



## Clinical Study Protocol

Protocol Number: REP 401

**An open-label, randomized, active controlled, parallel comparison study of the safety and efficacy of REP 2139-Mg in combination treatment with Pegasys® and Viread® and REP 2165-Mg in combination treatment with Pegasys® and Viread® in patients with HBeAg negative chronic hepatitis B infection.**

Approval Date:	Version 1.0 (Original Protocol): 05 May 2015
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	Version 1.2: 04 June 2015
	Amendment 1: 23 June 2015
	Amendment 2: 27 October 2015
	Version 2.0 Incorporating Amendment 1, 2 and 3: 15 February 2016
	Version 3.0 Incorporating Amendment 4: 28 July 2016
	<b>Version 4.0 Incorporating Amendment 5: 06 February 2017</b>

**Sponsor:** Replicor Inc.

Conduct: This clinical trial is being conducted in accordance with International Conference of Harmonization guidelines on-Good Clinical Practice and the ethical principles originated from the Declaration of Helsinki. It is confirmed that the Clinical Trial Protocol meets the applicable regulatory requirements applicable

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## Document History

Document	Date of Issue	Summary of Change
Original Protocol No. 1.0	May 05, 2015	NA
Version 1.1	May 12, 2015	<p>NAP therapy to be given throughout the entire course of Pegasys® or Zadaxin® exposure (48 weeks instead of 24 weeks) with entry into follow up at the end of 48 weeks.</p> <p>For the crossover patients the transition to 48 weeks of NAP plus immunotherapy is the identical to the experimental group patients. Title corrected to reflect updated clinical trial design.</p> <p>Statistical analysis section updated to reflect updated clinical trial design.</p>
Version 1.2	June 04, 2015	<p>The list Prohibited and/or Restricted Treatments in the Section 19 has been revised to exclude the hematologic growth factors.</p>
Version 2.0	February 15, 2016	<p>Incorporating of Amendment 1 dated June 23, 2015: addition of globulin testing to the list of Chemistry Laboratory Assessments in Section 19 (previously 20).</p> <p>Incorporating of Amendment 2 dated October 27, 2015: Exclusion criterion 14 has been revised to include concomitant treatment with any anticoagulant; Exclusion of any anticoagulant therapy during the REP 401 protocol and permit the use of antibiotics, anti-fungals and antivirals not active against HBV.</p> <p>Amendment 3: Inclusion criteria for serum HBV DNA changed from &lt; 10,000 copies / ml to &lt;7,000 copies / ml to facilitate recruitment.</p> <p>Removal of control and experimental groups (20 patients) for Zadaxin treatment arms and removal of Zadaxin treatment from protocol due to recruitment difficulties. (see Fig. 1). Changes throughout the text to be consistent with the revised design. Addition of provisions for interim analysis.</p>

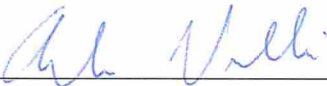
Document	Date of Issue	Summary of Change
Version 3.0	28 July, 2016	<p>Amendment 4:</p> <p>Modifications to clarify language:</p> <ul style="list-style-type: none"> <li>- as to those places in the protocol which discuss the baseline used for calculating HBsAg reductions for crossover eligibility. These clarifications established that the baseline value for serum HBsAg is to be taken from the result obtained at the second screening visit (visit 2);</li> <li>- technical changes throughout the text to provide conformity between tables/footnotes removing of excessive text; rewording, correction of misprints, omissions and a grammar mistake</li> </ul>
Version 4.0	06 February, 2017	<p>Amendment 5:</p> <p>Modifications to provide:</p> <ul style="list-style-type: none"> <li>- guidance on the supportive therapy in the study patients to prevent thrombocytopenia and leucopenia resulting from Pegasys® exposure;</li> <li>- guidance on the proactive management of thrombocytopenia by Pegasys® and NAP dose reduction;</li> <li>- guidance on the restoration of Pegasys® and NAP dosing with normalization of platelet counts and absolute neutrophil count;</li> <li>- clarification to dose modification in case of Grade 3 AE related to study drug;</li> <li>- clarification on ALT/AST laboratory abnormalities recording;</li> <li>- clarification on Vitamin D supplementation;</li> <li>- technical changes throughout the text to provide conformity between tables/footnotes, correction of misprints.</li> </ul>

**PROTOCOL APPROVAL SIGNATURE PAGE****Sponsor:**

All persons who made a significant contribution to the preparation of the trial protocol (protocol development committee) should sign this page.

I have read and understand the contents of the clinical protocol REP 401 dated February 06, 2017 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Principal Investigators are informed of all relevant information that becomes available during the conduct of this study.

It is confirmed that the Clinical Trial Protocol, the Case Report Forms (CRFs) and Annexes contain all the necessary information and provisions to conduct the trial, that the trial is being conducted and documented in full in accordance with this protocol, and that the legal provisions and agreements described above are met.

  
\_\_\_\_\_  
Signature

FEB 6 2017  
Date

Andrew Vaillant  
Chief Scientific Officer, Replicor Inc.

  
\_\_\_\_\_  
Signature

Feb 6, 2017  
Date

Michel Bazinet  
Chief Executive Officer, Chief Medical Officer, Replicor Inc.

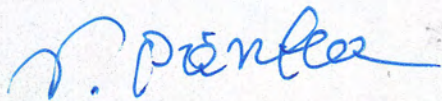


**PRINCIPAL INVESTIGATOR'S AGREEMENT**

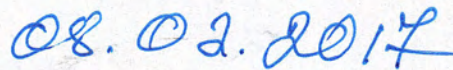
I have read and understand the contents of the clinical protocol REP401 dated February 06, 2017 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current Good Clinical Practices and applicable regulatory requirements.

Principle Investigator:

Address:



\_\_\_\_\_  
Signature of Principal Investigator



\_\_\_\_\_  
Date

**PRINCIPAL INVESTIGATOR'S AGREEMENT**

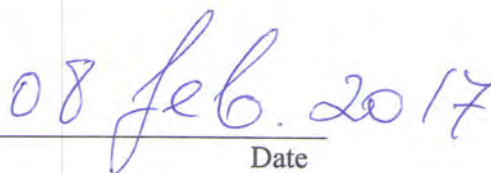
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Principle Investigator:

Address:



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Signature of Principal Investigator



\_\_\_\_\_  
Date



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I have read and understand the contents of the clinical protocol REP401 dated February 06, 2017 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current Good Clinical Practices and applicable regulatory requirements.

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*Moscalu*  
Signature of Principal Investigator

*10 Feb. 2017*  
Date

# 1. SYNOPSIS

## Clinical Protocol REP 401

Protocol Title: An open-label, randomized, active controlled, parallel comparison study of the safety and efficacy of REP 2139-Mg in combination treatment with Pegasys® and Viread® and REP 2165-Mg in combination treatment with Pegasys® and Viread® in patients with HBeAg negative chronic hepatitis B infection.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

REP 2139-Mg: 250 mg intravenously (IV) once weekly (given in combination with Pegasys® and Viread®). Planned total REP 2139-Mg exposure scheduled to be 12 g per patient (0.25g / week x 48 weeks).

REP 2165-Mg: 250 mg intravenously (IV) once weekly (given in combination with Pegasys® and Viread®). Planned total REP 2165-Mg exposure scheduled to be 12 g per patient (0.25g / week x 48 weeks).

Peginterferon alfa-2a (Pegasys®): 180 µg subcutaneous (SC) once weekly, for 48 or 72 weeks (except following stopping rules below).

Tenofovir disoproxil fumarate (TDF, Viread®): 300mg orally every day for 24 weeks prior to and during Pegasys®)

Study Phase: Phase IIb

## Research Hypothesis:

Treatment with the nucleic acid polymer (NAP) REP 2139-Ca has been shown effective in eliminating HBsAg from the blood of patients. Although REP 2139-Ca has been shown to be safe in human patients, it shares the same class effect as other phosphorothioate oligonucleotides in that it accumulates in the liver with repeated dosing. REP 2165 is a version of REP 2139 which is designed to have an increased rate of degradation to slow down liver accumulation while keeping its antiviral activity intact. The antiviral efficacy of REP 2165 has been shown to be comparable to REP 2139 in a pre-clinical model of HBV infection with significantly less accumulation in the liver. As such, REP 2165 is expected to have comparable antiviral efficacy in human patients with reduced liver accumulation during treatment.

REP 2139-Mg and REP 2165-Mg are improved NAP formulations relative to REP 2139-Ca which do not impact the antiviral activity of NAPs but are expected to have better tolerability.

Elimination of serum HBsAg with REP 2139-Mg or REP 2165-Mg will lead to:

Creation of a favourable immunological activation in the absence of HBsAg

Appearance of free anti-HBs

Clearance of HBV virions in the blood.

Synergistic immunostimulation with conventional dosing of Pegasys® and improved control of HBV infection in the presence of Viread®.

### **Endpoint(s):**

Primary objective:

To evaluate the safety of REP 2139-Mg and REP 2165-Mg when dosed in combination with pegylated interferon alfa-2a in patients with chronic HBV infection having previous and continuing therapy with TDF.

Secondary objectives:

To evaluate the effect of REP 2139-Mg and REP 2165-Mg administration on the following:

- reduction of serum HBsAg
- reduction of serum HBV viremia
- potentiation of the immunostimulatory effect of pegylated interferon alfa-2a (as measured by changes in anti-HBs)
- rate of restoration of immunological control over HBV infection during follow-up.

### **Study Design:**

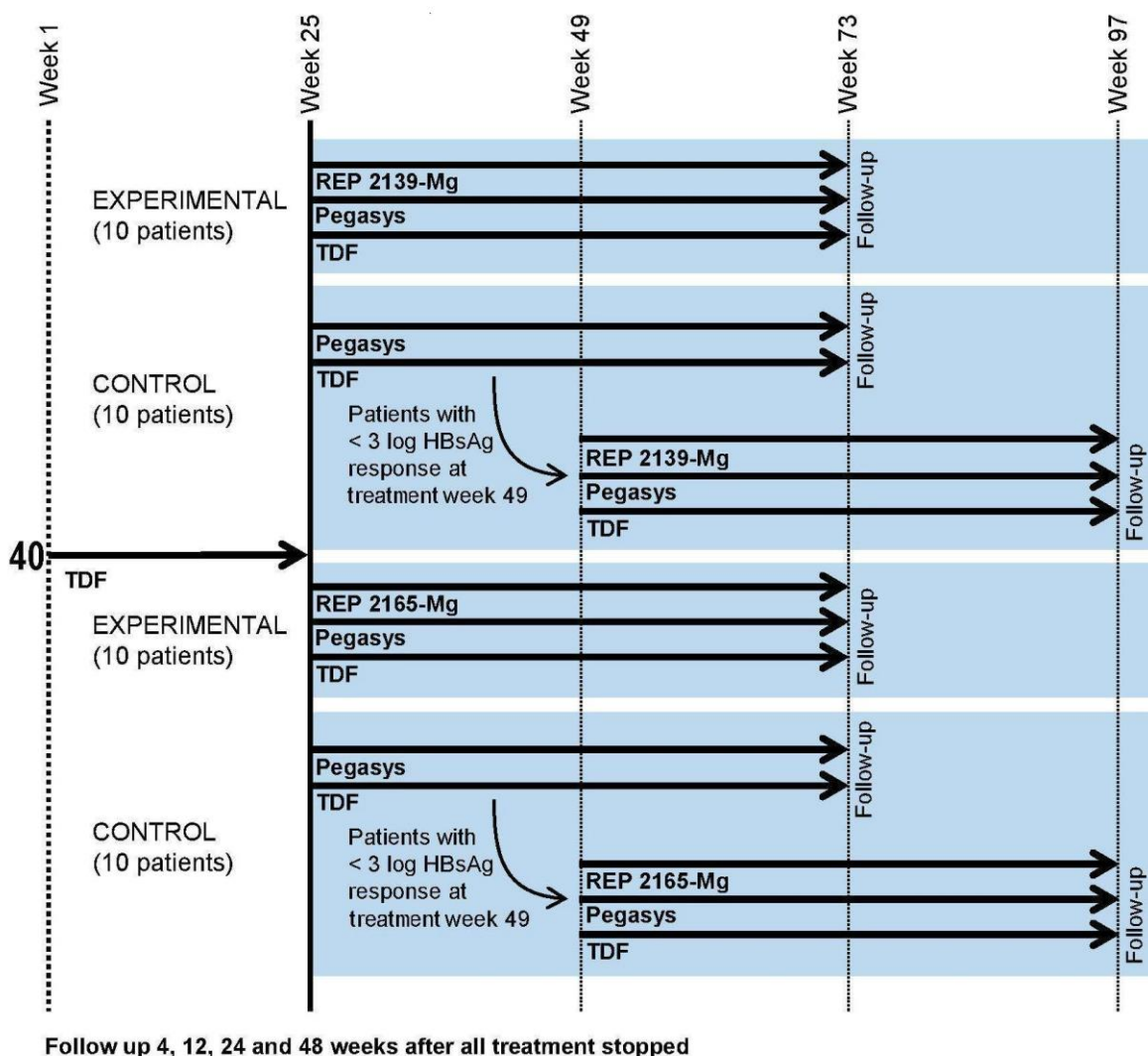
Treatment Period (Experimental Group):

1. Viread® monotherapy (24 weeks, 300mg qD) followed by:
2. Triple combination therapy for 48 weeks:
  - a. REP 2139-Mg 250mg qW or REP 2165-Mg 250mg qW
  - b. Pegasys® 180 ug qW
  - c. Viread® 300 mg

Treatment Period (Control Group):

1. Viread® monotherapy (24 weeks, 300mg qD) followed by:
2. Combination therapy for 24 weeks:
  - a. Pegasys® 180 ug qW
  - b. Viread® 300 mg qD followed by:
3. After 24 weeks of Pegasys® exposure, serum HBsAg reductions (as measured at Visit 28) relative to baseline (established at Screening Visit 2) be determined. Patients with  $\geq 3$  log reduction in serum HBsAg transition directly to (4) below. Patients with  $< 3$  log reduction in serum HBsAg crossover to 48 weeks of triple combination treatment as follows:
  - a. REP 2139-Mg or REP 2165-Mg 250mg qW

- b. Pegasys® 180 ug qW
  - c. Viread® 300 mg qD
- 4. Combination therapy for 24 weeks:
  - a. Pegasys® 180 ug qW
  - b. Viread® 300 mg qD



Follow up 4, 12, 24 and 48 weeks after all treatment stopped

Figure 1. Design of the REP 401 trial.

Planned REP 2139-Mg or REP 2165-Mg exposure not to exceed 12g.

Planned Pegasys exposure will not exceed 48 weeks (experimental group) or 72 weeks (control group).

Follow up: Minimum of 48weeks.

Dosing interval: REP 2139-Mg / REP 2165-Mg: once weekly  
Pegasys®: once weekly  
Viread®: once daily

Dosing route: REP 2139-Mg / REP 2165-Mg: IV, maximum speed of 250 mg/hour slow infusion  
Pegasys®: subcutaneous injection  
Viread®: oral

Dose level: REP 2139-Mg / REP 2165-Mg: 250 mg (not to exceed 12g total exposure)  
Pegasys®: 180ug (not to exceed 48 or 72 weeks of total exposure)  
Viread®: 300mg

Number of patients: 20 experimental (randomly assigned (1:1 ratio)  
(10 with REP 2139-Mg and 10 with REP 2165-Mg)  
  
20 control (randomly assigned (1:1 ratio)  
(10 randomly assigned to crossover to REP 2139-Mg and 10 randomly assigned to crossover to REP 2165-Mg)

#### **Pre-treatment assessment:**

Preliminary screening (pre-screening) performed during the pre-treatment period will consist of tests to determine if patients have heavy metal intoxication, and tests to determine whether patients have an autoimmune hepatitis. Patients determined to not have heavy metal intoxication and autoimmune hepatitis will proceed to the screening process (see inclusion / exclusion criteria below). All eligible patients will have their serum 25OH vitamin D levels brought into the optimal range (150 nmol / L) by supplementation with vitamin D<sub>3</sub> (5,000 IU PO QD) during a one month period prior to Pegasys® starting from study Visit 6. If during the study 25OH vitamin D level exceeds 150 nmol / L, vitamin D supplementation should be withheld until 25OH vitamin D  $\leq$  75nmol / L.

Patients will also be asked to take mineral supplements (containing calcium, magnesium, zinc, copper, manganese, molybdenum, chromium, boron and vanadium) starting one month before (at study Visit 6) starting and during Pegasys® treatment and an iron supplement at any time during or after treatment if haematological blood tests suggest the development of an iron deficiency. The investigators can prescribe a locally available iron supplement, if needed.



**Dosing regimen (see Fig. 1):**

All patients are to start daily Viread® therapy (300mg qD).

After 24 weeks of Viread® therapy, all patients are to continue Viread® therapy and start once weekly Pegasys® therapy (180ug qW)

Patients in the experimental group will also start 48 weeks of NAP therapy (REP 2139-Mg or REP 2165-Mg, both 250mg qW)

Patients in the control group (receiving no NAP therapy) are eligible to crossover to 48 weeks of REP 2139-Mg or REP 2165-Mg triple combination therapy if declines in serum HBsAg measured at Visit 28 are < 3 log from baseline (established at Screening Visit 2).

Patients in the control group eligible for crossover to NAP therapy will enter into combination therapy with NAPs and Pegasys® / Viread ® therapy for 48 weeks after which patients will enter into follow-up.

Patients in the control group not eligible for crossover to NAP therapy (decline of serum HBsAg > 3 log from baseline which is defined as Screening Visit 2) will enter into follow-up after 48 weeks of Pegasys® / Viread® therapy without receiving any NAP therapy.

**Follow-up:**

There will be 4 (four) visits during the follow-up period: at 4<sup>th</sup>, 12<sup>th</sup>, 24<sup>th</sup> and 48<sup>th</sup> week after treatment has ended. During these visits patients will be seen to monitor the durability of their antiviral response off treatment and to monitor their liver function.

**Table 1. Brief Study and Treatments Schedule**

Study Week	Experimental	Control group (no crossover)	Control group (crossover)
Wk-1	Pre-screening	Pre-screening	Pre-screening
Wk 1	Start of screening period	Start of screening period	Start of screening period
Wk 3	Complete screening / Start (first dose) Viread®	Complete screening / Start (first dose) Viread®	Complete screening / Start (first dose) Viread®
Wk 22	Start mineral supplementation	Start mineral supplementation	Start mineral supplementation
Wk 27	Start (first dose) Pegasys® and REP 2139-Mg or REP 2165-Mg	Start (first dose) Pegasys®	Start (first dose) Pegasys®
Wk 51	Continue Pegasys® and REP 2139-Mg or REP 2165-Mg	Continue Pegasys®	Continue Pegasys®, start REP 2139-Mg / REP 2165-Mg (in eligible patients)
Wk 52	Continue Pegasys® and REP 2139-Mg or REP 2165-Mg	Continue Pegasys®	Continue Pegasys® and REP 2139-Mg / REP 2165-Mg
Wk 74	Stop (last dose) Pegasys® / Viread® and REP 2139-Mg or REP 2165-Mg (EOT)	Stop (last dose) Pegasys® / Viread® (EOT)	Continue Pegasys® and REP 2139-Mg or REP 2165-Mg
Wk 75	Enter follow-up	Enter follow-up	Continue Pegasys® and REP 2139-Mg or REP 2165-Mg
Wk 98	Continue follow-up	Continue follow-up	Stop (last dose) Pegasys® / Viread® and REP 2129-Mg or REP 2165-Mg (EOT)
Wk 99	Continue follow-up	Continue follow-up	Enter follow-up
Wk 122	Stop follow-up (EOS)	Stop follow-up (EOS)	Continue follow-up
Wk 146			Stop follow-up (EOS)

**Table 2. Scheduled Procedures and Assessments**

<b>Procedure / Test</b>	<b>Frequency</b>
Inclusion and Exclusion Criteria	Pre-screening, screening visit
Medical History	Pre-screening visit
Vital Signs	Every visit
Physical Examination	Every visit
Height	Pre-screening visit
Weight /	Every visit
Adverse Events Review	Every Visit
Verification of Viread® compliance	At study week 10, 18, 22, 26 and every visit afterwards on treatment
Verification of prior / concomitant medications	Every visit
Verification of mineral supplement compliance	Every three (3) months starting at study week 34
Verification of Vitamin D3 supplement compliance	Every two (2) months starting at study week 30
ECG	Screening, at the start of Pegasys® and every 8 weeks afterwards on treatment, EOT, FW4, 12 and 24
Ultrasound.	Screening, after 12 and 24 weeks of NAP treatment, EOT, FW 24
Fibromax / Fibroscan	Screening, end of NAP treatment, EOT, FW24, FW48
HBV DNA	Screening, study weeks 1, 3, 10, 18, 26, 27 and then every four weeks during Viread® treatment, EOT, FW 4, 12, 24 and 48
HBsAg	Screening, study weeks 1, 3, 10, 18, 26, 27 and then every four weeks during Viread® treatment, EOT, FW 4, 12, 24 and 48
Anti-HBs	Screening, study weeks 1, 3, 10, 18, 26, 27 and then every four weeks during Viread® treatment, EOT, FW 4, 12, 24 and 48
HBeAg / Anti-HBeAg	Screening, start and end of REP 2139-Mg / REP 2165-Mg treatment, EOT, FW24, FW48
anti HIV 1+2 / anti-CMV / anti-HCV	Screening
Anti-HDAg	Screening, end of REP 2139-Mg / REP 2165-Mg treatment, EOT, FW24, FW48
ALT / AST / Alkaline Phosphatase	Screening, at the start of and every week during treatment with Pegasys® and Viread® treatment, EOT, FW4, 12, 24 and 48
GGT	Screening, at the start of and every 4 weeks during treatment with Pegasys® and / Viread®, EOT, FW 4, 12 and 24

**Table 2. Scheduled Procedures and Assessments (continued)**

<b>Procedure / Test</b>	<b>Frequency</b>
Total bilirubin	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
Creatinine	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
Biochemistry	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
Urinalysis	Screening, weeks 3, 10, 18, 22, 26, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
25 OH vitamin D	Screening, at the start of treatment with Pegasys® and Viread® and every 8 weeks afterwards on treatment, FW24 and FW48
Heavy metal analysis	Pre-screening visit
Electrolytes	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
Hematology	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
INR / PTT / aPTT	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
Lipid profile	Screening, at the start of and every two weeks during treatment with Pegasys® and Viread®, EOT, FW 4, 12 and 24
AFP	Screening, EOT and FW24
ANA	Pre-screening, end of NAP treatment, EOT and FW24
Serum pregnancy test	24 hours prior to first administration of Viread® (at the end of screening period) and Pegasys®
Urine pregnancy test	Every 4 weeks on treatment, FW4 , FW12 and FW24
AMA, LKM1	Pre-screening Visit
Frozen serum (4 X 1 cc aliquots) collected	Screening, weeks 3, 26, 27 and every 4 weeks afterwards on treatment, EOT, FW4, FW12, FW24 and FW48.
Thyroid function tests	Screening, at the start of Pegasys®, every three months on and at the end of Pegasys® treatment.

