CLINICAL STUDY PROTOCOL

MYR 202

A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination with Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients with Chronic Hepatitis D

Version: 3.0

Including Amendment(s): N/A

Date: 25 December 2017

Investigational Product: Myrcludex B, lyophilized powder for solution for injection

Study Sponsor: Hepatera LLC, Russia

Sponsor's Address: 12/19 Verkhnyaya Radischevskaya Ul, Bld. 1, Moscow, 109240

Sponsor`s legal representative: MYR GmbH

Sponsor`s legal representative address: Weinbergsweg 66, 61348 Bad Homburg, Germany

Phase: II

EudraCT number: 2016-000395-13

Replaces all previous versions of this protocol

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Protocol Synopsis

Protocol Code: MYR 202 Investigational Product: Myrcludex B

Study Title:	A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination with Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients with Chronic Hepatitis D
Clinical Phase	Phase II
Background Information:	HDV is a small RNA virus, which requires helper functions from HBV for virion assembly and propagation, and uses the HBV envelope for virus release and infection of new cells. About 5-15% of chronically HBV infected are co-infected with HDV. Several studies have shown that chronic HDV infection leads to more severe liver disease than chronic HBV mono-infection, with an accelerated course of fibrosis progression, an increased risk of hepatocellular carcinoma and early decompensation in the setting of cirrhosis. A recent 28 years follow-up study on hepatitis delta patients from Italy showed that 25% of patients with cirrhosis developed HCC and that liver failure was the cause of death in about three fifths of patients (Romeo et al, 2009). Liver cirrhosis and cancer occur 10-15 years earlier in HBV/HDV co-infection, and the 5-year mortality of co-infected individuals is twice that of HBV mono-infection (German Guideline for Prophylaxis, Diagnostics and Treatment of HBV infection, Cornberg et al. 2007). Current treatment options for patients with delta hepatitis are very limited as interferon alfa is able to clear HDV only in very few patients and is associated with significant side-effects. PEG-INF-a has also been used in small trials to treat delta hepatitis with sustained virological response rates of about 20%. Moreover, nucleoside and nucleotide analogues used for the treatment of HBV infection have been shown to be ineffective against HDV. A huge medical need remains for treating of chronic HDV infection as 75% of HBV/HDV co-infected individuals lack therapeutic options entirely.
Trial Population:	The study will enroll patients with chronic HDV infection, positive HDV RNA test at Screening, Patients who failed previous interferon therapy or for whom, in the opinion of the investigator, such therapy is contraindicated (including history of interferon intolerance), as well as cirrhotic patients are allowed. Cirrhotic patients will be included after an interim safety evaluation and upon a separate notification by the sponsor.
Number of Subjects	It is planned to screen up to 200 patients, and randomize 120 patients in the 1:1:1:1 ratio to one of the four treatment arms. This is a multinational trial. In Germany, it is planed to include up to 30 patients.
Study Design:	This is a multicenter, open-label, randomized clinical trial. Taking into consideration the screening failure rate, approximately

	up to 200 patients will be screened, and 120 patients will be randomized in the 1:1:1:1 ratio to one of the four treatment arms: **Arm A (30 patients):** Myrcludex B, 2 mg/day subcutaneously (s.c.) for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy. **Arm B (30 patients):** Myrcludex B, 5 mg/day subcutaneously (s.c.) for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy. **Arm C (30 patients):** Myrcludex B, 10 mg/day subcutaneously (s.c.) for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy. **Arm D (30 patients):** tenofovir treatment for 48 weeks. The main part of the study includes Screening period of 28 days (Days -28/-1), pre-treatment period for patients, for whom a preliminary therapy with tenofovir of up to 84 days is indicated, baseline randomization visit (Day 1), and study period of 24 weeks. Follow-up period will be 24 weeks for all treatment arms. <u>Screening</u> The following procedures will be done during screening (up to 28 days before the first dose of the study drug or pre-treatment phase): informed consent form signing, physical examination (including weight), safety laboratory tests, serology tests (HIV, HCV, HBsAg and HBeAg antibodies, HBsAg, HBeAg), HCV RNA in patients with HCV antibodies, antibodies to HDV, HDV RNA, transient liver elastometry (Fibroscan), abdominal ultrasound, urine pregnancy test, breath alcohol test, urine drug screening (test strips), evaluation of inclusion/ exclusion criteria. <u>Tenofovir Pre-treatment Period</u> All patients, who meet all inclusion and none of the exclusion criteria and who have not received treatment with nucleoside/ nucleotide analogues for at least 12 weeks before the planned start of study treatment, will be receiving protocol-defined nucleotide analogue (tenofovir) for 12 weeks prior to randomization. <u>Randomization Visit</u> All patients, who meet inclusion/ exclusion criteria and who received treatment with nucleoside/ nucleotide analogues for at least 12 weeks before the planned start of study treatment or underwent protocol-specified tenofovir pre-treatment, will be asked to attend Randomization Visit. The following tests and procedures are performed at this visit: physical examination (including weight), safety laboratory tests, virology parameters, serum fibrosis marker, immunogenicity, HBV and HDV genotyping and resistance analysis (in patients who have not underwent prior treatment with tenofovir). All assessments at this visit will be regarded as baseline for safety monitoring. Upon completion of all protocol-defined procedures, patients are randomly assigned to one of the 4 treatment arms and

	receive study medication for the first 28 days of use. Treatment Period Treatment with the study medication in combination with tenofovir or tenofovir alone will last for 24 weeks, followed by a 24-week follow-up period. Treatment will be performed in the outpatient settings. Follow-up Period Follow-up period lasts for 24 weeks. During this period, patients will receive treatment with tenofovir. Assessments Time points for study assessments are shown in Study Schedule. 1. Pharmacokinetics For a more precise investigation of the possible study drug accumulation all the patients of each Myrcludex B treatment arm will be included in this sub-study. Blood samples for pharmacokinetic study are to be collected at Week 4, 8, 12, 16, 20, 24 (1 hour +/- 15 min after Myrcludex B administration). Blood samples from the patients are to be collected on at randomization visit (1 hour +/- 15 min after Myrcludex B administration). Study Duration Up to 64 weeks, including Screening. Interim and Final Data Analysis When the last patient completes 24-week treatment period, viral load data from all treatment arms, obtained up to Week 24, will be analyzed based on PCR results for HDV RNA (negative PCR results for HDV RNA or decrease by ≥2 log from baseline at Week 24 will be the endpoint). These data will be included into the Interim Report of this clinical trial. When the last patient completes follow-up period, study data will be analyzed for all subjects completing 48-week treatment period, Final Study Report will be prepared and submitted to regulatory authorities.
Study Endpoints:	**Efficacy Endpoints** **Primary Efficacy Endpoint:** • HDV RNA negativation or decrease by ≥2 log10 from baseline to Week 24. **Secondary Efficacy Endpoints:**

	• Durability of HDV RNA response to 24 weeks post treatment • Combined response: HDV RNA negativation or ≥2 log decline and normal ALT at treatment week 24 • Changes in ALT values at Week 24 and Week 48 compared to baseline. • Lack of fibrosis progression based on transient elastometry (Fibroscan) at Week 24 compared to baseline. • Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 and Week 48 compared to baseline. • Changes in HBsAg (decreased levels, disappearance of HBsAg, antibodies to HBsAg) at Week 24 and Week 48 compared to baseline. • Change in HBV DNA levels at Week 24 and Week 48 compared to baseline. **Safety Endpoints** • Adverse events, physical examination, vital signs, 12-lead ECG, hematology, coagulation panel, blood chemistry, urinalysis, blood bile acids levels. • Development of anti- Myrcludex B antibodies.
Investigational Product Doses	Study Drug Phase IIa study in HDV patients demonstrated efficacy of the 2 mg dose. The 10 mg dose showed the most prominent effect in a phase Ib/IIa study in patients with chronic hepatitis B. Concomitant Medication for Hepatitis B Infection Tenofovir, used for concomitant treatment for hepatitis B infection, is approved to treat chronic HBV infection. Tenofovir dose will be selected based on Summary of Product Characteristics.
Inclusion Criteria:	1. Age from 18 to 65 years inclusively at the time of signing Informed Consent Form. 2. Positive serum HBsAg for at least 6 months before Screening. 3. Positive serum anti-HDV antibody for at least 6 months before screening. 4. Positive PCR results for serum HDV RNA at Screening. 5. Patients with liver cirrhosis, irrespective of previous interferon treatment[1]. 6. Patients without liver cirrhosis, who failed prior interferon treatment or for whom, in the opinion of the Investigator, such

[1] Patients with liver cirrhosis should be included in case the interim analysis (Section 9.4. Interim and Final Data Analysis) will provide positive safety assessment. The sponsor will notify the centers on the results of the analysis and the permission to enroll cirrhotic patients.

	treatment is currently contraindicated (including history of interferon intolerance)[2]. 7. Alanine aminotransferase level >1 x ULN, but less than 10 x ULN. 8. Previous nucleotide/nucleoside analogue treatment within at least 12 weeks prior to the planned start of study treatment or subject's willingness to take tenofovir for at least 12 weeks prior to the planned start of study treatment. 9. Negative urine pregnancy test for females of childbearing potential. 10. Inclusion criteria for female subjects: • Postmenopausal for at least 2 years, or • Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization), or • Abstinence from heterosexual intercourse throughout the study, or • Willingness to use highly effective contraception throughout the study and for 3 months after the last dose of the study medication. 11. Male and female subjects must agree to use a highly effective contraception[3] throughout the study and for 3 months after the last dose of the study medication. 12. Male subjects must agree not to donate sperm throughout the study and for 3 months after the last dose of the study medication.
Exclusion Criteria:	1. Child-Pugh score of B-C or over 6 points. 2. HCV or HIV coinfection. Subjects with anti-HCV antibodies can be enrolled, if screening HCV RNA test is negative. 3. Creatinine clearance <60 mL/min. 4. Total bilirubin ≥ 2mg/dL. Patients with higher total bilirubin values may be included after the consultation with the Study`s Medical Monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia. 5. Any previous or current malignant neoplasms, including hepatic carcinoma.

[2] Patients with previous interferon treatment can be enrolled only at least 30 days after the last interferon dose.

[3] According to CTFG Recommendations related to contraception and pregnancy testing in clinical trials dated 15 Sep 2014, the following birth control methods should be considered as highly effective: 1) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); 2) progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); 3) intrauterine device (IUD); 4) intrauterine hormone-releasing system (IUS); 5) bilateral tubal occlusion; 6) vasectomised partner; 7) sexual abstinence.

	6. Systemic connective tissue disorders. 7. NYHA (New York Heart Association) class III-IV congestive heart failure. 8. Patients with uncontrolled arterial hypertension (BP >150/100 mm Hg despite antihypertensive treatment) within 3 months prior to start of clinical phase of the study. 9. Previous or unstable concurrent diseases or conditions that in investigator`s opinion prevent subject's enrolment into the study. 10. Patients with mental disorders or social circumstances that preclude them from following protocol requirements. 11. Current or previous decompensated liver disease, including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminaemia, ascites, and esophageal varices hemorrhage. 12. Patients with history of pancreatitis or pancreatic insufficiency. 13. WBC count <3000 cells/mm^3. 14. Neutrophil count <1500 cells/mm^3. 15. Platelet count <60,000 cells/mm^3. 16. Proof of use of prohibited psychotropic agents at Screening. 17. Use of interferons within 30 days before Screening. 18. History of solid organ transplantation. 19. Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study. 20. History of disease requiring regular use of systemic glucocorticosteroids. 21. Pregnant or breast-feeding females. 22. Participation in another clinical study within 30 days prior to Screening. 23. Prior treatment with Myrcludex B in previous studies.
Statistical Analysis:	Primary efficacy analysis will be based on the following efficacy endpoint: • Negative PCR results for HDV RNA or decrease by ≥2 log from baseline at Week 24. Treatment arms will be compared using the Wald test for Superiority by Margin of 5%; 95% Clopper-Pearson confidence interval will also be calculated for treatment response rates (for each treatment arm). Each experimental treatment arm (Myrcludex B) will be compared to the control arm receiving tenofovir alone. Each Myrcludex B treatment arm will be compared to the control arm separately. Hypotheses will be tested sequentially, using Bonferroni-Holm method. Null hypotheses will be defined for each prior test, and appropriate p-values will be calculated (based on data obtained in the study). After that, null hypotheses will be rejected in

	descending order of respective p-values for critical values of type I error (α), calculated as α/(k – i + 1), where k is the number of planned comparisons and i is the sequential number of the comparison. Qualitative secondary endpoints (ALT normalization and disappearance of HBsAg/ seroconversion) will be analyzed using the Fisher's exact test. Quantitative secondary endpoints (serum fibrosis marker, HBsAg and HBV DNA) will be presented as absolute values and changes from baseline. To compare treatment arms on the basis of endpoints two-sided Wilcoxon rank sum test will be employed with adjustment at the significance level of 0.0167. If the assumptions necessary for carrying out parametric approach are not violated, parametric analogues of the above methods will be used: ANOVA/ ANCOVA, the Student's t-test for dependent samples. The assumptions will be verified using graphical methods. Numerical safety data will be presented as summary tables of descriptive statistics for each treatment arms. Descriptive statistics will be provided for each numerical safety endpoint. AEs will be tabulated per treatment group and System Organ Class (SOC) at Preferred Term (PT) level of MedDRA. SAEs will be reported in form of narratives. Vital sign and laboratory data as well as change from baseline will be summarized (where applicable) by visit of assessment and by treatment group. In addition, shifts in laboratory parameters will be presented by treatment group.

List of Abbreviations

AE	- Adverse event
AFP	- Alpha fetoprotein
ALT	- Alanine aminotransferase
AP	- Alkaline phosphatase
AST	- Aspartate aminotransferase
AUC_{0-t}	- Area under curve from dosing to time t
AUC_{tau}	- Area under curve over the dosing interval
cccDNA	- Covalently closed circular deoxyribonucleic acid
CHB	- Chronic hepatitis B
CHD	- Chronic hepatitis B with delta-agent
CK	- Creatine kinase
C_{max}	- Maximal concentration
C_{mean}	- Mean concentration
C_{min}	- Minimal concentration
CRF	- Case Report Form
CRP	- C-reactive protein
CT	- Computer tomography
CTCAE	- Common Terminology Criteria for Adverse Events
CTFG	-Clinical Trial Facilitation Group
DLT	- Dose-limiting toxicity
DNA	- Deoxyribonucleic acid
ECG	- Electrocardiogram
FDA	- U.S. Food and Drug Administration
GCP	- Good Clinical Practice
GCP	- Good Clinical Practice
GGT	- Gamma-glutaminetransferase
GMP	- Good Manufacturing Practice
HBeAg	- Hepatitis B virus e-antigen
HBsAg	- Hepatitis B virus s-antigen
HBV	- Hepatitis B virus
HCC	- Hepatocellular carcinoma
HCV	- Hepatitis C virus
HDV	- Hepatitis delta (D) virus

HED	- Human equivalent dose
HLA	- Human leukocyte antigen
HPLC	- High-performance liquid chromatography
HPLC-MS	- High-performance liquid chromatography - mass spectrometry
IC	- Ion chromatography
ICF	- Informed Consent Form
ICH	- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	- Independent ethics committee
IL	- Interleukin
IMP	- Investigational medicinal product
IMPD	- Investigational Medicinal Product Dossier
INF-α	- Interferon-alfa
INR	- International normalized ratio
IP	- Investigational product
IRB	- Institutional Review Board
IU	- International unit
IWRS	- Interactive Web-Response System
LDH	- Lactate-dehydrogenase
MBX	- Myrcludex B
MCH	- Mean corpuscular hemoglobin
MCHC	- Mean corpuscular hemoglobin concentration
MCV	- Mean corpuscular volume
MedDRA	- Medical Dictionary for Regulatory Activities
MRI	- Magnetic resonance imaging
MRT	- Mean residence time
NCI	- National Cancer Institute (USA)
NOAEL	- No Observed Adverse Effect Level
NOEL	- No Observed Effect Level
NTCP	- Na+- taurocholate cotransporter polypeptide
NYHA	- New York Heart Association
PBMC	- Peripheral mononuclear blood cells
Ph. Eur.	- European Pharmacopoeia
PK	- Pharmacokinetics
RH	- Relative humidity

RIA	- Radioimmunoassay
s.c.	- Subcutaneous
SAE	- Serious adverse event
SAP	- Statistical Analysis Plan
Scr	- Screening period
SOC	- System Organ Class
SOP	- Standard Operating Procedure
SUSAR	- Suspected unexpected serious adverse reaction
$T_{1/2}$	- Terminal half-life
TEC	- Therapeutic effect concentration
T_{max}	- Time to reach maximum concentration
TMF	- Trial Master File
TNFα	- Tumor necrosis factor α
TRAE -	Therapy related adverse event
ULN	- Upper limit of normal
WFI	- Water for injection

1. Administrative Study Structure

1.1. Protocol Identification

Study Title:	A Multicenter, Open-label, Randomized Clinical Study to Assess Efficacy and Safety of 3 Doses of Myrcludex B for 24 Weeks in Combination with Tenofovir Compared to Tenofovir Alone to Suppress HBV Replication in Patients with Chronic Hepatitis D
Protocol Number:	MYR 202
Version:	Country-specific version 3.0 (Germany)
Date:	25 December 2017

