the second drug injection on Day 14.

Blood sampling must be performed before the first drug injection MXB on Day 15.
For patients in Arm F participating in the pharmacokinetic study, there are no window periods for visits in days 1 and 2, blood sampling for evaluation the pharmacokinetics must be performed before and after the first dose of Myrcludex B. The second part of pharmacokinetic study may be performed with deviation +1 day (i.e. Days 15-16 of the study). Directly during the visits the following window periods for blood sampling to evaluate pharmacokinetics are allowed:

- in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00 (hh:min) after the injection of Myrcludex B – a window of ±5 minutes,
- in 6:00, 8:00, 10:00, 12:00, 14:00, 24:00 (hh:min) after the injection of Myrcludex B – a window of ±10 minutes.

Patients participating into the pharmacokinetic substudy (PK-substudy) will be hospitalized before the start of study treatment and will stay in the hospital during Days 1, 2, 14, 15. Other visits of pharmacokinetics (PK-main study) will be done outpatiently.
Blood samples will be frozen and sent to the central laboratory for analysis by the means of the validated analytical method. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

6.5 Immunogenicity

Assessment of immunogenicity will be performed in the groups of therapy with the studied drug Myrcludex B. Blood sampling for the detection of the antibodies to Myrcludex B will be determined during the treatment period (before the drug injection [Day 1], at 12, 24, 48 treatment weeks) and during the follow-up period (at 4, 12, 24 weeks after the end of treatment).
Blood samples will be frozen and sent to the central laboratory. The evaluation will be performed by the method of radioimmunoassay. Detailed instructions for the collection, preparation and sending of blood samples will be provided in the Laboratory manual.

6.6 Patient Diary

Before the treatment is started, the Patient Diary will be issued to all patients to collect the information about investigational drugs intake with Instructions on the preparation and administration of the study drug injections Myrcludex B and peginterferon alfa-2a.and Instructions about Tenofovir intake. A detailed description of the collection of therapeutic data is presented in Section 5.3.6, 5.3.7.

6.7 Justification of the selected study parameters

All selected parameters of the efficacy, safety, pharmacokinetics, immunogenicity, and genetic evaluation are standard, reliable, significant and generally accepted in clinical studies of drugs for the treatment of chronic viral hepatitis.

The above studies are planned to determine the compliance of patients with the criteria for participating in the study and to assess the treatment safety, efficacy, and to obtain new data on the study drug Myrcludex B. Each of these analyzes will require 2 to 9 mL of blood. On average, approximately 720 mL of blood will be collected for an entire 19-month (1.5-year) study for such analyzes in patients of the peginterferon alfa-2a (Arm A) group, approximately 790 mL of blood - in patients with the Myrcludex B monotherapy and combination therapy, approximately 915 mL of blood - in patients in Arms B, C, F additionally participating in the pharmacokinetic substudy.

In case of clinically significant laboratory abnormalities of grade 3 and 4 in accordance with the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.0, or in case of inability to analyze the sample collected (e.g., in case of hemolysis, damage during transportation, etc.), the additional blood volume will be required for repeated analyzes.

If repeated blood tests or the treatment safety monitoring are necessary, additional visits can be performed. After an unscheduled visit, the next visit is performed according to the previously approved schedule as per protocol.

7 ADVERSE EVENTS

7.1 Definitions

Adverse event; AE: any untoward change in the patient's health status whom the drug was prescribed to, regardless of the causal relationship with its use.

An adverse event can be any unfavorable and unintended change (including a laboratory abnormality), a symptom or a disease whose time of occurrence does not exclude a causal relationship with the use of the drug, regardless of the presence or absence of the relationship with the use of the drug.

Adverse events, for example, can include:

- New symptom/disease,
- New diagnosis,
- Clinically significant 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 AE only if their intensity, rate of occurrence or features have changed during the study. The principle investigator will register such changes as AEs.

Surgical procedures as such are not considered as AEs; they are measures taken to treat diseases requiring an operative treatment. An AE can become such a condition, stipulating the necessity of an operative treatment.

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.

The planned/recommended surgical treatment and condition(s) that determine the use of operative measures are not considered as AEs if the cause of the operative treatment was identified prior to the enrollment into the study.

All adverse events should be registered in the patient's case report form.

Adverse drug action; ADR: any noxious and unintended responses to a medicinal product related to its use in any dose. The phrase "drug reaction" means that the causal relationship with the drug is evaluated as at least possible, i.e. the relationship is not ruled out.

Unexpected adverse drug reaction: an adverse reaction, which nature, severity or outcome do not correspond to information in the current Instruction for medical use or in the Investigator Brochure for an unauthorized drug.

Serious adverse event; SAE or serious adverse reaction; serious ADR: any untoward medical event that, regardless of the drug dose:

- results in death,
- is life-threatening,

Note: the term "life-threatening" in the definition of "seriousness" means an immediate danger to the patient's life at the time the medical event develops. This category does not include adverse events that could hypothetically lead to the patient's death if their intensity was higher.

- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- results in a congenital anomaly/birth defect in children whose parents received the drug.