Detailed schedule, procedures and assessments at each visit for each study arm are described in the Section 19.

### **Study Population:**

1. Signed Written Informed Consent
  - Freely given informed consent for pre-screening to establish patient eligibility for the study must be obtained from subjects prior to any pre-screening assessment.
  - Freely given informed consent for clinical trial participation including informed consent for any screening procedures conducted to establish patient eligibility for the study must be obtained from subjects prior to any screening procedure.
2. Males or females 18-55 years of age
3. HBsAg > 1000 IU / ml at screening
4. HBV DNA > 7000 copies / ml at screening
5. Seronegative for HIV, HCV, CMV (IgM) and HDV (anti-HDAg) as determined at screening visit
6. HBeAg negative, anti-HBe positive
7. Evidence of fibrosis at screening
8. Non cirrhotic: absence of advanced cirrhosis based on fibroscan evaluation at screening.
9. Willingness to utilize adequate contraception while being treated with REP 2139-Mg or REP 2165-Mg and for 6 months following the end of the treatment in the study
  - Any woman of childbearing potential (WOCBP) who agrees to use an effective methods of birth control for the entire duration of the study.
  - Sexually active men who agree to use an effective method of birth control if their partners are WOCBP for the entire duration of the study and a minimum of 24 weeks after the last dose of study drugs or of Peginterferon/NUCs (or the time specified by the country-specific Peginterferon/NUC label, whichever is longer).
10. Body Mass Index (BMI)  $\geq 18$  kg/m<sup>2</sup> and  $\leq 30$ kg/m<sup>2</sup> at screening
11. Adequate venous access allowing weekly intravenous therapies and blood tests

### **Exclusion Criteria**

1. Women with positive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG).
2. Breast-feeding women.
3. HBeAg positive as determined at screening visit
4. Positive HCV antibody, or HIV-1/HIV-2 or CMV antibody (IgM) or anti-HDV antibody test at screening
5. Evidence of chronic liver disease caused by diseases other than chronic HBV infection (such as but not limited to: severe NAFLD (nonalcoholic hepatic steatosis), Wilson's disease, hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, significant biliary disease, and toxin exposure).
6. Medical History and Concurrent Diseases (see Section 17) for the full list of the concurrent diseases and conditions to be checked in medical history).
7. Physical and Laboratory Test Findings
  - a) Evidence of significant heavy metal load in whole blood as determined at pre-screening visit.
  - b) Antinuclear antibody (ANA) titer  $\geq 1:640$ , and AMA or LKM-1 antibody positive as determined at pre-screening visit
  - c) hemoglobin < 12.0 g/dL (males), < 10.0 g/dL (female) at screening
  - d) platelet count < 90,000/mm<sup>3</sup> as determined at screening visit

- e) creatinine clearance (CrCl) (as estimated by Cockcroft and Gault)  $\leq 50$  mL/min or confirmed creatinine persistently  $> 1.5$  mg/dl as determined at screening visit
  - f) total serum bilirubin  $> 25$   $\mu$ mol/L as determined at screening visit.
  - g) INR  $\geq 2.0$  as determined at screening visit
  - h) PTT  $\geq 2.0 \times$  ULN as determined at screening visit
  - i) serum albumin  $\leq 3.5$  g/dL (35 g/L) as determined at screening visit
  - j) ALT  $> 10 \times$  ULN as determined at screening visit
  - k) ANC  $\leq 1,500$  cells/mm<sup>3</sup> as determined at screening visit
  - l) Diagnosed or suspected hepatocellular carcinoma as evidenced by screening alpha-fetoprotein (AFP) of  $\geq 100$  ng/mL. If AFP is  $\geq 50$  ng/mL and  $< 100$  ng/mL, absence of mass/findings suspicious for HCC must be demonstrated by ultrasound/CT/MRI within the screening period.
  - m) Diabetes mellitus as evidenced by HbA1C  $\geq 8.5\%$  at screening
  - n) QTc interval  $> 500$  msec.
8. Known hypersensitivity to drugs with a similar biochemical structure to REP 2139-Mg or REP 2165-Mg (e.g. other phosphorothioate oligonucleotides) or Pegasys® (e.g. other interferons), Viread® (e.g. other nucleoside analog polymerase inhibitors such as entecavir).
  9. Any other criteria or known contraindication that would exclude the subject from receiving REP 2139-Mg, REP 2165-Mg, Pegasys®, Viread®.
  10. Prisoners or subjects who are involuntarily incarcerated.
  11. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
  12. Employees, family members, or students of the investigator or clinical site
  13. Individuals who participated in another clinical study of a medicinal product or medical device within 90 days of signing Informed Consent Form
  14. Concomitant Treatments with any of the following medications:
    - a. Any anticoagulant
    - b. Blood products within 30 days prior to study enrollment
    - c. Hematologic growth factors within 90 days prior to study enrollment
    - d. Use of any investigational product within 1 year prior to study enrollment
    - e. Systemic antibiotics, antifungals, or antivirals for treatment of active infection within 14 days of enrollment.
    - f. Previous exposure to immunotherapy with 6 months prior to enrollment.

## Study Assessments:

### Primary Endpoint

The primary endpoint, determined at treatment week 49, 73 (or 97 week), first post-treatment follow-up visit and at week 48 post-treatment follow-up, is the safe completion the combination regimens of REP 2139-Mg, Viread® and Pegasys® and REP 2165-Mg and Viread® and Pegasys® as detailed in Fig 1:

- Proportion of subjects who develop treatment emergent cytopenic abnormalities: anemia, as defined by Hb  $< 10$  g/dl, and/or neutropenia as defined by PMN  $< 1,000/\mu$ l, and/or thrombocytopenia as defined by platelets  $< 50,000/\mu$ l)
- Proportion of subjects who develop liver dysfunction (as defined by bilirubin  $> 2 \times$  ULN, chronic elevations in ALT or AST  $> 10 \times$  ULN  $> 8$  weeks in duration) by the end of treatment



- Proportion of subjects who develop renal impairment (as defined by serum creatinine > 1,5 mg/dl for > 4 weeks) by the end of treatment
- Proportion of subjects with AEs, SAEs, dose reductions, and discontinuations due to AEs through end of treatment
- Proportion of subjects with treatment emergent laboratory abnormalities by toxicity grade
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

#### Key Secondary Endpoints

Secondary endpoints will be determined at treatment week 49, 73 (or 97 week), first post-treatment follow-up visit and at week 48 post-treatment follow-up:

- Proportion of patients who achieve serum HBsAg < 50 IU/ml.
- Proportion of subjects who achieve anti-HBs titers above 10 mIU/ml
- Proportion of patients who suppress serum HBV DNA
- Proportion of subjects who maintain HBsAg and HBV DNA suppression during follow-up.
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

#### Statistical Analysis:

##### *Primary safety endpoint*

The primary safety endpoint, determined at treatment week 49, 73 (or 97 week), first post-treatment follow-up visit and at week 48 post-treatment follow-up, is the safe completion the combination regimens of REP 2139-Mg, Viread® and Pegasys® and REP 2165-Mg and Viread® and Pegasys® as detailed in Fig 1:

- Proportion of subjects who develop treatment emergent cytopenic abnormalities: anemia, as defined by Hb < 10 g/dl, and/or neutropenia as defined by PMN < 1,000/μl, and/or thrombocytopenia as defined by platelets < 50,000/μl),
- Proportion of subjects who develop liver dysfunction (as defined by bilirubin > 2X ULN, chronic elevations in ALT or AST > 10X ULN >8 weeks in duration), by the end of treatment
- Proportion of subjects who develop renal impairment (as defined by serum creatinine > 1,5 mg/dl for > 4 weeks), by the end of treatment
- Proportion of subjects with AEs, SAEs, dose reductions, and discontinuations due to AEs through end of treatment,
- Proportion of subjects with treatment emergent laboratory abnormalities by toxicity grade
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg.

Proportions will be derived at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and at week 48 post-treatment follow-up. The proportions will be derived for each treatment arm and for the pooled, non-switching patients of control groups with identical treatments. Similarly, proportions will be derived for pooled groups of identical treatment regimens of equal treatment durations.

Comparison will be made in twofold manner. Primarily experimental groups will be compared against their appropriate controls at each of the time points mentioned above.

Secondarily any experimental treatment (REP 2139-Mg or REP 2165-Mg) will be compared against its appropriate control considering identical length of application of the experimental treatment. E.g. proportions of the first treatment arm at treatment week 49 will be compared to [switching] control group at week 73 as both measures are connected with 24 weeks of REP 2139-Mg treatment.

The above analyses will include the calculation of point estimates of the proportions, a difference in proportions (where it is appropriate) and the corresponding 2-sided 95% Clopper-Pearson confidence intervals for all pair-wise treatment comparisons.

### ***Secondary efficacy endpoints***

Secondary efficacy endpoints will be determined at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and at week 48 post-treatment follow-up:

- Proportion of patients who achieve serum HBsAg < 50 IU/ml.
- Proportion of subjects who achieve anti-HBs titers above 10 mIU/ml
- Proportion of patients who suppress serum HBV DNA
- Proportion of subjects who maintain HBsAg and HBV DNA suppression during follow-up.
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

will be analysed with the methods described for primary safety endpoints.

### ***Antiviral activity***

Efficacy analysis uses treatment regimens and treated subjects. Analyses of antiviral activity will be based on HBsAg, anti-HBs and HBV DNA measurements closest to the planned visits and within pre-defined visit windows.

### ***Adverse events***

The investigators will determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at Replicor Inc. AEs will be presented by system organ class and preferred term.

If a subject had an AE with different intensities over time, then only the greatest intensity will be reported for a study period.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) of the US National Institutes of Health table for grading the severity of adverse experiences (2004) (Appendix 2). The laboratory value during the study period with the highest toxicity grade will be reported for each test. Treatment emergent laboratory abnormalities are those with highest on-treatment toxicity grade greater than the baseline toxicity grade. Levels and changes from baseline in selected laboratory tests over time will be summarized by treatment regimen for treated subjects using observed values.

Rate, severity, relatedness and relationship to administration of NAP therapy of any AEs per administration of NAP therapy and subject will be evaluated from the screening visit until the completion of the study separately for the different study periods. The following periods are defined:

- Pre-screening visit with signing of the Informed Consent to undergo the assessments defined in the protocol as pre-screening, and ends at the date of screening or withdrawal.

- Screening which starts with signing of the Informed Consent to participate in the study and ends at the day before the first dose of the investigational treatment or withdrawal.
- Treatment period, which starts with the first application of the investigational treatment and ends with study completion according to the protocol or withdrawal.
- Follow-up period, which starts the day after the last application of investigational treatment and ends with study completion according to the protocol or withdrawal.

Treatment-emergent adverse events (TEAEs) are defined as AEs that develop or worsen during the treatment period extended with 10 days from the application of the last dose of the investigational treatment. AEs occurring before the start of application of investigational treatment or beyond the treatment period extended with 10 days will only be listed.

AEs will be coded using MedDRA. Analyses will be performed by primary SOC and PT. AEs will primarily be classified by MedDRA PT. Aggregate incidences at the SOC level will be shown as well.

Deaths will be listed for enrolled subjects without regard to study period. The frequencies of the following safety events will be summarized by treatment regimen for treated subjects:

- SAEs (separated by on treatment and follow-up)
- AEs leading to discontinuation of study therapy
- AEs (related and regardless of relationship to study therapy) by intensity (separated by on treatment and follow-up)
- Treatment emergent laboratory abnormalities by toxicity grade.

#### ***Laboratory safety parameters***

The following approaches will be taken for the statistical analysis of the laboratory safety variables:

- Calculation of descriptive statistics (number of subjects, mean, standard deviation, median, 25% and 75% quantile, minimum, maximum) by visit for measured values and for the change from baseline at the completion visit.
- Shift tables displaying intra-individual changes from baseline to the different visits using categorized laboratory variables. Categorization will be done by converting the central lab specific normal ranges into missing, low, normal and high.
- Range change abnormal (RCA): A laboratory value that was either normal or high at baseline and low post-baseline (RCAL) or that was normal or low at baseline and high post-baseline (RCAH).
- Listing of CS laboratory values.

#### ***Vital Signs***

Vital signs will be summarized using descriptive statistics.

#### ***Physical examinations***

Any unfavorable findings recorded between the screening and the study completion visit will be recorded as an AE and summarized using descriptive statistics.

## 2. LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AMA	Anti-mitochondrial antibodies
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
anti-Hbe	Hepatitis B e-antigen antibody
anti-HBs	Hepatitis B surface antigen antibody
anti-HDAg	Hepatitis D antigen antibody
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body Mass Index
BUN	Blood urea nitrogen
cEVR	Complete early virologic response
cccDNA	Closed covalent circular DNA
CHB	Chronic Hepatitis B
CI	Confidence interval
CMV	Cytomegalovirus
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
CS	Clinically significant
CT	Computed tomography
CTA	Clinical trial agreement
Ctrough	Observed through serum/plasma concentration
CYP-450	Cytochrome P450
DAIDS	The Division of AIDS table for grading the severity of adult and pediatric adverse events
DILI	Drug-induced liver injury
dL	Deciliter
DNA	Deoxyribonucleic acid
DRM	Data Review Meeting
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EVR	Extended virologic response
eRVR	Extended rapid virologic response
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen
HbeAg	Hepatitis B e- antigen

Term	Definition
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCO <sub>3</sub>	Bicarbonate
Hct	Hematocrit
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HDAg	Hepatitis D antigen
HDV	Hepatitis D virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN $\alpha$	Interferon $\alpha$
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
ITTS	Intent to Treat Set
IU	International units
IWRS	Interactive Web Response System
Kg	Kilogram
LDH	Lactate dehydrogenase
LKM1	Anti-Liver Kidney Microsomal Antibodies
LLN	Lower limit of normal
LOD	Limit of detection
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	Milliliter
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
ng	Nanogram
NAP	Nucleic Acid Polymer
NUCs	Nucleoside analogs
PBMCs	Peripheral blood mononuclear cells
PID	Patient identification number
PMN	Polymorphonuclear
PRO	Patient reported outcomes
PT	Prothrombin time
PT	Preferred Term
PPS	Per Protocol Set
PPT	Partial prothrombin time
QD	Every day
RBC	Red blood cell
RGT	Response-guided therapy
RNA	Ribonucleic acid
RVR	Rapid virologic response

Term	Definition
Rz	Randomization
SAE	Serious adverse event
SC	Subcutaneous
SDMB	Safety Data Monitoring Board
SDpRS	Safety Data prior to Randomization Set
SDS	Safety Data Set
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOC	Standard of care
SVR	Sustained virologic response
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of normal
WBC	White blood cell
Wk	Week
WOCBP	Women of child-bearing potential



### 3. INTRODUCTION

#### Rationale for proposed therapy

Hepatitis B virus (HBV) has affected more than 2 billion people worldwide and left more than 350 million of these individuals with chronic HBV (CHB) infection which causes progressive liver disease which progresses from fibrosis to cirrhosis and potentially liver cancer (HCC). According to recent WHO data, more than 750,000 people die every year from the complications of HBV infection, underlying the global impact of this disease.

Approved treatments for HBV infection include immunotherapies (like pegylated-interferon [Pegasys®] and thymosin alpha-1[Zadaxin®]) and HBV polymerase inhibitors (entecavir and tenofovir disoproxil fumarate). These therapies do have antiviral effect (reduction in the viral load in the blood) but rarely lead to patients achieving a functional cure (immunological control of their infection after treatment has stopped). As such, there is an urgent need for more effective treatments for CHB infection.

HBV infection is difficult to treat due to maintenance of an active and stable reservoir of viral genetic material (cccDNA) in the nucleus, and constant flood of HBsAg into the circulation, which blocks immune function, preventing establishment of immune control (including control of cccDNA) and inhibits the action of immunotherapy.

Although the most successful currently approved therapeutic approach to treating HBV infection is immunotherapy, its effects are hampered by the persistence of HBsAg throughout therapy and as a result only 10-15% of patients completing a 48 week regimen of immunotherapy achieve functional cures. It is important to note that in all patients who achieved a functional cure after immunotherapy, HBsAg was completely eliminated. The rest of these patients, whose infection returns after therapy routinely experience a 0.5 to 1 log drop in HBsAg levels in the blood, suggesting the critical importance of complete HBsAg clearance in achieving a functional cure.

HBsAg is an abundant viral protein found in the blood of patients with chronic hepatitis B which has been shown to have important immuno-inhibitory activities in multiple peer-reviewed papers and is a major factor responsible for the chronicity of these infections. HBsAg interferes with many aspects of the immune response targeting both innate and adaptive immunity. See:

1. Cheng et al., 2005 Journal of Hepatology, 43: 465-471.
2. Op den Brouw et al., 2009 Immunology, 126: 280-289.
3. Vanlandschoot et al., 2002 J. Gen. Virol., 83: 1281-1289.
4. Xu et al., 2009 Molecular Immunology, 46: 2640-2646.
5. Wu et al., 2009 Hepatology, 49: 1132-1140.

### 4. STUDY RATIONALE

The rationale for conducting this study with Viread®, Pegasys® and REP 2139-Mg or REP 2165-Mg is based on the efficacy and safety data observed in recent proof of concept clinical trials with REP 2139-Ca and recent pre-clinical data comparing the tolerability, liver

accumulation and antiviral activity of REP 2139 and REP 2165. NAPs act against HBV infection by blocking the intracellular formation and release of subviral particles (which are the major source of HBsAg in the blood of infected patients) from infected hepatocytes and can effectively reduce and or eliminate HBsAg from the serum of infected patients.

REP 2139-Ca has been shown to reliably eliminate HBsAg from the blood of patients infected with chronic HBV. We have previously shown that the removal of HBsAg with our drug is associated with an improvement of the immune response against HBV which results in spontaneous resolution of the infection in 25 % of patients treated with monotherapy. More importantly, we have also recently shown that removing HBsAg dramatically improves the response of patients with HBV to pegylated interferon alfa-2a (Pegasys®), and thymosin alfa-1 (Zadaxin®) and is associated with the production of high levels of antibodies against HBsAg called anti-HBs. These results in a high rate of sustained virological responses in HBV (see effects in human patients below).

REP 2139 is a fourth generation NAP designed to improve compound stability and reduce immunostimulatory (pro-inflammatory) activity compared to REP 2055. These modifications (5-methylation of cytosines and 2' O methylation of the ribose sugar in each nucleotide) are naturally occurring modifications in human nucleic acid and are known to be well tolerated in clinical trials. Current interim analysis of the 12 patients in the REP 102 protocol assessing safety and efficacy of REP 2139-Ca has shown that 10 patients have achieved substantial reductions or effective clearance of serum HBsAg which was accompanied by the appearance of free anti-HBs antibodies > 10mIU/ml and concomitant reductions (up to 6 logs) of HBV DNA to levels < 5,000 IU/ml. One patient on REP 2139-Ca monotherapy achieved HBV DNA < 116copies/ml. Short term combination treatment with Pegasys® or Zadaxin® in patients having achieved HBsAg seroclearance resulted in dramatic increases of serum anti-HBsAg in many cases exceeding 1,000 mIU/ml. Of the 9 patients who received combination therapy, 8 have experienced complete control of their HBV infection off treatment (HBV DNA < 116 copies/ml, no detectable serum HBsAg and anti-HBsAg > 50mIU/ml. Four of these patients are still experienced a SVR 96-100 weeks post treatment.

In another small proof of concept phase II trial the tolerability of triple combination treatment with REP 2139-Ca, Pegasys® and entecavir was confirmed in two additional patients (transitioning from previous entecavir monotherapy) who achieved SVR with only 17 weeks of NAP exposure during 48 weeks of Pegasys® and entecavir therapy.

Treatment of HBV with polymerase inhibitors (including entecavir and TDF) has been shown to reduce the cccDNA copy number within infected hepatocytes in patients with chronic HBV infection (Werle-Laspottle et al., 2004 and Wong et al., 2013) which likely has a positive impact on the speed with which immune recovery in the presence of NAPs and immunotherapy can suppress and subsequently maintain long term control of cccDNA function. Prior exposure of patients to entecavir or TDF likely reduces the cccDNA load that needs to be controlled by the immune response when it is re-awakened when patients enter combination therapy with NAPs and immunotherapy and represent the best current possible treatment option for achieving SVR.

Access to Viread® is limited at the trial site and there is little or no available patient population currently on entecavir or Viread® therapy. Therefore, all patients in the trial will receive 24 weeks of Viread® exposure (to begin the reductions of intrahepatic cccDNA

stores) prior to add on combination therapy with NAPs and immunotherapy. This pre-exposure to Viread® maximizes the chance that patients will achieve SVR with the proscribed 48 weeks of NAP exposure as detailed below.

REP 2165 is an improved version of REP 2139 which is designed to breakdown faster and be more rapidly eliminated without compromising antiviral activity, thus reducing total systemic drug exposure without compromising antiviral effect.

Both NAPs REP 2139 and REP 2165 are formulated as magnesium chelate complexes. NAP chelate complexes neutralize the chelation-related side effects which are common during parenteral administration of phosphorothioated oligonucleotides (NAPs belong to this chemical class) without affecting the pharmacological activity of NAPs. Magnesium chelates (compared to the previous calcium chelate formulation used for REP 2139) have improved solubility, allowing for a more convenient drug product with a higher drug concentration and the clinical experience with mineral injectables demonstrates that magnesium chelates will also have improved tolerability compared to calcium chelates. In a report prepared by the United Kingdom Medicine Information Pharmacists Group for NHS healthcare professionals, the use of magnesium (as magnesium sulphate) injected subcutaneously was shown to be safer than other electrolytes such as potassium or calcium. High doses of magnesium sulphate can be safely administered intravenously, intramuscularly or subcutaneously.

### **Treatment Duration Rationale**

The Replicor Study will evaluate the efficacy and safety of the combination of REP 2139-Mg or REP 2165-Mg and peginterferon alfa-2a (Pegasys®) as an add-on therapy in patients receiving previous and continuing tenofovir disoproxil fumarate (Viread®) treatment. Patients will receive 24 weeks of TDF monotherapy to lower intra-hepatocyte cccDNA burden. Following this, patients will continue on TDF therapy (to continue to lower cccDNA) while receiving 48 weeks of NAP + immunotherapy. The expected reduction of circulating HBsAg induced by NAPs (REP 2139 or REP 2165) will potentiate the action of the simultaneous exposure to immunotherapy (Pegasys®).