1.2. Sponsor's and Authorized Representatives' Contact Information

Study Sponsor:	Name of the contact person: Yana Deloveri. Position: CEO Organization: OOO Hepatera, Russia Sponsor's Address: 12/19 Verkhnyaya Radischevskaya Ul, Bld. 1, Moscow, 109240 Telephone/fax: +7 (495) 726-52-53. E-mail: deloveri@ammaxwell.ru
Sponsor`s Legal Representatvive	Name of the contact person: Dr. Alexander Alexandrov Position: Medical Director Organization: MYR GmbH Address: Weinbergsweg 66, 61348 Bad Homburg, Germany Telephone: +491777168259 E-mail: alexandrov@myr-pharma.com
Study Management and Monitoring:	Name of the contact person: Anton Chugunov Position: Project Manager Organization: Smooth Clinical Trials Address: 153, business center „LIGOV", floor 10, Ligovsky pr., Saint-Petersburg, 192007, Russia Telephone: +7 812 913 04 23 E-mail: chugunov@smoothdd.com

1.3. Signature Page

MYR 202	
Sponsor: Name: Yana Anatolyevna Deloveri. Position: Director General Organization: OOO Hepatera, Russia Sponsor's Address: 12/19 Verkhnyaya Radischevskaya Ul, Bld. 1, Moscow, 109240	…… Date …… Signature
Sponsor's legal representative: Name of the contact person: Dr. Alexander Alexandrov Position: Medical Director Organization: MYR GmbH Address: Weinbergsweg 66, 61348 Bad Homburg, Germany	…… Date …… Signature
Lead clinician Prof. Dr. Heiner Wedemeyer Dept. of Gastroenterology, Hepatology and Endocrinology Medizinische Hochschule Hannover Carl-Neuberg Str. 1 30625 Hannover, Germany	…… Date …… Signature

1.4. Sites contact list and Principal Investigators

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

Clinical Site 19	Medical Company “Hepatolog” LLC, 36A, Serdobskaya str., 430063, Samara, Russia
Principal Investigator	Vyacheslav Gennadievich Morozov, MD, PhD, DMSc
Clinical Site 20	Federal budgetary research institution Central Research Institute of Epidemiology 111123, Russia, Moscow, ul. Novogireevskaya, house 3a
Principal Investigator	Vladimir Petrovich Chulanov
Clinical Site 41	Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover Carl-Neuberg-Str. 1, 30625 Hannover
Principal Investigator	Prof. Dr. Heiner Wedemeier
Clinical Site 42	UniversitätsKlinikum Heidelberg – Medizinische Klinik, Abteilung Klinische Pharmakologie & Pharmakoepidemiologie Im Neuenheimer Feld 410 - 69120 Heidelberg
Principal Investigator	Prof. Dr. Walter Haefeli
Clinical Site 43	Ifi-Institut für interdisziplinäre Medizin an der Asklepios Klinik St. Georg, Haus L Lohmühlenstr. 5 20099 Hamburg
Principal Investigator	Prof. Dr. Jörg Petersen
Clinical Site 44	Universitätsklinikum Hamburg-Eppendorf Medizinische Klinik Studienambulanz Hepatologie - Haus O28 Martinistr. 52 20246 Hamburg Germany
Principal Investigator	Dr. Julian Schulze-zur-Wiese

1.5. Investigator's Signature

I have read the protocol and appendices. I understand the content and intend to fully comply with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by the Sponsor in the form of a protocol amendment.

Investigator:

Signature: _____

Full Name: _____

Institution: _____

Date: _____ (DD/MMM/YYYY)

1.6 Central Laboratories Contact List

1) Central laboratory №1 (Immunogenicity)

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2) Central laboratory №2 (Virology)

Medizinische Hochschule Hannover

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

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Dr. Birgit Bremer, Email: Bremer.Birgit@mh-hannover.de

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

Universitätsklinikum Heidelberg

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

Im Neuenheimer Feld 672

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MD, Prof. Stephan Urban, Email: Stephan.Urban@med.uni-heidelberg.de

4) Central laboratory №4 (PK)

Universitätsklinikum Heidelberg

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

Im Neuenheimer Feld 410

D-69120 Heidelberg, Germany

Contacts:

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

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

Universitätsklinikum Hamburg-Eppendorf

Zentrum Innere Medizin (Zentrum Innere Medizin, I. Medizinische Klinik, AG Virushepatitis)

Büro: Raum 332, 3.OG, Haus O58

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DM, Prof. Maura Dandri, Email: m.dandri@uke.de

Dr. Marc Lütgehetmann, Email: m.luetgehetmann@uke.uni-hamburg.de

6) Central laboratory № 6 (separate bile acids)

Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology

Auerbachstr. 112

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2. Study Rationale

Hepatitis delta is liver inflammation caused by infection with hepatitis D virus, which requires presence of HBsAg for complete replication and transmission. Hepatitis D virus is a hepatotropic virus with a small RNA genome, HDV antigen. HDV is necessarily associated with HBV infection, as HDV ribonucleoprotein buds through the HBsAg secretory pathway. HDV genome is a single-stranded RNA of 1,680 bases; it has historical homology with viroids or plant virus satellite RNA [1]. The HDag consists of 2 isoforms, the small 24 kD protein which is required for the replication, and the larger 27 kD protein which is needed for virion formation [2]. Eight genotypes of HDV exist, whereas genotype 1 is the most common in the world and in Europe [3].

In general, hepatitis delta is a highly pathogenic virus causing acute and chronic liver disease. Although benign course of the disease has been described [4], patients with hepatitis delta usually have progressive liver disease leading to compensated or decompensated cirrhosis. Evidence was reported in the literature, that unlike HBV, HDV can be associated with direct cytotoxicity which may hasten fibrosis process [5, 6]. However, the immune system plays the major role in the clearance of the infected hepatocytes; levels of HDV viremia are not directly associated with histological changes [7]. There is no histological feature distinctive of hepatitis delta from other types of viral hepatitis. Biopsy specimens of patients with chronic hepatitis delta exhibit portal and periportal inflammation, fragmentary necrosis, often accompanied by fibrosis and cirrhosis. Marked intraglobular infiltration by mononuclear cells and degenerative changes in hepatocytes [8] is seen. Clinically, hepatitis delta may cause acute or fulminant hepatitis, chronic infection may lead to asymptomatic carrier state or evolve to rapidly progressive chronic liver disease.

Chronic Hepatitis delta develops in 70–90% of patients with HDV superinfection. The liver disease associated with HDV runs a more progressive course than chronic hepatitis B and may lead to cirrhosis within 2 years in 10–15% of patients [9]. Hepatitis delta is considered the most severe form of viral hepatitis in humans [10], and is associated with progression of liver disease, development of cirrhosis and decompensation [11, 12].

A tertiary clinic study with a longitudinal cohort of patients has shown a clear trend to worse survival in HBeAg negative patients with HDV, in comparison to HBV monoinfected [13]. In regions endemic for HDV infection, the liver disease is representing a major health care challenge. A study from Italy has shown existence of anti-HDV antibodies in as many as 40% of patients with liver cirrhosis in 1987. Although this number has declined to 11% in 2000 [14], the HDV-caused disease is still a significant burden. A longitudinal study has shown that 20% of hepatitis delta patients develop a liver-related first time event during the median follow up time of 4 years, vs only 8.5% of HBV monoinfected patients [15]. At baseline, 19.8% of the patients of this cohort had cirrhosis, compared to 7.3% of CHB patients. HDV was a cause of death for 60% of patients in a 28-year study from Italy [16]. HDV co-infection is associated with faster progression to fibrosis and cirrhosis, earlier onset of hepatic complications and likelihood of liver transplantation [17-19]. Liver cirrhosis and cancer occur 10-15 years earlier in HBV/HDV co-infection and the 5-year mortality of co-infected individuals is twice that of HBV monoinfection [20]. Chronic HDV infection causes cirrhosis and HCC with annual rates of 4% and 2.8%, respectively [16].

In average, 5-10% of HBsAg positive patients who admit to tertiary centres in Europe are tested positive for HDV. The calculation of total number of people affected by hepatitis delta in the EU has yielded the estimate of 145,000 persons. Accounting for EU population of 505,665,700 (2013), the expected prevalence of HDV among EU citizens, under these assumptions, is 2.9 in 10,000, where best-and worst case assumptions (the limits of the 95 per cent credibility interval)

are 1.6 and 4.7 in 10,000, respectively. The worst-case scenario is below the Orphan Drug designation threshold of 5 in 10,000 people affected by the condition.

Very limited literature data could be identified to estimate HDV prevalence in the US. A recent study utilizing data of a tertiary center database revealed HDV prevalence of 8% among HBsAg carriers [21]. 11% of injection drug users were tested positive for HDV in Baltimore; in those with chronic HBV infection, 50% were HDV positive [22]. In average, 5-10% of HBsAg positive patients who admit to tertiary centers are tested positive for HDV. The calculation of total number of people affected by hepatitis delta in the US has yielded the estimate of 63,800 persons (worst-case scenario). This is below the Orphan Drug designation threshold of 200,000 people affected by the condition.

The therapeutic options for HDV co-infected patients are very limited. Only interferons show some degree of efficacy in a small proportion of patients with approximately 25% of virological and biochemical response. Antiviral agents active against HBV do not work against HDV [18]. Several clinical trials were recently performed investigating the use of pegylated interferon alpha in hepatitis delta. The two largest trials in this indication, HIDIT-1 and HIDIT-2, did show only very modest long-term virological results. In the HIDIT-1 clinical trial, pegylated interferon was tested in combination with nucleotide analogue adefovir dipivoxil versus either drug alone in 91 chronically HDV infected patients [23]. At test week 48, 23% of patients on combination therapy, 24% on pegylated interferon monotherapy, and no patients on adefovir reached HDV RNA negativation. The effect was sustained through follow up week 24. However, the follow up study revealed that from 16 individuals who have reached HDV RNA negativity at the end of treatment, 9 tested positive within the median follow up of 4.5 years (0.5-5.5 years) [24]. In the HIDIT-2 clinical trial, 120 patients received pegylated interferon alpha with or without tenofovir disoproxil fumarate for 96 weeks. The prolongation of the interferon treatment to 96 weeks and addition of nucleotide analogue tenofovir did not improve sustained virological response rates: 30% of patients in the combination arm and 23% of patients in the monotherapy arm were HDV RNA negative 24 weeks after the end of treatment. Of note, 20 patients (16%) did not complete at least week 80 of treatment. A trial involving 49 patients treated with pegylated interferon alpha 2b has shown 33% of HDV RNA negativation at the end of treatment (48 weeks) and 25% at the end of follow up [25].

In summary, there is an urgent unmet medical need for new medications to treat chronic HDV infection, as currently no treatment options exist for 75% of patients with HBV/HDV coinfection.

2.1. Study Drug Name and Description

2.1.1. General Properties

Myrcludex B (MXB) is a myristoylated N-terminal and amidated C-terminal 47-amino acid lipopeptide. All amino acids are of L-forms.

Molecular formula	C248H355N65O72 (net)
Molecular weight	5398.9 g/M (mean weight, net)
Salt	Acetate
Presentation	White to off-white powder
Solution	Clear, colorless

MXB is a 47 amino acids long, N-terminally myristoylated, HBV-L-protein derived lipopeptide. It blocks the entry of HBV into hepatocytes by binding to and inactivating an NTCP/SLC10A1, a bile acid liver transporter serving as essential HBV and HDV entry receptor. MXB was shown

to be effective against hepatitis B and delta virus in non-clinical in vitro and in vivo models. In a clinical trial, viral load reductions could be shown with best response in 10mg once daily cohort. For HDV and HBV, similar degree of efficacy was shown in vitro. In an immune deficient animal model, prevention of HDV infection and inhibition of HBV spread was demonstrated. In the clinical trial, a profound decline of HDV RNA viremia was shown at a daily dose of 2mg, including negativation in 2/7 patients. This suggests a pronounced dependence of HDV persistence on de novo infection of hepatocytes and thus a higher sensitivity against entry inhibition. This might be linked to pathophysiological properties of HDV/HBV co-infection: generally higher degree of immune reaction and inflammation, and possible pronounced cytopathic effects of HDV when compared to HBV. Moreover, HDV RNA represents a unique marker to measure response in the clinical trials; negativation of HDV RNA is a widely used endpoint for clinical trials in this indication.

MXB will be supplied used to date in sterile vials with a nominal content of 2.0 mg and 5.0 mg of Myrcludex-B Acetate. The vial content has to be reconstituted in 1 mL sterile WFI prior to administration. The containers and closures are intended for single use. MXB is intended for parenteral administration. During the Phase 1 trial, single intravenous dosages of up to 20mg were applied to healthy volunteers. In the Phase 1b/2a, subcutaneous dosages of up to 10mg daily were applied to chronically HBV and HDV infected patients for the period of up to 24 weeks with excellent safety profile.

Further information is available in the Investigator Brochure.

2.2. Summary of Pre-clinical and Clinical Data

2.2.1. Pre-clinical Studies

MXB blocks the entry of HBV into hepatocytes by binding to and inactivating an essential HBV entry receptor recently described as NTCP [26]. Myrcludex B acts when the virus has attached, and presumably is redirecting HBV entry path to a non-productive cellular channel.

Antiviral effect was investigated [36] in the HBV and HDV inhibition tests in cell lines susceptible to HBV and HDV infection: HepaRG cell line, Tupaia belangeri and PHH primary hepatocytes [27, 28]. Secreted HBeAg and HBsAg were measured in cell culture supernatant using ELISA as infection markers. Infected cells were calculated using immunofluorescence technique with determination of the count of HBcAg-positive cells (HBV) and HDV-Ag-positive cells (HDV). IC_{50} was 14.5 pM to 9.5 nM, depending on the viral load and cell culture. No signs of *in vitro* toxicity measured by LDH release were reported at MBX concentrations of up to 50 µM.

The *in vivo* antiviral activity of acylated HBV derived peptides similar to MXB was tested in immunodeficient uPA/RAG-2 mice transplanted with susceptible hepatocytes from Tupaia belangeri and PHH. The mice were infected with HBV and the infection was competed by different concentrations of the active peptide or a control peptide. In this model, systemic application of the peptides allowed the complete prevention of the establishment of a HBV infection at 200 µg/kg, the lowest dose tested [29]. Myrcludex B is an optimization product of peptides evaluated in this study. MXB was then tested in uPA/SCID mice transfected with human hepatocytes after infection with HBV. Significant inhibition of HBV spread in the liver was observed in MBX-treated animals, compared to placebo-treated animals, as measured by serum HBV DNA and HbsAg levels and immunohistology data [30].

Possible secondary pharmacology effects were explored in a single dose chimpanzee study. The chimpanzee is the only relevant animal model as it expresses the receptor for HBV and can reliably develop acute and chronic infection. The intravenous application of 300 µg/kg MXB did not produce any substance-related clinical or laboratory changes.

For the evaluation of the single dose toxicity, a study in CD® rats was performed (single high dose was applied in limit test). The study included evaluation of safety pharmacology parameters (Irwin screen). I.v.administration of 12.5 mg MXB/kg b.w. to rats did not reveal any signs of toxicity. No mortality did occur.

The evaluation of some toxicology parameters (clinical signs, clinical chemistry/hematology evaluations) was included into a single dose chimpanzee secondary pharmacology and pharmacokinetic study.

The repeat dose toxicity was evaluated after daily subcutaneous injection in rats (7 days, 4 weeks, 6 months) and in dogs (3 months). The studies incorporated cytokine evaluation (4 week rat) and safety pharmacology evaluations (3 months dog study).

In all studies completed so far, no signs of test item related mortality, systemic or local intolerance, body weight and body weight gain, food and drinking consumption, hematology and clinical biochemistry parameters were observed. Macroscopic necropsy evaluation or histological evaluation did not reveal any signs of test item related changes.

2.2.2. Clinical Experience with Myrcludex B

Three clinical studies have been conducted on Myrcludex-B and two ongoing under clinical trial applications:

- Study MYR 101: A Phase 1 Study in Healthy Volunteers (Germany)-completed
- Study MYR 201: A Phase 1b/2a clinical trial in HBV (Russia) - completed
- Study MYR 102: A Phase 1 Drug Interaction Study in Healthy Volunteers (Germany) - completed
- Study MYR 201 (substudy): A Phase 1b/2a study in hepatitis delta patients (Russia) – ongoing
- Study MYR 202: A Phase 2 study of different doses of Myrcludex B on top of tenofovir in hepatitis delta (international)

A Phase I single-dose study (MYR 101) was conducted in 36 healthy male volunteers. Selected dose groups were 0.3 µg, 3 µg, 10 µg, 100 µg, 800 µg, 3 mg, 5 mg, 10 mg, and 20 mg for intravenous application and subcutaneous administration was carried out with 800 µg, 5 mg, and 10 mg. Each dose was administered to a cohort of 3 consecutive volunteers. For all cohorts and both administration routes administration of MXB was uneventful and well tolerated. After administration, there were no relevant changes in vital signs (blood pressure, heart rate, respiratory rate, and body temperature), 12-lead ECGs, and safety laboratory values. Overall, 85 AEs were observed in 29 individuals, none of these was serious. Events were equally distributed between cohorts and no organ system was predominantly affected. Seventy-four events were mild in nature, nine moderate, and only two were severe (grade3) according to CTC-AE 4.0 criteria (increased lipase; increased amylase). Anti-drug antibodies were measured until 6 months after exposure and were negative for all individuals.