Hospitalization in the absence of a precipitating AE developed during treatment (i.e. not associated with the development of a new AE or the deterioration of a previous disease) may meet the criteria of "seriousness", but may not be an adverse event and, therefore, avoids the need to be immediately reported to the sponsor. Hospitalization for routine or elective treatment/operative treatment should not be registered as a SAE, provided that there are no complications or consequences that meet the above mentioned seriousness criteria.

In addition, serious adverse events/reactions may include important medical events if, based on his/her medical experience, the investigator believes that without medical intervention, this event can lead to one of the outcomes described above. Examples of such medical events include intensive treatment of allergic bronchospasm in the intensive care unit or at home; pathological changes in the blood system, or convulsions that do not require hospitalization; development of drug dependence or abuse.

The terms "serious" and "severe" adverse events are not synonymous. The term "severe" is used to describe the intensity/severity of an adverse event (mild, moderate, severe), and the event may have a relatively minor medical significance (e.g., severe headache). This term is different from the evaluation of "seriousness", which is based on the outcome of an event or measures taken in connection with the development of events that are life-threatening or pose the risk of disability of the patient. The evaluation of seriousness (not severity) is the basis for determination of the need to be reported to the regulatory authorities.
Suspected unexpected serious adverse reaction, SUSAR: unexpected serious adverse reaction, which relation to the drug is regarded as at least possible.
Information on the development of SUSAR is subject to expedited reporting and should be sent to the Institutional Review Board/Independent Ethics Committee and the appropriate regulatory authority within the time limits established by local regulatory requirements.

7.2 Methods of adverse event detection

Adverse events can be detected by a physician investigator (e.g., as based on the examination findings or laboratory test results), self-reported by the patient, or information thereon can be obtained during visits specified in the study protocol, during which the investigator will ask the patient "Have you ever had any health problems since your previous visit?"
In addition, a field for the patient to enter information about any complaints and/or health abnormalities during the treatment period will be assigned in the Patient diary in the registration form for the performed planned injections and taking Tenofovir.

7.3 Other significant adverse events

7.3.1 Local Reactions at the Myrcludex B Injection Site

Local reactions at the Myrcludex B injection site belong to adverse event of special interest that will be actively monitored during the study.
At each visit as per this study protocol, the doctor will evaluate the Myrcludex B injection site, all observed changes should be recorded in the CRF, and if the condition is regarded by the investigator as a clinically significant event, then it should be recorded as an adverse event.
When registering data on AEs, the recommendations in Section 7.4.1 should be followed.

7.4 Registration of adverse events

Adverse events are recorded in the original medical records and the relevant sections of the patient's case report form.
During this study, adverse events will be recorded after the first dose of the study drug/reference product and until the end of the patient's participation in the study. Adverse or unexpected symptoms or illnesses identified between the signing of the informed consent and the administration of the first study drug dose should be recorded as a medical history.
To identify the adverse events in this study, an evaluation of the patient health abnormalities will be made (based on physical examination findings, results of laboratory and instrumental study methods) from the data obtained during the Screening, at other Visits of the planned study and accepted reference values. Moreover, at the moment of inclusion into the study Investigator will ask the patient about complaints and symptoms. Then will ask about appearance of new complaints and symptoms during the study. Also information registered in Patient’s diary and spontaneous patient’s reports about appearance of new complaints and symptoms will be used.
After receiving the necessary information, the physician investigator will classify the patient's condition as "norm", "clinically insignificant deviations" or "clinically significant deviations". If the observed deviations were not previously recorded and, according to the investigator's assessment, are clinically significant, or the patient's condition will worsen compared to the data obtained during the Screening, the observed deviations will be classified as adverse events (AEs) and identified under the severity as per CTCAE
The following information should be specified during the registration of adverse events:

- The nature of adverse event (it is preferably to indicate the diagnosis, not the list of symptoms);
- Date of development and resolution of the manifestation (and time, if applicable);
- Severity of the adverse event;
- The relationship with the study drug/reference product/Tenofovir (in the opinion of the investigator);

- Measures taken in connection with the adverse event (not applied, the indication of concomitant treatment, etc.);
- Measures taken with regard to ongoing treatment (permanent drug withdrawal, temporary drug withdrawal, dose reduction, etc.);
- Correspondence of the adverse event to the criteria of a serious adverse event;
- Outcome of the adverse event;
- Additional information about the adverse event (if applicable).

Information about drugs and other types of treatment, which is indicated in connection with the development of an adverse event, must be recorded in the original medical records and the relevant sections of the patient's case report form.

7.4.1 Evaluation of the Severity of an Adverse Event

The severity of AEs is evaluated in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE, version 4.0.
Description of the severity of adverse events under CTCAE is listed on the official website of the National Cancer Institute:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
If the CTCAE does not provide a detailed description of the observed adverse event, its severity must be evaluated and recorded according to the description in the subsection "Other, specify".
If the severity of the AE changes during its development, a maximum severity score should be recorded.