### **Rationale to Support Open-Label Study**

This study will be open label due to: 1) it is a pilot study; 2) the efficacy and safety of REP 2139-Mg and REP 2165-Mg has not yet been established in a large population of patients; 3) registration of AE which makes true-blinding unrealistic; 4) the small amount of patient enrollment.

## 5. RESEARCH HYPOTHESIS

Clearance of serum HBsAg with REP 2139-Mg or REP 2165-Mg will lead to:

- a) the appearance of anti-HBs, which will in turn clear serum HBV.
- b) the appearance of anti-HBs, which will prevent the entry of HBV viruses into hepatocytes.
- c) the creation of a permissive environment in which host immunity can begin to control HBV infection.
- d) a synergistic effect on the immunostimulatory action of Pegasys® which may further increase the chance of patients achieving control of their HBV infection off treatment.
- e) these effects are likely to be accelerated in patients with suppression of infectious HBV by continuous therapy with HBV polymerase inhibitors such as entecavir or tenofovir disoproxil fumarate which have been shown to reduce intra-hepatic cccDNA burden.

### Objectives

#### Primary Objective

To demonstrate that REP 2139-Mg or REP 2165-Mg are well tolerated when given intravenously to patients with HBV infection in combination with Pegasys® and TDF (Viread®).

#### Key Secondary Objectives

To demonstrate the efficacy of REP2139-Mg and REP 2165-Mg in the above combination regimens in achieving the following outcomes in patients with HBV infection:

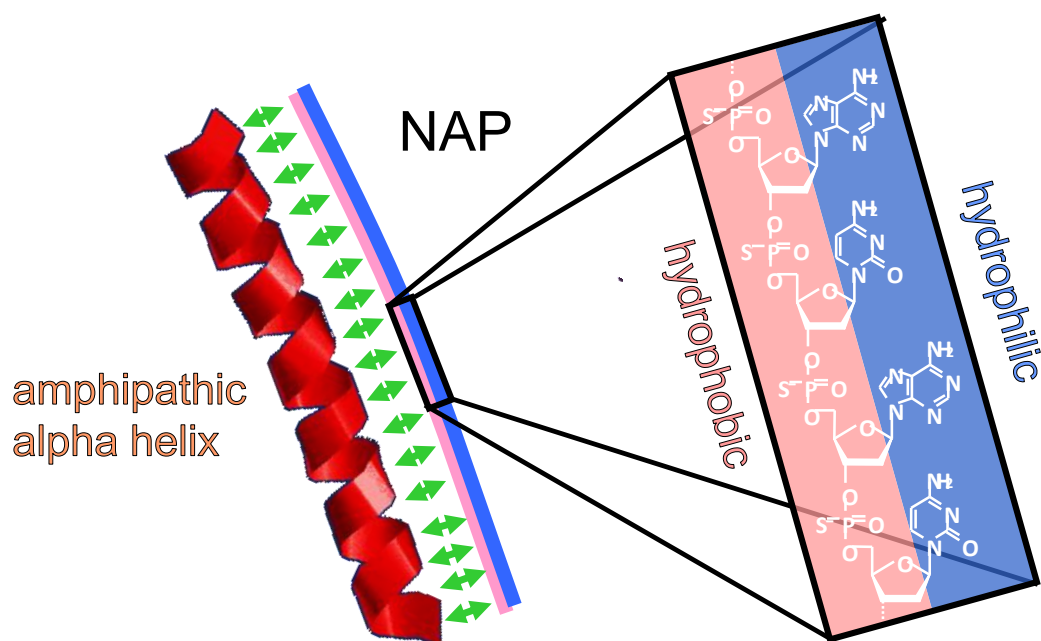
- a) to reduce or clear serum HBsAg
- b) to reduce or clear serum HBV DNA
- c) to produce a synergistic effect with Pegasys® (as measured by anti-HBs production).
- d) to establish control of HBV infection off treatment (HBV DNA).

## 6. PRODUCT DEVELOPMENT BACKGROUND

### Background of NAPs (Nucleic Acid Polymers)

#### IN VITRO MECHANISM OF ACTION OF NAPs

NAPs are amphipathic polymers synthesized using phosphorothioate oligonucleotide chemistry. NAPs interact with large, exposed amphipathic targets in a size dependent but sequence independent fashion via multiple lateral interactions with the target interface (see below).



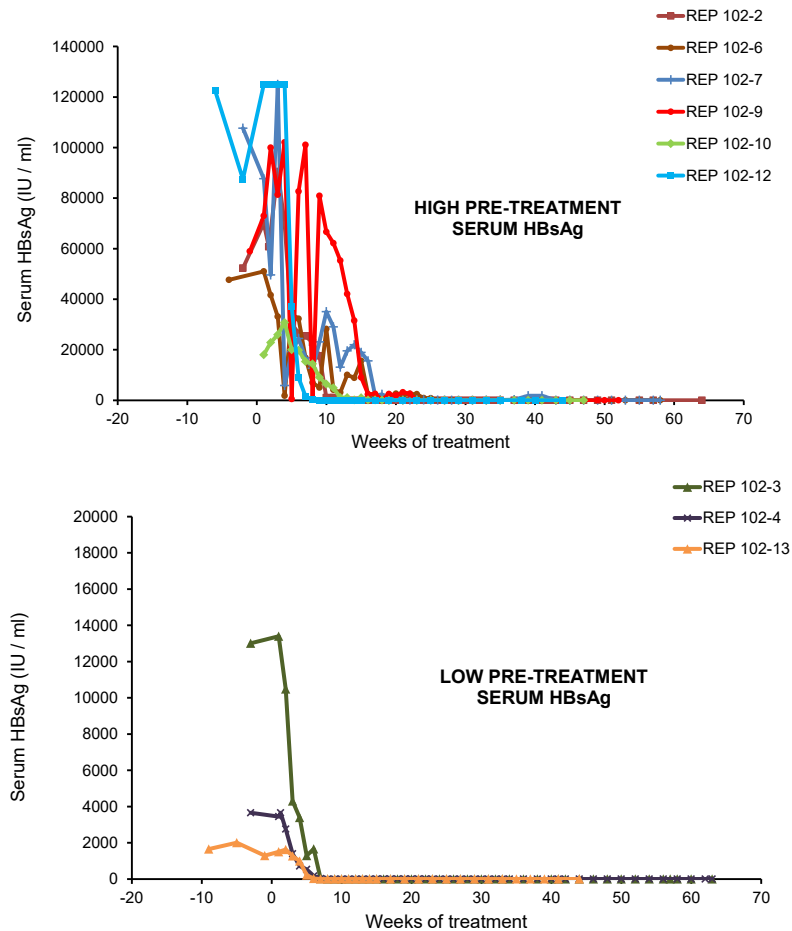
#### NAP-TARGET INTERACTION IN HBV

NAPs target a large amphipathic surface on apolipoprotein H (Apo H or beta-2-glycoprotein) whose interaction with HBsAg is important for the formation of HBV subviral particles. In HBV infected cells, NAP treatment does not affect the production of HBsAg but blocks ApoH / HBsAg interactions and prevents HBsAg assembly into subviral particles which in turn prevents their release from infected hepatocytes.

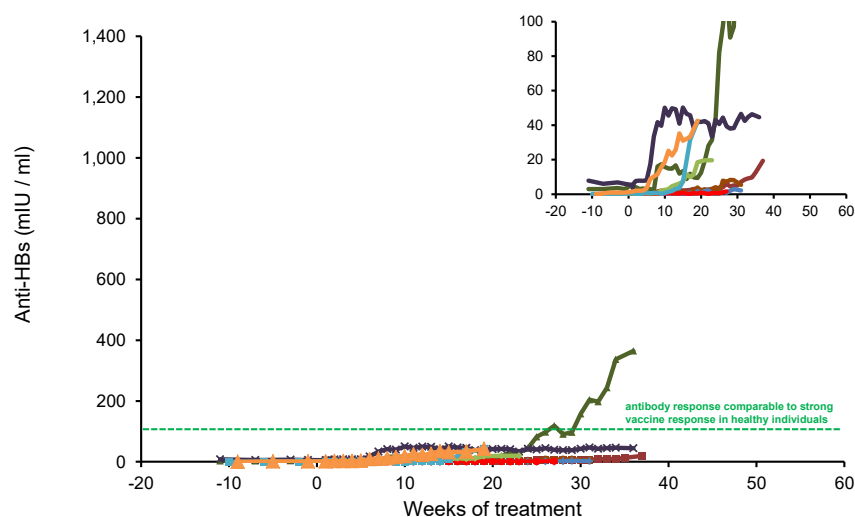
#### CLINICAL EFFECT OF NAP THERAPY IN PATIENTS WITH CHRONIC HBV

A small group of patients (predominantly genotype C and D) with immunotolerant HBeAg+ chronic HBV infection were exposed to once weekly REP 2139-Ca therapy (500mg via IV infusion) in a phase I/II proof of concept trial conducted at the Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh under ethics committee approval. Viremia in the serum of these patients was monitored by the Abbott Architect® quantitative assay (HBsAg and anti-HBs) and the Roche Cobas® quantitative assay (HBV DNA).

Weekly treatment with REP 2139-Ca rapidly resulted in the elimination of serum HBsAg in patients regardless of their pre-treatment HBsAg setpoints (see below).

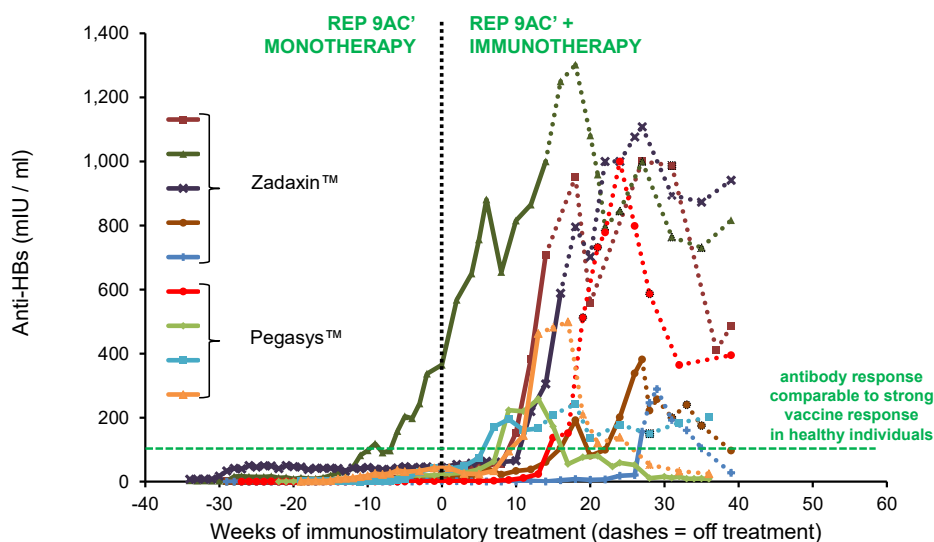


Concomitant with reduction or elimination of serum HBsAg by REP 2139-Ca was the appearance of free anti-HBsAg antibodies in most patients (see below – inset shows expanded scale).



As mentioned above, in a previous proof of concept trial conducted at the same trial site, NAP monotherapy resulted in the achievement of durable immunological control off treatment in ~25% of patients (these patients have stable control of their HBV infection

5years off treatment). Therefore, at this point in the current trial, these patients who had cleared serum HBsAg were subjected to add on immunotherapy (see below) with either Zadaxin® (thymosin  $\alpha$ 1 – 1.6mg SC twice weekly) or Pegasys® (pegylated interferon  $\alpha$ -2a – 90-180 $\mu$ g SC once weekly).

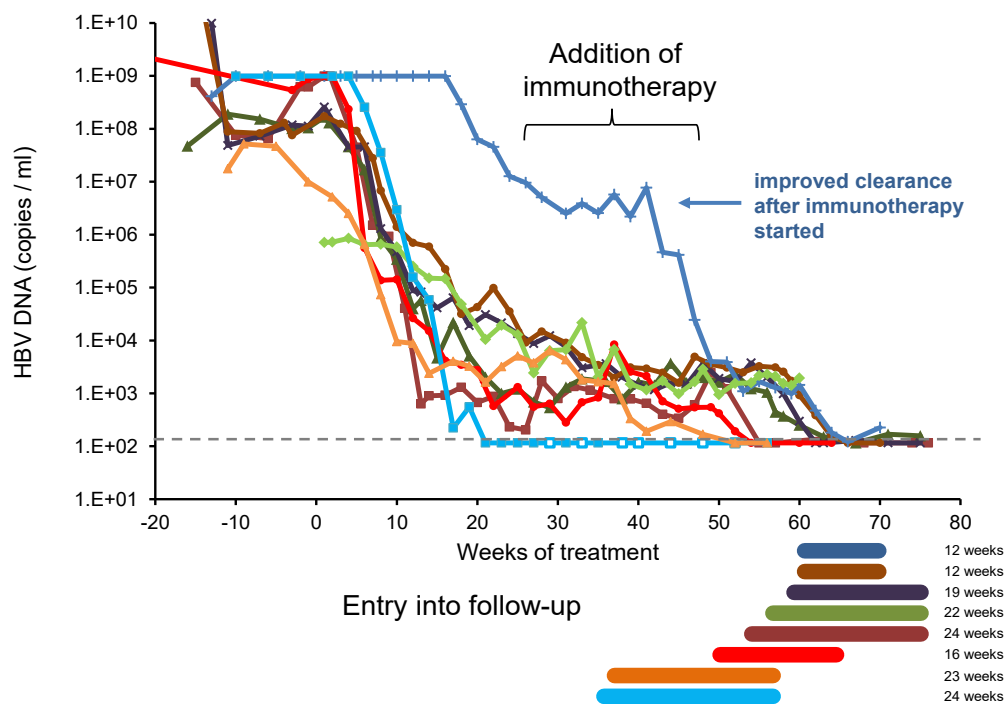


Improvement in anti-HBs titers with short term exposure to immunotherapy. Dashes represent antibody production after cessation of all treatment. Note antibody responses in all patients have been synchronized to the start of add-on immunotherapy (week 0) in the continuing presence of REP 2139-Ca.

With add-on immunotherapy, all patients experienced substantial improvement in their anti-HBs response with as few as 6 weeks of add-on immunotherapy and most had attained anti-HBs responses greatly exceeding those typically observed with a strong vaccine response in healthy patients after only 13 weeks of add-on immunotherapy. In patients where treatment has been halted, the anti-HBs response either persists or continues to improve in most patients after immunotherapy is halted (dotted lines). Data for all patients above was synchronized to the start of immunotherapy (time = 0).

Importantly, removal of HBsAg appears to greatly improve the efficacy of immunotherapy in all patients, with profound increases in the adaptive immune response observed in all patients with short duration immunotherapy (13 weeks versus 48 weeks conventionally used with Zadaxin® or Pegasys® monotherapy).

The effect of REP 2139-Ca monotherapy and subsequent add-on immunotherapy has a profound effect on the clearance of HBV virus from the blood (see below). Initial “unmasking” of the existing immune response by REP 2139-Ca monotherapy (generally from weeks 0 – 30) appears to result in dramatic rates of HBV clearance in all patients comparable to or exceeding HBV viral clearance observed with NUCs. Initiation of short duration combination therapy with Zadaxin® or Pegasys® lead to control of HBV infection in 8 of 9 patients 12-24 weeks after treatment was removed (see below).



Reduction in serum HBV DNA with REP 2139-Ca monotherapy, with add-on immunotherapy with Pegasys® or Zadaxin® and control of viremia off treatment. Bracket indicates the time when immunotherapy was started (which was different for each patient). Bars below indicate when all treatment was halted for each patient and the duration of on-going follow-up. Weeks of treatment (are indicated in the X-axis).

These results strongly suggest that a permanent control of HBV infection, eventually leading to complete suppression or elimination of HBV infection can be achieved by the robust activation of the immune response after NAP-mediated serum HBsAg clearance.

This therapeutic approach is likely to be effective in all patients, regardless of genotype, infectious status or ethnic background.

### REP 2139 versus REP 2165

REP 2165 is a version of REP 2139 which is engineered to break into small pieces so that it is more easily eliminated. This is achieved by the use of three “adenosine breaks” as described below.



REP 2165:  
REP 2139 ENGINEERED TO DEGRADE MORE EASILY

COMPOUND	SEQUENCE	FORMULATION
REP 2139	ACACACACACACACACACACACACACACACACACAC (all linkages phosphorothioated)	magnesium chelate complex
REP 2165	ACACACACACACACACACACACACACACACACACAC (all linkages phosphorothioated)	magnesium chelate complex

**All nucleotide modifications occur naturally in humans:**

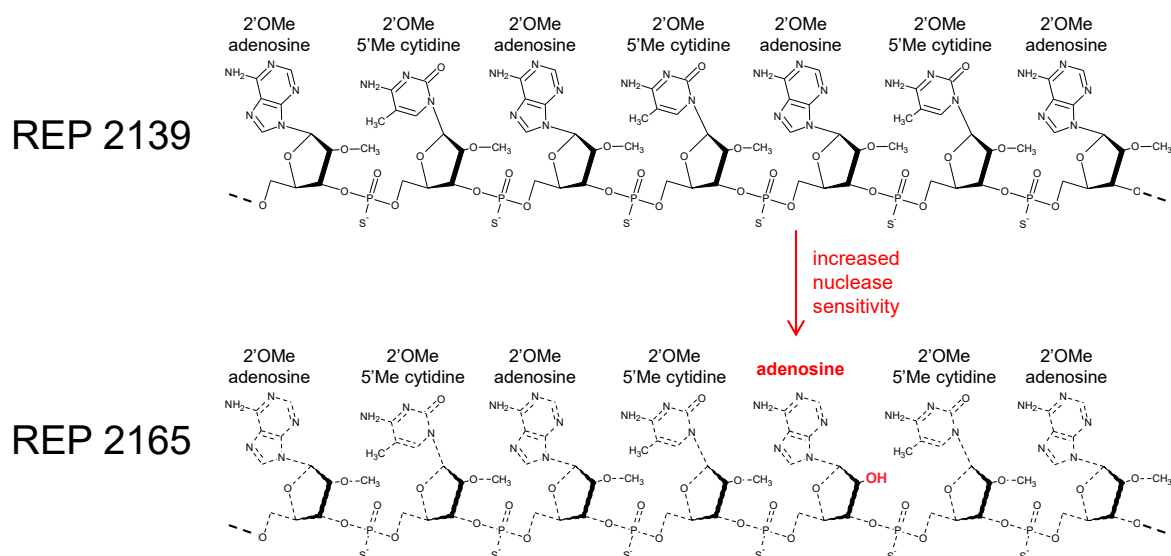
A = 2'O methyl riboadenosine

C = 2'O methyl - 5'methylcytidine

**A** = unmodified riboadenosine → accelerates nuclease cleavage

The above figure shows that both REP 2139 and REP 2165 have the exact same sequence and the same length giving them the same amphipaticity. The only difference between these 2 molecules is that of the 20 adenosines (A) present, 3 adenosines do not have the 2'Omethyl modification. The absence of this modification allows nuclease activity to more easily break REP 2165 into 4 smaller pieces. Smaller pieces of nucleic acids are more easily eliminated from the body. Both adenosine versions (2'O methyl modified or unmodified) are naturally occurring in the human body. Previous observations suggest that NAPs interact with apo-H only initially following the administration and then move on to different cellular compartments where there is no useful interaction. There is therefore no advantage of accumulating NAPs in the liver once the initial desired interaction has occurred. Faster elimination of NAPs could reduce side effects including minimizing the elimination of minerals via chelation of divalent cations.

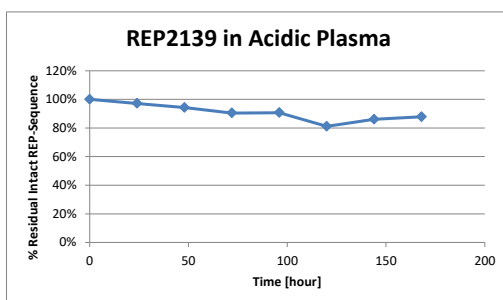
REP 2165:  
STRUCTURAL DETAILS OF “ADENOSINE” BREAK



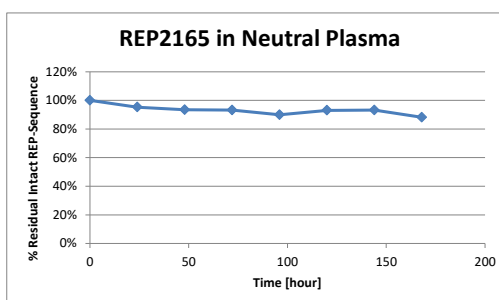
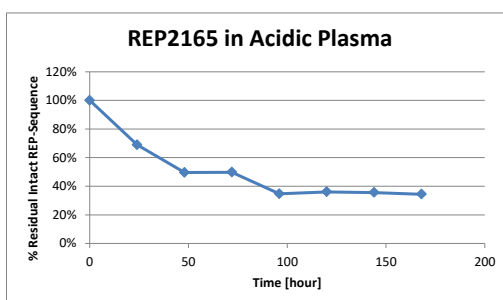
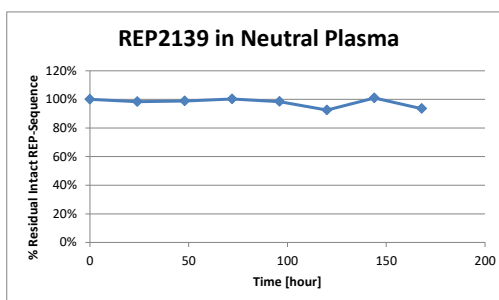
In neutral human plasma, REP 2165 is stable but in acidified human plasma, which simulates the intracellular nuclease activity, REP 2165 is degraded over time.