MXB has been well tolerated in all volunteers, no SAE and no dose limiting toxicities occurred. The AEs were mostly mild in nature and self-limiting and no pattern suggesting a relationship with Myrcludex B or unexpected off-target effects were seen. There was no dose-dependency of AE frequency or severity. This matches the observations from animal studies, where Myrcludex B exhibited a highly specific and exclusive binding to hepatocyte. Therefore, MXB had a good safety profile even in the cohorts with high doses in this trial.

Myrcludex B showed strong dose dependent pharmacokinetics; the area-under-the-time-plasma-concentration curve (AUC) increased disproportionally while the clearance and volume of distribution decreased with higher doses. The bioavailability of the drug after subcutaneous administration was estimated to be 88%. The release after subcutaneous administration was best described by a parallel slow and fast first-order process, where 59% of the bioavailable dose was absorbed fast and the remaining 41% of the dose was absorbed slowly with absorption half-lives of 1.3 h and 5.4 h, respectively. A simulation of the impact of various doses of Myrcludex B on the occupancy of the binding target revealed that at doses of 10 mg most of the binding target was occupied >80 % for at least twenty hours in a simulated steady-state after subcutaneous administration

A Phase 1 drug interaction study (MYR 102) in healthy volunteers investigated the influence of receptor-saturating dose on PK of anti-HBV drug tenofovir. Twelve healthy volunteers received 245 mg of oral tenofovir disoproxil for 5 days alone followed by 6 days of co-administration of 10 mg subcutaneous myrcludex B. Plasma samples were collected and myrcludex B, tenofovir, and plasma bile acids were quantified. Repeatedly, a 30 µg midazolam microdose was administered to determine the impact of the antivirals on CYP3A activity.

The combination of Myrcludex B and tenofovir was well tolerated. A total of 28 adverse events occurred in 10 out of 12 participants, 12 of which were considered to be at least possibly related to tenofovir or myrcludex B treatment (anemia (2), first-degree atrioventricular block (1), diarrhea (1), nausea (1), injection site hypersensitivity (2), increased ALT (5), increased amylase (1), increased AST (1), increased lipase (2), muscular weakness (1), and headache (1)). With the exception of one grade 3 increase in lipase levels, all treatment-related adverse events were mild. Lipase levels showed marked day to day fluctuations in this participant. Two volunteers experienced localized hypersensitivity reactions for about 30 min after each administration of myrcludex B (erythema, pruritus) without accompanying signs of systemic anaphylaxis.

Myrcludex B did not have a significant effect on tenofovir pharmacokinetics including renal tenofovir clearance. Myrcludex pharmacokinetic parameters after first and repeated dosing were comparable to those observed in two other clinical studies with the substance. Therefore, a clinically relevant influence of tenofovir on myrcludex B concentrations seems unlikely. Estimated metabolic clearance of midazolam exhibited a downward trend with a gradual decrease during the course of the study. Geometric mean values were 1022 ml/min (95% CI: 801.5, 1303) without co-medication, 869.1 ml/min (679.8, 1111) under tenofovir, and 724.8 ml/min (592.5, 886.7; p-value 0.02 vs. baseline) under tenofovir and myrcludex B treatment.

Differences were significant between baseline and co-administration of tenofovir and myrcludex B, but not between tenofovir monotherapy (baseline immediately before start of myrcludex B) and combination therapy. Therefore, our results did neither confirm nor rule out an influence of myrcludex B on CYP3A activity. The small and clinically irrelevant inhibition of CYP3A activity by tenofovir or its prodrug might account for the statistically inconclusive results. Co-administration of regular tenofovir doses with myrcludex B was well tolerated and revealed no clinically relevant change in either drug`s pharmacokinetics or CYP3A activity, suggesting that these drugs can be safely combined without dose modification.

Phase 1b/2a study in 48 chronic HBV infection is completed (MYR 201). HBeAg negative patients with increased ALT levels and viral load above 10,000 copies per mL were randomized into following cohorts:

Cohort A: 0.5 mg MXB daily sc / 12 weeks + 12 weeks follow up

Cohort B: 1 mg MXB daily sc / 12 weeks + 12 weeks follow up

Cohort C:	2 mg MXB daily sc / 12 weeks + 12 weeks follow up
Cohort D:	0.5 mg Entecavir daily orally / 24 weeks
Cohort E	5 mg MXB daily sc / 12 weeks + 12 weeks follow up
Cohort F	10 mg MXB daily sc / 24 weeks + 12 weeks follow up

Safety and tolerability, plasma pharmacokinetic parameters, immunogenicity and virological responses are assessed in this trial. Levels of HBsAg, HBV DNA and ALT are used to assess efficacy.

A dose-dependent decrease in viral load was reported at week 12 of treatment. 6 of 8 patients (75%) of the 10mg cohort had a decline in serum HBV DNA of more than 1log10 in comparison to baseline. The patients of 10mg cohort continued the treatment for 24 weeks, maintaining HBV DNA levels achieved at week 12. At lower dose levels, no per cohort dose dependency was observed; per cohort, at most 25% of lower dose patients achieved >1 log10 HBV DNA reduction at week 12. Normal ALT was reported in 50%-75% of patients receiving Myrcludex B at week 12, irrespective of dose level. No effect on HBsAg was observed.

A a total of 69 adverse events were reported during the study. Overall, in the Myrcludex B treatment groups the AEs were predominantly clustered in the same 4 SOCs: General disorders and administration site condition; Investigations; Skin and subcutaneous tissues disorders; Blood and lymphatic system disorders. In the Entecavir treatment group all the AEs were in the 3 SOCs: General disorders and administration site condition; Infections and infestations; Respiratory, thoracic and mediastinal disorders. A total of 45 adverse events were considered as treatment-related (TRAE). In general, treatment-related AEs were of mild severity (a total of 41 events). The events of moderate severity were erythema, gamma-glutamyltransferase increased, reticulocyte increased, injection site dermatitis. Neither treatment group had any reports of AEs judged to be severe. There were 2 AEs considered to be serious: drug withdrawal syndrome reported for 1 patient of the Myrcludex B 1 mg group (Arm B) and 1 patient of the Myrcludex B 2 mg group (Arm C). There were no patients who prematurely discontinued participation in the study due to AE/SAE. There were no deaths in the study. Levels of bile acids are important secondary pharmacodynamics parameter, as a bile acid transporter NTPC is the target of MXB. A dose-dependent, asymptomatic increase of bile acids which are NTCP substrates (ie taurocholate and glycocholate) was detected; whereas lithocholic acid (non-substrate for NTCP) levels were not affected. Antibodies to MXB were detected in 58% of patients of MXB dose groups. No correlation was observed between the appearance of antibodies and pharmacodynamic parameters. Elevated levels of bile acids, which are a secondary pharmacodynamic parameter and are indicative for drug-target binding, were detected independent of antibody positivity. Virological and biochemical response was not different in patients who were antibody-positive versus antibody-negative.

A Phase 2a study is currently ongoing in hepatitis delta patients. 24 patients with chronic hepatitis delta, determined by presence of anti-HDV antibody in serum and HBsAg positivity for more than 6 months were included in the study and randomized into the following 3 arms, 8 patients each:

Arm A: Myrcludex B 2mg once daily sc for 24 weeks, followed by pegylated interferon alpha, 180µg weekly sc for 48 weeks

Arm B: Pegylated interferon alpha, 180µg weekly sc for 48 weeks; addition of Myrcludex B 2mg once daily sc for the first 24 weeks

Arm C: Pegylated interferon alpha, 180µg weekly sc for 48 weeks

Currently, 24 week efficacy data is available. Six of the seven and 7/7 of patients with data available experienced >1log10 HDV RNA decline at week 24 during Myrcludex B monotherapy (A) or combination therapy (B) while this response was observed in 7/7 of group C patients. HDV RNA became negative in 2 and 5 patients of groups A and B, and in 2 patients of group C.

ALT values declined at week 24 in 6/7 (A), 4/7 (B) and 2/7 (C) patients. One patient in A had negative HDV RNA and normal ALT at week 24. A tendency to ALT decline in comparison to baseline was observed in group A. Interestingly, median ALT levels demonstrated a tendency to decrease in Myrcludex monotherapy arm, from 66 U/L to 40 U/L (p=0.06). No such tendency was demonstrated in arms B and C.

In summary, strong antiviral effect of MXB on HDV as monotherapy, as well as possible additive effect to pegylated interferon anti-HDV activity was demonstrated. MXB administration as monotherapy induced marked decrease in hepatitis activity measured by decline in ALT levels. MXB demonstrated very good safety and tolerability profile in this study with only 4 TAEs and did not add to pegylated interferon toxicity.

In conclusion, available data demonstrated favorable safety and efficacy profile of MXB and warrants further clinical application of the product.

2.3. Information About Comparator / Background medication

Tenofovir (Viread®) is a highly effective HBV polymerase inhibitor approved for the treatment of chronic hepatitis B. Nucleoside/ nucleotide analogues are widely used by clinicians to treat background HBV infection in HDV patients. The dose of tenofovir used in the study will be according to the label for HBV infection.

2.4. Rational for the study, dose selection and risk-benefit assessment

The study is designed to evaluate the benefit of 3 MXB doses versus observation in patients suffering from hepatitis delta with very limited therapeutic options; the patients will be randomized 1:1:1:1 into 3 treatment arms and an observation arm. Patients with compensated cirrhosis at screening will be stratified to allow similar distribution into each treatment arm. If patients were not receiving treatment with nucleoside/nucelotide analogue, the comparator/background drug will be initiated after the eligibility confirmation, for 12 weeks prior to randomization visit; patients who previously received tenofovir will continue the dosing; patients on different nucleoside/nucleotide analogue will be switched to tenofovir. Observation is considered an adequate control group, as daily placebo injections for 24 weeks are regarded not feasible and ethically questionable.

In the Phase 2a study, effects on HDV RNA including negativations were observed within 24 weeks. Therefore, 24 weeks are considered adequate time frame for the evaluation of the primary endpoint. There will be a follow up of 24 weeks on comparator/background drug to study the durability of achieved responses.

Patients with ALT >10 fold ULN, creatinine clearance < 60 mL/min, total bilirubin > 2 mg/dL, decompensated liver disease or liver carcinoma will not be allowed to enter the trial. Patients with presence of anti-HCV antibodies but with negative HCV RNA at screening will be permitted to participate.

The dose of 2mg is theoretically sufficient to reach liver concentrations above in vitro IC90. In an ongoing Phase 2a study in patients with chronic hepatitis delta infection, 2mg of Myrcludex B dosed subcutaneously once daily for 24 weeks followed by or in addition to pegylated interferon alpha showed benefit with good tolerability.

In a Phase 2a study in HBV, the dose of 10mg once daily subcutaneous dosing for 24 weeks showed most pronounced effects on HBV DNA. The use of 10mg dose is further supported by pharmacokinetic modeling, showing that this dose should lead to 80% saturation of NTCP for at least 15 hours.

The intermediate dose of 5mg will be investigated as well. Administration of 5mg dose can reach the target saturation for several hours. In *in vitro* experiments, cells susceptible to HBV/HDV infection were rendered unsusceptible by limited exposure to MXB (15-30 minutes), and maintained this status for 24 hours. It can be anticipated, that if the target saturation is important for increasing the antiviral effect, the use of 5mg dose may already be sufficient. Moreover, the increase in bile acid concentrations in 5mg and 10mg dose groups in the Phase 2a HBV study was similar, suggesting that both doses had similar effect on NTCP bile acid transporter function.

It is not expected that the background medication anti-HBV polymerase inhibitor alone will influence HDV replication. The goals of the study are to investigate the effect of Myrcludex B on HDV RNA levels on the background of effective HBV replication suppression and to determine if there are synergistic effects of both medications on HBsAg levels decline.

The primary endpoint is HDV RNA negativity or significant decline at treatment week 24 in comparison to tenofovir only arm. Negative HDV RNA result is a standard parameter used in clinical studies and routine practice for monitoring of treatment success in HDV infection. Additional summaries of patients who had durable response during the treatment free follow-up will be summarized. Most important secondary endpoint will be ALT normalization showing the decline in hepatitis activity, which is important in this patient population.

Analysis of qualitative secondary endpoints (ALT normalization and HBsAg Loss/Seroconversion) will be handled using the Fisher's exact test. Analysis of quantitative secondary endpoints (Serum fibrosis marker, HBsAg and HBV DNA) will be summarized over time (actual value and the change from baseline value). Treatment group comparisons for these endpoints will be made using a two-sided Wilcoxon Rank-Sum test with an adjusted alpha of 0.0167. Each endpoint will also be summarized during treatment free follow-up. No statistical testing is planned for this analysis.

The sample size calculation is based on following considerations: the study is powered to detect 34% increase in HDV RNA negativation or 2log10 decrease (37% activity in treatment arms) vs observation, assuming 3% spontaneous HDV RNA negativation in the observation arm. 30 patients per arm were calculated to achieve two-sided alpha of 0.0167 with 80% power, accounting for multiple comparisons as 3 doses are investigated in the trial.

Standard methods will be applied for safety monitoring, recording and treatment delay(s), dose modification and discontinuation.

Considering all above information, the trial as described in the current protocol is justifiable. The scheduled treatment may be of benefit for included subjects, while the risks remain well-predictable and acceptable. Moreover, the trial will provide crucial information in the course of clinical development of Myrcludex B.

2.6. Study Population

The study will enroll male and female patients, 18 to 65 years of age (inclusively), with chronic HDV infection, positive HDV RNA results at Screening, in order to evaluate Myrcludex B efficacy in this population.

Initial evidence of Myrcludex B efficacy in patients with chronic HDV infection was obtained in a phase Ib/IIa clinical trial. In this trial led to a decrease in HDV RNA and ALT values. Three out of 24 subjects enrolled into the phase Ib/IIa study had liver cirrhosis, and 9 had a history of previous interferon therapy. Potential benefit of Myrcludex B was demonstrated in this population of patients, for whom therapeutic options are particularly limited.

The current study will enroll patients with chronic HDV infection, who failed previous interferon therapy or for whom, in the opinion of the investigator, such therapy is contraindicated (including history of interferon intolerance), as well as cirrhotic patients. Inclusion of such patients is ethically appropriate and justified by data obtained in the previous study.

Up to 200 patients will be screened. 120 patients will be participating in this trial (up to 30 thereof in Germany).

Only subjects who sign informed consent form and who meet all eligibility criteria will be enrolled into this study.

3. Study Objectives and Endpoints

Primary Objective

To investigate the efficacy of MXB and to compare 3 doses of MXB versus observation on background therapy with tenofovir in hepatitis delta patients.

Secondary Objectives

To investigate further efficacy parameters as well as safety and tolerability, as well as to assess pharmacokinetics and immunogenicity, of three doses of MXB in hepatitis delta patients.

Primary Efficacy Endpoint:

- HDV RNA negativation or decrease by ≥2 log10 from baseline to Week 24

Secondary Efficacy Endpoints:

- Durability of HDV RNA response to 24 weeks post treatment
- Combined response: HDV RNA negativation or ≥2 log decline and normal ALT at treatment week 24
- Changes in ALT values at Week 24 and Week 48 compared to baseline.
- Lack of fibrosis progression based on transient elastometry (Fibroscan) at Week 24 compared to baseline.
- Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 and Week 48 compared to baseline.
- Changes in HBsAg (decreased levels, disappearance of HBsAg, antibodies to HBsAg) at Week 24 and Week 48 compared to baseline.
- Change in HBV DNA levels at Week 24 and Week 48 compared to baseline.

Safety Endpoints

- Adverse events, physical examination, vital signs, 12-lead ECG, hematology, coagulation panel, blood chemistry, urinalysis, blood bile acids levels.
- Development of anti- Myrcludex B antibodies.