Clinically significant laboratory abnormalities of the severity grade 3 and 4 under CTCAE should be confirmed by repeated analyzes within 3 calendar days from the moment the results have received (in the central laboratory).
The severity of each AE is not synonymous with its seriousness. The definition of a serious adverse event (SAE) is given in Section 7.1. It should be also kept in mind even a SAE does not necessarily have a severe intensity. In contrast, a severe AE is not necessarily a serious one (e.g., a full-blown headache is a severe AE, but not a SAE).
To assess the severity of local reactions at the drug injection site, and fever, the recommendations in Sections 7.4.1.1-7.4.1.2 should be followed.

7.4.1.1 Evaluation of the severity of local reactions at the drug injection site

If local reactions occur at the injection site, AE registration and severity Evaluation should be performed according to the classification given in Table 3.

Table 3 Evaluation of local reactions at the drug injection site

Adverse event	**Mild (Grade I)**	**Moderate (Grade II)**	**Severe (Grade III)**	**Extremely severe (life-threatening) (Grade IV)**
Dermatitis at the drug injection site	Reddening, itchy skin	Diffuse maculopapular rash OR dry skin flaking	Bubbles OR wet skin flaking OR ulceration	ANY OF THE FOLLOWING: mucosal lesions, suspected Stevens-Johnson syndrome, erythema multiform, necrosis requiring an operative treatment, exfoliative dermatitis
Reaction at the drug injection site	Hyperemia	Induration <10 mm OR inflammation OR phlebitis	Induration ≥10 mm OR ulceration	Skin necrosis

7.4.1.2 Evaluation of the severity of fever

If an adverse even 'Fever' occurs, the following classification should be used to assess the AE severity:

Mild (Grade I)	Body temperature <38 ° C, a clinically significant change is observed compared with the patient's baseline at the time of enrollment.
Moderate (Grade II)	Body temperature is ≥ 38°C and < 40°C.
Severe (Grade III)	Body temperature is ≥ 40°C, accompanied by hypotension and/or other symptoms and signs that are clinically significant.

7.4.2 Evaluation of the causal relationship of an adverse event with the study drug/reference product/Tenofovir

To evaluate the causal relationship of AE with the study drug/reference drug/Tenofovir, all available information should be taken into account, which may help in the identifying of this relationship, in particular the mode of action of the drug, information on known adverse drug reactions according to the Investigator's Brochure/Instructions for medical use, AE characteristics, temporary relation of AEs and drug injection, the time of resolution of AEs and other possible causes of AEs that may include:

- Intake of other drugs or exposure to chemicals;
- Natural history of the underlying disease or other conditions;
- Study procedures;
- Impact of other factors.

Based on the analysis of the information obtained, the investigator defines the causal relationship of the adverse event using the following categories:

Definite	Clinical manifestations of AEs, laboratory abnormalities occur during the period of the drug injection, cannot be explained by the presence of existing diseases and the influence of other factors; manifestations of AEs regress after withdrawal of the drug and develop again with the repeated drug injection.
Likely	Clinical manifestations of AEs, laboratory abnormalities are associated with the time of the drug injection, are unlikely to be related to concomitant diseases or other factors, regress after the drug withdrawal; the response to reassignment is unknown.
Possible	Clinical manifestations of AEs, laboratory abnormalities are related to the time of the drug injection, but they can be explained by the presence of concomitant diseases or by taking other medications and the influence of chemical compounds; information on the response to the drug withdrawal is unclear.
Unlikely	Clinical manifestations of AEs, laboratory abnormalities occur in the absence of a clear temporality with the drug; there are other factors (drugs, diseases, chemicals) that can be the cause of their occurrence.
Non-estimable	Clinical manifestations of AEs, laboratory abnormalities, attributed to AE, are difficult to be evaluated; additional data are needed for evaluation, or these data are currently being analyzed.
There is no relationship	An AE, in the investigator's opinion, is not related to the drug.

7.4.3 Evaluation of the outcome of an adverse event

The outcome of an adverse event should be recorded in the original medical records and the patient's case report form using the following categories:

- Complete resolution
- In the process of resolution
- No resolution
- Resolution with sequelae
- Fatal outcome
- Unknown

7.5 Monitoring the dynamics of an adverse event

If an adverse event or its complications are not resolved, the investigator should conduct follow-up monitoring of the patient's condition. The follow-up is performed until the adverse event and its

consequences are resolved or stabilized to a state that, in the opinion of the investigator, is acceptable, or until the cause of the development of the adverse event not related to the use of the study drug/reference product/Tenofovir is identified.

7.6 Investigator's liability to report a serious adverse event

The investigator must immediately report the occurrence of a serious adverse event the sponsoring company and/or the authorized organization within 24 hours from the date of its detection (or receipt of information on the detection). The information is provided in the form of a SAE report.
The information on SAEs should also be recorded in the source documentation and should coincide with the data given in the sections "Adverse event", "Concomitant treatment", "Laboratory test results" of the CRF.
Before sending the SAE form, the sponsor's monitor should be informed about that by phone.