## REP 2139 and REP 2165: COMPARATIVE 7 DAY STABILITY IN HUMAN PLASMA

(intracellular)



(extracellular)



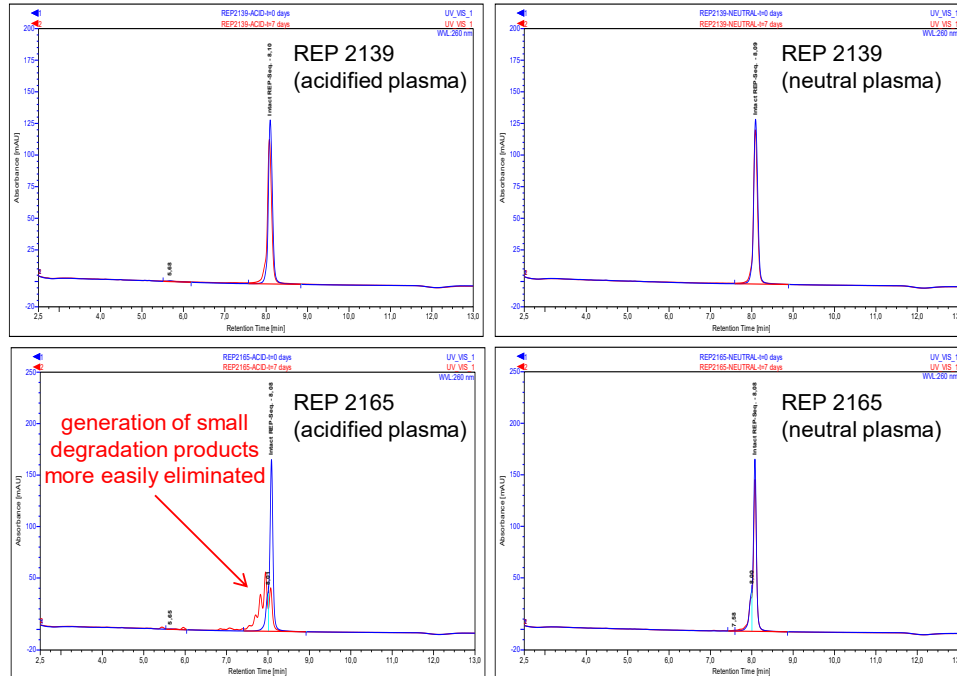
**REP 2165 is designed to be stable in plasma so it enters cells intact and then  
to breakdown as it passes through the cell**

This enhanced degradation of REP 2165 in acidified human plasma due to cleavage at the adenosine breaks will make REP 2165 more easily eliminated, thus resulting in reduced accumulation of drug in the liver.

## REP 2165 DEGRADATION INTO SMALLER FRAGMENTS WILL FACILITATE CLEARANCE

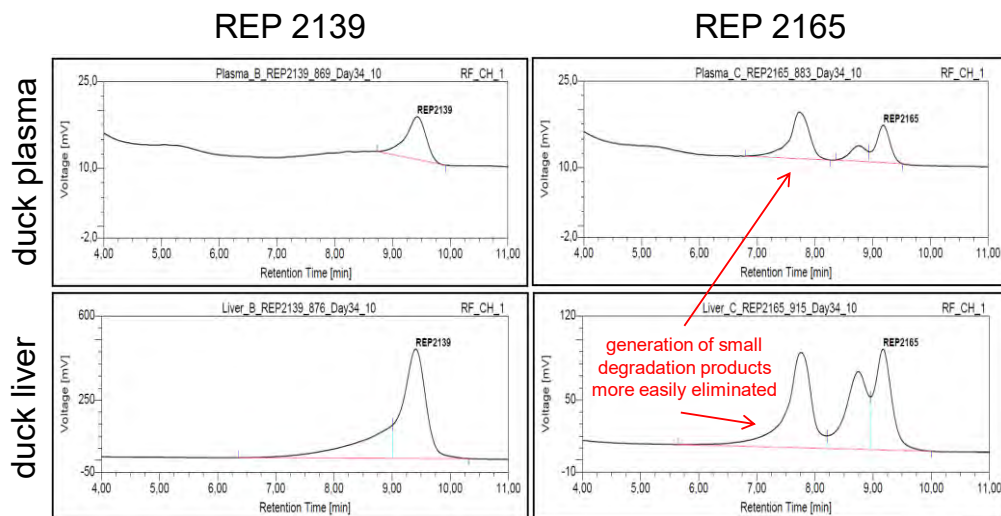
(HPLC analysis of REP 2139 and REP 2165 degradation products in human plasma)

**0 DAYS INCUBATION** **7 DAYS INCUBATION**



Duck HBV infection of Pekin ducks is an accepted surrogate animal model for HBV infection in humans. In Pekin ducks harbouring DHBV infection, REP 2139 and REP 2165 were dosed 3 times per week for three weeks. At the end of treatment, the degradation patterns of REP 2139 and REP 2165 in the plasma and liver of these ducks was assessed by HPLC and demonstrated that REP 2165 underwent the same degradation in the liver and plasma (likely from drug transit through the liver) as was observed in human plasma.

**REP 2165 DEGRADATION IS SIMILAR IN  
PEKIN DUCK IN VIVO AND HUMAN PLASMA  
(HPLC analysis of duck liver and plasma at end of treatment)**



Given that REP 2165 was undergoing the expected degradation to slow down drug accumulation in the liver, the antiviral effect of REP 2139 and REP 2165 as well as the total ac

**REP 2165 ANTIVIRAL ACTIVITY IN VIVO IS COMPARABLE TO REP 2139  
WITH SIGNIFICANTLY LESS LIVER ACCUMULATION  
(10mg / kg 3x / week for three weeks in duck HBV (DHBV) infected Pekin ducks)**

<b>Antiviral activity (at end of treatment)</b>	<b>REP 2139</b>	<b>REP 2165</b>	<b>Normal saline (control)</b>
clearance of serum DHBsAg	4/5 ducks	3/5 ducks	0/5 ducks
increase in anti-DHBV antibodies	3/5 ducks	3/5 ducks	0/5 ducks
reduction in serum DHBV DNA	4/5 ducks	5/5 ducks	0/5 ducks
reduction in liver DHBV DNA	4/5 ducks	5/5 ducks	0/5 ducks
<b>NAP accumulation in the liver at end of treatment (average std. dev.)</b>	<b>131472.2 26204.3 ng / g tissue (n=5)</b>	<b>21718.1 3085.1 ng / g tissue (n=5)</b>	<b>no drug present</b>

Importantly, the antiviral activity of REP 2165 was comparable to REP 2139 in vivo in DHBV infected Pekin ducks with substantially less accumulation of drug in the liver at the end of treatment. This provides a clear rationale for the use REP 2165 in the treatment of human patients with HBV infection. Due to these two NAPs having identical sequences, the good tolerability profile of REP 2139 will be duplicated or improved upon with REP 2165.

## **Packaging**

The REP 2139-Mg drug product container is a 5cc borosilicate vial with a polyethylene cap enclosure packaged individually. Each vial contains 4.2cc of 62.5 mg/ml REP 2139 magnesium chelate complex (50 mg/ml  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ ) in water which is sterilized by filtration through a 22  $\mu\text{m}$  filter. REP 2139-Mg is certified sterile and its pyrogen content meets or exceeds the criteria for allowable pyrogen content for injectable medications.

The REP 2165-Mg drug product container is a 5cc borosilicate vial with a polyethylene cap enclosure packaged individually. Each vial contains 4.2cc of 62.5 mg/ml REP 2165magnesium chelate complex (50 mg/ml  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ ) in water which is sterilized by filtration through a 22  $\mu\text{m}$  filter. REP 2165-Mg is certified sterile and its pyrogen content meets or exceeds the criteria for allowable pyrogen content for injectable medications.

## **Storage and drug infusion**

REP 2139-Mg / REP 2165-Mg:

A 5cc syringe is used to withdraw the entire contents from one vial and aseptically transfer this 4cc to an IV bag of normal saline (100 – 250cc) which will then be infused over 2 hours. The drug product is stored refrigerated between 4 and 30 °C.

## **7. BACKGROUND OF PEGASYS®**

Peg-interferon  $\alpha$ -2a (Pegasys®) is used for the treatment of chronic hepatitis B in adults with compensated liver disease, HBV viremia, elevated ALT and histologically proven inflammation of the liver or liver fibrosis.

Through an unselective stimulation of T-cells, peg-interferon  $\alpha$ -2a strengthens the immune response to the hepatitis B virus. This can result in an immunological control of the virus with formation of anti-HBs antibodies. Peg-interferon  $\alpha$ -2a is usually considered the only available therapy for chronic hepatitis B that can induce an immunological control of the infection.

Patients with psychiatric disease, use of myelosuppressive substances, thyroid, cardiac or autoimmune disease, HIV or after transplantation should not be treated with peg-interferon  $\alpha$ -2a because of the risks of severe side effects.

## **8. BACKGROUND OF VIREAD®.**

Tenofovir disoproxil fumarate (Viread®) is also an antiviral drug used for the treatment of chronic hepatitis B in adults with compensated liver disease, active viral replication and persistently elevated ALT values, as well as histologically proven active inflammation and/or fibrosis or decompensated liver disease.

Tenofovir disoproxil fumarate belongs to the group of nucleotide reverse transcriptase inhibitors (NtRTI). Chemically it is a nucleotide analogue which like Entecavir is

incorporated into the viral DNA which inhibits viral replication. This happens by inhibition of the HBV reverse transcriptase (the hepatitis B virus, though a DNA virus, transcribes its DNA into RNA via the reverse transcriptase, where after it is transcribed into DNA again).

## **9. NON-CLINICAL SAFETY STUDIES**

Data from REP 2139 and REP 2165 non-clinical studies can be found in the REP 2139-Mg and REP 2165-Mg Investigator Brochure (IB).

## **10. CLINICAL EXPERIENCE WITH REP 2139-CA AND PEGASYS® or ZADAXIN®**

To date 32 courses of NAP therapy have been administered (8 with REP 2055, 17 with REP 2139-Cain Asia and 7 with REP 2139-Ca in Moldovawith regular weekly administration in the 400-500mg range in regimens lasting 15-62 continuous weeks. Detailed information on the toxicological effects of REP 2139-Ca treatment can be found in the REP 2139-Mg or REP 2165-Mg IBs.

The calcium chelate formulation of REP 2139-Ca, currently employed in treating patients prevents the common administration-related side effects typically observed with this chemical class (phosphorothioate oligonucleotides, as was the case with REP 2055 in the first proof of concept trial). The use of magnesium chelate formulations of REP 2139 and REP 2165 is expected to result in further improvements in administration tolerability without altering antiviral activity.

The addition of either Zadaxin® (n=5) or Pegasys® (n=4) or transition from Zadaxin® to Pegasys® (n=2) while on REP 2139-Ca therapy introduced no additional side effects with these immunotherapies compared to these immunotherapies given alone.

## **11. CLINICAL EXPERIENCE WITH REP 2139-CA, PEGASYS® AND ENTECAVIR.**

In a supplemental trial, two patients who originally responded to REP 2055 therapy but failed to achieve sufficient control of infection were placed on a daily regimen of 0.5mg of entecavir (ETV). After more than a year on ETV, these patients received combination add-on therapy with REP 2139-Ca and Pegasys® at the same time (while continuing ETV). This triple combination therapy was not associated with any additional side effects. More detailed information on these patients can be found in the REP 2139-Ca IB.

## **12. OVERALL RISK/BENEFIT ASSESSMENT**

### **Key Risks Associated with the Use of REP 2139-Mg and REP 2165-Mg**

32 patients have been treated with NAPs (8 with REP 2055 and 24 with REP 2139-Ca) in clinical trials. Reviewing the safety data from those clinical studies did not reveal any major safety concerns (please see the REP 2139-Mg and REP 2165-Mg Investigational Brochures for additional information) but indicated the importance of mineral supplementation in patients receiving NAP therapy. The number and types of side effects reported in those studies were similar to those observed in other studies that used phosphorothioated oligonucleotides (typically as antisense agents) except that symptoms related to mineral deficiency were more frequent due to liver dysfunction and poor dietary access to minerals and underlying heavy metal intoxication in the locale where the patients lived. In general, these events were mild to moderate in nature and did not affect the ability of patients to take drug as directed.

REP 2165 is chemically identical to REP 2139 except for three “adenosine breaks” which serve only to increase its elimination from the subject. Because of its almost identical chemical properties to REP 2139, the existing REP 2139 safety data stands as a reasonable and reliable predictor of the expected safety profile of REP 2165 in human patients.

REP 2055 and REP 2139-Ca treatment of patients with HBV infection has resulted in the development of short term, asymptomatic liver flares consisting of AST and ALT > 1.5X ULN not exceeding 10 weeks in duration and where AST > 10X ULN and ALT > 20X ULN does not persist for more than 2-4 weeks during which all other aspects of liver function remained normal (serum bilirubin, albumin and globulin). These liver flares were concomitant with the rapid and dramatic reduction in serum viremia and resolved spontaneously after serum viremia was either eliminated (in a few patients) or reached a plateau in the 1000-2000 IU/ml range (in most patients). Flares resolved spontaneously with continued REP 2139-Ca treatment exposure. These flares are analogous to those observed during interferon treatment and are currently treated as evidence of a desirable cytolytic clearance of infected hepatocytes in the liver due to a restored immune response and are not currently attributed to toxicity exposure to NAPs. All patients receiving REP 2139-Mg or REP 2165-Mg treatment in this proposed study have a high likelihood of developing these liver flares. Typical flares on REP 2139-Ca monotherapy and REP 2139-Ca combined with immunotherapy are described below.

### Liver Flares observed with REP 2139-Ca in mono- and combination therapy.

Patient	Monotherapy (REP 2139-Ca)				Combination therapy (REP 2139-Ca + Pegasys® or Zadaxin®)			
	ALT		AST		ALT		AST	
	max	duration > 1.5x baseline	max	duration > 1.5x baseline	max	duration > 1.5x baseline	max	duration >1.5x baseline
REP 102-2	670	5 weeks	320	5 weeks	absent			
REP 102-3	155	6 weeks	108	3 weeks	absent			
REP 102-4	170	2 weeks	139	3 weeks	193	6 weeks	206	6 weeks
REP 102-6	717	9 weeks	285	8 weeks	229	10 weeks (biphasic)	165	7 weeks (biphasic)
REP 102-7	281	8 weeks	145	8 weeks				
REP 102-9	600	6 weeks	249	5 weeks	182	9 weeks	116	6 weeks
REP 102-10	absent				246	11 weeks	225	11 weeks
REP 102-12	550	14 weeks	203	5 weeks	absent			
REP 102-13	145	6 weeks	absent		362	8 weeks	241	7 weeks

Of the 32 patients exposed to NAPs, three patients have not experienced a reduction in their serum HBsAg.

NAPs (as is the case for all oligonucleotides) chelate minerals in the blood (especially calcium, magnesium and zinc) and chronic exposure to these compounds can lead to increased rates of mineral elimination in the urine and subsequent mineral deficiency. In patients with normal liver function this appears to be easily compensated, however in patients with chronic hepatitis B, this chronic leaching of minerals may be more difficult to compensate. Therefore, vitamin D levels and mineral stores should be optimized before treatment and maintained during treatment and for a minimum of 6 months post REP 2139-Mg or REP 2165-Mg exposure to prevent the development of mineral deficiencies and associated symptoms. This is a precaution and is not expected to be problematic in patients in this study as they have daily access to minerals and vitamin D in their diet and will be supplemented.

#### Magnesium versus calcium chelate

REP 2139 and REP 2165 are formulated as a magnesium chelate complex instead of a calcium chelate complex. Interaction data has shown that oligonucleotides preferentially chelate with magnesium versus calcium (magnesium can displace already chelated calcium) which is reflected in the preferential elimination of magnesium in patients receiving oligonucleotide therapy (see also Mata et al 2000 Clin. Toxicol. 38: 383-387). The magnesium sulfate used in the preparation of the chelate complex of REP 2165 will have an improved tolerability profile, will be better suited to prevent additional chelation with other divalent minerals in the blood and more effectively replace the most preferentially eliminated mineral under oligonucleotide treatment.



### **Risks Associated with the Use of Pegasys®**

Peginterferon  $\alpha$ -2a is associated with numerous side effects, including influenza-like symptoms such as fever, myalgia, fatigue, and arthralgia. Other side effects, some of which have sometimes been associated with fatal outcomes, include rash, autoimmune disorders, neurologic and psychiatric disorders (including depression and suicidal ideation), insomnia, cardiac disorders (including ischemia), thyroid disorders, hematologic abnormalities (including thrombocytopenia and neutropenia), worsening of liver function tests, pulmonary and ophthalmologic disorders, and severe infection. Subjects with known or potential contraindications to Peginterferon  $\alpha$ -2a therapy, including but not limited to, autoimmune hepatitis, history of cardiac disease, chronic pulmonary disease (including interstitial lung disease and sarcoidosis), poorly controlled depression, and autoimmune disease (including Crohn's disease and ulcerative colitis), will be excluded from the study, and all subjects will be monitored for the occurrence of AEs. In clinical studies of Peginterferon  $\alpha$ -2a, 9% of subjects with HCV developed binding antibodies to Peginterferon  $\alpha$ -2a, and 3% of subjects developed low-titer neutralizing antibodies.<sup>2</sup>

### **Risks Associated with the Use of Viread®**

Side effects which are reported during the use of Tenofovir disoproxil fumarate are hypophosphatemia, vertigo, diarrhea, vomiting, nausea, skin rashes, fatigue, cephalgias, abdominal pain, flatulence, elevation of transaminases, hypokalemia, pancreatitis, rhabdomyolysis, muscular fatigue, elevation of creatinine, lactic acidosis, hepatic steatosis, hepatitis, angioedema, osteomalacia, myopathy, acute kidney injury, kidney failure, acute tubular necrosis, proximal renal tubulopathy (Fanconi syndrome included), nephritis (acute interstitial nephritis included), nephrogenic diabetes insipidus, hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia, lactic acidosis, lipodystrophy, immune reactive syndromes, osteonecrosis and hepatomegaly.

Tenofovir disoproxil fumarate has the potential for CYP450-induced interactions. This may lead to elevation of the concentration of Tenofovir disoproxil fumarate or the simultaneously used drug, whose active tubular secretion is also transmitted through the transport proteins hOAT 1/3 or MRP 4. If simultaneously used with Tacrolimus it is recommended to monitor closely the renal function. The concurrent use with protease inhibitors leads to elevation of the AUC of Tenofovir disoproxil fumarate and reinforcement of its side effects.

Like with all NUCs, there have been reported cases of lactic acidosis. In the event of development of any metabolic or lactic acidosis, progressive hepatomegaly or elevation of ALT, treatment must be discontinued. Close monitoring of liver function during treatment and follow up is recommended.

## **13. POTENTIAL BENEFITS OF REP 2139-Mg OR REP 2165-Mg TREATMENT**

Patients undergoing combination treatment with REP 2139-Mg or REP 2165-Mg in combination with and Pegasys® and Viread® are expected to have a high likelihood of achieving an effective immunological recovery capable of permanent control or eventual elimination of their HBV infection.

## **14. ETHICAL CONSIDERATIONS**

### **Good Clinical Practice**

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and as well as other valid national regulations.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to Replicor Inc. immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

### **Institutional Review Board/Independent Ethics Committee**

Before study initiation the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates. The investigator should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

### **Informed Consent**

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects, they will not be included in the study.

Each investigator will be provided with an appropriate sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

**Investigators must:**

- 1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- 2) Allow time necessary for subject to inquire about the details of the study.
- 3) Obtain an informed consent signed and personally dated by the subject and by the person who conducted the informed consent discussion.
- 4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions is completed for new information.
- 5) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements and the subjects' signed informed consent document.

The consent form must also include a statement that Replicor Inc. and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., subjects with dementia) will not be included in the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

## **15. STUDY DESIGN AND DURATION**

This is a Phase IIb open-label randomized, multicenter study to investigate the safety and efficacy of NAP therapy in combination treatment with Pegasys® and Viread® and Viread® in patients with HBeAg negative chronic hepatitis B infection. This is a pilot study in order to assess safety and efficacy of the proposed combination therapy in patients with HBV infection.

Approximately 200 subjects will be screened to randomize 40 subjects in this open-label trial. Forty chronic HBV infected subjects enrolled will be randomly allocated in either experimental (20 patients) or control group (20 patients) in a 1:1:1:1 ratio to receive study treatments:

**Experimental Group:**

1. Viread® monotherapy (24 weeks, 300mg qD) followed by:
2. Triple combination therapy for 48 weeks:
  - a. REP 2139-Mg 250mg qW or REP 2165-Mg 250mg qW
  - b. Pegasys® 180ug qW
  - c. Viread® 300mg qD.

## Control Groups

1. Viread® monotherapy (24 weeks, 300mg qD) followed by:
2. Combination therapy for 24 weeks:
  - a. Pegasys® 180ug qW
  - b. Viread® 300mg qD followed by:
3. After 24 weeks of Pegasys® exposure, serum HBsAg reductions (as measured at Visit 28) relative to baseline (established at Screening Visit 2) will be determined. Patients with  $\geq 3$  log reduction in serum HBsAg transition directly to (4) below. Patients with  $< 3$  log reduction in serum HBsAg crossover to 48 weeks of triple combination treatment as follows:
  - a. REP 2139-Mg 250mg qW or REP 2165-Mg 250mg qW
  - b. Pegasys® 180ug qW
  - c. Viread® 300mg qD.
4. Combination therapy for 24 weeks:
  - a. Pegasys® 180ug qW
  - b. Viread® 300mg qD

It is expected that all subjects who are on study will complete the protocol-defined durations for treatment and follow-up. All subjects who discontinue after randomization should enter, complete and comply with the protocol-specified follow-up procedures at FU Week 4, FU Week 12, FU Week 24 and FU Week 48 as outlined below. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated or for the treatment of either a psychiatric or physical illness).

If a subject is withdrawn before completing the study, the reason for withdrawal must be recorded on the appropriate case report form (CRF) page. If a subject withdraws during pre-screening period, the reason for withdrawal must be recorded in patient medical documentation.

Subject who does not qualify for the study based on the assessments during pre-screening and screening period or who withdraws from the study before the randomization visit will be replaced to achieve target number of randomized patients (forty). Subjects who withdraw from the study after receiving one dose of Pegasys® will not be replaced.

## Duration of Study Participation

Subjects will undergo an one week pre-screening period which starts one week (7 days) before the Screening visit with signing of the Informed Consent to undergo the assessments defined in the protocol as pre-screening, and ends at the date of Screening Visit which is the date of signing of Informed Consent to participate in the study.

Each subject will then undergo a two week (14 days) screening period which starts at the date of Screening Visit which is the date of signing of Informed Consent to participate in the study and ends at the date of study visit 3 or withdrawal.

Each subject then enters into the pre-treatment period which starts at the date of study Visit 3 and ends at the date of Randomization at study Visit 8.

See also Section 18 “Selection and Timing of Dose for each Subject” for the allowed visit window extension.

The total duration of this study for each subject is a maximum 2.5 years or 123 weeks (3 years or 147 weeks in the case of control group patients who crossover to REP 2139-Mg / REP 2165-Mg). This duration consists of 1 week of pre-screening, 2 weeks of screening, 24 weeks of pre-treatment and 48 (or 72) weeks of treatment plus 48 weeks post-treatment follow-up.

Day 1 of the conduction of this study is the day the first patient is enrolled. All patients should be recruited in a timeline of 3 months which can be extended to accommodate recruitment of all patients. The last day of this study is the day the last patient finishes his follow-up (End of Study).

The overall study schema is described by a study flowchart in Figure 1.