4. Study Design

4.1. Summary of Study Design

Taking into consideration the screening failure rate, approximately 200 patients will be screened, and 120 patients will be randomized in the 1:1:1:1 ratio to one of the four treatment arms:

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

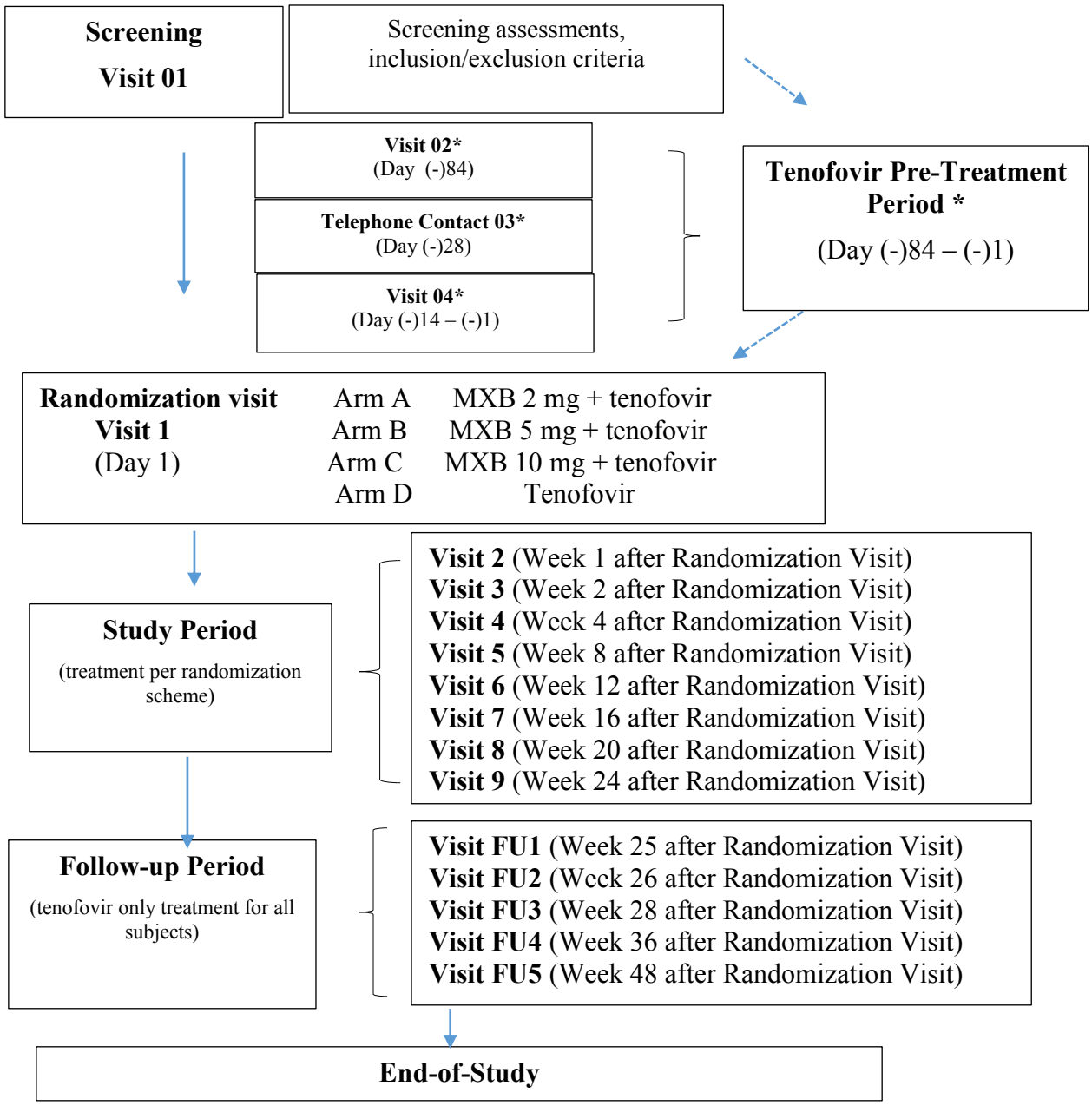
Arm B (30 patients): Myrcludex B, 5 mg/day subcutaneously (s.c.) for 24 weeks + tenofovir with a further follow-up period of 24 weeks of continued tenofovir therapy.

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

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

The main part of the study includes screening period of 28 days (Days -28/-1), pre-treatment period for patients, for whom a preliminary therapy with tenofovir of up to 84 days is indicated, baseline randomization visit (Day 1), and study period of 24 weeks. Follow-up period will be 24 weeks for all treatment arms.

Figure 1a. Phase II Study Scheme



* Only subjects who require tenofovir pre-treatment *(Pretreatment period - PreT)*.

Table 1. Study Flowchart

Procedures	SCR	PreT*				RV	Study Period								Follow-up Period					Early Termination
Visits	01	02	03	04		1	2	3	4	5	6	7	8	9	FU1	FU2	FU3	FU4	FU5	Final Visit
Day (D)/ Week (W)	D –28/-112* -1	D -84	D - 28	D -14 - 1		D1	W1/D8 ± 2D	W2/D15 ± 2D	W4/D28 ± 2D	W8 ± 2D	W12 ± 2D	W16 ± 2D	W20 ± 2D	W24 ± 2D	FUW1/ W25 ± 2D	FUW2/ W26 ± 2D	FUW4/ W28 ± 5D	FUW12/ W36 ± 5D	FUW24/ W48 ± 2D	D X
Informed Consent	X																			
Demographics and Medical History	X																			
Physical Examination (including weight)	X	X		X*		X					X			X					X	X
Height	X																			
Vital Signs	X	X		X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X										X			X					X	
Urine Pregnancy Test [1]	X			X*		X			X	X	X	X	X	X						
Urine Drug Screening (test strips)	X																			
Urinalysis	X					X			X		X			X				X	X	X
Serology	X																			
AFP Test	X																			
Abdominal Ultrasound	X																			
Breath Alcohol Test	X					X														
Inclusion/Exclusion Criteria	X			X*		X														
Transient Elastometry	X													X						
Randomization						X														
Dispensing of Study Medication (for 28 days of treatment)						X			X	X	X	X	X							
Dispensing of Tenofovir (nucleotide analogue therapy)		X*				X			X	X	X	X	X	X			X	X		
Compliance Assessment			X*	X*			X	X	X	X	X	X	X	X						
Dispensing and Review of Subject Diaries						X	X	X	X	X	X	X	X	X						
PK main study (for all subjects)						X			X	X	X	X	X	X						
HBV/HDV Genotyping (frozen samples)		(X)				(X)****														
NTCP Polymorphism (frozen cell pellet)						X														
Hematology, coagulation panel	X	X**		X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (complete panel)	X					X					X			X					X	X
Blood chemistry (abbreviated)		X**		X*			X	X	X	X		X	X		X	X	X	X		

Procedures	**SCR**	**PreT***				**RV**	**Study Period**								**Follow-up Period**					**Early Termination**
Visits	01	02	03	04		1	2	3	4	5	6	7	8	9	FU1	FU2	FU3	FU4	FU5	Final Visit
Day (D)/ Week (W)	D –28/- 112* -1	D -84	D - 28	D -14 - 1		D1	W1/D8 ± 2D	W2/D15 ± 2D	W4/D28 ± 2D	W8 ± 2D	W12 ± 2D	W16 ± 2D	W20 ± 2D	W24 ± 2D	FUW1/ W25 ± 2D	FUW2/ W26 ± 2D	FUW4/ W28 ± 5D	FUW12/ W36 ± 5D	FUW24/ W48 ± 2D	D X
Total Blood Bile Acids						X	X	X	X	X	X	X	X	X	X	X			X	X
Blood Bile Acids (frozen samples)						X	X	X	X	X	X	X	X	X	X	X			X	X
HDV RNA (ambient samples)	X																			
HDV RNA (frozen samples)		X*				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA		X*				X					X			X				X	X	X
HBsAg (frozen samples)		X*				X			X	X	X	X	X	X			X	X	X	X
HBeAg and anti-HBeAg antibodies	X													X***					X***	
Immunogenicity (frozen samples)						X					X			X				X	X	
Serum Fibrosis Marker (frozen samples)						X								X					X	
Resistance Test (frozen samples)		(X)				(X)****								X						
Adverse Events	X	X*	X*	X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications*****	X	X*	X*	X*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Only subjects who require pre-treatment with tenofovir *(Pretreatment period - PreT)*.

** Done, if laboratory test at Screening was performed over 14 days ago.

***Only for patients who are HBeAg-positive at Screening.

****In patients who need pre-treatment with tenofovir, the sample should be taken at visit 02 and omitted at RV Visit

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

(1) Women of childbearing potential only.

Overview of study visits.

- Screening Period of 28 days (Visit 01);
- Tenofovir Pre-Treatment Period for subjects requiring pre-treatment with tenofovir for up to 12 weeks (84 days) (starting from the moment when screening results become available that allow to assess inclusion/exclusion criteria for this study); this period includes the following:
    - Visit 02 (attending the study site) – start of tenofovir treatment 84 days before planned randomization visit;
    - Visit 03 (telephone contact) – telephone call to the subject 28 days before planned randomization visit;
    - Visit 04 (attending the study site) – up to 14 days before planned randomization visit.
- Randomization Visit (Visit 1 – Day 1);
- Treatment Period of up to 24 weeks (Visits 2-9 at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 after Randomization Visit);
- Follow-up Period of 24 weeks (Visits FU1-FU5 at Weeks 25, 26, 28, 36, and 48 after Randomization Visit, respectively).

Screening Period

The following procedures will be done at Screening, Visit 01 (up to 112 days prior to the first dose of Myrcludex B in case of pre-treatment with tenofovir; up to 28 days before the first dose of the study drug for subjects, who do not require tenofovir pre-treatment): informed consent form signing, physical examination (including weight measurement), laboratory tests, serology tests (HIV, HCV, HBsAg and HBeAg antibodies, HBsAg, HBeAg), HCV RNA in patients with HCV antibodies, antibodies to HDV, HDV RNA, abdominal ultrasound, urine pregnancy test, breath alcohol test, urine drug screening (test strips), evaluation of inclusion/ exclusion criteria.

Transient elastometry (Fibroscan) to assess fibrosis will be perfomed during screening.

If the subject requires pre-treatment period for nucleotide analogue treatment, he/she receives tenofovir for the entire pre-treatment period (84 days of dosing).

Tenofovir Pre-Treatment Period

Tenofovir Pre-treatment Period is included in order to allow to enroll patients, who did not receive prior treatment with nucleoside/nucleotide analogues. This will ensure a more homogeneous population of subjects participating in this clinical trial. Total duration of this period will be 12 weeks.

Tenofovir Pre-treatment Period includes the following:

- Visit 02 (attending the study site) – start of tenofovir treatment 84 days before planned randomization visit;
- Visit 03 (telephone contact) – telephone call to the subject 28 days before planned randomization visit to collect compliance data, concomitant treatments and adverse events;
- Visit 04 (attending the study site) –up to 14 days before planned randomization visit (physical examination, laboratory tests, counting of tenofovir tablets, compliance

assessment, repeated evaluation of inclusion/exclusion criteria, concomitant treatments and adverse events).

Randomization Visit

All patients, who meet inclusion/ exclusion criteria and who received treatment with nucleoside/ nucleotide analogues for at least 12 weeks before the planned start of study treatment or underwent protocol-specified tenofovir pre-treatment, will be asked to attend Randomization Visit. The following tests and procedures are performed at this visit: physical examination, safety laboratory tests, virology parameters, serum fibrosis marker, immunogenicity. All assessments at this visit will be regarded as baseline for safety monitoring (and should not be qualified as the inclusion/exclusion criteria). Upon completion of all protocol-defined procedures, patients are randomly assigned to one of the 4 treatment arms and receive study medication for the first 28 days of use.

Treatment Period

Treatment with the study medication in combination with tenofovir or tenofovir alone will last for 24 weeks, followed by a 24-week follow-up period. Treatment will be performed in the outpatient settings.

Follow-up Period

Follow-up period lasts for 24 weeks. During this period, patients will receive treatment with tenofovir.

4.2. Pharmacokinetic Study

For a more precise investigation of the possible study drug accumulation all the patients of each Myrcludex B treatment arm will be included in this sub-study.

Blood samples for pharmacokinetic study are to be collected at Randomization Visit, at Week 4, 8, 12, 16, 20, 24 (1 hour +/- 15 min after Myrcludex B administration).

4.3. Randomization

Subjects are randomized in the 1:1:1:1 ratio into arms A, B, C and D using a digital randomization scheme.

In order to minimize bias, subjects will be stratified based on the presence of liver cirrhosis (yes/no). Stratification is aimed on enrolling comparable number of cirrhotic subjects into each of the treatment arms. In this open-label study, neither subjects, nor investigators will be blinded to treatment assignments.

More details are given in the Randomization Plan.

4.4. Study Periods and Procedures

Any deviations from protocol-defined procedures must and reported to the Sponsor and CRO. Study procedures and visits are described below. Unscheduled visits may be performed, if deemed necessary by the Investigator, and must be documented in the CRF.

4.4.1. Screening Procedures

Inclusion and exclusion criteria will be verified during Screening Period (up to 112 days prior to the first dose of Myrcludex B in case of pre-treatment with tenofovir; up to 28 days before the first dose of the study drug for subjects, who do not require tenofovir pre-treatment).

The following procedures will be done in the outpatient settings at Screening Visit (Visit 01):

- Subjects receive information about the study and provide written informed consent to participate in the study (ICF must be signed and dated by the subject and the responsible Investigator);
- Medical history and demographics;
- Recording of concomitant medications including the previous therapy of hepatitis with interferon medications regardless of treatment prescription ;
- SAE recording;
- Physical examination including weight;
- Height;
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate);
- 12-lead ECG;
- Hematology, coagulation panel;
- Blood chemistry (complete panel);
- Serology;
- Urinalysis;
- Abdominal ultrasound;
- Transient elastometry (Fibroscan) ;
- AFP test;
- HDV RNA (ambient samples, central laboratory) ;
- HBeAg and anti-HBeAg antibodies;
- Alcohol breath test;
- Urine drug screening (test strips);
- Urine pregnancy test (for women of childbearing potential only)
- Assessment of inclusion/exclusion criteria;

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be ask to return to the clinic within 4 weeks after Screening for Randomization Visit.

Only subjects with positive HDV RNA test obtained from central laboratory may be enrolled into the study.

If pre-treatment with nucleotide analogue is indicated (subject has not received nucleotide/nucleoside analogues for at least 12 weeks prior to enrollment), patient will be asked to attend Visit 02 of the Tenofovir Pre-Treatment Period.

During Screening Period, subjects are monitored for adverse events. However, all unfavorable medical events (other than serious adverse events) that occurred during the screening period will be recorded as medical history of patients.

4.4.2. Tenofovir Pre-Treatment Period Procedures and Assessments

If a patient, who has not received nucleotide/nucleoside analogues for at least 12 weeks prior to enrollment, consents to taking part in the study and meets all of the inclusion criteria and none of the exclusion criteria, tenofovir pre-treatment period will be performed for up to 84 days prior to Randomization Visit.

Eligibility of subgroup subjects for whom pre-treatment with tenofovir is indicated will be confirmed based on data obtained at Visit 04 (no more than 14 days prior to the first dose of the study medication).

Tenofovir pre-treatment period includes the following:

Visit 02 (at the study site) – outpatient settings. The following procedures are performed at this visit:

- Recording of concomitant medications;
- SAE recording;
- Physical examination including weight;
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate);
- Hematology, coagulation panel (if more than 14 days elapsed since blood collection at Screening);
- Blood chemistry (abbreviated panel; if more than 14 days elapsed since blood collection at Screening);
- HBV/HDV genotyping (frozen samples);
- Resistance testing (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA and HBsAg (frozen samples);
- Dispensing of tenofovir.

Visit 03 (by telephone) – is a telephone contact with the patient 28 days before planned randomization date. The following procedures are performed at this visit:

- Recording of concomitant medications;
- SAE recording;
- Assessment of compliance, as reported by the subject.

Visit 04 (at the study site), in the outpatient settings, 14 days before planned randomization date. The following procedures are performed at this visit:

- SAE recording;

- Recording of concomitant treatment;
- Physical examination including weight;
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate);
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Urine pregnancy test (for women of childbearing potential only)
- Calculation of medication (tenofovir) taken;
- Assessment of compliance;
- Assessment of inclusion/exclusion criteria.

Subjects must return used and unused tenofovir bottles to the study site for assessment of compliance (after that unused bottles will be returned to the patient for continuation of therapy). Investigator enters compliance data into the CRF.

Investigator must reassess subject's eligibility based on inclusion/exclusion criteria, and if the subject meets all inclusion criteria and none of the exclusion criteria, Visit 1 will be scheduled for randomization procedure.

During pre-treatment period, subjects are monitored for adverse events (will be recorded as indicators to be included in patient's medical history, except for serious adverse events).

4.4.3. Randomization Visit

All eligible subjects will be asked to attend Randomization Visit (Visit 1, Day 1). At Randomization Visit, upon completion of all scheduled procedures, subjects are randomized to one of the four treatment arms.

Treatment and visits will be done in the outpatient settings.

Subcutaneous injections of the study medication and oral intake of tenofovir must be done every 24 ± 1 hour after the first dose. However patient can adjust the introduction of the second and subsequent doses of the study drug under a convenient schedule which should be reflected in the patient's diary. Administration of subsequent doses of the drug should be carried out every 24 ± 1 hours from the time set by the schedule.

The following procedures and baseline assessments will be performed at Randomization Visit:

- AE recording;
- Confirmation of meeting inclusion/ exclusion criteria based on results obtained during Screening;
- Randomization;
- Dispensing subject diary;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir for 28 days of treatment;
- Recording of concomitant treatment;

- Physical examination including weight;
- Vital signs;
- Hematology and coagulation panel;
- Blood chemistry (complete panel);
- Total blood bile acids ;
- Blood bile acids (frozen samples);
- Urinalysis;
- HDV RNA (frozen samples);
- HBV DNA and HBsAg (frozen samples);
- HBV/HDV genotyping (frozen samples): only if no sample was taken at visit 02;
- Resistance testing (frozen samples); only if no sample was taken at visit 02
- Urine pregnancy test (for women of childbearing potential only)
- Alcohol breath test;
- Immunogenicity (frozen samples);
- Serum fibrosis marker (frozen samples);
- NTCP polymorphism (frozen cell pellet);
- Blood sample for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).