If a serious adverse event is detected, it is necessary to send the completed SAE report form by fax and/or e-mail within 24 hours:
Sponsor company
Fax: +7 (495) 726-52-53
E-mail: pharmacovigilance@ammaxwell.ru
Authorized organization
E-mail: safety@smothdd.com

7.7 The sponsor's liability to provide safety information during the clinical study

Reporting of suspected unexpected serious adverse reactions (SUSARs)
The Pharmacovigilance Officer will send expedited reports on suspected unexpected serious adverse reactions (SUSARs) to the Institutional Review Board/ Independent Ethics Committee and the appropriate regulatory authorities within the time limits established by local regulatory requirements. The requirements for reporting of suspected unexpected serious adverse reactions are applied to both the study drug and the reference product and Tenofovir.
The submission of other reports on the treatment safety.
The Pharmacovigilance Officer will send other safety information that can change the benefit/risk ratio of the study drug/reference product/Tenofovir, or serve as a basis for changes in the recommendations for their prescription, as well as the basis for reviewing the possibility of further study, to the Institutional Review Board/ Independent Ethics Committee and the appropriate regulatory authority.
In addition to the expedited reporting, throughout the study, the sponsoring company will prepare annual reports on the treatment safety, containing all new information obtained during the reporting period. Such reports will be sent to the Institutional Review Board/ Independent Ethics Committee and the appropriate regulatory authority within the time limits established by local regulatory requirements.

7.8 Pregnancy

Pregnancy is not an adverse event as such, except cases when there are reasons to believe that the study drug/reference product/Tenofovir led to a decrease in the effectiveness of contraceptives. Congenital abnormalities and developmental disorders in patient children are classified as serious adverse events. Planned medical abortions, as well as other serious complications of pregnancy (including spontaneous abortion) are classified as serious adverse events. Planned artificial abortions in the absence of complications are not considered as adverse events.
All cases of pregnancy identified during the clinical study (including pregnancy of female partners of male patients enrolled into the study) should be duly recorded.
When the pregnancy is confirmed, the investigator must notify the contract research organization/sponsoring company thereof in the form of a pregnancy report. Then, information on the pregnancy should be provided.
Pregnancy in female patients and female partners of male patients is subject to registration, from the first day of administration of the study drug/reference product to the completion of the final procedures of the study.
Each pregnancy outcome (spontaneous abortion, elective abortion, the birth of a healthy child or child with congenital anomalies or malformations) should also be recorded.

8 STATISTICAL CONSIDERATIONS

8.1 General Information

The statistical analysis will be carried out under supervision of the responsible biostatistician in accordance with the requirements of the ICH GCP and other applicable guidelines and regulatory documents.
Before the statistical analysis is carried out, data from different centers will be combined into a common data set.
Statistical analysis will be described in the Statistical Analysis Plan in details, which will be finalized before the study database lock. All deviations from the Statistical Analysis Plan will be presented in depth in the clinical study report.
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. Calculation of pharmacokinetic parameters will be done in the WinNonlin software package or using other applicable software.

8.2 Populations for the study data analysis

The following populations will be used for statistical analyses:

- Safety set: all patients who received at least one dose of the study drug/reference product/Tenofovir.
- Full analysis set (FAS): All randomized patients of the Safety set.
- Per protocol set: all FAS patients who completed the study without significant protocol deviations and for those who have data about primary efficacy endpoint.

Significant protocol deviations include, but are not limited to:

– Inclusion of a patient with a violation of inclusion/exclusion criteria, which may affect the treatment efficacy
– Administration of concomitant treatment prohibited by this study protocol
– Other deviations from protocol, which will be regarded as significant from point of view of primary efficacy endpoint by the decision of Data review meeting

- Pharmacokinetic set (PK set): all patients, who had the study drug Myrcludex B injected at least once, and for whom data on the blood drug concentration were obtained.

8.3 Demographic and Baseline Characteristics

The descriptive statistics will be used to describe demographic and baseline parameters and characteristics for the analysis of general population and treatment groups. The arithmetic mean, a 95% confidence interval for the mean, standard deviation, medians and quartiles will be calculated for quantitative variables. The frequencies of the values, percentages, and 95% confidence intervals for the frequencies under the Clopper-Pearson method will be calculated for dichotomous variables.

8.4 Prior and Concomitant Therapy

Drugs of prior and concomitant treatment will be coded using the WHO Drug dictionary (the latest version at the time of the study database lock). The results will be presented for the Safety Set in the form of tables per treatment group and the entire population, as well as in the form of listings.

8.5 Efficacy Analysis

Efficacy Analysis will be performed for the Full analysis set. Additionally, the efficacy analysis will be performed for the per protocol set.
Primary efficacy endpoint:

- Proportion of patients with a negative PCR finding on HDV RNA (undetectable level of HDV RNA) at week 72 (end of the follow up period)

The frequencies and proportions of participants with HDV RNA response will be presented. The Fisher's exact test will be used to compare groups.
Secondary efficacy endpoints:

- Proportion of patients with a negative PCR finding on HDV RNA (undetectable level of HDV RNA)

at weeks 24 and 48

- Proportion of patients with an HDV RNA response (decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) at weeks 24, 48 and 72
- Proportion of patients with ALT normalization in weeks 24, 48 and 72
- Proportion of patients with combined treatment response (negative PCR result of HDV RNA and ALT normalization) at weeks 24, 48 and 72
- The proportion of patients with a combined response to therapy ((decrease ≥ 2 log10 HDV RNA or an undetectable level of HDV RNA) and normalization of ALT) at weeks 24, 48 and 72
- Proportion of patients with HBsAg response (HBsAg negativation or >1 log10 IU/mL decline) at weeks 24, 48 and 72
- Proportion of patients with the HBsAg negativation with the appearance of anti-HBsAg antibodies and without it at weeks 48 and 72
- Proportion of patients with a negative PCR result of HBV DNA at weeks 24, 48 and 72
- The intensity of liver fibrosis based on results of transient elastometry at weeks 48 and 72
- Changes in the results of liver biopsy before and after the treatment.