### **Randomization**

Patients who meet all eligibility criteria will be randomized to study treatment at study Visit 8. The investigator is not allowed to grant any exceptions.

### **Blinding/Unblinding**

Not applicable.

## **16. STUDY ENDPOINTS**

### **Primary Endpoints**

The primary endpoints, determined at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and at week 48 post-treatment follow-up, is the safe completion the combination regimens of REP 2139-Mg, Viread® and Pegasys® and REP 2165-Mg and Viread® and Pegasys® as detailed in Fig 1:

- Proportion of subjects who develop treatment emergent cytopenic abnormalities: anemia, as defined by Hb < 10 g/dl, and/or neutropenia as defined by PMN < 1,000/μl, and/or thrombocytopenia as defined by platelets < 50,000/μl)
- Proportion of subjects who develop liver dysfunction (as defined by bilirubin > 2X ULN, chronic elevations in ALT or AST > 10X ULN >8 weeks in duration) by the end of treatment
- Proportion of subjects who develop renal impairment (as defined by serum creatinine > 1,5 mg/dl for > 4 weeks) by the end of treatment
- Proportion of subjects with AEs, SAEs, dose reductions, and discontinuations due to AEs through end treatment
- Proportion of subjects with treatment emergent laboratory abnormalities by toxicity grade

- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

An analysis of primary endpoints will be conducted after all subjects complete 48 weeks of NAP therapy, and 72 weeks (or 96 weeks) of all study and first post-treatment follow-up visit. An additional analysis will be conducted when all subjects complete the Week 48 post-treatment follow-up visit.

### **Key Secondary Endpoints**

Secondary endpoints will be determined at treatment week 49, 73 (or week 97) , first post-treatment follow-up visit and at week 48 post-treatment follow-up:

- Proportion of patients who achieve serum HBsAg < 50 IU/ml.
- Proportion of subjects who achieve anti-HBs titers above 10 mIU/ml
- Proportion of patients who suppress serum HBV DNA
- Proportion of subjects who maintain HBsAg and HBV DNA suppression during follow-up.
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

## **17. SELECTION OF SUBJECTS**

The goal is to randomize 40 subjects to one of the treatment arms described in Fig. 1, ensuring that the following characteristics are balanced between groups. The randomization will be stratified by:

- Serum HBsAg at screening: Group 1:  $\leq 5000$  IU / ml, Group 2:  $> 5000$  IU / ml
- Serum HBV DNA at screening: Group 1:  $\leq 10^5$  copies / ml, Group 2:  $> 10^5$  copies / ml
- Age: Group 1:  $\leq 40$  years old, Group 2:  $> 40$  years old

For entry into the study, the following criteria MUST be met.

### **Recruitment Methods**

Subjects will be recruited from those individuals, who are registered in the site database, spontaneously come to the individual study sites or who are referred by other physicians. Preliminary screening(pre-screening) performed will consist of a test to determine if patients have heavy metal intoxication, and tests to determine whether patients have an autoimmune hepatitis. Patients determined to not have heavy metal intoxication and autoimmune hepatitis will proceed to the screening process.

This is a multicenter study however subject recruitment will not be performed in a competitive manner. The site-specific number of patients to be randomized will be agreed and determined in the Investigator Clinical Trial Agreement.

### **Inclusion Criteria**

1. Signed Written Informed Consent

- Freely given informed consent for pre-screening to establish patient eligibility for the study must be obtained from subjects prior to any pre-screening assessment.
- Freely given informed consent for clinical trial participation including informed consent for any screening procedures conducted to establish patient eligibility for the study must be obtained from subjects prior to any screening procedure.

2. Males or females 18-55 years of age

3. HBsAg > 1000 IU / ml at screening

4. HBV DNA > 7000 copies / ml at screening

5. Seronegative for HIV, HCV, CMV (IgM) and HDV (anti-HDAg) as determined at screening visit

6. HBeAg negative, anti-HBe positive

7. Evidence of fibrosis at screening

8. Non cirrhotic: absence of advanced cirrhosis based on fibroscan evaluation at screening.

9. Willingness to utilize adequate contraception while being treated with REP 2139-Mg or REP 2165-Mg and for 6 months following the end of the treatment in the study

- Any woman of childbearing potential (WOCBP) who agrees to use an effective methods of birth control for the entire duration of the study.
- Sexually active men who agree to use an effective method of birth control if their partners are WOCBP for the entire duration of the study for 6 months following the end of treatment.

10. Body Mass Index (BMI)  $\geq 18$  kg/m<sup>2</sup> and  $\leq 30$ kg/m<sup>2</sup> at screening

11. Adequate venous access allowing weekly intravenous therapies and blood tests

**Exclusion Criteria**

1. Women with positive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG).
2. Breast-feeding women.
3. HBeAg positive as determined at screening visit
4. Positive HCV antibody, or HIV-1/HIV-2 or CMV antibody (IgM) or anti-HDV antibody test at screening
5. Evidence of chronic liver disease caused by diseases other than chronic HBV infection (such as but not limited to: severe NAFLD (nonalcoholic hepatic steatosis), Wilson's disease, hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, significant biliary disease, and toxin exposure).

## 6. Medical History and Concurrent Diseases

- a) Current evidence of or history of variceal hemorrhage, hepatic encephalopathy, or ascites requiring diuretics or paracentesis or evidence of any of these findings on physical examination performed at screening
- b) Documented or suspected HCC as evidenced by previously obtained imaging studies or liver biopsy.
- c) Current evidence of or history of pancreatitis
- d) Current evidence of or history of renal dialysis, including hemodialysis or peritoneal dialysis
- e) History of bone marrow or organ transplant (other than cornea or hair), including liver transplant, or therapy with an immunomodulatory agent, cytotoxic agent, or systemic corticosteroids within 2 months of screening
- f) Current or known history of cancer (except adequately treated in situ carcinoma of the cervix, or basal or squamous cell carcinoma of the skin) within 5 years prior to screening
- g) Subjects with clinically significant ECG abnormalities (indicative of arrhythmia, myocardial ischemia or other serious cardiovascular disorder) at the time of screening in the opinion of the investigator
- h) Active substance abuse, such as alcohol, or inhaled or injected drugs, as defined by Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), Diagnostic Criteria for Drug and Alcohol Abuse (see Appendix 1) within 12 months prior to screening.
- i) The use of illicit drugs within the past two years prior to screening.
- j) Prior or current history of cardiomyopathy or significant ischemic cardiac or cerebrovascular disease, including history of angina, myocardial infarction, or interventional procedure for coronary artery disease (including angioplasty, stent procedure, or cardiac bypass surgery)
- k) Confirmed uncontrolled hypertension (patients with screening systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg should be excluded unless discussed with Replicor Inc.)
- l) Presence of diabetes (controlled or uncontrolled).
- m) Prior or current history of clinically significant hemoglobinopathy or hemolytic anemia
- n) History of or evidence of hyperthyroidism at screening.
- o) Subjects with pre-existing ophthalmologic disorders considered clinically significant on eye exam during physical examination.
- p) Prior or current history of severe chronic obstructive pulmonary disease, interstitial lung disease or sarcoidosis
- q) History of immunologically mediated disease (including but not limited to, rheumatoid arthritis, inflammatory bowel disease, moderate to severe psoriasis [mild psoriasis is allowed], and systemic lupus erythematosus)
- r) History of or current severe psychiatric disease, especially untreated or unstable depression, psychotic disorder such as bipolar disease and history of hospitalization for suicidal ideation/attempt
- s) Active seizure disorder as defined by either untreated seizure disorder or continued seizure activity within the past year prior to screening despite treatment with anti-seizure medication



- t) Has, in the opinion of the investigator, any physical exam findings, laboratory abnormalities, or other medical, social, or psychosocial factors that may negatively impact compliance or subject's safety by participation in this study; this should include conditions which may affect hematologic parameters such as prior or current history of porphyria cutanea tarda and/or hemophilia
- u) Fibroscan and Fibromax showing current evidence advanced cirrhosis at screening or known history of decompensated cirrhosis based on radiologic criteria or biopsy results and clinical criteria
- v) Poor venous access making IV infusion too difficult
- w) Inability to provide informed consent
- x) Inability or unwillingness to provide weekly blood samples.
- y) Patients not willing to come every week to receive therapy or to give blood.

## 7. Physical and Laboratory Test Findings

- a) Evidence of significant heavy metal load in whole blood as determined at pre-screening visit.
  - b) Antinuclear antibody (ANA) titer  $\geq 1:640$ , and AMA or LKM-1 antibody positive as determined at pre-screening visit
  - c) Hemoglobin  $< 12.0$  g/dL (males),  $< 10.0$  g/dL (female) at screening
  - d) Platelet count  $< 90,000/\text{mm}^3$  as determined at screening visit
  - e) Creatinine clearance (CrCl) (as estimated by Cockcroft and Gault)  $\leq 50$  mL/min or confirmed creatinine persistently  $> 1.5$  mg/dl as determined at screening visit
  - f) Total serum bilirubin  $> 25 \mu\text{mol/L}$  as determined at screening visit.
  - g) INR  $\geq 2.0$  as determined at screening visit
  - h) PTT  $\geq 2.0 \times \text{ULN}$  as determined at screening visit
  - i) Serum albumin  $\leq 3.5$  g/dL (35 g/L) as determined at screening visit
  - j) ALT  $> 10 \times \text{ULN}$  as determined at screening visit
  - k) ANC  $\leq 1,500$  cells/ $\text{mm}^3$  as determined at screening visit
  - l) Diagnosed or suspected hepatocellular carcinoma as evidenced by screening alpha-fetoprotein (AFP) of  $\geq 100$  ng/mL. If AFP is  $\geq 50$  ng/mL and  $< 100$  ng/mL, absence of mass/findings suspicious for HCC must be demonstrated by ultrasound/CT/MRI within the screening period.
  - m) Diabetes mellitus as evidenced by HbA1C  $\geq 8.5\%$  at screening
  - n) QTc interval  $> 500$  msec.
8. Known hypersensitivity to drugs with a similar biochemical structure to REP 2139-Mg or REP 2165-Mg (e.g. other phosphorothioate oligonucleotides) or Pegasys® (e.g. other interferons), or Viread® (e.g. other nucleoside analog polymerase inhibitors such as entecavir).
9. Any other criteria or known contraindication that would exclude the subject from receiving REP 2139-Mg, REP 2165-Mg, Pegasys®, or Viread®.
10. Prisoners or subjects who are involuntarily incarcerated.
11. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
12. Employees, family members, or students of the investigator or clinical site
13. Individuals who participated in another clinical study of a medicinal product or medical device within 90 days of signing Informed Consent Form
14. Concomitant Treatments with any of the following medications:
- a) Any anticoagulant
  - b) Blood products within 30 days prior to study enrollment
  - c) Hematologic growth factors within 90 days prior to study enrollment

- d) Use of any investigational product within 1 year prior to study enrollment
- e) Systemic antibiotics, antifungals, or antivirals for treatment of active infection within 14 days of enrollment.
- f) Previous exposure to immunotherapy with 6 months prior to enrollment.

## **18. TREATMENTS**

All protocol-specified investigational and non-investigational medicinal products (IMP, NIMP) are considered study drugs.

In accordance with International Conference on Harmonization (ICH) / Good Clinical Practice (GCP) guidelines, investigators will ensure that:

- Investigational product deliveries are correctly received by a responsible person (e.g., a pharmacist or delegated research staff member).
- Investigational product deliveries are recorded.
- Investigational product is appropriately handled and stored.
- Investigational product is only dispensed to study subjects in accordance with the protocol.
- Any unused (including returned) investigational product is returned to Replicor or its authorized representative for destruction (or locally destroyed if such a written agreement with Replicor is reached in advance).

### **Study Treatments**

Replicor will provide study drugs labelled in accordance with applicable guidelines/regulations and with Annex 13 of the Good Manufacturing Practice (GMP) guide. Refer to Table 3 for more details on study treatments.

**Table 3. Study Drugs Description**

<b>Product Description and Dosage Form</b>	<b>Potency</b>	<b>Primary Packaging (Volume)/Label Type</b>	<b>Secondary Packaging (Qty)/Label Type</b>	<b>Appearance</b>	<b>Storage Conditions (per label)</b>
REP 2139-Mg (IMP)	250mg	4.2cc of 62.5 mg/ml in a 5cc borosilicate vial/ open label	Plastic bags containing 1vial (sufficient for one 250mg dose)	solution is clear and colorless to light yellow	Store at 4-30°C in the original package. Do not freeze or shake
REP 2165-Mg (IMP)	250mg	4.2cc of 62.5 mg/ml in a 5cc borosilicate vial/open label	Plastic bags containing 1vial (sufficient for one 250mg dose)	solution is clear and colorless to light yellow	Store at 4-30°C in the original package. Do not freeze or shake
Pegasys® (IMP)	180 µg/0.5 mL	0.5 mL pre-filled syringe/open label	Outer carton 1 syringe, open-label	Solution is clear and colorless to light yellow	Store at 2-8°C in the original package. Keep the prefilled syringes in the outer carton to protect from light. Do not freeze or shake.
			•		
Viread® (IMP)	300mg	Sealed plastic bottle containing 30 tablets/ open label	Outer carton, 1 bottle	Almond shaped, light blue, film-coated tablet	Store at <30°C in the original package to protect from light.

**Table 3. Study Drugs Description (continued)**

<b>Product Description and Dosage Form</b>	<b>Potency</b>	<b>Primary Packaging (Volume)/Label Type</b>	<b>Secondary Packaging (Qty)/Label Type</b>	<b>Appearance</b>	<b>Storage Conditions (per label)</b>
Bone Restore (NIMP)	Vitamin D3250 IU; Calcium - 175 mg; Magnesium - 75 mg; Zinc – 0.5 mg; Manganese – 0.25 mg; Silicon extract (herb) – 1.25 mg; Boron – 0.75 mg (per capsule)	Sealed plastic bottle containing 120 capsules		white capsule	Store at <25°C in the original package to protect from light.
Only Trace Minerals (NIMP)	Zinc - 20 mg; Copper - 2 mg; Manganese - 2 mg; Chromium - 400 mcg; Molybdenum - 250 mcg; Boron - 3 mg; Vanadyl sulfate - 3.75 mg (per capsule)	Sealed plastic bottle containing 90 capsules		white capsule	Store at <25°C in the original package to protect from light.
Magnesium Caps (NIMP)	Magnesium - 500 mg (per capsule)	Sealed plastic bottle containing 100 capsules		white capsule	Store at <25°C. In the original package to protect from light.
Vitamin D3 (NIMP)	5000 IU (per softgel)	Sealed plastic bottle containing 60 soft gels		pale yellow soft gel	<25°C in the original package to protect from light.

## **Investigational Product**

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, investigational products are: REP 2139-Mg, REP 2165-Mg, Pegasys®, and Viread®. For additional information on REP 2139-Mg or REP 2165-Mg, please refer to the REP 2139-Mg / REP 2165-MgIB. For additional information on Pegasys® or Viread®, please refer to their respective package inserts or Summary of Product Characteristics (SmPC)/reference labels.

## **Non-investigational Medicinal Products**

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational medicinal products are mineral / vitamin supplements as follows:

Bone Restore (by Life Extension Foundation)  
Magnesium (by Life Extension Foundation):  
Only Trace Minerals (by Life Extension Foundation)  
Vitamin D3 (by Life Extension Foundation)

For detailed information on these supplements please refer to their respective package inserts/instructions for use.

Unscheduled visits to replenish mineral supplements supply for patients can be arranged if needed.

## **Storage, Handling, Dispensing, Accountability of Study Drugs**

The sponsor will supply all study medication. The investigational product will be shipped to sites under temperature controlled conditions. The PI (or designee) will then confirm receipt of the supplies and will forward the temperature monitor as instructed. If there is a temperature deviation, the PI (or designee) will follow the procedures specified in the study manual.

All study drugs must be stored under conditions specified on their labels. The drug storage area at the clinic must be locked and have controlled access. The PI (or designee) should ensure that the study drug is stored in accordance with the environmental conditions as determined by Replicor Inc. in the Study Manual. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact Replicor Inc immediately. Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures,

reconstitution, and use of required processes (e.g., required diluents, administration sets). Please refer to Section 22 for information on study drug record retention and information below for destruction and return instructions.

### **Destruction of Study Drug**

For this study, the used study drugs (those supplied by Replicor Inc. or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxic or biologics)

On-site destruction is allowed provided the following minimal standards are met:

On-site disposal practices must not expose humans to risks from the drug.

On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drugs.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

### **Return of Study Drug**

All unused and/or partially used NAP therapies that were supplied by Replicor Inc. must be returned to Replicor Inc. The return of NAP therapies will be arranged by the responsible Study Monitor.

### **Selection and Timing of Dose for Each Subject.**

The pre-treatment assessment for this study is 3 weeks. This period will include a Pre-screening Visit (one week) to exclude heavy metal intoxication and autoimmune hepatitis and Screening Visit to perform screening assessment and may include unscheduled visits to perform re-testing, if required for safety reasons. In case of delays in processing of the pre-screening samples, the Screening Visit assessments should start after the pre-screening testing results are available with the less invasive procedure. In this case visit window between Pre-Screening and Screening Visit can be extended until Pre-Screening testing results and their assessment completed.

Eligible subjects should start dosing within at least 2 weeks of the date of Screening Visit, but this interval can be extended if required to 4 weeks if tests results required to confirm patient exclusion are delayed.

At Visit 3 after all procedures have been performed, eligible subjects will start Viread® treatment. Subjects will be dosed as follows:

1. All patients will receive 24 weeks of daily Viread® therapy (300mg qD).
2. After 24 weeks of Viread®, at Visit 8 patients will be randomized to receive the following therapy in addition to their continuing Viread®:
  - a. 24 weeks of Pegasys® (180ug qW)
  - b. 48 weeks of Pegasys®(180ug qW) + REP 2139-Mg (250mg qW) or
  - c. 48 weeks of Pegasys® (180ug qW) + REP 2165-Mg (250mg qW) or
3. Patients receiving (2a) above are eligible to crossover to (2b) or (2c) if they do not experience a > 3 log reduction in serum HBsAg (as measured at Visit 28) relative to baseline (established at Screening Visit 2) during their (2a) therapy.

When REP 2139-Mg or REP 2165-Mg are being dosed with Pegasys®, the Pegasys® injection should be administered after the infusion of REP 2139-Mg or REP 2165-Mg is completed.

If a subject cannot appear for a scheduled study visit, the patient will be called and a new visit will be arranged as soon as possible. If a new visit cannot be arranged within the previous 3 days before or next 3 days after the scheduled visit, the medication dose will be omitted and continued at the next scheduled study visit. Unscheduled visits to perform re-testing can be arranged, if required for safety reasons.

## Dose Modifications

Dose modifications refer to dose adjustments necessary for the management of REP 2139-Mg or REP 2165-Mg, Pegasys®, and SAEs. Investigators are encouraged to follow Tables 1, 2, and 3, respectively. These tables are based on recommendations from the Pegasys® and Viread® package inserts, and the REP 2139-Ca clinical data in HBV-infected subjects, and have been modified as necessary for this study.

Dose modification decisions should be based on central laboratory results when possible. Dose adjustment should be done at visit when laboratory samples were collected or at the next scheduled visit. Dose modifications may occur for medical reasons, and when done contrary to the instruction below lead to deviations of the study protocol. In this case Replicor and the principal investigator should be informed and the patient should receive further treatment and regular check ups. The following examinations should be continuously documented.

**Table 4: Dose Reductions of REP 2139-Mg / REP 2165-Mg, Pegasys® and Viread®**

Assigned Treatment	Starting Dose	1st Dose Reduction	2nd Dose Reduction
REP 2139-Mg	250 mg	200 mg	150 mg
REP 2165-Mg	250 mg	200 mg	150 mg
Pegasys®	180 µg	135 µg	90 µg
Viread®	300 mg	--	--



**Table 5: REP 2139-Mg / REP 2165-Mg, Pegasys® and Viread® Dose Modification Guidelines**

Toxicity	Dose Modifications	Additional Instructions
<b>Adverse Events (see appendix 2)</b>		
<p>≥ Grade 3 AE considered related to study drug and clinically significant excluding ALT, AST and platelet abnormalities. For ALT, AST, bilirubin, ANC and platelet abnormalities the dose reductions are specified below.</p>	<p>Hold dose until ≤ Grade 1 or baseline value, and then restart Pegasys® and/or NAP at 1st dose reduction level (in some cases restarts at the 2nd reduction level may be needed)restart Viread ® .</p>	<p>Following improvement of the adverse reaction, dose increases to or toward the starting dose may be considered and agreed with Principal Investigator.</p> <p>Permanently discontinue and enter patient into early follow-up if either of the following is true:</p> <p>1) Event occurs or recurs when subject is receiving Pegasys® at the 2nd dose reduction level;</p> <p>2) Event is not resolving within 14 days of the date that treatment was held (no more than 4 continuous weeks of dosing can be held).</p>
<b>Hematological Abnormalities:</b>		
<b>ANC</b>		
≥750/mm <sup>3</sup>	Maintain the starting dose	
≥ 500 to < 750/ mm <sup>3</sup>	Reduce Pegasys® to 1st dose reduction level (in some cases restarts at the 2nd reduction level may be needed)	<p>Following improvement of the ANC value, dose increases to or toward the starting dose may be considered as agreed to by the Principal Investigator.</p> <p>Permanently discontinue with early entry into follow-up if event persists for 4 weeks when subject is receiving Pegasys® at the 2nd dose reduction level.</p>
< 500/ mm <sup>3</sup>	Hold dose until ANC > 1,000/mm <sup>3</sup> , and then restart Pegasys® treatment initially at the 2nd dose reduction level.	<p>Following improvement of the ANC value, dose increases to or toward the starting dose may be considered as agreed to by Principal Investigator.</p> <p>Permanently discontinue with early entry into follow-up and consult medical monitor if either of the following is true:</p> <p>1) Event persists for 4 weeks when subject is receiving Pegasys® at the 2nd</p>

		dose reduction level; 2) Event is not resolving within 14 days of the date that treatment was held (no more than 4 sequential doses can be held).
<b>Platelets</b>		
$\geq 100,000/\text{mm}^3$	Maintain the starting dose	
$\geq 80,000/\text{mm}^3$ to $< 100,000/\text{mm}^3$	Reduce Pegasys® to 1st dose reduction level.	In such cases following the normalization of platelet counts $\geq 100,000/\text{mm}^3$ , restore the dose to the starting dose.
$\geq 50,000/\text{mm}^3$ to $< 80,000/\text{mm}^3$	Reduce Pegasys® to 2nd dose reduction level.	In such cases following the normalization of platelet counts, re-escalate the dose as follows:  $\geq 100,000/\text{mm}^3$ – to 1st reduction level $\geq 150,000/\text{mm}^3$ - to the starting dose
$\geq 25,000$ to $< 50,000/\text{mm}^3$	Hold Pegasys® and reduce REP 2139-Mg / REP 2165-Mg to 2nd dose reduction level.	In such cases following the normalization of platelet counts, re-escalate the dose of Pegasys® as follows:  $\geq 60,000/\text{mm}^3$ – restart at 2nd reduction level $\geq 100,000/\text{mm}^3$ – to 1st reduction level $\geq 150,000/\text{mm}^3$ - to the starting dose,  and REP 2139-Mg / REP 2165-Mg : - $\geq 60,000/\text{mm}^3$ – escalate to 1st reduction level $\geq 100,000/\text{mm}^3$ – escalate to the starting dose  Permanently discontinue with early entry into follow-up if event persists for 4 weeks when subject is receiving REP 2139-Mg / REP 2165-Mg at the 2nd dose reduction level.
$< 25,000/\text{mm}^3$	Permanently discontinue all treatment with early entry into follow-up.	