Subject receives study medication, tenofovir, and all other study materials for Days 1 through 28 of the study.

All assessments done at this visit will be regarded as baseline for safety monitoring and should not be considered as inclusion/ exclusion criteria.

4.4.4. Treatment Period Procedures and Assessments

Patients start treatment at the Randomization Visit. Subcutaneous injections of the study medication and oral intake of tenofovir must be done every 24 ± 1 hour after the first dose. However patient can adjust the introduction of the second and subsequent doses of the study drug under a convenient schedule which should be reflected in the patient's diary. Administration of subsequent doses of the drug should be carried out every 24 ± 1 hours from the time set by the schedule. Subject visits must take place in compliance with the schedule described in this section and detailed in the Study Flowchart.

Randomization Visit, visits in weeks 1, 2, 4, 8, 12, 16, 20, and 24, follow-up visits at weeks 1, 2, 4, 12, and 24.

Week 1/ Day 8 ± 2 days/ Visit 2: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;

- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance.

Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

Week 2/ Day 15 ± 2 days/ Visit 3: the following procedures will be:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance.

Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

Week 4/ Day 28 ± 2 days/ Visit 4: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Urinalysis;
- Urine pregnancy test (for women of childbearing potential only)
- Total blood bile acids;
- Blood bile acids (frozen samples);

- HDV RNA (frozen samples);
- HBsAg (frozen samples),
- Blood sample for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration), frozen sample.
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

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

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- Urine pregnancy test (for women of childbearing potential only)
- HDV RNA (frozen samples);
- HBsAg (frozen samples),
- Blood samples for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

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

- AE recording;
- Physical examination including weight;
- Measurement of vital signs;
- 12-lead ECG;
- Hematology, coagulation panel;
- Blood chemistry (complete panel);
- Urinalysis;
- Urine pregnancy test (for women of childbearing potential only)
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples),
- Blood samples for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).
- Immunogenicity (frozen samples);
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

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

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);

- Urine pregnancy test (for women of childbearing potential only)
- HDV RNA (frozen samples);
- HBsAg (frozen samples),
- Blood samples for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

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

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Urine pregnancy test (for women of childbearing potential only)
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBsAg (frozen samples),
- Blood samples for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).
- Recording of concomitant treatment;
- Evaluation of the correctness of patient diaries filling (copies of the completed pages should be stored in the primary documentation);
- Assessment of compliance;
- Dispensing of study medication for 28 days of treatment;
- Dispensing of tenofovir.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

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

- AE recording;
- Physical examination including weight;
- Measurement of vital signs;
- 12-lead ECG;
- Hematology, coagulation panel
- Coagulation panel;
- Blood chemistry (complete panel);
- Urinalysis;
- Urine pregnancy test (for women of childbearing potential only)
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Blood samples for pharmacokinetic study (1 hour +/- 15 min after Myrcludex B administration, frozen sample).
- HBeAg and anti-HBeAg antibodies (frozen samples) – only for subjects with positive HBeAg test at Screening;
- Transient elastometry (Fibroscan);
- Serum fibrosis marker (frozen samples);
- Resistance test (frozen samples);
- Immunogenicity (frozen samples);
- Recording of concomitant treatment;
- Subject diary review;
- Assessment of compliance;
- Dispensing of tenofovir for 56 days.

Subjects must return used and unused study drug vials, as well as used and unused tenofovir bottles to the study site. Investigator reviews records in the subject diary and enters compliance data into the CRF. Subject diary is part of source documents.

4.4.5. Post-treatment Assessments

Upon completion of treatment period, subjects enter the follow-up period that lasts for 24 weeks. During the follow-up period, all subjects continue taking tenofovir.

FU Week 1 – Study Week 25 ± 2 days/ FU Visit 1: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- Recording of concomitant treatment.

FU Week 2 – Study Week 26 ± 2 days/ FU Visit 2: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Blood chemistry (abbreviated panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- Recording of concomitant treatment.

FU Week 4 – Study Week 28 ± 5 days/ FU Visit 3: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel
- Coagulation panel;
- Blood chemistry (abbreviated panel);
- HDV RNA (frozen samples);
- HBsAg (frozen samples);
- Recording of concomitant treatment;
- Dispensing of tenofovir for 56 days.

All subjects must return used tenofovir bottles to the study site.

FU Week 12 – Study Week 36 ± 5 days/ FU Visit 4: the following procedures will be performed in the outpatient settings:

- AE recording;
- Measurement of vital signs;
- Hematology, coagulation panel;
- Coagulation panel;
- Blood chemistry (abbreviated panel);
- Urinalysis;
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Immunogenicity (frozen samples);
- Recording of concomitant treatment;
- Dispensing of tenofovir for 56 days.

All subjects must return used tenofovir bottles to the study site.

FU Week 24– Study Week 48 ± 2 days/ FU Visit 5 (End-of-Study Visit)**:** the following procedures will be performed in the outpatient settings:

- AE recording;
- Physical examination including weight;
- 12-lead ECG;
- Measurement of vital signs;
- Hematology,
- Coagulation panel;
- Blood chemistry (complete panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- Urinalysis;
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- HBeAg and anti-HBeAg antibodies - only for subjects with positive HBeAg test at Screening;
- Immunogenicity (frozen samples);

- Serum fibrosis marker (frozen samples);
- Recording of concomitant treatment.

All subjects must return used and unused tenofovir samples to the study site.

4.5. Premature Discontinuation, Study Drug Interruption, Dose Adjustments

If a study participant discontinues MXB injections, for example, due to an adverse event, every effort must be made to motivate the the subject to continue participating in the study and undergoing all study procedures and follow-up, including tenofovir treatment. If this is not possible or inapplicable for the study participant, he/she will prematurely discontinue the study participation.

Before withdrawing subjects assigned to 5 mg and 10 mg MXB doses, Investigator should consider reducing the study drug dose: doses are reduced from 10 mg to 5 mg and from 5 mg to 2 mg per day. During dose adjustments AE monitoring must continue. If Investigator believes, that the treatment may be continued at the 2 mg dose level, the subject should continue with this dose and undergo all study procedures and follow-up.

If Investigator believes, that the subject requires temporary interruption in the MXB or tenofovir treatment, he/she should discuss it with the Sponsor's Medical Monitor.

If a study participant from any of the MXB treatment arms discontinues tenofovir, but continues with the MXB treatment, he/she should continue participation in the study. If a subject discontinues tenofovir treatment during follow-up period, every effort should be made to motivate the subject to continue with participation in the study.

Subjects discontinuing from the study will complete End-of-Treatment Visit, that includes the below assessments, within 14 days after the last dose of the study medication:

At the End-of Treatment Visit, the following procedures will be performed in the outpatient settings:

- AE recording;
- Physical examination including weight;
- Measurement of vital signs;
- Hematology;
- Coagulation panel;
- Blood chemistry (complete panel);
- Total blood bile acids;
- Blood bile acids (frozen samples);
- HDV RNA (frozen samples);
- HBV DNA (frozen samples);
- HBsAg (frozen samples);
- Urinalysis;
- Recording of concomitant treatment.

4.6. Management of Hepatitis Exacerbations

Hepatitis flair is defined as ALT increase as ALT > 2 × baseline or 10 × ULN.

Hepatitis exacerbations during MXB treatment

In case a hepatitis flair occurred during the treatment period, and no singes of hepatic function worsening are detected (bilirubin increase ≥ 2mg/dL, INR ≥1.7), the treatment should be continued under close monitoring of hepatic function. Unscheduled visits to monitor patient`s status and laboratory parameters should be discussed with sponsor`s medical monitor.

In case hepatic function worsening occurred, MXB treatment should be stopped and background therapy continued. At investigator`s discretion, switch to other commercially available anti-HBV therapy may be appropriate.

Hepatitis exacerbation after cessation of MXB treatment

MXB has been shown to significantly decrease HDV replication in previous studies. As with any effective antiviral treatment, the therapy stop may lead to viral rebound and hepatitis exacerbation.

In case of hepatitis exacerbation accompanied with HDV RNA replication increase is detected during the follow-up phase of the trial, at investigator`s discretion a therapy with interferon alpha can be initiated.

4.7. Description of Study Procedures

This section provides description of assessments. More details are given in the Laboratory Manual.

Demographics and Medical History

The following demographic details are to be collected during Screening:

- Date of birth;
- Sex;
- Race.

Information about underlying disease, other concurrent or previous conditions (deemed relevant by Investigator) and information about the previous interferon treatment of hepatitis regardless of the treatment prescription must also be entered into CRF. Information on any concomitant treatment / therapy should be collected from the time of screening.

Vital Signs and physical examination

Respiration rate, blood pressure, heart rate and body temperature will be measured regularly during the study. Time points for measuring vital signs are indicated in the study schedule. Vital signs are entered into CRF.

A complete physical examination and body weight determination will be done in this study at time points indicated in the Study Flowchart. The results must be entered into CRF.

Height

Height will be measured at time points indicated in the Study Flowchart and will be entered into CRF.

Urine Pregnancy Test

Urine pregnancy test is required for women of childbearing age. Pregnancy testing will be done locally, using test strips. The result will be documented in the CRF.

Drug Screening (urine test using test strips)

Urine test strips will be used to detect traces of methadone, benzodiazines, cocaine, amphetamines, cannabinoids, opiates, barbiturates, tricyclic antidepressant. The result will be documented in the CRF.

Alcohol Breath Test

Alcohol levels in exhaled oxygen will be measured using electronic breathalyzer. The result will be documented in the CRF.

Abdominal Ultrasound

Abdominal ultrasound is done at Screening. Special attention must be paid to liver structure. All abnormalities must be reported in the Medical History section of the CRF.

Serum Alpha-Fetoprotein

Serum alpha-fetoprotein will be measured for all subjects at Screening. The alpha-fetoprotein test is intended to rule out hepatocellular carcinoma. The result will be documented in the CRF.

Transient Elastometry

Transient elastometry (Fibroscan) is done at screening and at the End-of-Treatment Visit period to assess liver fibrosis staging. The result will be documented in the CRF.

Blood Tests for Safety Assessments

Safety blood tests will be performed by local center laboratories at time points indicated in the Study Schedule. Laboratory results will be entered into CRFs. Investigator must review laboratory results in the CRF and comment on values outside of the reference range or values that significantly differ from the previous results.

Clinical laboratory tests to be done during the study are listed below:

Hematology and Coagulation Panel

- WBC differential (percentage): neutrophils, eosinophils, basophils, monocytes, lymphocytes;
- WBC differential (absolute counts): neutrophils, eosinophils, basophils, monocytes, lymphocytes;
- RBC count;
- WBC count;
- Hematocrit;
- Hemoglobin;
- Platelets;

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

Blood Chemistry

Complete blood chemistry panel:

- Sodium;
- Potassium;
- Chloride;
- C-reactive protein;
- Total protein;
- Albumin;
- Total bilirubin;
- Direct (unconjugated) bilirubin;
- Total cholesterol;
- Creatinine;
- Blood urea;
- Glucose;
- Gamma glutaminetransferase;
- Alanine aminotransferase;
- Alkaline phosphatase;
- Aspartate aminotransferase;
- Lipase;
- P-amylase;
- Phosphate.

Abbreviated blood chemistry panel:

- Albumin;
- Total bilirubin;
- Creatinine;
- Gamma glutaminetransferase;
- Alanine aminotransferase;
- Aspartate aminotransferase;
- Phosphate;

- Lipase.
- P-amylase;

Blood Bile Acids

Specific bile acid levels will be analyzed by central laboratory in Germany. Samples will be collected in compliance with instructions provided by the central laboratory and stored at -20°C before courier shipment to the central laboratory.

Serology Screening

- HIV antibodies;
- HCV antibodies;
- HDV antibodies;
- Non-quantitative HBsAg test for eligibility assessment;
- Non-quantitative HBeAg test;
- HBeAg antibodies.

The above laboratory tests will be done at local laboratory of the study site, unless specified otherwise. In case of positive HCV antibodies test, HCV RNA test must be done. If the result for HCV RNA test is negative, the patient can be enrolled into the study.

Safety Urinalysis

Urinalysis will be done as indicated in the Study Flowchart. Results are entered into CRF.

The following parameters will be measured:

- pH;
- Specific gravity;
- Protein;
- Glucose;
- Bilirubin;
- Urobilinogen;
- Ketones;
- Erythrocytes;
- Leukocytes;
- Nitrites.

Urinalysis will be done at the local laboratory of study site.

Protocol-specified laboratory tests performed at local laboratories will be done in compliance with local standard operating procedures.

Laboratory tests performed at central laboratory will be done using the following methods:

Virology Tests

The following virology parameters will be evaluated in the study: HDV RNA, HBsAg and HBV DNA. Samples of venous blood will be collected at specified time points.

- HDV RNA by quantitative PCR;
- HBsAg levels by quantitative immunoassay;
- HBV DNA by quantitative PCR;
- HBV genotyping – once as a part of the study during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated, using sequencing technique;
- HDV genotyping – once as a part of the study during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated, using sequencing technique;
- Resistance testing – at the start of the study and at end of treatment, using sequencing technique. The first blood sample should be collected for analysis during the 02 Pre-T visit for patients whom the pre-treatment period with tenofovir has been indicated, or during the randomization visit – if no pre-treatment period is indicated.

These tests will be done by central virology laboratory.

Blood samples will be collected in sterile, air-locked single-use plastic K2-EDTA Vacutainer® vials. All plasma samples will be stored at -20°C until shipment to the central laboratory. Vials are shipped to the central laboratory in validated freezer containers at -20°C or -80°C.

Plasma samples for HDV RNA collected at Screening are stored and shipped to the central laboratory in ambient conditions.

Determination of antibodies to HBsAg will be performed at the end of the study in a central virology laboratory using appropriate back-up samples (for HBsAg determination) in patients with negative result of quantitative HBsAg determination at Week 24 and Week 48 of active treatment. The samples are not to be taken separately for this analysis.

NTCP Polymorphism

NTCP polymorphism is assessed once during the study (at baseline), at the central laboratory, using sequencing technique.

Serum Fibrosis Marker

EIA test for serum fibrosis marker, alpha-2-macroglobulin, will be done at the start of the study, at the end of treatment and at the end of follow-up period, at site local laboratory. The result will be documented in the CRF.

Immunogenicity

Anti-MXB antibodies will be determined only in subjects receiving Myrcludex B by ELISA technique.

Plasma PK Parameters

Blood samples will be collected in sterile, air-locked single-use plastic Li-Heparin Vacutainer® vials. The volume of the blood samples for this test must be at least 4 mL.

Plasma levels of Myrcludex B will be measured using a validated HPLC-MS/MS technique. Quantitative analysis of concentration will be done by the Central Laboratory.

Blood amount taken during the study

The total amount of blood taken for the study will be approximately 648 ml. In account with the 12-week course of pre-treatment with tenofovir the blood volume increases on 30 ml.

If there is a need to conduct re-analyzes or safety monitoring of investigational therapy, additional visits can be scheduled. After the unscheduled visit, the next visit is to be carried out in accordance with previously approved plan and protocol.

To determine Myrcludex B effects or physiological effect of increased level of bile acids on the metabolism or inflammation, blood samples collected in the study can be analyzed for parameters that characterize carbohydrate and lipid metabolism and also play a role in the development of vascular diseases.

Subject Diary

During Treatment Period subjects receive diaries to record the following information:

- Adverse events, specifically injection site reaction;
- Date and time of each dose of the study medication and the nucleotide analogue medication.

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

4.8. Study Completion, Interruption and Termination, Individual Study Site Termination and Subject Withdrawal

4.8.1. Study Completion

A subject is considered to complete the study, when he/she completes all study procedures listed in Section 4.4 of the protocol.

Completion of study participation is defined as the date of the last visit or the last scheduled procedure per Section 4.4 of the study protocol. Completion of the whole study is defined as the last visit of the last enrolled subject.

The Sponsor has the right to suspend or terminate the study at any time, due to reasons, that include, but are not limited to safety issues, ethical considerations and significant violations of pre-defined rules and requirements. If the study is suspended or terminated for safety concerns, the Sponsor will in a timely manner inform the contract research organizations (CROs), investigators, IEC and the competent as well as local regulatory authorities of suspension/termination and reasons for this decision.

4.8.2. Study Suspension or Early Termination

Investigator and Sponsor reserve the right to terminate the study at any moment. If necessary, procedures will be agreed upon after consultation of both parties. If the study is terminated early or suspended, the Sponsor has to immediately notify investigators/ institutions and authorized bodies of

termination or suspension stating the reasons for termination or suspension. Local ethics committee, the competent and local authorities have to be notified by the Sponsor or investigator/ institution, as well (as per regulatory requirements) specifying reasons for termination or suspension of the study. At the study termination, the Sponsor and the investigator will ensure compliance with regulations for the best protection of patients' interests.

The most probable reasons for suspension or early termination of the study may be serious and unexpected adverse reactions in the majority of patients during the first study days, noncompliance with study rules, and impossibility to conduct the study according to the protocol.