As part of the study of efficacy, HBV, HDV genotyping, resistance assay and NTCP polymorphism will be performed additionally.
Secondary efficacy endpoints will be analyzed similarly to the primary endpoint if it is applicable. For the HBV, HDV genotyping findings, the incidence of the HBV and HDV genotypes is given for the Safety set.
All data on the efficacy endpoints will be listed in the form of listings.

8.6 Safety Analysis

The safety data will be analyzed descriptively in the Safety Set:
All AEs will be classified using the latest version of the MedDRA dictionary. The analysis will include counting the number of AEs and SAEs, the number (proportion) of study subjects with registered AEs and SAEs, the number (proportion) of patients with AEs related to the study drug/reference product/Tenofovir, the number (proportion) of patients with AEs that required the discontinuation of treatment and the premature drop-out of the study.
Data on AEs will be presented in the tables indicating the system-organ class (SOC) and the preferred term (PT) for all treatment groups and the whole population.
The physical examination findings will be shown in the tables per treatment group with frequency values for each organ and system groups by time points of assessment.
The ophthalmological examination findings will be shown in the listing.
The analysis results of other safety indicators (vital sings, ECG, hematology, blood chemistry, urine analysis, coagulogram, urinalysis, total blood bile acids test, TSH and T4 blood test) will be presented in the tables using methods of descriptive statistics (meanings by assessment visits and changes compared with base meanings if it's applicable. Results on conformity to normal values will also be presented.
All safety data will additionally be presented in the form of listings.

8.7 Analysis of pharmacokinetic parameters

The pharmacokinetic analysis will be performed in the PK set (Arms B, C, F). The following indicators will be evaluated by the method of non-compartmental analysis:

- C_{max} – maximum concentration
- T_{max} – time of maximum concentration
- K_{el} – elimination rate constant
- $T_{1/2}$ – elimination half-life
- CL/F – total clearance
- AUC_{0-t} – area under the curve "drug concentration-time" from time 0 to the sampling time (t) of the last sample
- $AUC_{0-\infty}$ – area under the curve "drug concentration-time" from time 0 to infinity

The pharmacokinetic analysis results will be presented in the form of tables with descriptive statistics per a treatment group. The analysis results and the initial concentrations will also be presented in the form of listings.

8.8 Immunogenicity analysis

Evaluation of immunogenicity will be performed in the treatment groups taking the study drug Myrcludex B. These immunogenicity estimates will be analyzed in the Safety Set. The results will be presented in the tables using descriptive statistics methods per a treatment group and for the whole population. Values for each patient will be presented in the form of listings.

8.9 Sample size justification

This clinical study is an exploratory, controlled, parallel-arm study with a control arm, five test arms performed to demonstrate differences in the monotherapy of investigational drug, the combination of the study drug with standard treatment and the combination investigational drug with Tenofovir versus the standard treatment. The study results will be used to select the optimal treatment regimen with Myrcludex B in the next phase.

The primary endpoint (negative result of PCR on HDV RNA at week 72) was used to justify the minimum size of treatment arms.

The calculation of the sample size was carried out according to the method described in the book by Chow Sh.-Ch., Sample Size Calculations in Clinical Research [Chow Sh.-Ch., Shao J., Wang H., 2008], by means of the TrialSize package for the R programming language. The results of the previous MYR 201 substudy, data at the 24 treatment week were used: in Group of peginterferon therapy peginterferon alfa-2a 180 μg for 48 weeks, the proportion of participants with negative PCR result of HDV RNA was 29% (2 of 7 participants), in arm of combined therapy Myrcludex B 2 mg + peginterferon alfa-2a 180 μg for 24 weeks, followed by peginterferon alfa-2a 180 μg for 24 weeks, the proportion of participants with a negative PCR result of HDV RNA was 71% (5 of 7 participants). It is expected that five clinical study groups will demonstrate efficacy comparable to combined therapy results in MYR 201 substudy. Under such assumptions and a given critical value of the significance level of 0.10, the group size n = 15 will make it possible to reach the power of a study more than 60%.

Considering the exploratory nature of the study, the calculated number of arms can be considered sufficient to obtain conclusions about the optimal dosing schedule to be used in clinical studies of the following phases.

8.10 Interim analysis

The interim analysis will be performed when efficacy and safety data are available after the end of follow up period of participants in the first phase of the clinical study (Arms A-D).

Considering the fact that the study is exploratory, there is no provision for adjusting the level of significance due to intermediate analysis. Premature termination of the study by results of intermediate analysis is not planned.

8.11 Procedures for Accounting Missing Data and Data Queries

For the statistical safety analysis, the replacement of missing data is not planned. The missing data on the primary efficacy criterion will be considered as a treatment non-response.