**Table 5: REP 2139-Mg / REP 2165-Mg, Pegasys® and Viread® Dose Modification Guidelines (continued)**

Toxicity	Dose Modifications	Additional Instructions
<b>Liver Abnormalities<sup>a</sup>:</b>		
<b>ALT or AST</b>		
> 10 x ULN for > 4 weeks, regardless of baseline value when bilirubin > 2 x ULN	Hold Pegasys® until ALT or AST $\leq 5$ x ULN or $\leq 3$ x baseline value, whichever comes first, and then restart Pegasys® at the 1st dose reduction level. If recurs, hold dose until ALT or AST $\leq 5$ x ULN or $\leq 3$ x baseline value, whichever comes first, and then restart Pegasys® at the 2nd dose reduction level.	Permanently discontinue with early entry into follow-up and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving Pegasys® at the 2nd dose reduction level; 2) Event is not resolving within 14 days of the date that treatment was held (no more than 4 sequential doses can be held); 3) There is evidence of liver decompensation.
> 5 x ULN and > 3 x baseline value for > 10 weeks when bilirubin > 2 x ULN	Hold Pegasys® until ALT or AST $\leq 5$ x ULN or $\leq 3$ x baseline value, whichever comes first, and then restart Pegasys® at the 1st dose reduction level. If recurs, hold dose until ALT or AST $\leq 5$ x ULN or $\leq 3$ x baseline value, whichever comes first, and then restart Pegasys® at the 2nd dose reduction level.	Permanently discontinue with early entry into follow-up and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving Pegasys® at the 2nd dose reduction level; 2) Event is not resolving within 14 days of the date that treatment was held (no more than 4 sequential doses can be held); 3) There is evidence of liver decompensation.
<b>Bilirubin</b>		
Total bilirubin > 2.5 x ULN and direct bilirubin > 3 x ULN, regardless of ALT values	Hold dose until total bilirubin $\leq 1.5$ x ULN and direct bilirubin $\leq 3$ x ULN, and then restart Pegasys® at the 1st dose reduction level. If recurs, hold dose until total bilirubin $\leq 1.5$ x ULN and direct bilirubin $\leq 3$ x ULN, and then restart Pegasys® at the 2nd dose reduction level	Permanently discontinue with early entry into follow-up and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving Pegasys® at the 2nd dose reduction level; 2) Event is not resolving within 14 days of the date that treatment was held (no more than 4 sequential doses can be held); 3) There is evidence of liver decompensation.

**Table 5: REP 2139-Mg / REP 2165-Mg, Pegasys® and Viread® Dose Modification Guidelines (continued)**

Toxicity	Dose Modifications	Additional Instructions
<b>Liver Abnormalities<sup>a</sup>:</b>		
<b>Child-Pugh score</b>		
≥ 6	Permanently discontinue Pegasys®.	

<sup>a</sup>When subjects have clinical jaundice or evidence of impairment of liver function which require dose modification, subjects must be monitored no less than weekly to ensure improvement and will also have a thorough clinical evaluation. Dose modification decisions should be based on Central Laboratory results.

Clinical jaundice is considered to be an important medical event for this study and should be reported as an SAE (see Section 20 for reporting details).

When subjects have clinical signs of liver abnormalities (e.g., jaundice), dose is to be held until liver laboratory results are known.

If subject meets drug discontinuation criteria, please contact Replicor to discuss the case, prior to discontinuation.

Subjects who meet criteria for treatment discontinuation based on impairment of liver function should also have a clinical work-up which includes consideration of the following:

- a) Serologies for hepatitis A, hepatitis B, hepatitis E, hepatitis delta, herpes simplex virus (HSV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV)
- b) Detailed medical history including concomitant medication use (including herbal or over-the counter medications), drug and alcohol intake
- c) Early consultation with a hepatologist should be considered (if not already being managed by a hepatologist)
- d) Imaging studies for a possible extrahepatic cholestasis (i.e., ultrasound)

Initial liver-related laboratory abnormalities should be confirmed in 3-5 days prior to the reporting of a potential drug induced liver injury (DILI) event and discussed with the sponsor. All confirmed occurrences of potential DILIs, meeting the defined criteria (see above), must be reported as SAEs (see Section 20 for reporting details). Subjects who meet criteria for DILI should be strongly considered for liver biopsy, provided clinical parameters do not contraindicate this.

**Table 5: REP 2139-Mg / REP 2165-Mg, Pegasys®, and Viread® Dose Modification Guidelines (continued)**

Toxicity	Dose Modifications	Additional Instructions
<b>Renal Impairment</b>		
<b>Creatinine Clearance</b>		
30-50 mL/min	Maintain the starting dose.	
30 mL/min	Reduce Pegasys® to 1st dose reduction until CrCl is $\geq 30$ mL/min, and then restart Pegasys® treatment at the starting dose	
<b>New Ocular Symptom(s):</b>		
New decrease or loss of vision or other clinical significant ocular sign or symptom	Interrupt all study treatments.	Complete eye examination must be performed by an ophthalmologist. Further management should be discussed with central medical monitor before restarting therapy.
<b>New or Worsening Neuropsychiatric Signs or Symptoms (including Depression):</b>		
Mild	No change	Evaluate weekly by visit or phone until symptoms improve.
Moderate	Reduce Pegasys® to 1st dose reduction level (in some cases, reduction to 2nd dose reduction level may be needed).	Evaluate weekly (with visit at least every other week). Consider psychiatric consultation if no improvement. If improved and stable for 4 weeks, may resume normal visit schedule (while continuing with reduced dosing).
Severe	Permanently discontinue Pegasys®	Psychiatric therapy necessary.

## **Dose Interruptions**

Should drug interruption/suspension be necessary for any laboratory abnormality or AE, the following rules must be applied, (dose interruptions due to lack of compliance that deviate from these rules should be discussed with Replicor Inc. to determine the proper course of action):

- No more than 4 sequential doses of REP 2139-Mg or REP 2165-Mg or Pegasys® or 28 doses of Viread® can be held, and if not reinitiated within these timeframes from the day of the interruption, the subject must discontinue all study drug treatment and enter follow-up.
- Subjects with new onset or worsening depression on study should be treated with antidepressants at the discretion of the investigator.
- Subjects with other neuropsychiatric disorders on study should be managed at the discretion of the investigator.
- Weekly monitoring of the laboratory abnormality or AE that led to interruption of study drug(s) is required until resolution or discontinuation of study drug(s).

## **Permitted Concomitant Treatment**

Acetaminophen should be the analgesic of choice but will not be permitted at doses higher than 3 g/day. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible and should be limited to an ibuprofen equivalent dose of  $\leq 1.8$  g/day. Acetaminophen and NSAIDs should not be taken simultaneously.

Additionally, the locally sourced folic acid / B complex vitamin supplement Benevion® is recommended for use as supportive therapy for thrombocytopenia and leucopenia. (see Appendix 3 for dosing guidance).

## **Prohibited and/or Restricted Treatments**

During the screening period, every effort should be made to adjust any concomitant medication of a subject that is prohibited or restricted during the course of the study. Further adjustments may be made once the patient is participating in the study, and/or after the subject has completed the treatment.

### Prohibited medications are:

- Any anticoagulant
- Blood products
- Investigational products not specified in this protocol.
- Medications with known or potential anti-HBV activity other than the assigned study treatment are prohibited during the on-treatment period. These medications should not be used in the post-treatment period unless approved by Replicor.
- Long-term treatment ( $\geq 2$  weeks) with agents that are immunosuppressive or have a high risk for nephrotoxicity or hepatotoxicity.
- Any prescription or herbal product which is not prescribed by the investigator or licensed physician for treatment of a specific clinical condition

### Other Restrictions and Precautions:

If the subject is on chronic medications, a consistent dosing schedule is recommended for the duration of this study when medically possible.

Subjects receiving theophylline therapy should undergo frequent monitoring of serum theophylline levels due to the identified increase in theophylline levels with Peginterferon  $\alpha$ -2a.

### **Rescue Medication**

Not applicable

### **Treatment Compliance**

All investigational drug products, except Viread® and mineral supplements, used in this protocol will be administered under supervision.

Treatment compliance will be checked at regular intervals.

Refer to the study manual for guidance on treatment compliance check.

Subjects will be encouraged to comply with the Viread® and mineral supplementation regimen. If a subject misplaces the provided mineral supplementation, the study center may replace the misplaced ones.

### **Discontinuation of Subjects from Treatment**

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- a) Withdrawal of informed consent (subject's decision to withdraw for any reason)
- b) Any clinical AE, abnormal laboratory test results or inter-current illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- c) Termination of the study by competent local authorities, Replicor Inc. or the Principal Investigator
- d) Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- e) Use of an investigational product other than study medication
- f) Subjects who appear to have no reduction in serum HBsAg relative to pre-treatment levels at the end of 24 weeks of therapy with REP 2139-Mg or 2165-Mg.
- g) Evidence of confirmed hepatic decompensation
- h) ALT > 2 x baseline and 10x ULN and total bilirubin > 2 x ULN for > 12 weeks,
- i) Platelets < 25,000/mm<sup>3</sup>
- j) Any Grade 4 AE considered REP 2139-Mg or REP 2165-Mg related

- k) Severe neuropsychiatric signs and symptoms (including depression) for both new and worsening events that are considered clinically significant by the investigator.
- l) Criteria for potential drug-induced liver injury (pDILI): initial liver-related laboratory abnormalities should be confirmed in 3-5 days prior to the reporting of a potential DILI event and discussed with Replicor Inc. All confirmed occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 20 for reporting details). Potential DILI is defined as concurrent:

$ALT \geq 5 \times$  baseline or nadir value, whichever is lower for  $> 12$  weeks

**AND**

$ALT \geq 10 \times$  ULN for  $> 12$  weeks

**AND**

Total bilirubin  $\geq 2 \times$  ULN

**AND**

No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including but not limited to, acute viral hepatitis, cholestasis, pre-existing hepatic disease excluding HBV, or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

Subjects who meet the pDILI criteria should discontinue study treatment (all drugs). If a subject meets drug discontinuation criteria, please contact Replicor to discuss the case, prior to discontinuation. For subjects who meet criteria for discontinuation based on liver abnormalities, it is strongly recommended that the following evaluations be performed:

- a) Imaging studies for a possible extrahepatic cholestasis (i.e., ultrasound)
- b) When etiology remains unclear, liver biopsy (if clinically feasible).

If discontinuation of therapy is required, this must occur no later than the next study visit. The principal or co-investigator will decide for treatment discontinuation and the patient will be informed in his next study visit.

It is expected that all subjects who are on study will complete the protocol-defined durations for treatment and follow-up. However, if alternative HBV therapy is initiated in the post-treatment period for any reason, subject must withdraw from the study once the post-treatment Week 4 visit has occurred.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined above. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

### **Retained Samples for Bioavailability/Bioequivalence**



Not applicable.

## **19. STUDY ASSESSMENTS AND PROCEDURES**

The various assessments that will be conducted during the study are described in this section.

**Table 6.1 Schedule of Assessments and Procedures:  
Pre-screening, Screening and Pre-treatment period for all groups**

VISIT	Visit1, 1 week Pre- Screening	Visit2, 2-week Screening	Visit3	Visit4	Visit5	Visit6	Visit 7
STUDY WEEK (Wk)	Wk -1	Wk 1	Wk3	Wk10	Wk18	Wk22	Wk26
Informed Consent	X	X					
Review of Inclusion/Exclusion Criteria	X	X					
Demography	X						
Historical HBV test results		X					
Medical History	X						
Review of Adverse Events		X	X	X	X	X	X
Review of prior / current Concomitant Medication		X	X	X	X	X	X
Vital Signs <sup>a</sup>		X	X	X	X	X	X
Height	X	X					
Weight	X	X	X	X	X	X	X
ECG <sup>b</sup>		X					
Ultrasound <sup>c</sup>		X					
Physical Exam		X <sup>d</sup>	X	X	X	X	X
Serum Pregnancy Test (females only)		X					X <sup>e</sup>
Urine Pregnancy test (females only) <sup>f</sup>				X	X	X	
Urinalysis <sup>g</sup>		X	X	X	X	X	X
Virology sample collection		X <sup>h</sup>	X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		X <sup>i</sup>
Fibroscan / Fibromax		X					
Chemistry sample collection	X <sup>j</sup>	X <sup>g</sup>					
Hematology sample collection <sup>g</sup>		X					
Coagulation profile <sup>g</sup>		X					
Thyroid function tests sample collection <sup>k</sup>		X					
AFP (Alfa fetoprotein) sample collection, HCC Assessment <sup>l</sup>		X					
Immunology Sample Collection <sup>m</sup>	X						
Frozen serum (4 X 1 cc aliquots) collected		X	X				X
Viread Dispensing			X	X	X	X	X
Verification of Viread Compliance				X	X	X	X
Mineral Supplementation Dispensing						X	

**NOTES:**

<sup>a</sup> Seated BP, axillary temperature, HR, RR

<sup>b</sup> ECG while the subject is resting in a supine position, after the subject has been supine for at least 5 minutes.

<sup>c</sup> Ultrasound evaluations will include thyroid gland and abdomen.

<sup>d</sup>Physical exam at Screening should include eye exam as described below in the “Method and Timing of Assessments”

<sup>e</sup> Serum pregnancy test should be done 24 hours before start of Treatment Period of the study.

<sup>f</sup>Urine pregnancy test will be done and read at the site before study drug administration.

<sup>g</sup>Refer to the Study Laboratory Manual for the details of lab tests scheduled for each visit. The full list of the lab tests to be performed throughout the study can be found in the section “Method and Timing of Assessments” below.

<sup>h</sup>HBV DNA, HBsAg, anti-HBs, HBeAg, anti-HBeAg, anti-HDAg, anti-HIV 1+2, anti-CMV, anti-HCV

<sup>i</sup>HBV DNA, HBsAg, anti-Hbs

<sup>j</sup>Whole blood toxicities including cadmium, lead, mercury. The results will be retained in patient medical records. If patient is eligible for the study, these results will be captured in the CRF.

<sup>k</sup>Thyroid function tests include, total T3, total T4, TSH; reflex to anti-TPO, if results are abnormal

<sup>l</sup> If AFP is  $\geq 50\text{ng/mL}$  and  $\leq 100\text{ng/mL}$ , absence of mass/findings suspicious for HCC must be demonstrated by ultrasound/CT/MRI

<sup>m</sup> Immunology panel at pre-screening includes ANA, AMA, and LKM1. AMA, LKM1 results will be retained in patient records in order to confirm absence of immune hepatitis. If a patient eligible for the study, these results will be captured in the CRF.

**Table 6.2 Schedule of Assessments and Procedures: Treatment Period**  
**Experimental Group NAP Treatment plus Pegasys® plus Viread®**

VISIT	Visit 8 Rz	Visit 9, 13, 17, 21, 25, 29, 33 37,41,45, 49,53	Visit 10 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54	Visit 11, 15, 19, 23,27, 31, 35, 39,43, 47, 51	Visit 12, 28, 36, 52	Visit 16, 24, 40, 48	Visit 20, 44	Visit 32	Visit55 EOT
STUDY WEEK (Wk)	Wk27	Wk 28, 32, 36, 40, 44, 48, 52, 56,60,64, 68,72	Wk 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73	Wk 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70	Wk 31, 47, 55, 71	Wk 35, 43, 59, 67	Wk 39, 63	Wk 51	Wk 74
Review of Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Vital Signs (prior to administration of treatment) <sup>a</sup>	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Physical Exam	X <sup>b</sup>	X	X	X <sup>b</sup>	X	X	X	X <sup>b</sup>	X <sup>b</sup>
ECG <sup>c</sup>	X					X		X	X
Ultrasound <sup>d</sup>	X						X	X	X
Urine Pregnancy test (females only) <sup>e</sup>				X					X
Urinalysis <sup>f</sup>	X		X		X	X	X	X	X
Virology sample collection	X <sup>g</sup>				X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>i</sup>
Fibroscan / Fibromax									X
Chemistry samples collection <sup>f</sup>	X	X	X	X	X	X	X	X	X
Hematology sample collection <sup>f</sup>	X		X		X	X	X	X	X
Coagulation profile <sup>f</sup>	X		X		X	X	X	X	X
Thyroid function tests sample collection <sup>j</sup>	X						X	X	X
AFP (Alfa fetoprotein) sample collection, HCC Assessment									X
Immunology (ANA) Sample Collection									X
Frozen serum (4 X 1 cc aliquots) collected	X				X	X	X	X	X
Viread Administration	X	X	X	X	X	X	X	X	X
NAP Therapy (REP 2139-Mg or REP 2165-Mg) administration	X	X	X	X	X	X	X	X	X

**Table 6.2 Schedule of Assessments and Procedures: Treatment Period**  
**Experimental Group NAP Treatment plus Pegasys® plus Viread® (continued)**

VISIT	Visit 8 Rz	Visit 9, 13, 17, 21, 25, 29, 33 37,41,45, 49,53	Visit 10 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54	Visit 11, 15, 19, 23,27, 31, 35, 39,43, 47, 51	Visit 12, 28, 36, 52	Visit 16, 24, 40, 48	Visit 20, 44	Visit 32	Visit55 EOT
STUDY WEEK (Wk)	Wk27	Wk 28, 32, 36, 40, 44, 48, 52, 56,60,64, 68,72	Wk 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73	Wk 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70	Wk 31, 47, 55, 71	Wk 35, 43, 59, 67	Wk 39, 63	Wk 51	Wk 74
Record of Symptoms during NAP therapy administration	X	X	X	X	X	X	X	X	X
Blood Pressure (post NAP therapy infusion)	X	X	X	X	X	X	X	X	X
Pegasys administration	X	X	X	X	X	X	X	X	X
Viread Dispensing	X							X	
Verification of Viread Compliance	X	X	X	X	X	X	X	X	X
Mineral Supplementation Dispensing	X							X	

**NOTES:**

<sup>a</sup>Seated BP, axillary temperature, HR, RR

<sup>b</sup>Physical exam should include eye exam as described below in the “Method and Timing of Assessments”

<sup>c</sup>ECG while the subject is resting in a supine position, after the subject has been supine for at least 5 minutes.

<sup>d</sup> Ultrasound evaluations will include thyroid gland and abdomen.

<sup>e</sup> Urine pregnancy test will be done and read at the site before study drug administration.

<sup>f</sup>Refer to the Study Laboratory Manual for the details of lab tests scheduled for each visit. The full list of the lab tests to performed throughout the study can be found in the section “Method and Timing of Assessments” below.

<sup>g</sup>HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg

<sup>h</sup>HBV DNA, HBsAg, anti-Hbs

<sup>i</sup>HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg, anti-HDAg

<sup>j</sup>Thyroid function tests include, total T3, total T4, TSH; reflex to anti-TPO, if results are abnormal

**Table 6.3 Schedule of Assessments and Procedures: Treatment Period**  
**No Cross-Over Control Group Pegasys® plus Viread®**

VISIT	Visit 8 Rz	Visit 9,13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53	Visit 10 14,18, 22 26,30, 34, 38, 42, 46, 50, 54	Visit 11, 15,19, 23, 27, 31, 35, 39, 43, 47, 51	Visit 12, 28, 36, 52	Visits 16, 24, 40, 48	Visit 20, 44	Visit 32	Visit 55 EOT
STUDY WEEK (Wk)	Wk 27	Wk 28, 32, 36, 40, 44, 48, 52, 60, 64, 68, 72	Wk 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73	Wk 30,34, 38, 42,46, 50, 54, 58, 62, 66, 70	Wk 31, 47, 55, 71	Wk 35,43, 59, 67	Wk 39, 63	Wk 51	Wk 74
Review of Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Vital Signs (prior to administration of treatment) <sup>a</sup>	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Physical Exam	X <sup>b</sup>	X	X	X <sup>b</sup>	X	X	X	X <sup>b</sup>	X <sup>b</sup>
ECG <sup>c</sup>	X					X		X	X
Ultrasound <sup>d</sup>	X						X	X	X
Urine Pregnancy test (females only) <sup>e</sup>				X					X
Urinalysis <sup>f</sup>	X		X		X	X	X	X	X
Virology sample collection	X <sup>g</sup>				X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>h</sup>
Fibroscan / Fibromax									X
Chemistry samples collection <sup>f</sup>	X	X	X	X	X	X	X	X	X
Hematology sample collection <sup>f</sup>	X		X		X	X	X	X	X
Coagulation profile <sup>f</sup>	X		X		X	X	X	X	X
Thyroid function tests sample collection <sup>i</sup>	X						X	X	X
AFP (Alfa fetoprotein) sample collection, HCC Assessment									X
Immunology (ANA) Sample Collection									X

**Table 6.3 Schedule of Assessments and Procedures: Treatment Period  
No Cross-Over Control Group Pegasys® plus Viread® (continued)**

VISIT	Visit 8 Rz	Visit 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53	Visit 10 14,18, 22, 26, 30, 34, 38, 42, 46, 50, 54	Visit 11, 15,19, 23,27, 31, 35, 39, 43, 47, 51	Visit 12, 28, 36, 52	Visits 16, 24, 40, 48	Visit 20, 44	Visit 32	Visit 55 EOT
STUDY WEEK (Wk)	Wk 27	Wk 28, 32, 36, 40, 44, 48, 52, 60, 64, 68, 72	Wk 29, 33, 37, 41,45, 49, 53, 57, 61, 65, 69, 73	Wk 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70	Wk 31, 47, 55, 71	Wk 35,43, 59, 67	Wk 39, 63	Wk 51	Wk 74
Frozen serum (4 X 1 cc aliquots) collected	X				X	X	X	X	X
Viread Administration	X	X	X	X	X	X	X	X	X
Pegasys administration	X	X	X	X	X	X	X	X	X
Viread Dispensing	X							X	
Verification of Viread Compliance	X	X	X	X	X	X	X	X	X
Mineral Supplementation Dispensing	X							X	

**NOTES:**

<sup>a</sup> Seated BP, axillary temperature, HR, RR

<sup>b</sup> Physical exam should include eye exam as described below in the “Method and Timing of Assessments”

<sup>c</sup> ECG while the subject is resting in a supine position, after the subject has been supine for at least 5 minutes.