The possible reasons for the study termination by the Sponsor may include the increased risk for patients' life and health, significant deviations during the study, etc. In case the study is terminated by the Sponsor, the company has to notify the CROs, investigators, as well as the local ethics committees, competent and local authorities. The Sponsor has the right to stop the study at any moment.

Investigator has the right to stop the participation of her/his center if in their opinion increased risk for patients' life and/or health is not acceptable. In this case the investigator has to notify the CRO/ Sponsor and the local ethics committee.

If the study is terminated early or suspended for any reason, the investigator should immediately notify enrolled patients and ensure they are adequately treated and followed up.

4.8.3. Premature Discontinuation of Study Site by the Sponsor

A study site may be prematurely closed, or its activities suspended in case the study staff significantly deviates from requirements of GCP, protocol and/or regulatory authorities, contract obligations, and cannot ensure adequate study conduct.

4.8.4. Early Termination of Patient's Participation

For patients, who were included in the study and finished participation not according to the protocol, i.e. were excluded from the study, the Final Visit section of the CRF will be completed with obligatory reporting of the reason for the patient's withdrawal. The following may be among the reasons:

- Investigator decides that the patient has to be excluded for safety reason.
- Inclusion by mistake.
- Serious protocol deviation, protocol violation.
- Serious adverse event, including death (report date).
- Adverse event.
- Patient undergoes/ needs additional treatment which may affect study results.
- Positive pregnancy test (for female patients).
- Patient did not come for a visit or is lost to follow up.
- Subject's consent withdrawal or non-compliance.

4.9. List of Data Entered Directly into CRF

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the

reconstruction and evaluation of the trial. Source data is contained is source documents (originals or certified copies).

All source data including AE information will first be recorded in source documents (medical charts, case histories), and then transferred to CRF. CRF will not contain any data not reflected in the source documents, except when original printouts are available or data can be entered directly into the system, as stated in the Monitoring Manual.

Completed CRFs will be checked against source data by Study Monitor. All deviations and errors must be corrected by Investigator and documented in Monitor's Report.

5. Selection and Withdrawal of Study Participants

This study will enroll subjects with chronic HDV infection and detectable HDV RNA replication level.

5.1. Inclusion Criteria

Subjects must meet all of the below inclusion criteria in order to be eligible for participation in this study.

1. Age from 18 to 65 years inclusively at the time of signing Informed Consent Form.

2. Positive serum HBsAg for at least 6 months before Screening.

3. Positive serum anti-HDV antibody for at least 6 months before Screening.

4. Positive PCR results for serum HDV RNA at Screening.

5. Patients with liver cirrhosis, irrespective of previous interferon treatment.[4]

6. Patients without liver cirrhosis, who failed prior interferon treatment or for whom, in the opinion of the Investigator, such treatment is currently contraindicated (including history of interferon intolerance)[5].

7. Alanine aminotransferase level >1 x ULN, but less than 10 x ULN.

8. Previous nucleotide/nucleoside analogue treatment within at least 12 weeks prior to the planned start of study treatment or subject's willingness to take tenofovir for at least 12 weeks prior to the planned start of study treatment.

9. Negative urine pregnancy test for females of childbearing potential.

10. Inclusion criteria for female subjects:

- Postmenopausal for at least 2 years, or
- Surgically sterile (total hysterectomy or bilateral oophorectomy, bilateral tubal ligation, staples, or another type of sterilization), or
- Abstinence from heterosexual intercourse throughout the study, or
- Willingness to use highly effective contraception throughout the study and for 3 months after the last dose of the study medication.

[4] Patients with liver cirrhosis should be included in case the interim analysis (Section 9.4. Interim and Final Data Analysis) will provide positive safety assessment. The sponsor will notify the centers on the results of the analysis and the permission to enroll cirrhotic patients.
[5] Patients with previous interferon treatment can be enrolled only at least 30 days after the last interferon dose.

11. Male and female subjects must agree to use a highly effective contraception[6] throughout the study and for 3 months after the last dose of the study medication.

12. Male subjects must agree not to donate sperm throughout the study and for 3 months after the last dose of the study medication.

5.2. Exclusion Criteria

Patients meeting any of the below exclusion criteria cannot take part in this study.

1. Child-Pugh score of B-C or over 6 points.

2. HCV or HIV coinfection. Subjects with anti-HCV antibodies can be enrolled, if screening HCV RNA test is negative.

3. Creatinine clearance <60 mL/min.

4. Total bilirubin ≥ 2mg/dL. Patients with higher total bilirubin values may be included after the consultation with the Study`s Medical Monitor, if such elevation can be clearly attributed to Gilbert's syndrome associated with low-grade hyperbilirubinemia.

5. Any previous or current malignant neoplasms, including hepatic carcinoma.

6. Systemic connective tissue disorders.

7. NYHA (New York Heart Association) class III-IV congestive heart failure.

8. Patients with uncontrolled arterial hypertension (BP >150/100 mm Hg despite antihypertensive treatment) within 3 months prior to start of clinical phase of the study.

9. Previous or unstable concurrent diseases or conditions that in investigator's opinion prevent subject's enrolment into the study.

10. Patients with mental disorders or social circumstances that preclude them from following protocol requirements.

11. Current or previous decompensated liver disease, including coagulopathy, hyperbilirubinemia, hepatic encephalopathy, hypoalbuminaemia, ascites, and esophageal varices hemorrhage.

12. Patients with history of pancreatitis or pancreatic insufficiency.

13. WBC count <3000 cells/mm^3.

14. Neutrophil count <1500 cells/mm^3.

15. Platelet count <60,000 cells/mm^3.

16. Proof of use of prohibited psychotropic agents at Screening.

17. Use of interferons within 30 days before Screening.

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[6] According to CTFG Recommendations related to contraception and pregnancy testing in clinical trials dated 15 Sep 2014, the following birth control methodsshould be considered as highly effective: 1) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); 2) progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); 3) intrauterine device (IUD); 4) intrauterine hormone-releasing system (IUS); 5) bilateral tubal occlusion; 6) vasectomised partner; 7) sexual abstinence.

18. History of solid organ transplantation.

19. Current alcohol abuse or alcohol abuse within 6 months prior to enrolment in this study.

20. History of disease requiring regular use of systemic glucocorticosteroids.

21. Pregnant or breast-feeding females.

22. Participation in another clinical study within 30 days prior to Screening.

23. Prior treatment with Myrcludex B in previous studies.

5.3. Subject Withdrawal Criteria

5.3.1. Withdrawal Criteria

Study subjects can withdraw from the study at any moment and without having to explain their decision. However, Investigator will make every reasonable effort to document exact reasons for subject's decision to withdraw and enter them into CRF.

Subjects may be withdrawn from the study in the following circumstances:

1. Investigator believes that it is not in the subject's best interests to continue participation in the study.

2. Investigator decides to withdraw the study subject due to a serious protocol deviation/violation.

3. Concurrent disease or progression of the underlying disease that, in the opinion of Investigator, can significantly affect evaluation of subject's clinical status.

4. In case of suspected pancreatitis, the treatment with the study medication should be stopped and further diagnostic procedures undertaken. Patients should be informed about the symptoms of pancreatitis and contact the investigator immediately in case of occurrence of such symptoms.

5. Use of prohibited medication is required.

6. Unacceptable toxicities, as defined in Toxicity Management Section of the Protocol, or a reaction that, in the Investigator's opinion, precludes further study procedures or requires discontinuation of the subject from the study.

7. Subject's decision to discontinue from the study for any reason.

8. Unsatisfactory compliance, defined as missing study drug doses for 3 consecutive days or 4 missed doses over 28 days.

9. Pregnancy during the study.

10. Sponsor, regulatory authority or IRB/IEC decide to terminate the study.

11. Subject is lost to follow-up.

The following protocol violations may require withdrawing subject from the study. In such cases, decision regarding subject's continuation with the study will be made by the Sponsor alone or after discussion with the Investigator.

- Failure to inform the Sponsor about AE in a timely manner (if Investigator becomes aware of the AE, and this is documented).
- Concurrent disease or condition that interferes with protocol-required procedures, which, in the Investigator's opinion, can bias interpretation of the subject's condition.

- Need to use other medications, other than the study drug, that do not significantly affect study results.
- Other protocol violations that are not considered significant by Investigator or Sponsor.

Subject may be immediately withdrawn from the study at any stage of the study.

In case of a serious disease or intolerance of the study medication, Investigator is responsible for deciding, whether the subject must be withdrawn from the study. Subjects withdrawn from the study due to a serious concurrent disease or for safety reasons will receive appropriate standard medical care and will be followed until resolution or stabilization of their condition. In such cases, Investigator must notify the Sponsor in advance and provide sufficient medical rationale for his/her decision.

Patients will also be considered withdrawn, if they are lost to follow-up, i.e. when a patient withdraws from the study without notifying the Investigator.

As excessive dropout rate may render study results not interpretable, unnecessary withdrawals should be avoided.

5.3.2. Withdrawn Subject Data

Investigator is responsible for documenting the reason(s) for subject's withdrawal from the study after randomization and entering all relevant information into CRF. Investigator must complete the Final Visit page in the CRF, indicating detailed information about the reason for the subject's withdrawal from the study. If the subject was withdrawn due to an AE, the primary term or a laboratory test must be reported in the CRF, and Investigator must make every effort to accurately report all AE characteristics.

Investigator will report information about withdrawn subjects to the Sponsor and site monitor within 24 hours, including the reason for subject withdrawal:

- Investigator's mistake;
- Adverse events;
- Serious adverse events;
- Pregnancy;
- Protocol violations;
- Subject's decision to withdraw;
- Subject's failure to attend visits or lost to follow-up;
- Other reasons (specify).

5.3.3. Replacement of Subjects

If a subject was randomized in the study, but did not start treatment with the study medication, he/she will be replaced. Subjects discontinued during the pre-treatment period will be considered screening failures and will be replaced. Subjects who received at least one dose of the study drug will not be replaced.

5.3.4. Follow-Up of Withdrawn Subjects

In case of a SAE, subject must be followed until SAE resolution or reaching stable conditions by collecting information about symptoms and history by telephone, and during unscheduled visits, required to ensure subject's safety.

If, in the opinion of treating physician, a non-serious adverse event requires follow-up, information about symptoms and the course of the event can be collected by telephone and at visits to the study site.

If Investigator considers an SAE to be probably related to the study medication, subject will be followed and treated appropriately until SAE resolution, irrespective of the time that elapsed from SAE occurrence.

If a subject withdraws from the study on his/her own request, every effort will be taken to follow-up the (S)AEs until their resolution and/or reaching stable conditions.

6. Treatment of Patients

6.1. Myrcludex B

6.1.1. Formulation

Myrcludex B is produced as lyophilized powder for solution for injection. Myrcludex B is supplied in sterile vials, the contents of which must be diluted in 1 mL of sterile water for injection.

Composition:

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

Excipients: water for injection, sodium carbonate, sodium hydrocarbonate, mannitol, hydrochloric acid, and sodium hydroxide are used for solution of the drug substance before aseptic filling and lyophilization. Pharmaceutically pure substances are used.

Physical Formulation: white or grayish-white powder.

Solution Appearance: clear and colorless.

6.1.2. Container Closure System

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

Primary Packaging

Container: 2 R vial for injection, colorless glass, Ph. Eur. Hydrolytic class I.

Closure Element: lyophilization rubber stopper for 2R vials, Ph. Eur. type I (diameter 13 mm).

Secondary Packaging

Closure Element: 13 mm flip clap seal, aluminum with a plastic disk.

Container closure system is for single use only. Vials and lyophilization rubber stoppers are sterile, all materials are tested before use.

6.1.3. Drug Storage and Handling

At study site, the drug should be stored at -20±5°C, protected from light.

At home, the drug is can be stored at +5°C (in refrigerator).

Deviation of the cold chain conditions is allowed (storage at room temperature up to 3 days).

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

6.2. Dosing and Administration of Myrcludex B

Study site staff will instruct patients on subcutaneous administration of the drug. Training materials will be provided to the patients separately.

Arm A: Myrcludex B 2 mg/day SC

During the treatment period at each visit patients randomized into Arm A will receive study drug kits to be used over 28 days, including:

30 vials of Myrcludex B 2.0 mg

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

30 single-use syringes

Patients will be instructed to reconstitute the entire content of the Myrcludex B 2.0 mg vial contents with 1 mL of water for injection, and to carry out a self-administration once per day. The drug should be diluted immediately before injection. Reconstituted solution is stable for 2 hours.

Arm B: Myrcludex B 5 mg/day SC

During the treatment period at each visit patients randomized into Arm B will receive study drug kits to be used over 28 days, including:

30 vials of Myrcludex B 5.0 mg

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

30 single-use syringes

Patients will be instructed to reconstitute the entire content of the Myrcludex B 5.0 mg/vial with 1 mL of water for injection and to carry out a self-administration once per day. The drug should be diluted immediately before injection. Reconstituted solution is stable for 2 hours.

Arm C: Myrcludex B 10 mg/day SC

During the treatment period at each visit patients randomized into Arm C will receive study drug kits to be used over 28 days, including:

60 vials of Myrcludex B 5.0 mg

30 vials of sterile water for injection (5 mL minimum)

60 single-use syringes

Patients will be instructed to reconstitute the entire content of the two Myrcludex B 5.0 mg/vials with 1 mL of water for injection each, and to carry out a self-administration once per day. Interval between both injections should be 1-30 minutes.

The drug should be diluted immediately before injection. Reconstituted solution is stable for 2 hours.

Dose Adjustment

Dose adjustment in Arm A is not allowed.

In arms B and C, dose may be adjusted in case of toxicity. Further details are provided inn Section 4.5, Premature Discontinuation, Study Drug Interruption, Dose Adjustments.

Missed Dose

In case of a missed dose the following procedure is to be followed:

If a patient remembered of the missed dose before 4 hours have lapsed from the daily administration time frame, the dose should be administered. The next day, the planned dose should be administered at the initially set up time. If more than 4 hours have passed from the planned time point, the dose should not be administered and should be considered missed, and the next day the planned dose should be administered at the initially set up time.

The missed dose should be reported in a patient's diary and CRF. Patient should notify the investigator of the missed dose by phone.

6.3. Previous and Concomitant Medications

Patients who previously received treatment for HBV with another nucleoside/ nucleotide analogue will be switched to tenofovir in the beginning of the study (randomization visit).

Tenofovir (VIREAD®) will be provided by Gilead Sciences (Ireland) in market package for Germany in the form of film-coated tablets of 245 mg tenofovir disoproxil, N30 vials in a cardboard box. Primary and secondary drug packaging will be labeled according to requirements of the German legislation.

VIREAD® (tenofovir disoproxil 245 mg, equivalent to tenofovir disoproxil fumarate 300 mg), film-coated tablets.

Trademark: VIREAD®

Registration Numbers:

EU/1/01/200/001

EU/1/01/200/002

INN: tenofovir disoproxil (fumarate)

Chemical Name: 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]metoxy]phosphenyl]metoxy]propyl] adenine fumarate

Manufacturer: Patheon Inc., Canada,

Gilead Sciences (Ireland),

Marketing Authorization Holder: Gilead Sciences, Ireland

Formulation

Film-coated tablets, 245 mg (tenofovir disoproxil)

Contents

Each film-coated tablet contains:

Active Ingredient: tenofovir disoproxil 245 mg equivalent to tenofovir disoproxil fumarate 300 mg;

Excipients:

Tablet Core: pregelatinized starch, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, magnesium stearate;

Film Coat: glycerol triacetate (E1518), indigo carmine aluminum lake (E132), hypromellose (E464), lactose monohydrate, titanium dioxide (E171).

Description

Film-coated almond-shaped light blue tablets, 16.8 mm × 10.3 mm, "GILEAD" and "4331" engraved on one side and "300" – on another.

Formulation

Film-coated 245 mg tenofovir disoproxil tablets. 30 tablets in a HDPE vial with dessicator (silica gel) sealed by a child resistant cap.

Storage Conditions

In a dry place protected from light, at temperature not exceeding 30°C.

Keep away from children.

Shelf Life

5 years.

Do not use after expiration date printed on the package.

6.4. Prohibited Products

- Systemic glucocorticosteroids.
- Prohibited psychotropic agents, drugs, and psychoactive substances.
- Use of immunomodulatory agents and antiviral drugs, apart from tenofovir, should be discussed with the medical monitor.

6.5. Methods to Control Patients' Compliance with Study Procedures

At screening or randomization, patients undergo laboratory and instrumental examinations to confirm they meet or do not meet inclusion/ exclusion criteria. Female patients will additionaly undergo pregnancy test.

During the study, each visit also implies concomitant therapy reporting, evaluation of treatment compliance and AEs. These procedures also confirm patients' compliance with study procedures.

7. Efficacy Assessments

7.1. Efficacy Endpoints

Primary Endpoint

- HDV RNA negativation or decrease by ≥2 log10 from baseline to Week 24.

As Myrcludex B has no direct effects on HDV replication levels, but prevents HBV entry into hepatocytes by blocking HBV and HDV receptor NTCP/SLC10A1, thus suppressing viral spread in the liver, HDV RNA decrease by ≥2 $\log^{10}$ can most probably indicating a 100-fold decrease in the number of infected cells. This information is needed to establish duration of treatment with Myrcludex B, required for HDV RNA negativation / complete viral elimination in an individual patient, depending on the viral load decrease progress.