Recovery missed meanings in analysis of efficacy and pharmacokinetics algorithm is described in details in the statistical analysis plan.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Source documentation is the original documents, data and records (for example, medical histories, laboratory reports, medical records, records of automatic devices, etc.). All information contained in the 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, is considered as the source data.

If there is an electronic system of source documentation or laboratory data registration, all relevant data will be transferred to the study database or entered into the study database in electronic form directly from the source documents. If there is no source documentation, the data will be entered directly into the electronic CRF.

The investigator undertakes to provide direct access to the patient records and source documentation for monitoring, auditing or inspections conducted by the sponsor, the sponsor's authorized representatives, or control and permission authorities.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Qualification of the investigator

The investigator must have the education, occupational training and experience that let him/her claim responsibility for the proper conduct of a clinical study. The qualification of the investigator must meet the regulatory requirements and be confirmed by his/her *curriculum vitae* and/or other documents.
The investigator should know in detail how to use the study drug in accordance with the protocol, the current version of the Investigator's Brochure, product information and other sources provided by the sponsoring company.
The investigator should maintain a list of persons with the necessary qualifications who carry out certain activities in the study on his/her behalf.

10.2 Study Monitoring

The monitoring will be carried out by a clinical study specialist (monitor), who will monitor the activities of the study from the beginning to the end in accordance with the organization's standard operating procedures (SOPs), GCP and relevant regulatory documents.
The monitoring plan will be described in the Guidance on monitoring in detail. The monitor will monitor the study, the filling of the CRFs and the source documentation in, record maintenance and proper accountability of the study drugs. For these purposes, the monitor will visit study centers at appropriate time intervals, as well as maintain constant communication, oral and written, with the center staff. It is extremely important that the monitor is given access to all documents (related to the study and its individual study subjects) at any time and immediately upon request. In turn, the monitor will comply with all confidentiality preservation requirements, as described in the informed consent form. The principal investigator and his/her team members are expected to cooperate with the monitor, to be present for some time during the monitoring visits to answer questions and provide missing information.

10.3 Inspection and Audit

Regulatory authorities, Institutional Review Board/ Independent Ethics Committee and organizations authorized by the study's sponsoring company can conduct inspections and audits. The audit objective is to perform a comprehensive and independent review of the activities and documentation related to the study performed to verify the compliance of these activities, as well as the procedures for collecting, analyzing and reporting the data to the protocol, standard operating procedures, good clinical practice and regulatory requirements. The principal investigator and authorized study center staff should provide direct access to the source documentation, CRFs and other study documents.
If representatives of control and permission authorities apply to the center with the issue of performance of an inspection, investigators should immediately inform Hepatera LLC and the clinical study monitor.

11 ETHICS

11.1 Declaration of Helsinki

The investigator will ensure that the study is performed in full compliance with the ethical principles described in the current version of the World Medical Association Declaration of Helsinki.

11.2 Good Clinical Practice

This study will be conducted in accordance with all the requirements of this protocol, the standard operating procedures of the sponsoring company and/or the contract research organization, in accordance with applicable regulatory requirements and the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP).

11.3 Study Approval

Prior to the start of the study, the clinical study protocol, the patient information sheet and the informed consent form and other applicable study documents will be submitted for examination to the regulatory authority and the Institutional Review Board/ Independent Ethics Committee. The study is possible only after a written approval from the authorized regulatory authority and the Institutional Review Board/ Independent Ethics Committee has been obtained.

Changes to the clinical study protocol will be documented in the form of a protocol amendment, and can be implemented only after the protocol amendment is considered and approved by the authorized regulatory authority and the Institutional Review Board/ Independent Ethics Committee. The procedures for amending the clinical study protocol should be in accordance with the applicable regulatory and ethical committee requirements.

11.4 Procedure for obtaining the written informed consent

It is the responsibility of the investigator to obtain the patient's written informed consent before any procedures as a part of the study. Before signing, the patient should be informed about the objectives, methods, expected benefits and potential risks of the study. The patient should be given one original of the patient information sheet and the informed consent form in his/her native language. The second original of the signed and dated informed consent form must necessarily be kept in the investigator file.

Patients will be informed of any new information that may affect their consent to participate in the study. The presentation of this information should also be documented in an appropriate manner.

11.5 Confidentiality

All documents and information, relating to the study, provided to the investigator by the sponsoring company are strictly confidential. The investigator and his/her staff undertake to use this information only in this study.

The investigator undertakes to ensure the security of the personal data of patients participating in the study in accordance with applicable local regulatory requirements. The necessary personal data of the study subjects (e.g., socio-demographic parameters) will be collected solely for the achievement of the study objectives and in the minimum amount. The CRF will not record the names, addresses, medical record/out-patient medical record numbers.

No disclosure of information identifying the patient participating in the clinical study is allowed. To protect personal data, each patient will be assigned a unique patient number (identification code). If a patient name and surname are mentioned in any document, then before submitting a copy of such a document to the sponsoring company, that name should be erased.

Before being enrolled into the study, the patients will be familiarized with the confidentiality policy and the use of their personal data, including the need for access to them by the monitor and other authorized persons (in case of auditing, inspection, etc.).