<sup>d</sup> Ultrasound evaluations will include thyroid gland and abdomen.

<sup>e</sup> Urine pregnancy test will be done and read at the site before study drug administration.

<sup>f</sup> Refer to the Study Laboratory Manual for the details of lab tests scheduled for each visit. The full list of the lab tests to performed throughout the study can be found in the section “Method and Timing of Assessments” below.

<sup>g</sup> HBV DNA, HBsAg, anti-Hbs,

<sup>h</sup> HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg, anti-HDAg

<sup>i</sup> Thyroid function tests include total T3, total T4, TSH; reflex to anti-TPO, if the results are abnormal

**Table 6.4 Schedule of Assessments and Procedures: Treatment Period  
Cross-Over in the Control Group Pegasys® plus Viread®**

VISIT	Visit 32	Visit 33, 37, 41, 45, 49, 53, 57 61, 65, 69, 73, 77	Visit 34 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78	Visit 35, 39, 43, 47, 51, 55, 59, 63, 67, 71, 75	Visit 36, 52, 60, 76	Visit 40, 48, 64, 72	Visit 44, 68	Visit 56	Visit 79 EOT
STUDY WEEK (Wk)	Wk 51	Wk 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96	Wk 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97	Wk 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94	Wk 55, 71, 79, 83, 91, 95	Wk 59, 67	Wk 63, 87	Wk 75	Wk 98
Review of Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Vital Signs (prior to administration of treatment) <sup>a</sup>	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Physical Exam	X <sup>b</sup>	X	X	X <sup>b</sup>	X	X	X	X <sup>b</sup>	X <sup>b</sup>
ECG <sup>c</sup>	X					X		X	X
Ultrasound <sup>d</sup>	X						X	X	X
Urine Pregnancy test (females only) <sup>e</sup>				X					X
Urinalysis <sup>f</sup>	X		X		X	X	X	X	X
Virology sample collection	X <sup>g</sup>				X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>i</sup>
Fibroscan / Fibromax	X								X
Chemistry samples collection <sup>f</sup>	X	X	X	X	X	X	X	X	X
Hematology sample collection <sup>f</sup>	X		X		X	X	X	X	X
Coagulation profile <sup>f</sup>	X		X		X	X	X	X	X
Thyroid function tests sample collection <sup>j</sup>	X						X	X	X
AFP (Alfa fetoprotein) sample collection, HCC Assessment									X
Immunology (ANA) Sample Collection									X
Frozen serum (4 X 1 cc aliquots) collected	X				X	X	X	X	X
Viread Administration	X	X	X	X	X	X	X	X	X
NAP Therapy (REP 2139-Mg or REP 2165-Mg) administration	X	X	X	X	X	X	X	X	X



**Table 6.4 Schedule of Assessments and Procedures: Treatment Period  
Cross-Over in the Control Group Pegasys® plus Viread® (continued)**

VISIT	Visit 32	Visit 33, 37, 41, 45, 49, 53, 57 61, 65, 69, 73, 77	Visit 34 38, 42, 46, 60, 64, 58, 62, 66, 70, 74, 78	Visit 35, 39, 43, 47, 51, 55, 59, 63, 67, 71, 75	Visit 36, 44, 60, 76	Visit 40, 48, 64, 72	Visit 44, 68	Visit 56	Visit 79 EOT
STUDY WEEK (Wk)	Wk 51	Wk 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96	Wk 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97	Wk 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94	Wk 55, 71, 79, 95, 83, 91	Wk 59, 67	Wk 63, 87	Wk 75	Wk 98
Record of Symptoms during NAP therapy administration	X	X	X	X	X	X	X	X	X
Blood Pressure (post NAP therapy infusion)	X	X	X	X	X	X	X	X	X
Pegasys administration	X	X	X	X	X	X	X	X	X
Viread Dispensing								X	
Verification of Viread Compliance		X	X	X	X	X	X	X	X
Mineral Supplementation Dispensing								X	

**NOTES:**

<sup>a</sup> Seated BP, axillary temperature, HR, RR

<sup>b</sup> Physical exam should include eye exam as described below in the “Method and Timing of Assessments”

<sup>c</sup> ECG while the subject is resting in a supine position, after the subject has been supine for at least 5 minutes.

<sup>d</sup> Ultrasound evaluations will include thyroid gland and abdomen.

<sup>e</sup> Urine pregnancy test will be done and read at the site before study drug administration.

<sup>f</sup> Refer to the Study Laboratory Manual for the details of lab tests scheduled for each visit. The full list of the lab tests to be performed throughout the study can be found in the section “Method and Timing of Assessments” below.

<sup>g</sup> HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg

<sup>h</sup> HBV DNA, HBsAg, anti-Hbs

<sup>i</sup> HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg, anti-HDAg

<sup>j</sup> Thyroid function tests include total T3, total T4, TSH, reflex to anti-TPO, if the results are abnormal

**Table 6.5 Schedule of Assessments and Procedures:  
Follow-Up Period for all groups\***

Follow-Up Week (FW)		FW4	FW12	FW24	FW48
Experimental NAP Therapy plus Pegasys plus Viread / Control no cross-over Pegasys plus Viread )	VISIT	Visit 56	Visit 57	Visit 58	Visit 59 EOS
	STUDY WEEK (Wk)	Wk 78	Wk 86	Wk 98	Wk 122
Control cross-over Pegasys plus Viread	VISIT	Visit 80	Visit 81	Visit 82	Visit 83 EOS
	STUDY WEEK (Wk)	Wk 102	Wk 110	Wk 122	Wk 148
Review of Adverse Events		X	X	X	X
Review of prior / current Concomitant Medication		X	X	X	X
Vital Signs <sup>a</sup>		X	X	X	X
Weight		X	X	X	X
Physical Exam		X	X	X	X
ECG <sup>b</sup>		X	X	X	
Ultrasound <sup>c</sup>				X	
Urine Pregnancy test (females only) <sup>d</sup>		X	X	X	
Urinalysis <sup>e</sup>		X	X	X	
Virology sample collection		X <sup>f</sup>	X <sup>f</sup>	X <sup>g</sup>	X <sup>g</sup>
Fibroscan / Fibromax				X	X
Chemistry sample collection <sup>e</sup>		X	X	X	X
Hematology sample collection <sup>e</sup>		X	X	X	
Coagulation profile <sup>e</sup>		X	X	X	
AFP (Alfa fetoprotein) sample collection, HCC Assessment <sup>h</sup>				X	
Immunology (ANA) Sample Collection				X	
Frozen serum (4 X 1 cc aliquots) collected		X	X	X	X

**\*Any treated patient who is discontinued from the study after randomization for AEs or for safety reasons should be followed-up according to this schedule.**

<sup>a</sup> Seated BP, axillary temperature, HR, RR

<sup>b</sup> ECG while the subject is resting in a supine position, after the subject has been supine for at least 5 minutes.

<sup>c</sup> Ultrasound evaluations will include abdomen only.

<sup>d</sup> Urine pregnancy test will be done and read at the site before study drug administration.

<sup>e</sup> Refer to the Study Laboratory Manual for the details of lab tests scheduled for each visit. The full list of the lab tests to be performed throughout the study can be found in the section "Method and Timing of Assessments" below.

<sup>f</sup> HBV DNA, HBsAg, anti-HBs

<sup>g</sup> HBV DNA, HBsAg, anti-HBs, HBeAg, anti-HBeAg, anti-HDAg

<sup>h</sup> If AFP is  $\geq 50$  ng/mL and  $\leq 100$  ng/mL, absence of mass/findings suspicious for HCC must be demonstrated by ultrasound/CT/MRI

## **Methods and Timing of Assessments**

Subjects who are registered in the site database will be contacted by the investigators, spontaneously come to the individual study sites or who are referred by other physicians.

Subjects from site database, who were contacted by the investigators, spontaneously came to the study site or who were referred by other physicians will be provided with a written informed consent form to undergo pre-screening tests to be assessed for eligibility.

One-week preliminary screening (Pre-screening visit) performed during the pre-treatment period will consist of tests to determine if patients have heavy metal intoxication, and tests to determine whether patients have an autoimmune hepatitis. Patients determined to not have heavy metal intoxication and autoimmune hepatitis will proceed to the screening process (see eligibility criteria above).

At Screening visit subjects will be provided with a written informed consent form, given the opportunity to ask any questions concerning the study and will sign an informed consent form prior to participating in any study procedures. After giving written informed consent, subjects will undergo a required 2-week screening period to be assessed for eligibility.

Subjects who do not meet the inclusion/exclusion criteria will be considered screening failures and will not be eligible for the study.

Subjects that have met all inclusion/exclusion criteria after the 2-week screening period will enter the pre-treatment period at Visit 3, and will be randomly assigned one of the treatments at Visit 8.

Subjects who withdraw (for any reason) during the screening period without investigational product administration will be considered screening failures.

### **Historical HBV test results**

The historical HBV test results include the first test results when HBV had been detected in a subject, and the most recent prior to screening results from the subject history. In case the first test results when HBV had been detected in the subject are the most recent results, this should be recorded in the eCRF as such. The historical HBV results must be available for subject medical records at the screening visit.

### **Medical History**

A complete medical history including evaluation for past (up to 5 years) or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatological, psychiatric, genitourinary, obstetrical, surgical history or any other diseases or disorders will be performed at pre-screening.

All subjects must record the initial diagnosis of HBV as “chronic hepatitis B infection.” Any past or present symptoms of hepatitis should also be recorded (e.g., discomfort/pain etc.).

## **Adverse Events Assessments**

Subjects will be closely monitored throughout the study for AEs. Data evaluation for safety will proceed in real time as data become available. Adverse events will be recorded and subjects who discontinue assigned therapy early should proceed to all post-treatment follow-up visits. All study drug-related AEs must be followed until resolution or stabilization.

All subjects will have AEs recorded from the time of signature on the ICF at pre-screening until the final visit (FU Week 48). Any ongoing SAEs should be followed until stabilization or resolution.

An AE is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new inter-current illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to ICF signature as part of medical history and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. Symptoms and/or conditions related to hepatitis B (discomfort/pain, etc.) will not be captured as AEs for this study unless the severity increases from baseline, the characterization of the symptom changes from baseline, or meets the criteria of a SAE.

## **Prior Medications**

All prior medications within 30 day of the signature of the ICF should be recorded. All chronic hepatitis-related prior medications (including hepatoprotectors) should be recorded regardless of time.

## **Concomitant Medications**

All subjects will have concomitant medications and procedures recorded from the time of signature on the ICF until the final follow up visit (Week 122 or Week 146).

A complete list of all medications (prescription, OTC, nutritional, fiber supplements, etc.), dose, dosing regimen, and start and stop dates used prior to and during the study will be recorded. Refer to the Section 18 for a listing of permitted and prohibited concomitant medications.

## **Vital Signs**

Vital signs (seated blood pressure by standard sphygmomanometer reading, temperature, respiration rate and heart rate), weight at each visit from the time of signature on the ICF at pre-screening visit until the final follow up visit (FU Week 48) including any unscheduled visits. Seated or supine blood pressure will be also measured 5 minutes after the completion of each infusion of NAP therapy. Height measurement will be performed at pre-screening/screening only and weight measurement for calculation of BMI will be performed at each visit.

## **Electrocardiogram**

An ECG with a will be performed at study visits outlined above (or at the early termination visit) and if clinically indicated, at any unscheduled visits. The ECG performed while the subject is resting in a supine position will be recorded. The ECG should be recorded after the subject has been supine for at least 5 minutes.

The Investigator will examine the ECG for signs of cardiac disease that would exclude the subject from participating in the study at Screening. If the Investigator is uncertain about whether an ECG result finding excludes a subject, Replicor should be contacted to discuss the case prior to randomization.

All ECG tracings will be clearly identified with the subject's identity and the results retained as source data in the subject's notes.

In order to confirm that the ECG has been reviewed, the ECG report must be signed and dated by the Investigator (or designee).

## **Physical Examinations**

All subjects should be evaluated by qualified study site personnel, capable of making proper safety assessments based on the clinical history obtained from the patient at every visit and any unscheduled visit.

A full physical examination will be performed at the Screening visit, whereas a targeted physical exam will occur at Randomization and during on-treatment visits and the post-treatment visits. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms or concerns. Targeted physical exam includes assessment of heart, lung, and abdomen and eye exam. The eye exam is limited to:

1. No conjunctival inflammation (no red eye) on plain observation.
2. Evaluate normal eye movements following the finger.
3. Adequate bilateral pupil contraction when exposed to light.

## **Ultrasound**

At Screening visit, at the start, every three months and at the end of Pegasys® treatment ultrasound evaluations will include examination of thyroid gland and abdomen. Ultrasound will be performed at study visits outlined above (or at the early termination visit) and if clinically indicated, at any unscheduled visits.

The Investigator will obtain the ultrasound report signed and dated by qualified medical provider performed the ultrasound. If the Investigator is uncertain about whether an Ultrasound report finding excludes a subject, Replicor should be contacted to discuss the case prior to randomization and further during the study.

All Ultrasound reports will be clearly identified with the subject's identity and the results retained as source data in the subject's notes.

In order to confirm that the Ultrasound report has been reviewed, the Ultrasound report must be signed and dated by the Investigator (or designee).

### **Fibroscan**

Fibroscan for evaluation of liver stiffness will be at study visits outlined above (or at the early termination visit) and if clinically indicated, at any unscheduled visits.

The Investigator will obtain the Fibroscan report signed and dated by qualified medical provider performed the fibroscan. If the Investigator is uncertain about whether a Fibroscan report finding excludes a subject, Replicor should be contacted to discuss the case prior to randomization and further during the study.

All Fibroscan reports will be clearly identified with the subject's identity and the results retained as source data in the subject's notes.

In order to confirm that the Fibroscan report has been reviewed, the Fibroscan report must be signed and dated by the Investigator (or designee).

### **Pregnancy Testing**

All female subjects of child bearing potential who participate in the study will have a serum pregnancy test at Screening and at visit 7 and urine pregnancy test at all subsequent visits will be performed every 4 weeks. The serum pregnancy analysis will be done by the central lab, while the urine pregnancy tests will be performed and read by the study site. The subject may not receive investigational product until the investigator has verified that the results of these pregnancy tests are negative.

Any pregnancies that occur in women who have received study drug must be reported (see Section 20).

### **Laboratory Assessments**

The assessments listed below will be analyzed by a central laboratory except the urine pregnancy tests (performed and read by the study site). Only data for the procedures and assessments specified in this protocol should be either recorded on the laboratory pages of the case report form or by another mechanism as agreed upon between the investigator and Replicor Inc. (e.g., provided electronically). If the units of a test result differ from those provided on the CRF, the recorded laboratory values must specify the correct units. Additional procedures and assessments may be performed as part of the subject's standard medical care. All laboratory tests will be performed by a central laboratory

It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the reference ranges from the central laboratory. All clinically significant laboratory abnormalities are to be recorded as AEs on the AE eCRF (clinically significant laboratory abnormalities at screening will result in a subject being ineligible for the study and should not be captured as an AE). Any abnormal values that persist should be followed at the discretion of the Investigator.

The Investigator should file all copies of the reports, including faxes with the subject's medical chart.

## **Toxicity Laboratory Assessments**

Whole blood toxicities including cadmium, lead, and mercury will be performed at pre-screening visit.

## **Immunological Assessment**

At Pre-screening visit immunological profile will include anti-nuclear antibody (ANA), anti-mitochondrial antibodies (AMA) and anti-liver kidney microsomal antibodies<sup>1</sup> (LKM1) at Pre-screening visit. ANA testing will be also performed at the end of NAP treatment, end of all treatments in the study and at FU Week 24.

## **Hematology Laboratory Assessments**

Hematology laboratory including RBC count, hemoglobin, hematocrit, WBC count and differential (including ANC), Reticulocyte count, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Cell Distribution Width and platelet count Mean Platelet Volume, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils will be collected at the visits as outlined above (or at the early termination visit); and any Unscheduled visits (only if clinically indicated).

## **Chemistry Laboratory Assessments**

Serum chemistries sodium, potassium, chloride,  $\text{HCO}_3$ , phosphate, calcium, magnesium, 25OH Vitamin D3, blood urea nitrogen (BUN), urea, creatinine, glucose, HbA1c, albumin, globulin, total protein, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), Gamma- Glutamyl Transferase (GGT), uric acid, triglycerides (fasting), total cholesterol (fasting), HDL (fasting), LDL (fasting) will be collected at the visits outlined above (or at the early termination visit); and any Unscheduled visits (only if clinically indicated).

### Note regarding fasting

On those scheduled visits where lipid measurements are to be taken, patients are required to fast after dinner from the previous evening until completion of the blood test during the scheduled visit. Patients can and should be encouraged to eat before treatment after the blood has been withdrawn.

## **Fibromax**

FibroMAX® is the combination of up to five non-invasive liver tests: FibroTest® diagnoses hepatic fibrosis, ActiTest® assesses viral necro-inflammatory activity, SteatoTest® diagnoses hepatic steatosis (otherwise known as ‘fatty liver’) – the most common cause of ALT and GGT abnormalities, ActiTest® assesses viral necro-inflammatory activity, AshTest® diagnoses severe alcoholic steatohepatitis (ASH) in excessive drinkers, NashTest® diagnoses non-alcoholic steatohepatitis (NASH) and includes ten serum markers with the age, sex, height and weight of the patient: Alpha-2-macroglobulin, Haptoglobin, Apolipoprotein A1, GGT, total bilirubin, ALT, AST, total cholesterol, triglycerides, Blood glucose (fasting).

## **Thyroid Function Laboratory Assessments**

The thyroid function will be assessed by the following tests: serum thyroid-stimulating hormone (TSH) concentration, serum total thyroxine (T4) concentration and total

triiodothyronine (T3) concentration (reflex to anti-TPO if results are abnormal) at the start, every three month and at the end of Pegasys® treatment.

### **Coagulation Profile**

Coagulation profile including prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR) will be collected at the visits as outlined above (or at the early termination visit); and any Unscheduled visits (only if clinically indicated).

### **HCC Assessment**

Sampling for alpha-fetoprotein (AFP) will be performed at Screening, at the end of treatment visit and follow-up visit 24. If AFP is  $\geq 50$  ng/mL but  $< 100$  ng/mL at screening, absence of a mass must be demonstrated by US/CT/MRI imaging within the screening period.

### **Virology Assessments**

Serum virology will include anti-HIV 1+2, anti-CMV (IgG, IgM), anti-HCV performed at screening only and HBV DNA, HBsAg, anti-Hbs, HBeAg, anti-HBeAg, anti-HDAg at screening and at the visits as scheduled (or at the early termination visit); and any Unscheduled visit (only if clinically indicated).

### **Serum Frozen Sample**

At the visits outlined above the collected serum sample should be aliquoted into 4 (four) Eppendorf Safe Lock Tubes™, 1mL in each tube. Tubes should be frozen at -20°C to -25°C, and retained at the refrigerator with regular temperature monitoring. Additional information on frozen samples and their storage will be provided in the Lab Manual.

### **Urinalysis**

Urinalysis including specific gravity, pH, glucose, protein, ketones, nitrites, WBC and RBC will be performed at the visits as outlined above (or at the early termination visit); and any Unscheduled visits (only if clinically indicated). Microscopy will only be performed if any clinically significant abnormalities are observed in urinalysis.

### **Randomization and Administration of the Study Drugs**

At Study Week27 (Randomization, Visit 8) the clinical site will use the IWRS to randomize the study subject and obtain the treatment assignment for that subject. The IWRS will stratify automatically at randomization for age; serum HBsAg and serum HBV DNA to ensure balance between treatment groups based on the assessment results obtained from Screening. Prior to the randomization, subjects will have a subject number. They will be given their randomization number only after the screening assessments and pre-treatment period have been completed and it has been verified that the subject is still eligible to receive the one of the study treatments. The Study Manual should be referred for the details of the randomization procedure.

Each subject will start Viread® pre-treatment and will be instructed to intake Viread® in the proper method, including the dose, and will then intake their first dose in clinic. This will be documented (date and time of receiving the first dose of Viread®) in the individual subject's record and CRF.



During pre-treatment period each subject will be dispensed with Viread® in the amount sufficient for eight (8) weeks at Visit 3. Subjects should bring their used and unused product and dosing diaries with them to the clinic at Visit 4, 5, 6 and 7, and the investigators will verify subject compliance.

During treatment period each subject will be dispensed with Viread in the amount sufficient for four (4) weeks. Subjects should bring their used and unused product and dosing diaries with them to the clinic at each study visit thereafter, and the investigators will verify subject compliance.

At Visit 6 (Study Week 22) each subject will start mineral supplementation (containing vitamin D<sub>3</sub>, calcium, magnesium, zinc, copper, manganese, molybdenum, chromium, boron and vanadium) on the next day after the study visit 6.

Each subject will be dispensed with mineral supplementation (containing calcium, magnesium, zinc, copper, manganese, molybdenum, chromium, boron and vanadium) in the amount sufficient for three (3) months. Subjects should bring their dosing diary and unused supplementation product, and empty bottles to the clinic at visits as outlined above every three (3) months thereafter, and the investigators will verify subject compliance, and with mineral supplementation (containing vitamin D<sub>3</sub>) in the amount for two (2) months.

Each subject will be dispensed with mineral supplementation (containing vitamin D<sub>3</sub>) in the amount sufficient for two (2) months. Subjects should bring their unused supplementation product and empty bottles to the clinic at visits as outlined above every two (2) months thereafter, and the investigators will verify subject compliance.

Subjects will be encouraged to comply with the study medication regimen and may be withdrawn from the study for reasons of non-compliance based on Sponsor and/or Investigator discretion. If a subject misplaces Viread® or mineral supplementation provided, the study center may replace them.

All subjects will start the assigned treatment at Study Week 27, visit 8.

At each study visit when administration of NAP therapy plus Pegasys® plus Viread® is scheduled subjects may be hospitalized overnight.

Due to the established poor response of serum HBsAg to therapy with nucleoside analogs such as entecavir or TDF (Chevaliez et al., 2013), Pegasys® (Brunetto et al., 2009) or combinations with both (Reijnders et al., 2011; Wiegand et al., 2011), patients in control groups are expected to not experience any significant declines in serum HBsAg and most (if not all) patients in all control groups are expected to be eligible to crossover into triple combination therapy (with NAPs) after 24 weeks of treatment with Pegasys® and Viread®

### **Recording symptoms and signs during infusion of NAP therapy**

Symptoms and signs during infusion are:

1. Chills
2. Fever
3. Peripheral tingling
4. Headache.

5. Any other relevant symptom developing during intravenous infusion.

**Note regarding capturing data**

Only data for the procedures and assessments specified in this protocol should be registered on a case report form. Additional procedures and assessments may be performed as part of the patient's standard medical care; however, data for these assessments should remain in the patient's medical record.