Secondary Endpoints

Secondary Efficacy Endpoints:

- Durability of HDV RNA response to 24 weeks post treatment
- Combined response: HDV RNA negativation or ≥2 log10 decline and normal ALT at treatment week 24
- Changes in ALT values at Week 24 and Week 48 compared to baseline.
- Lack of fibrosis progression based on transient elastometry (Fibroscan) at Week 24 compared to baseline.
- Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 and Week 48 compared to baseline.
- Changes in HBsAg (decreased levels, disappearance of HBsAg, antibodies to HBsAg) at Week 24 and Week 48 compared to baseline.
- Change in HBV DNA levels at Week 24 and Week 48 compared to baseline.

7.2. Efficacy Assessment Methods and Time Points

Protocol defines baseline data for Myrcludex B efficacy assessments as values obtained at Randomization Visit (Visit 1).

Efficacy assessments will be done as follows:

- HDV RNA negativation or decrease by ≥2 log10 from baseline (Visit 1) to Week 24 (Visit 9) will be analyzed by HDV RNA PCR.
- Durability of HDV RNA response to 24 weeks post treatment (FU Visit 5; Study Week 48) compared to end of treatment (Visit 9: Study Week 24) will be analyzed by HDV RNA PCR.
- Combined response: HDV RNA negativation or ≥2 log10 decline and normal ALT at treatment week 24 (Visit 9) compared to baseline (Visit 1) will be analyzed based on PCR data and blood chemistry results.
- Changes in ALT values at Week 24 (Visit 9) and Week 48 (FU Visit 5) compared to baseline (Visit 1) will be analyzed based on blood chemistry results.
- Lack of fibrosis progression at Week 24 (Visit 9) compared to baseline (Visit 01) will be assessed based on transient elastometry (Fibroscan) results.
- Changes (absence of increase) in fibrosis marker: serum alpha-2-macroglobulin at Week 24 (Visit 9) and Week 48 (FU Visit 5) compared to baseline (Visit 1).
- Changes in HBsAg (decreased levels, disappearance of HBsAg, antibodies to HBsAg) at Week 24 (Visit 9) and Week 48 (FU Visit 5) compared to baseline (Visit 1) will be assessed based on quantitative immunoassay results.
- Decreased HBV DNA levels at Week 24 (Visit 9) and Week 48 (FU Visit 5) compared to baseline (Visit 1) will be assessed based on quantitative HBV DNA PCR results.

8. Safety Assessment

8.1. Safety Endpoints

- Adverse events, physical examination, vital signs, 12-lead ECG, hematology, coagulation panel, blood chemistry, urinalysis, blood bile acids levels.
- Development of anti- Myrcludex B antibodies.

8.2. Adverse Events

Study subjects will be thoroughly monitored for serious adverse events (SAEs) by interviewing, physical examinations and laboratory tests from the moment of signing the informed consent form. The AEs reported after the first dose of the study drug will be collected and included in the statistical analysis. Monitoring will be conducted as per the schedule of procedures. AEs will be classified and reported in CRFs. Classification will be based on the following parameters: seriousness, severity, relation to the study drug, outcome, measures related to the study drug and other countermeasures undertaken. Classification will be done by the responsible investigator according to the definitions presented below.

The planned study implies reporting of all abnormalities in patients' health (based on results of physical examination, laboratory and instrumental examinations) compared to screening data, data collected at other visits of the planned study and approved reference values.

Having received necessary information the investigating physician will classify a patient's condition as "normal", "clinically insignificantly abnormal", or "clinically significantly abnormal". In case detected abnormalities have been considered by investigator as clinically significant, have not been previously reported, or exacerbation of a patient's condition takes place compared to screening data or data received before the first dose of study drug administration, the detected abnormalities will be classified as adverse events (AEs) and evaluated as per CTCAE, version 4.0.

In case the detected abnormalities have been reported at screening or before the first dose of study drug administration and no negative trend is evident, the detected abnormalities will be classified as clinically insignificant.

All documented abnormalities irrespective of their classification as AEs or clinically insignificant abnormalities will be analyzed for clinical study reports.

The protocol includes reporting of all AEs detected in patients after the first dose of study drug administration and throughout their participation in the study. An adverse event is defined as "any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug" according to the ICH Guideline for good clinical practice, E6(R1) .

An AE may be any unfavorable (including abnormal laboratory finding) symptom, complaint, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

All changes in laboratory, instrumental and physical parameters compared to normal and/or baseline will be reported by the investigating physician followed by the investigating physician's medical judgment of the detected abnormalities. In case the detected change meets the definition of an AE, the investigating physician should report the AE, otherwise, the detected change will be considered a clinically insignificant abnormality.

8.2.1. Definitions

The following definitions have been adopted in the protocol (italics mean citations from ICH E2A Guidelines "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting").

Adverse Event:

"any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug".

AEs include:

- new symptoms/ medical conditions,
- new diagnosis,
- changes in laboratory parameters,
- concomitant diseases and accidents,
- worsening of medical condition/ disease present before the start of the clinical study,
- disease recurrence,
- increased rate and severity of disease exacerbation episodes.

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

Surgical procedures are not AEs as such, but measures undertaken to treat diseases requiring surgical intervention. Condition requiring surgical intervention may be considered an AE. Planned hospitalization, surgery or conditions resulting in these measures are not AEs, if the condition resulting in necessary hospitalization/ surgery was evident before the enrollment of the subject.

All AEs (including SAEs) will be reported in CRFs.

AEs will be categorized as "serious" and "non-serious" (see below).

Serious Adverse Event:

"A serious adverse event (SAE) is any untoward medical occurrence that at any dose of the drug:

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

In addition, adverse events or reactions considered by the responsible investigator as **important medical or scientific events** may also be classified as "serious".

SAEs appearing after the study completion i.e. after the Follow-up Visit 05 are NOT to be reported, excluding cases when, in the investigator's opinion, the event could be the result of the study drug administration or any protocol procedure.

Death is an outcome of an AE, not an event as such. If no other information is included in a report of the lethal outcome due to "disease progression", it is implied that death is the result of progression of the disease treated by the study drug.

All deaths of study subjects should be reported over 30 days from the last dose of the study drug or up to 30 days from the last study evaluation which is earlier irrespective of relationship of the death with the study drug.

"At any dose" does not mean that the subject received the study drug at the moment an adverse event developed. The drug could be administered within the treatment course, treatment could be suspended before a SAE developed, but it could affect emergence of an AE.

"Life-threatening" means that the subject was at immediate risk of death at the time of the event. This does not include AEs that had they occurred in a more severe form, might have caused death.

Complications during hospitalization are considered AEs. If a complication results in prolongation of existing hospitalization, it is considered a SAE.

"In-patient hospitalization" is defined as admission to a hospital for medical reasons for any time period. It does not necessarily mean hospitalization over 24 hours. This category does not include consultations and care in an emergency room.

Investigator should try to diagnose an adverse event based on signs, symptoms and/or other clinical data. In such cases a diagnosis should be reported as an AE or SAE, not individual signs/ symptoms.

Expectedness:

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

Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute "unexpected" events.

8.2.2. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Both suspected (i.e. (possibly) related to the study drug) and "unexpected" serious adverse events are considered suspected unexpected serious adverse reactions (SUSARs).

If an investigator, who first reported an SAE, considered the SAE at least as "unlikely" related to the study drug and this SAE is "unexpected", then this SAE must be considered as a SUSAR.

All SUSARs meet the requirements for expedited reporting. Reports will be submitted to responsible ethics committees and competent regulatory authorities i.e. BfArM according to the applicable regulations.

8.2.3. Follow-Up Period and Documentation

In this study, adverse events will be recorded from the first dose of the study medication (Study Day 1 Visit) through the last visit of the follow-up period. All adverse medical events present before the first administration of the study medication will be reported as part of subject's medical history.

At each study visit the responsible investigator will question the subjects about adverse events. If necessary, AEs and SAEs will be documented in eCRFs and and/or reported in writing on a pre-specified SAE-form.

All subjects with AEs, both related and unrelated to the study drug, will be followed by the responsible investigator in order to report the outcome. Clinical course of AEs will be followed until complete resolving or stabilization.

8.2.4. Characteristics of Adverse Events

All AEs will be classified according to the following characteristics:

Intensity/ Severity

Severity of AEs during the study is assessed according to NCI-CTC, version 4.0, see http://ctep.cancer.gov.

- **Mild:** presence of signs and symptoms, but easily tolerated and not affecting everyday activities. Symptoms do not require therapy or medical evaluation, signs and symptoms are transient.
- **Moderate:** AEs result in inconvenience or discomfort of the subject and may affect everyday activities, but are usually reversed by simple therapeutic measures. Moderate AEs may affect body functioning to a certain extent.
- **Severe:** AEs forcing the subject to stop everyday activities and usually requiring systemic drug therapy or other treatment. Usually they result in disability.

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

AEs and adverse drug reactions seriousness, and not intensity (severity), will be used as a criterion of regulatory authorities notification.

Causal Relationship with the Study Drug

Investigator is responsible for assessment of relationship between AEs and the study drug. Investigator must establish if there is a reasonable probability that the study drug caused or contributed to emergence of an AE. Assessment of the causal relationship based on clinical evaluation often relies on the following criteria:

- Temporal relationship between an AE and the study drug administration.
- Probable biological mechanism of an AE emergence due to the study drug.
- Another possible nature of an AE.
- Previous reports of similar AEs related to the study drug or drugs of a similar class.
- Recurrence of an AE after reinitiation of therapy or resolving after treatment withdrawal, if applicable.

The following terms are used to assess relationship of an event with the study drug:

- **Related** – suspected probability that an AE may be related to the study drug.
- **Unrelated** – no suspected probability that an AE may be related to the study drug.

In case an event is considered an "unrelated" to the study drug, another etiology, diagnosis or rationale of an AE development should be reported.

Outcome

AE outcomes will be classified as follows:

- **Resolved/recovered:** all signs and symptoms of an AE disappear without sequelae by the moment of the last interview.
- **Resolving/ recovering:** intensity of signs and symptoms is decreasing, up to the last interview their clinical nature was changing typically for resolving.

- **Not resolved/ not recovered:** signs and symptoms of an AE almost did not change from the moment of the last interview.
- **Resolved/ recovered with sequelae:** actual signs and symptoms of an AE disappeared, but had sequelae related to the AE.
- **Death:** AE resulted in death. If the patient reported several AEs only the AE that resulted in death is qualified as such.
- **Unknown:** outcome is unknown or unlikely, and information cannot be supplemented or confirmed.

Actions Taken Regarding the Study Drug

The actions taken regarding the study drug should fall into one of the following categories:

- **Dose not changed:** the study drug dose remains unchanged.
- **Dose decreased:** the study drug dose is decreased.
- **Drug temporary discontinued:** interruption of the study drug therapy.
- **Drug withdrawn:** permanent termination of the study drug therapy.
- **Not applicable:** the issue is irrelevant (due to the subject's death or single administration of the drug, precluding possibility to change the dose).

Countermeasures:

The term "countermeasures" means special actions taken for treatment or relief in case of AEs in order to prevent sequelae. The following categories have been approved:

- **None:** no actions taken.
- **Drug treatment:** a newly prescribed drug, or modification of the study drug dose.
- **Other:** other countermeasures, e.g. surgery.

8.2.5. Investigator's Notifications of Serious Adverse Events

Investigator will submit notifications of all SAEs within 24 hours he/she learnt of the SAE by sending an SAE form to the PV-department of the KKS Heidelberg.

The reporting will be carried out by faxing of the SAE form to the number: **+49 (0)6221-56-33725**.

The initial report must be as complete as possible and contain information on the current disease and event, as well as assessment of the causal relationship between an AE and the study drug.

Detailed information on reporting of SAEs and a SAE form completion will be provided in the Safety Manual.

8.2.6. Second Assessment

All SAE will be subject to a second assessment by the second assessor designated by the Sponsor or his deputy. The second assessor will fill out a 'Second Assessment Form' for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours.

The 'Second Assessment Form' will contain the following information:

- assessment of relationship between SAE and the study drug,
- assessment of expectedness of SAE to the study drug (derived from IB),

- statement if the benefit/ risk assessment of the trial did change as a result of the current SAE.

In case of SUSARs or other safety issues, the expedited reporting will be carried out by a responsible Safety Officer or Safety Data Manager at KKS Heidelberg.

8.2.7. Expedited Reporting

SUSARs will be reported to the ethics committee and the competent regulatory authority within timeframes defined by regulatory documents, i.e. they are subject to the expedited reporting.

Participating investigators should report all SAEs to the responsible member of the safety department as soon as possible, but not later than 24 hours after the relevant information was received. (see above).

Expedited reporting is conducted by a responsible staff at the KKS (see above).

8.2.8. Pregnancy

In case of pregnancy of a female subject, the study drug treatment should be stopped immediately.

Pregnancy is not considered an AE, apart from cases when it is reasonably supposed that the study drug resulted in decreased efficacy of contraceptives. Congenital anomalies and developmental disturbances in subjects' children are considered SAEs. Medical abortions and other serious pregnancy complications (including spontaneous abortion) are classified as SAEs. Induced abortion without complications is not considered as an additional AE.

All pregnancy cases (including pregnancies in female partners of male study subjects) that occur during the clinical study must be appropriately documented. Upon confirmation of a pregnancy, Investigator must send a notification to the Sponsor and to the KKS Heidelberg. Sponsor and KKS Heidelberg will also be notified of the course of pregnancy and its outcome. Pregnancies in female subjects and partners of male subjects are to be documented starting from Day 1 of the study drug dosing and until the completion of the trial.

Pregnancy outcome (spontaneous abortion, elective termination, birth of a healthy child or a child with congenital anomalies or malformations) must be documented, even if the subject did not complete the participation in the clinical trial.

8.2.9. Reporting Requirements after the Study

All deaths within the study period and at least within 30 days after the last administration of the study drug must be reported irrespective of their reasons or relation to the study drug.

8.3. Clinical Laboratory Abnormalities and Other Abnormalities Considered AEs or SAEs

Laboratory abnormalities are usually not recorded as adverse events or serious adverse events unless they are associated with clinical signs and/or symptoms. However, laboratory abnormalities (e.g. clinical chemistry, hematology, urinalysis, etc.) independent from the underlying medical condition, in case of medical significance, such as requirement for medical or surgical intervention, or lead to study drug interruption or discontinuation should be recorded as AEs. In addition, laboratory or other abnormal assessments (e.g. electrocardiogram, X-rays, vital signs) that are associated with clinical signs and/or symptoms must be recorded as an AE or SAE if they meet the respective definitions described in the section. If the laboratory abnormality is part of a syndrome or diseased, the respective diagnosis must be recorded.

Severity of AEs will be assessed as per common toxicity criteria (CTCAE, Common Terminology Criteria for Adverse Events and Reactions of the National Cancer Institute, version 4.0, see http://ctep.cancer.gov). Special attention should be paid to injection site reactions and dermatitis as they may appear during treatment with Myrcludex B.

For adverse events associated with laboratory abnormalities, the event should be graded based on the clinical severity in the context of the underlying conditions, which may or may not be in agreement with the grading of the laboratory abnormality.

For possible renal toxicities, associated with the administration of the background medication Viread® (tenofovir), adverse events should be recorded in case creatinine clearance is <50 mg/dL – 0.48 mmol/L (two independent calculations), or serum phosphate is >0.5 mg/dL on two separate occasions. Tenofovir should be stopped and the renal function should be assessed weekly. Further management of the patient should be discussed with the study medical monitor.

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

In case detected changes in laboratory or instrumental examinations have been reported at screening or before the first dose of study administration and no negative trend is evident, the detected abnormalities will be classified as clinically insignificant.

All detected changes will be analyzed for the clinical study reports irrespective of their classification as AEs or clinical significance.

8.4. Toxicity Management

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within three calendar days of receipt of results and before study drug discontinuation, unless such a delay is not consistent with good medical practice.

- Clinical events and clinically significant laboratory abnormalities will be graded according to CTC AE version 4.0.

- When restarting study drug following resolution of the adverse event, the study drug should be restarted at full dose or modified dose which is dependent upon discussion with the Medical Monitor.

- Any recurrence of the study drug related grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of study drug.

- Any questions regarding toxicity management should be directed to the Medical Monitor.

Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the investigator.

Grade 3 Laboratory Abnormality or Clinical Event

- For grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

- For a grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ grade 2.

- If a toxicity recurs to ≥ grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and subjects managed according to local practice. Recurrence of events considered unrelated to study drug may not require permanent discontinuation.

Grade 4 Laboratory Abnormality or Clinical Event

- For grade 4 clinical event or clinically significant grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued and subjects managed according to local practice. The subject should be followed as clinically indicated until the event resolves to baseline, or is otherwise explained, whichever occurs first. Clinically significant grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed per algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for non-clinically significant grade 4 laboratory abnormality or clinical event considered unrelated to study drug.

8.5. Risks for Females of Childbearing Potential and Risk during Pregnancy

The risks of treatment with MXB during pregnancy have not been evaluated. Animal studies do not indicate direct or indirect harmful effects of MXB with respect to pregnancy. Please refer to the latest version of the Investigator's Brochure for additional information.