12 DATA HANDLING AND RECORD KEEPING

12.1 Records Retention

The Investigator agrees to retain all study records, including original medical records of patients (e.g., laboratory test results and instrumental examination findings, out-patient medical records, medical history) in accordance with the ICH GCP provisions and the regulatory requirements of the country where the study has been performed. These study records should be available for inspection/audit by the study sponsor and/or regulatory authorities.

The destruction of the study records is possible with the written permission of the sponsoring company.

The main documents that allow to evaluate the study and the quality of the data obtained should be archived in such a way as to ensure their integrity and complete safety during the retention period, as well as availability upon request of representatives of competent authorities.

12.2 Data Collection

All data obtained during the study will be recorded in the electronic CRF (eCRF). The investigator is responsible for ensuring that all sections of the CRF are correctly filled in and that the data is available for verification.

The validity of data in the CRF will be confirmed by the investigator's dated electronic signature and controlled by a data monitoring specialist.

13 SPONSORSHIP AND INSURANCE

13.1 Sponsorship

The study is sponsored by the sponsoring company Hepatera LLC. The detailed financial aspects of the study are presented in contractual agreement between the sponsoring company, the contract research organization and the study centers.

13.2 Insurance

The life and health of patients participating in this clinical study will be insured in accordance with local regulatory requirements. In the Russian Federation, the insurance is performed in accordance with the Decree of the Government of the Russian Federation No.714 dd. September 13, 2010 “On establishing standard rules for compulsory insurance of the life and health of patients involved in clinical trials of medicinal products”. The investigator will provide the patient with information on the terms and conditions of the policy of insurance, inform that the use of other treatment types and concomitant medications during the study (except for emergency cases) is allowed only with the consent of the investigator.

14 PUBLICATION OF THE CLINICAL STUDY RESULTS

The sponsoring company (Hepatera LLC, Russia) has exclusive rights to the study results. The investigators have the right to publish the study results only with the consent of the study's sponsoring company. Prior to submission for publication, the investigator is required to submit a copy of the planned publication to the representative of Hepatera LLC. All information obtained during the study shall be considered confidential.

15 REFERENCE LIST

1. Abbas Z, Ma K, Salih M, Jafri W. Interferon alpha for chronic hepatitis D (Review). 2011;(12).
2. Buti, M., Homs, M., Rodriguez-Frias, F., Funalleras, G., Jardí, R., Sauleda, S., … Esteban, R. (2011). Clinical outcome of acute and chronic hepatitis delta over time: A long-term follow-up study. Journal of Viral Hepatitis, 18, 434–442. doi:10.1111/j.1365-2893.2010.01324.x
3. Cole S., Gowans E., M. T. (1991). Direct evidence foe cytotoxicity accociated with expression of hepatitis delta virua antigen. Hepatology, 13(5), 845–51.
4. Cornberg, M., Protzer, U., Dollinger, M. M., Petersen, J., Wedemeyer, H., Berg, T., … Manns, M. P. (2007). [Prophylaxis, Diagnosis and Therapy of Hepatitis-B-Virus-(HBV-) Infection: upgrade of the guideline, AWMF-Register 021/011]. Zeitschrift Für Gastroenterologie, 45(6), 525–74. doi:10.1055/s-2007-963232
5. EMA. Guideline on the Clinical Evaluation of Medicinal Product Intended to Treatment of Hepatitis B. CHMP/EWP/6172/03, EMEA, 2006.
6. Gaeta, G. B., Stroffolini, T., Chiaramonte, M., Ascione, T., Stornaiuolo, G., Lobello, S., … Rizzetto, M. (2000). Chronic hepatitis D: a vanishing Disease? An Italian multicenter study. Hepatology (Baltimore, Md.), 32(4 Pt 1), 824–7. doi:10.1053/jhep.2000.17711
7. Gheorghe, L., Iacob, S., Simionov, I., Vadan, R., Constantinescu, I., Caruntu, F., … Grigorescu, M. (2011). Weight-based dosing regimen of peg-interferon α-2b for chronic hepatitis delta: a multicenter Romanian trial. Journal of Gastrointestinal and Liver Diseases : JGLD, 20(4), 377–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22187703
8. Gish, R. G., Yi, D. H., Kane, S., Clark, M., Mangahas, M., Baqai, S., … Glenn, J. S. (2013). Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. Journal of Gastroenterology and Hepatology, 28(9), 1521–5. doi:10.1111/jgh.12217
9. Glebe, D., Urban, S., Knoop, E. V., Çağ, N., Krass, P., Grün, S., … Gerlich, W. H. (2005). Mapping of the Hepatitis B Virus Attachment Site by Use of Infection-Inhibiting preS1 Lipopeptides and Tupaia Hepatocytes. Gastroenterology, 129(1), 234–245. doi:10.1053/j.gastro.2005.03.090
10. Gripon, P., Cannie, I., & Urban, S. (2005). Efficient inhibition of hepatitis B virus infection by acylated peptides derived from the large viral surface protein. Journal of Virology, 79(3), 1613–22. doi:10.1128/JVI.79.3.1613-1622.2005
11. Heidrich, B., Manns, M. P., & Wedemeyer, H. (2013). Treatment options for hepatitis delta virus infection. Curr Infect Dis Rep, 15(1), 31–38. doi:10.1007/s11908-012-0307-z
12. Heidrich, B., Yurdaydın, C., Kabaçam, G., Ratsch, B. a, Zachou, K., Bremer, B., … Wedemeyer, H. (2014). Late HDV RNA relapse after peginterferon alfa-based therapy of chronic hepatitis delta. Hepatology (Baltimore, Md.), 2–49. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24585488
13. Kucirka, L. M., Farzadegan, H., Feld, J. J., Mehta, H., Winters, M., Glenn, J. S., … Golub, E. T. (2011). Prevalence, Correlates and Viral Dynamics of Hepatitis Delta Among Injection Drug Users. J Infect Disease, 202(6), 845–852. doi:10.1086/655808.Prevalence
14. Lacombe K., Boyd A., Girard P., et al. (2007). Impact of chronic hepatitis C and/or D on liver fibrosis severety, 21(18), 2546–2549.
15. Lamers MH, Kirgiz ÖÖ, Heidrich B, Wedemeyer H, Drenth JPH. Interferon-α for patients with chronic hepatitis delta: a systematic review of randomized clinical trials. Antivir Ther. 2012;17(6):1029-37. doi:10.3851/IMP2306.
16. Man, A. De, Spreyi, R. I., Niesters, H. G. M., Heijtinka, R. A., Zondervan, P. E., Hop, W., & Schalm, S. W. (1995). Survival and complications of a cohort of patients with anti-Delta positive liver disese presenting in a tertiary referral clinic, 662–667.
17. Manesis, E. K., Vourli, G., Dalekos, G., Vasiliadis, T., Manolaki, N., Hounta, A., … Touloumi, G. (2013). Prevalence and clinical course of hepatitis delta infection in Greece: A 13-year prospective study. Journal of Hepatology, 59, 949–956. doi:10.1016/j.jhep.2013.07.005
18. Niro, G. A., & Smedile, A. (2012). Current concept in the pathophysiology of hepatitis delta infection. Current Infectious Disease Reports, 14(1), 9–14. doi:10.1007/s11908-011-0233-5
19. Niro, G., Gravinese, E., Martini, E., Garrubba, M., Facciorusso, D., Conoscitore, P., … Andriulli, A. (2001). Clearance of hepatitis B surface antigen in chronic carriers of hepatitis delta antibodies. Liver, 21(4), 254–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11454188
20. Radjef, N., Gordien, E., Ivaniushina, V., Gault, E., Anaïs, P., Drugan, T., … De, P. (2004). Molecular