**Primary Safety Data**

The laboratory results and AEs / SAEs after 48, 72 (or 96) weeks on treatment will be used to assess safety.

**Key Secondary Efficacy Data**

All HBV serum virology results will be used to assess efficacy.

## **20. ADVERSE EVENTS**

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

**Related:** There is a reasonable causal relationship between study drug administration and the AE.

**Not related:** There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

**Serious Adverse Events**

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- a) results in death
- b) is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- c) requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- d) results in persistent or significant disability/incapacity
- e) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy of a subject's partner, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

#### NOTE:

The following hospitalizations are not considered SAEs in this clinical study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

### **Serious Adverse Event Collection and Reporting**

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Serious adverse events, whether related or not related to study drug, and pregnancies, must be reported to Replicor Inc., within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission (if email is not available) to:

SAE Email Address: [mbazinet@Replicor.com](mailto:mbazinet@Replicor.com)  
[availlant@Replicor.com](mailto:availlant@Replicor.com)

SAE Facsimile Number: +1 514 496 9011

The study is one that captures SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact:     primary +1 514 951-6123 (Dr. Bazinet)  
                                  Alternate +1 514 862 2271 (Dr. Vaillant)

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Replicor Inc. using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

An Adverse reaction is an adverse event that is considered by either the investigator, sponsor or Replicor Inc. as related to the investigational product.

An unexpected Adverse Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for the investigational product)

### **Non-serious Adverse Events**

A non-serious adverse event is an AE not classified as serious.

#### **Non-serious Adverse Event Collection and Reporting**

The collection of non-serious AE information should begin at initiation of study drug.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see above). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study

treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

### **Laboratory Test Result Abnormalities**

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

If grading of laboratory abnormalities is reported as AEs or SAEs, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events should be used (see Appendix 2).

ALT and AST elevations will be reported as AEs when the laboratory results are  $> 5 \times \text{ULN}$ .

### **Pregnancy of a subject/subject's partner**

If, following initiation of the investigational product, it is discovered that a partner of a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 months after product administration, the investigator must immediately notify Replicor Inc. of this event in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

### **Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

### **Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not

required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## **21. STATISTICAL CONSIDERATIONS**

### **Sample size**

Due to the exploratory nature of the study no formal sample size determination was performed. Nevertheless the proposed design with the 40 subjects eligible for randomization is expected to answer at least the majority of the key research questions.

### **Randomization**

Subjects will be randomly allocated in a 1:1:1:1 ratio to 1 of 4 treatment groups. Assignment to treatment groups will be performed using covariate adaptive randomization (Pocock et al., 1975) using an IWRS. Access to this system is strictly limited, and randomization files and lists are kept confidential. Each subject will be allotted a unique randomization number for this study.

The following covariates will be taken into consideration to assure the maximally available balance during the randomization procedure.

- Serum HBsAg at screening: Group 1:  $\leq 5000$  IU / ml, Group 2:  $> 5000$  IU / ml
- Serum HBV DNA at screening: Group 1:  $\leq 10^5$  copies / ml, Group 2:  $> 10^5$  copies / ml
- Age: Group 1:  $\leq 40$  years old, Group 2:  $> 40$  years old

The study is open, so no blinding procedure will be applied.

### **Analysis sets and analyses**

#### **Analysis sets**

Analyses will be based on the following sets: total set, safety data set (SDS), intention-to-treat set (ITTs), and per-protocol set (PPS). Final decisions on memberships in different sets will be made in the Data Review Meeting (DRM) before database lock.

#### **Total Set**

The total set consists of all subjects included into the study, i.e., subject's informed consent has been obtained.

#### **Safety data set (SDS)**

The SDS is based on all subjects randomized to any study treatment group.

#### **Safety data prior to randomization set (SDpRS)**

The SDpRS is based on all subjects enrolled into the study. The documented failure to take at least one dose of Viread® prior to randomization will lead to the exclusion of the subject from the SDpRS.

#### **Intention to Treat Set (ITTs)**

The ITTS is the analysis set that is as complete and as close as possible to the ITT concept including all randomized subjects. For the definition of the ITTS, no distinction is made whether or not the subject received at least 1 dose of investigational treatment. Lack of any post-randomization efficacy measurement may lead to the exclusion of the subjects from ITTS which decision should be made during the DRM.

### **Per Protocol Set**

The PPS consists of all subjects of the ITTS without any major protocol deviation with a potential impact on the validity of the efficacy measurements. It is the set of subjects that participated in the study as intended. Major protocol deviations, their impact on the validity of the efficacy measurements, and their occurrence in individual subjects will be determined and documented in the Data Review Meeting prior to database lock, including major deviations from inclusion/exclusion criteria, major deviations from planned study medication dose and treatment schedule, and administration of prohibited concomitant medication. Subjects terminating prematurely will be included in the PPS, provided that there is no major protocol violation with impact on the validity of the efficacy measurements.

### **Efficacy analysis**

#### **ITT analysis**

The ITT analysis will be based on the ITTS with subjects analyzed as randomized. In case of missing data for a specific analysis variable, decisions have to be made whether appropriate imputation procedures are applied or if the subject will be excluded from the analysis of this variable; if both procedures are applied then the 2 analyses should be ranked as main analysis and as sensitivity analysis. Therefore, some subjects may not be included in the analysis of a particular efficacy variable, although they are part of the ITTS. The rules of application of imputation procedures will be specified in detail in the Statistical Analysis Plan (SAP).

#### **Per Protocol Analysis**

The Per-Protocol analysis will be based on the PPS. A subject must have at least 1 available valid post-baseline measurement of a specific variable during the treatment period in order to be analyzed for that variable. Depending on the analysis, a valid baseline value may also be required. Therefore, some subjects may not be included in the analysis of a particular efficacy variable, although they are part of the PPS.

#### **Safety analysis**

Safety analysis after administration of the first dose of investigational treatment will be performed on the SDS with subjects analyzed as treated.

Safety analysis of all enrolled subjects will be performed on the SDpRS for the Screening and the entire period prior to randomization.

### **Statistical Analyses and methods**

Longitudinal summaries of safety and efficacy endpoints will use pre-defined visit week windows. Windows around planned measurement times will be constructed based on the midpoint between planned study visits. Laboratory measurements will be summarized using US standard values and units.

On-treatment endpoints will be assessed with measurements from the start of study therapy through the last dose of study therapy plus 10 days. Follow-up endpoints will be assessed with measurements after the last dose of therapy plus 10 days. An extra care should be taken during defining the visit windows in visits where change in the investigational treatment is detected.

## **Subject disposition and characteristics**

### **Subject disposition**

The number of subjects screened, enrolled into the study, and completed the study, as well as the reason for discontinuing the NAP therapy or discontinuing a subject from the study, will be presented in summary tables by treatment arm (after randomization), total subjects (prior to and after randomization), and study period. The reason for discontinuing the NAP therapy or withdrawing a subject from the study will be listed by subject.

### **Subject Characteristics**

Descriptive statistics (mean, standard deviation, median, 25% and 75% quartiles, and minimum, maximum) will be calculated for all demographic variables. Percentages will be presented where appropriate. Age will be described as continuous.

## **Efficacy analysis**

### **Primary efficacy endpoint**

Not applicable. No primary efficacy endpoint is defined.

### **Secondary efficacy endpoints**

Secondary efficacy endpoints will be determined at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and 48 week post-treatment follow-up:

- Proportion of patients who achieve serum HBsAg < 50 IU/ml.
- Proportion of subjects who achieve anti-HBs titers above 10 mIU/ml
- Proportion of patients who suppress serum HBV DNA
- Proportion of subjects who maintain HBsAg and HBV DNA suppression during follow-up.
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg

Proportions will be derived at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and at week 48 post-treatment follow-up. The proportions will be derived for each treatment arm and for the pooled, non-switching patients of control groups with identical treatments. Similarly, proportions will be derived for pooled groups of identical treatment regimens of equal treatment durations.

Comparison will be made in twofold manner. Primarily experimental groups will be compared against their appropriate controls at each of the time points mentioned above. Secondly any experimental treatment (REP 2139-Mg or REP 2165-Mg) will be compared against its appropriate control considering identical length of application of the experimental treatment. E.g. proportions of the first treatment arm at treatment week 49 will be compared to [switching] control group at week 73 as both measures are connected with 24 weeks of REP 2139-Mg treatment.



The above analyses will include the calculation of point estimates of the proportions, a difference in proportions (where it is appropriate) and the corresponding 2-sided 95% Clopper-Pearson confidence intervals for all pair-wise treatment comparisons.

### **Antiviral activity**

Efficacy analysis uses treatment regimens and treated subjects. Analyses of antiviral activity will be based on HBsAg, anti-HBs and HBV DNA measurements closest to the planned visits and within pre-defined visit windows.

### **Safety analysis**

#### **Primary safety endpoint**

The primary safety endpoint, determined at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and 48 week post-treatment follow-up, is the safe completion the triple combination regimen of Viread®, Pegasys® and REP 2139-Mg or REP 2165-Mg as detailed in Fig 1.:

- Proportion of subjects who develop treatment emergent cytopenic abnormalities: anemia, as defined by Hb < 10 g/dl, and/or neutropenia as defined by PMN < 1,000/μl, and/or thrombocytopenia as defined by platelets < 50,000/μl),
- Proportion of subjects who develop liver dysfunction (as defined by bilirubin > 2X ULN, chronic elevations in ALT or AST > 10X ULN > 8 weeks in duration) by the end of treatment,
- Proportion of subjects who develop renal impairment (as defined by serum creatinine > 1.5 mg/dl for > 4 weeks) by the end of treatment,
- Proportion of subjects with AEs, SAEs, dose reductions, and discontinuations due to AEs through end of treatment,
- Proportion of subjects with treatment emergent laboratory abnormalities by toxicity grade,
- Differences in the above proportions between patients receiving REP 2139-Mg versus REP 2165-Mg.

Proportions will be derived at treatment week 49, 73 (or week 97), first post-treatment follow-up visit and at week 48 post-treatment follow-up. The proportions will be derived for each treatment arm and for the pooled, non-switching patients of control groups with identical treatments. Similarly, proportions will be derived for pooled groups of identical treatment regimens of equal treatment durations.

Comparison will be made in twofold manner. Primarily experimental groups will be compared against their appropriate controls at each of the time points mentioned above. Secondly any experimental treatment (REP 2139-Mg or REP 2165-Mg) will be compared against its appropriate control considering identical length of application of the experimental treatment. E.g. proportions of the first treatment arm at treatment week 49 will be compared to [switching] control group at week 73 as both measures are connected with 24 weeks of REP 2139-Mg treatment.

The above analyses will include the calculation of point estimates of the proportions, a difference in proportions (where it is appropriate) and the corresponding 2-sided 95% Clopper-Pearson confidence intervals for all pair-wise treatment comparisons.

#### **Secondary safety endpoints**

Not applicable.

### **Adverse events**

The investigators will determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at Replicor Inc. AEs will be presented by system organ class and preferred term.

If a subject had an AE with different intensities over time, then only the greatest intensity will be reported for a study period.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) of the US National Institutes of Health table for grading the severity of adverse experiences (2004) (Appendix 2). The laboratory value during the study period with the highest toxicity grade will be reported for each test. Treatment emergent laboratory abnormalities are those with highest on-treatment toxicity grade greater than the baseline toxicity grade. Levels and changes from baseline in select laboratory tests over time will be summarized by treatment regimen for treated subjects using observed values.

Rate, severity, relatedness and relationship to administration of NAP therapy of any AEs per administration of NAP therapy and subject will be evaluated from the screening visit until the completion of the study separately for the different study periods. The following treatment periods are defined:

- Pre-screening with signing of the Informed Consent to undergo the assessments defined in the protocol as pre-screening, and ends at the date of screening or withdrawal.
- Screening which starts with signing of the Informed Consent to participate in the study and ends at the day before the first dose of the investigational treatment or withdrawal.
- Treatment period, which starts with the first application of the investigational treatment and ends with study completion according to the protocol or withdrawal.
- Follow-up period, which starts the day after the last application of investigational treatment and ends with study completion according to the protocol or withdrawal.

Treatment-emergent adverse events (TEAEs) are defined as AEs that develop or worsen during the treatment period extended with 10 days from the application of the last dose of the investigational treatment. AEs occurring before the start of application of investigational treatment or beyond the treatment period extended with 10 days will only be listed.

AEs will be coded using MedDRA. Analyses will be performed by primary SOC and PT. AEs will primarily be classified by MedDRA PT. Aggregate incidences at the SOC level will be shown as well.

Deaths will be listed for enrolled subjects without regard to study period. The frequencies of the following safety events will be summarized by treatment regimen for treated subjects:

- SAEs (separated by on treatment and follow-up)
- AEs leading to discontinuation of study therapy
- AEs (related and regardless of relationship to study therapy) by intensity (separated by on treatment and follow-up)
- Treatment emergent laboratory abnormalities by toxicity grade.

### **Adverse events prior to randomization**

Adverse Events prior to randomization will be analyzed on SDpRS. This dataset contains all subjects of SDS and additionally contains those subjects who were withdrawn prior to randomization. Concept of treatment-emergent adverse event cannot be defined for this analysis.

AEs will be coded using MedDRA. Analyses will be performed by primary SOC and PT. AEs will primarily be classified by MedDRA PT. Aggregate incidences at the SOC level will be shown as well.

### **Laboratory safety parameters**

The following approaches will be taken for the statistical analysis of the laboratory safety variables:

- Calculation of descriptive statistics (number of subjects, mean, standard deviation, median, 25% and 75% quantile, minimum, maximum) by visit for measured values and for the change from baseline at the completion visit.
- Shift tables displaying intra-individual changes from baseline to the different visits using categorized laboratory variables. Categorization will be done by converting the central lab specific normal ranges into missing, low, normal and high.
- Range change abnormal (RCA): A laboratory value that was either normal or high at baseline and low post-baseline (RCAL) or that was normal or low at baseline and high post-baseline (RCAH).
- Listing of CS laboratory values.

### **Vital Signs**

Vital signs will be summarized using descriptive statistics.

### **Physical examinations**

Any unfavorable findings recorded between the screening and the study completion visit will be recorded as an AE and summarized using descriptive statistics.

### **Interim analysis**

An interim analysis of primary endpoints is planned to be performed after all patients completed treatment week 48 weeks of treatment.

The Interim Analysis will be based on a formally closed Interim Analysis Database and will be conducted according to the SAP for Interim Analysis

### **Analysis provided to Safety Data Monitoring Board**

Regular safety summary will be generated for the SDMB during the treatment period extended with 10 days from the last application of the investigational treatment. Summary will contain listings of withdrawn cases, AEs (TEAs), and laboratory abnormalities of the reported period.

### **Statistical Software**

The data obtained in this study will be analyzed statistically using SAS software, version 9.1 or higher. For this purpose, data will be transferred from the eCRF system to SAS following CDISC standards.

## **22. STUDY MANAGEMENT**

### **Compliance with Protocol and Protocol Revisions**

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with the local competent authorities and Replicor Inc. The investigator should not implement any deviation or change to the protocol without prior

review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

An amendment should be considered in the case of:

- medical impacts of the investigational product on the patient safety
- new insights that reduce the validity of the study
- change of the leading investigator of the study

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- a) IRB/IEC for review and approval/favorable opinion
- b) Replicor Inc.
- c) Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Replicor Inc.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

## **Monitoring**

The study monitor(s) must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Audit reports will be kept confidential.

The investigator must notify Replicor Inc. promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Replicor Inc.

## **Investigational Site Training**

The Sponsor will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

## **Records**

The investigator must retain all study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region

OR

At least 7 years after the approval of marketing application in the Republic of Moldova, but no more than 15 years have elapsed since the formal discontinuation of clinical development study of the investigational product in Republic of Moldova BUT at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product  
and

The investigator must contact Replicor Inc. prior to destroying any records associated with the study.

Replicor Inc. will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Replicor Inc.

### **Study Drug Records**

It is the responsibility of the investigator to ensure that a current disposition record of investigational products (those supplied by Replicor Inc.) is maintained at each study site where study drugs are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to Replicor Inc.
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

Replicor Inc. will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### **Case Report Forms**

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from

source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. The investigator must retain a copy of the CRFs including records of the changes and corrections.

### **Clinical Study Report and Publications**

The Principal Investigators will be Signatory Investigators to sign the clinical study report.

The data collected during this study are confidential and proprietary to Replicor Inc. Any publications or abstracts arising from this study require approval by Replicor prior to publication or presentation and must adhere to publication requirements as set forth in the Helsinki Declaration and the approved clinical trial agreement (CTA).

## **23. GENERAL DESIGNATIONS; AGREEMENTS AND ORGANIZATIONAL PROCEDURES**

### **Legal regulations**

This clinical trial will be conducted according to the Declaration of Helsinki and the regulations of Moldova in its valid form, as well as the ICH-GCP guidelines and other valid national regulations.

### **Information for the Principal Investigator**

The principal investigator will be completely informed about the preclinical and clinical knowledge of the investigational product, through the Investigator's Brochure. By the acquisition of new insights an updated version of the Investigator's Brochure will be handed over or an amendment for the Investigator's Brochure will be conducted

### **Organizational arrangements/ investigational meetings**

All principal investigators and their assistant personal which are involved in the study will meet before the initiation of the study. The attendance is obligatory.

In this meeting the clinical protocol and patient records will be discussed as well as the ethic, legal and scientific requirements to clinical studies according to the pharmaceutical products act and the ICH- recommendations for "good clinical practice". The meeting will be conducted for the coordination and standardization of the study procedures.

## **Data protection and medical confidentiality**

In the context of this study, all patient data in case report forms will be identified only with a patient number.

The patients will be informed that the obtained data, in the context of this study, will be coded without referring to the patient's name (pseudonymized) before submitting them elsewhere.

## **Case report forms and handling of them**

For each patient there will be a unique case report form. All relevant data will be kept in the medical record and will be documented on the case report form.

If there should be made corrections or complementation, they should be made in a way that the former entry is still readable. Additions and corrections should be signed and dated from the sub-investigators. Not self-explaining corrections have to be justified. Additions and corrections can be also conducted during the visit of a monitor.

Additions and corrections can be conducted only through authorized people. These are apart from the principal, co- and sub-investigators study nurses or specifically trained medicinal personnel. All people that do corrections or additions should have signed in the list of the investigational file.

## **Retention of study records**

After completion of the study and submission of the final report all study records will be archived. The principal investigator is obliged to keep the investigational records as stipulated in Section 22.

# **24. PREMATURE DISCONTINUATION OF THE STUDY**

## **Single Site**

The responsible clinical Investigator and Replicor have the right to discontinue a single site at any time during the study for reasonable medical or administrative reasons. Possible reasons for termination of the study could be, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol

## **Study as a Whole**

Replicor reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

The clinical trial will be discontinued before the last patient has finished his follow-up (follow-up will however be continued) when:

- a) There is early evidence that NAPs are not beneficial for the condition under study/a solid evidence that NAPs are not providing any benefit, OR

- b) there is early evidence that NAPs are, in contrary, harmful (the emergence of ADRs, SAEs, SUSARs ,
- c) It is not feasible to reach the planned outcomes.

Any possible early termination would have to be documented adequately with reasons being stated, and information would be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.)



## 25. REFERENCES

1. Hoffman La Roche. Pegasys® - pegInterferon alfa-2a injection, solution (prescribing information).
2. Gilead Sciences. Viread®- tenofovir dipivoxil fumarate tablets for oral use (prescribing information).
3. ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice: Recommended for Adoption at Step 4 of the ICH Process on 1 May 1996 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
4. ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting: Recommended for Adoption at Step 4 of the ICH Process on 27. October 1994 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
5. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports: Recommended for Adoption at Step 4 of the ICH Process on 30 November 1995 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
6. ICH Harmonized Tripartite Guideline: General Considerations for Clinical Trials: Recommended for Adoption at Step 4 of the ICH Process on 17 July 1997 by the ICH Steering Committee This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
7. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials: Recommended for Adoption at Step 4 of the ICH Process on 5 February 1998 by the ICH Steering Committee: This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.
8. Brunetto, M. et al. 2009 Hepatol. 49: 1141-1150.
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10. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975 Mar; 31(1):103-15.
11. Reijnders, J. et al. 2011 J. Hepatol. 54: 449-454.
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## **APPENDIX 1      DSM IV: DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE**

### **Criteria for Alcohol & Substance Abuse**

1) A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

a) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

b) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

c) Recurrent substance-related legal problems (e.g., arrests for substance related disorderly conduct)

d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

2) The symptoms have never met the criteria for Substance Dependence for this class of substance.

## **APPENDIX 2 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS**

## APPENDIX 3 GUIDANCE ON SUPPORTIVE THERAPY FOR THROMBOCYTOPENIA / LEUCOPENIA

### Thrombocytopenia

Platelet count	Beneveron BF® tablets	folic acid tablets
$> 150 \times 10^6 / \text{ul}$	none	none
$\leq 150 \times 10^6 / \text{ul}$	Start 1 pill daily	5mg
$\leq 100 \times 10^6 / \text{ul}$	1 pill daily	5mg
$\leq 80 \times 10^6 / \text{ul}$	1 pill daily	5mg
$\leq 60 \times 10^6 / \text{ul}$	1 pill daily	10mg
$\leq 50 \times 10^6 / \text{ul}$	1 pill daily	10mg

Notes:

- Folic acid dose can be reduced if significant gastritis develops.
- If implemented, Beneveron BF® and folic acid supplementation is recommended to be maintained during Pegasys® dosing till  $\text{PLT} \leq 150,000/\text{mm}^3$ .

### Leucopenia

WBC count	Beneveron BF® tablets	folic acid tablets
$> 4 \times 10^3 / \text{ul}$	none	none
$\leq 4 \times 10^3 / \text{ul}$	Start 1 pill daily	5mg

Notes:

- WBC counts between  $2 - 4 \times 10^3 / \text{ul}$  are not considered an adverse event and have no assignable DAIDS grade. However, the normal range for WBC counts at the test lab for the REP 401 trial is  $4 - 10 \times 10^3 / \text{ul}$ . The use of Beneveron BF® and folic acid as described above for leucopenia is prophylactic in nature and therefore, when patients are receiving Pegasys®, is introduced before leucopenia of a formally adverse nature develops ( $< 2 \times 10^3 / \text{ul}$ ).