Highly effective contraception should always be used by women of child bearing potential who are less than 2 years post-menopausal while participating in the study and for 30 days following the last dose of study medication.

Male subjects in the study who are sexually active must use highly effective contraception methods for the same period of time with their female partners of childbearing potential or agree to abstain from heterosexual intercourse.

According to CTFG Recommendations related to contraception and pregnancy testing in clinical trials dated 15 Sep 2014, the following birth control methods should be considered as highly effective：

1. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   - oral;
   - intravaginal;
   - transdermal;

_ 2. progestogen-only hormonal contraception associated with inhibition of ovulation:
   - oral;
   - injectable;
   - implantable;
3. intrauterine device (IUD);
4. intrauterine hormone-releasing system (IUS);
5. bilateral tubal occlusion;
6. vasectomised partner;
7. sexual abstinence.

A female subject must be instructed to discontinue all study drugs and inform the investigator **immediately** if she becomes pregnant during the study. Likewise, a male subject must inform the Investigator **immediately** if his partner becomes pregnant during the study.

The Investigator should report all pregnancies to the Sponsor within 24 hours of becoming aware of the pregnancy. The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE and is always to be handled as an SAE.

A spontaneous abortion is always considered to be a SAE and will be reported as described in the adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Sponsor.

Additionally all pregnancies that occur during the study should be reported using the Pregnancy Report CRF page. Monitoring of the subject should continue until the conclusion of the pregnancy. The outcome should be reported to the sponsor using the Pregnancy Outcome (and Abnormal Pregnancy Outcome, if applicable) CRF page(s). If the end of the pregnancy occurs after the study has been complete, the outcome should be reported directly to the sponsor. Pregnancies that occur after the subject has discontinued study drugs do not require monitoring.

9. Statistical Analysis

9.1. Analytical Methods

9.1.1. General Information

Statistical analysis of the study data will be performed under supervision of responsible biostatistician in compliance with applicable laws and regulations.

Prior to statistical analysis, data obtained at all sites will be combined into one data set.

If preliminary assumptions made at study planning are erroneous, analytical methods will be adjusted for a more appropriate analysis. If changes to the statistical analysis plan are significant and affect study results or their interpretation, a protocol amendment will be issued in a timely manner.

Statistical analysis is planned to be performed using IBM SPSS Statistics (IBM Corporation, Armonk, New York, USA), SAS (Statistical Analysis Software, SAS Institute Inc. Cary, NC, USA) or another commercially available software with a validated algorithm for statistical methods and appropriate documentation.

9.1.2. Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be analyzed for the complete analysis set and by treatment arms using descriptive statistics. For interval variables, arithmetic mean (with a 95% confidence interval for mean), standard deviation, median, 25^{th} and 75^{th} percentiles will be calculated. For nominal variables, frequency rates and confidence intervals for rates (95% Clopper-Pearson confidence intervals) will be presented.

9.1.3. Efficacy Analysis

Primary efficacy analysis will be based on the following efficacy endpoint:

- HDV RNA negativation or decrease by ≥2 log10 from baseline to Week 24.

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

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

Qualitative secondary endpoints (ALT normalization and disappearance of HBsAg/ seroconversion) will be analyzed using the Fisher's exact test. Quantitative secondary endpoints (serum fibrosis marker, HBsAg and HBV DNA) will be presented as absolute values and changes from baseline. To compare treatment arms on the basis of endpoints, two-sided Wilcoxon rank sum test will be employed with adjustment at the significance level of 0.0167. If the assumptions necessary for

carrying out parametric approach are not violated , parametric analogues of the above methods will be used: ANOVA/ ANCOVA, the Student's t-test for dependent samples. The assumptions will be verified using graphical methods.

9.1.4. Safety Analysis

Myrcludex B safety will be analyzed based on the following endpoints:

Primary Safety Endpoint:

- Incidence of treatment-related adverse events from Visit 1 to End-of-Study Visit.

Secondary Safety Endpoint:

- Nature and severity of treatment-related adverse events from Visit 1 to End-of-Study Visit.
- Incidence, nature and severity of all other adverse events, and assessment of physical examination results, vital signs, 12-lead ECG, hematology, coagulation panel, blood chemistry, urinalysis, blood bile acids, development of anti- Myrcludex B antibodies from Visit 1 to End-of-Study Visit.

These endpoints will be analyzed in Safety Set (see Section 9.7).

Treatment-related adverse event is defined as any AE that occurred after the start of study drug treatment or pre-existing condition that worsened after the start of study drug treatment and that has any degree of relationship to the study drug, with the exception of "unrelated". Information on AE will be presented overall and by severity as numbers (and proportions) of subjects.

Adverse events, including serious adverse events, will be classified using the latest version Medical Dictionary for Regulatory Activities (MedDRA) available at the time of database lock. Further analysis will include all AEs, SAEs, AEs requiring treatment discontinuation, and discontinuations due to AEs.

Incidence and severity of all AEs and treatment-related adverse events will be provided for all SOCs in accordance with MedDRA terminology. SAE will also be presented in the form of descriptions (narratives).

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

Safety data listings will also be included in the final analysis.

9.2. Planned Number of Subjects

This study is a comparative parallel-group clinical study with three treatment arms receiving study medication (2 mg, 5 mg and 10 mg) and one control arm (all three comparisons will be done independently) to test the hypothesis of superiority of the study medication over reference product.

The primary variable for this study is treatment response rate, defined as HDV RNA decrease by 2 log10 from baseline or absence of HDV RNA (after 24 weeks of treatment). This is a frequency parameter.

As warranted by study aim and objectives, the null hypothesis (H_0) will be defined the following way:

H_0: $\varepsilon \leq \delta$

and the alternative hypothesis (H_a) will be:

H_a: $\varepsilon > \delta$

where ε is the anticipated difference between treatment response rates in the experimental arm and the control arm, and δ is the threshold for clinically significant values (superiority threshold).

Considering study design, as well as type and nature of the primary endpoint (comparative study in parallel arms), sample size for each treatment arm can be calculated as follows:

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

where z_α and z_β are the respective z-function values for planned type I and II error values; p_1 and p_2 are the treatment response rates in the experimental and control arms, respectively; ε is the expected difference between treatment arms in the primary variable; k is the coefficient for uneven number of subjects per treatment arm (in this study k =1); n_1 and n_2 are the planned number of subjects for the experimental and control arms, respectively.

Thus, the sample size was calculated based on the following assumptions:

1. Critical level of significance for null hypothesis testing α = 0.0167 (Bonferroni adjustment).

2. Study power – at least 0.8 (80%), probability of type II error (β) will not exceed 0.2.

3. Superiority limit (clinical significance of the difference) δ will be assumed as 5%.

4. Expected difference in the primary variable between treatment arms will be at least 34.0%. Previous phase Ib/IIa clinical study in patients with chronic hepatitis D demonstrated efficacy in monotherapy arm in 57% of subjects after 24 weeks of treatment with a lower limit of confidence interval of approximately 37%.

5. Expected treatment response rate in the control arm is no more than 3% (in the absence of treatment and with nucleoside/nucleotide analogue therapy approved for hepatitis B in subjects with chronic hepatitis D, no response was observed; for example, study HIDIT-1 in 90 patients with chronic hepatitis D showed no effect on HDV RNA with monotherapy with adefovirm, a nucleotide analogue). It is believed, that spontaneous decrease in HDV RNA by 2 $\log^{10}$ can occur in no more than 3%.

Sample size has been calculated the following way:

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

Thus, to test the hypothesis of superiority of the study medication (separately for each dose level) over control arm, at least 28 subjects from each treatment arm need to be included into efficacy analysis. Assuming a dropout rate of no more than 5% of subjects in each treatment arm, at least 30 subjects need to be enrolled into each treatment arm.

When last subject completes 24 weeks of treatment, viral load (PCR results for HDV RNA) will be analyzed for all subjects in all treatment arms (primary endpoint is negative PCR results for HDV RNA or decrease by ≥2 log from baseline at Week 24).

9.3. Significance Level

One-sided significance level will be employed to test the primary variable (superiority by margin testing). Efficacy hypotheses will be tested sequentially, using Bonferroni-Holm method. This procedure allows to control the general probability of one or more type I errors (FWER - Familywise error rate). In the planned comparisons, type I error rate will not exceed 0.05, and significance levels for each sequential comparison will be calculated individually using the Bonferroni-Holm method (see above).

9.4. Interim and Final Data Analysis

When 10 patients of each arm will complete 28 days of treatment (starting from randomization visit), an Interim Safety Analysis will be performed. Based on the results of the analysis, the decision will be met by the sponsor, if cirrhotic patients can be included into the study.

When the last patient completes 24-week treatment period, an Interim Report will be compiled on efficacy and safety of the study treatment.

When the last patient completes follow-up period Final Study Report will be prepared.

9.5. Handling of Missing and Non-Evaluable Data

At interim analysis (when the last patient completes 24-week treatment period), missing data imputation for the primary efficacy endpoint will be based on Missing = Failure approach.

Detailed procedure of missing data imputation will be provided in the Statistical Analysis Plan.

9.6. Reporting of Any Deviations from Initial Statistical Plan

Detailed description of statistical analysis will be provided in Statistical Analysis Plan. Statistical Analysis Plan will be finalized before database closure and deviations from the final version of the Statistical Analysis Plan will be described (with rationale) in the Final Study Report.

9.7. Selection of Subjects for Statistical Analysis

The following analytical sets will be included into data analysis:

Safety Set: all subjects who received at least one dose of the study medication (Myrcludex B or Tenofovir) in the study period.

Modified Intent-to-Treat Set (mITT): all randomized subjects who started study treatment (Myrcludex B or Tenofovir) in the study period after randomization .

Per Protocol Set (PP): subjects from mITT set who completed24-week treatment period without major protocol deviations and with efficacy results for 24 weeks time point.

10. Direct Access to Source Data/ Documents

10.1. Access and Review of Source Data and Records

All information contained in source documents and certified copies and concerns clinical data, observations and other study-related activities, that is required for reconstruction and evaluation of the study is regarded as source data.

Direct access to source data and documents must be provided to the study monitor and authorized representatives (CRO), Sponsor's/CRO's auditor, regulatory inspectors, members of ethics committees and representatives of insurance companies.

10.2. Additional Information

Upon request, Investigator provides additional study-related data or copies of relevant pseudonymized source documents to the Sponsor. This may be relevant in such cases, when CRF records are illegible or contain errors. In special circumstances, or upon request form competent governmental authorities, access to complete study records may be required, provided that confidentiality requirements are met.

11. Quality Control and Assurance

11.1. Periodic Monitoring

Monitoring will be done by a clinical monitor according to SOPs of the clinical research organisation. At the beginning of the trial the responsible monitor will perform an Initiation visit at the trial site (prior to the inclusion of the first study participant). During regular On-site visits the monitor will review the entries into the CRFs on the basis of applicable source documents. The investigators must allow the monitor to verify all essential documents and must provide support to the monitor at any time. Frequency of monitoring will be defined in the Monitoring Manual. By frequent communications (letters, telephone, fax), the site monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

11.2. Audit and Inspection

Competent and local authorities and an auditor authorized by the Sponsor may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigators who must provide support at all times for these activities.

In case inspections will be announced to the Principal Investigator, the Sponsor and site monitor should be informed in time.

12. Ethical and Legal Issues

12.1. Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

12.2. Patient information leaflet and informed consent form

Before entering the study, the subject should provide the informed consent to the nature of the study, its methods and possible risks which must preliminary be explained to the subject. The subject must give the written informed consent. The signed informed consent form will be filed in the ISF. One copy of the patient leaflet and the written informed consent will be given to the subject. Subjects incapable of giving informed consent or minors are not allowed to participate in the study.

All documents provided to the subject must be written in understandable language. The data on person providing the information to the subject should also be indicated.

The participants will be informed as soon as possible if any new information may influence his/her decision to participate in the trial. The communication of this information will be documented.

12.3. Confidentiality

The data obtained in the course of the trial will be treated pursuant to the applicable national and EU regulations.

During the clinical trial, participants will be identified solely by means of their date of birth and an individual identification code (participant number). Trial findings will be stored in accordance with local data protection law and be handled with strict confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in their entirety.

The participant consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the participant-related data collected during the trial ensuring the data protection law.

The investigator will maintain a patient identification list (patient numbers with the corresponding patient names) to keep records identifiable. This list will be filed in the ISF.

Patients who did not consent to distribution of their pseudonymized data will not be included into the trial.

12.4. Responsibilities of Principal Investigator

A Principal Investigator will be appointed at each study center. He/she should ensure that all persons assisting in the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions. He should maintain a list of investigators at his study center and other appropriately qualified persons to whom he has delegated significant trial-related duties.

12.5. Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, patient information leaflet and informed consent form, and any other appropriate documents will be submitted to the local independent ethics committees (IEC) as well as to the competent higher federal authority. A written favourable vote of the IEC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of this clinical trial. The statement of IEC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the IEC participating in the applicable IEC meeting and a GCP compliance statement.

Before the first participant is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to IEC and the competent higher federal authority in written as protocol amendments. They have to be approved by the IEC and the competent higher federal authority.

The Lead Clinician and the CRO will keep a record of all communication with the IEC and the regulatory authorities.

12.6. Notification of Regulatory Authorities

Local regulatory authorities responsible for each investigator have to receive information before, during and in the end of the study according to the current legislation.

12.7. Continuous Information to Independent Ethics Committee

According to the applicable national laws, EU regulations and the GCP, the IEC and the competent higher federal authority will be informed of all suspected serious unexpected adverse reactions (SUSARs) occurring during the trial. Both institutions will be informed in case the risk/benefit assessment did change or any others new and significant hazards to participants' safety or welfare did occur.

The IEC and the regulatory authorities must be informed about the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase.

13. Data Management

13.1. Data collection

All data obtained during the study will be documented in the electronic CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that the entries can be verified against source data whenever applicable.

The correctness of entries in CRF will be confirmed by dated electronic signature of the responsible investigator and reviewed by the responsible monitor.

13.2. Data handling

CRF are provided for each subject in electronic format.

All protocol-required information collected during the study must be entered in English into the electronic CRF by the investigator or a designated representative. The data has to be recorded on source documents immediately, except for data that are available on original printouts or that were defined as direct entries in the monitoring manual. An explanation should be given for all missing data. If the investigator authorizes other persons to make entries into the CRFs, the names, positions, signatures, and initials of these persons must be recorded. The Investigator must verify that all data entries in the CRF are accurate and correct. Therefore completed CRF must be reviewed and signed by the Investigator.

All missing data or inconsistencies will be reported back to the center as queries and clarified by the responsible Investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

13.3. Storage and archiving of data

In accordance with ICH/GCP requirements the Investigator/the trial site will keep the electronic copy of the site-specific entries in the CRF and source data which confirm data obtained from patients as well as all documents indicated in section 8 “Essential documents for the conduct of a clinical trial” ICH/GCP, and all clinical trial documents as specified in by corresponding regulatory requirements. The Sponsor is responsible for archiving of TMF including all important trial documents. Furthermore, the Principal Investigator will archive all trial-specific data (the electronic copy of the site-specific entries in the CRF, source data and Investigator Site File (ISF) including participant identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to the local law and regulations.

14. Insurance

According to applicable national laws and EU regulations, an insurance policy has to be subscribed covering in its terms and provisions the legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.
The insurance was taken out at:

Great Lake Reinsurance (UK) PLC, 30 Fenchburch Street London EC3M 3AJ
Insurance number: DE400-02-16
Maximum limit 500,000€ per participating person

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The participant is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the participant must not undergo other clinical treatment, except for cases of emergency, without prior consultation with the responsible Investigator. The participant is bound to inform the Investigator immediately about any adverse events and additional drugs taken. The terms and conditions of the insurance will be handed out to the participant on request.
The insurance company has to be informed about all amendments that could affect participants' safety.

15. Publication and Other Use of Study Results

The Sponsor encourage the presentation and/or publication of the results of their studies, using only clean, checked and validated data in order to ensure the accuracy of the results.

At least forty-five (45) days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by Hepatera/MYR, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

16. Confidentiality

Information in this document is proprietary to the Sponsor and may be disclosed to the third parties only with the written consent from the Sponsor. The right to review this information will be granted only to the investigator(s) and members of the study site(s) staff, members of the independent ethics committee(s) and healthcare officials entitled to control the study conduct. Information sufficient to make a decision regarding consent to participate in the study will be provided to the patients whom the investigator plans to enroll.

17. Protocol Amendments and/or Revisions

Any changes to the study protocol must be agreed upon between Investigator and Sponsor prior to the implementation. Any deviations in the study process that occur after approval of the protocol must be documented in a form of addendums or amendments to the protocol and/or updated versions of the protocol. Depending on the nature of amendment, it needs to be submitted to the Ethics Committee and regulatory authorities as a notification or for approval. Ethics Committee approval will be required for any change that affects subjects' safety, study scale/design, involves increase in dose or duration of study drug treatment, increase in the number of subjects treated with the study medication, addition of a new test/procedure or elimination of a safety test. Any changes can only be implemented after they are approved by the Sponsor, all Investigators, and, if applicable, ethics committee and regulatory authorities, except for cases when such changes are required to avoid direct threat to life or health of subject participating in the clinical trial, or when the changes to the protocol involve administrative or logistics issues only.

18. References

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