Phylogenetic Analyses Indicate a Wide and Ancient Radiation of African Hepatitis Delta Virus , Suggesting a Deltavirus Genus of at Least Seven Major Clades Molecular Phylogenetic Analyses Indicate a Wide and Ancient Radiation of African Hepatiti. doi:10.1128/JVI.78.5.2537
21. Rizzetto, M. (2009). Hepatitis D: Thirty years after. Journal of Hepatology. doi:10.1016/j.jhep.2009.01.004
22. Romeo, R., Del Ninno, E., Rumi, M., Russo, A., Sangiovanni, A., de Franchis, R., … Colombo, M. (2009). A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology, 136, 1629–1638. doi:10.1053/j.gastro.2009.01.052
23. Verme, G., Amoroso, P., Lettieri, G., Pierri, P., David, E., Sessa, F., … Rizzetto, M. (1986). A histological study of hepatitis delta virus liver disease. Hepatology (Baltimore, Md.), 6(6), 1303–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3793008
24. Wedemeyer, H. (2010). Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. Journal of Hepatology, 52(5), 627–9. doi:10.1016/j.jhep.2010.02.001
25. Wedemeyer, H., & Manns, M. P. (2010). Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nature Reviews. Gastroenterology & Hepatology, 7, 31–40. doi:10.1038/nrgastro.2009.205
26. Wedemeyer, H., Yurdaydìn, C. et al. Prolonged therapy of hepatitis delta for 96 weeks with PEG-IFNa-2a plus Tenofovir or placebo does not prevent HDV RNA relapse: The HIDIT-2 study. EASL –ILC 2014.
27. Wedemeyer, H., Yurdaydìn, C., Dalekos, G. N., Erhardt, A., Çakaloğlu, Y., Değertekin, H., … Manns, M. P. (2011). Peginterferon plus adefovir versus either drug alone for hepatitis delta. The New England Journal of Medicine, 364(4), 322–331.
28. Yurdaydın, C., Idilman, R., Bozkaya, H., & Bozdayi, a M. (2010). Natural history and treatment of chronic delta hepatitis. Journal of Viral Hepatitis, 17(11), 749–56. doi:10.1111/j.1365-2893.2010.01353.x
29. Zachou, K., Yurdaydin, C., Drebber, U., Dalekos, G. N., Erhardt, A., Cakaloglu, Y., … Wedemeyer, H. (2010). Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. Liver International : Official Journal of the International Association for the Study of the Liver, 30(3), 430–7. doi:10.1111/j.1478-3231.2009.02140.x