Protocol Number: REP 301
Version 2.2 June 04, 2015

A study of the safety and efficacy of combination treatment with REP 2139-Ca and Pegasys™ in patients with hepatitis B / hepatitis D co-infection.

Protocol

Sponsor:

REPLICor Inc.
6100 Royalmount Avenue
Montreal, Quebec
Canada, H4P 2R2

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

RELEASE FROM CONFIDENTIALITY FOR THE PURPOSE OF PUBLIC DISCOSURE

Version 2.2 of the REP 301 protocol dated June 4, 2015 is authorized for public release by the Sponsor.

JUNE 6, 2017

Andrew Vaillant
Chief Scientific Officer
Replicor Inc.

Date

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Document History

Document	Date of Issue	Summary of Change
Original Protocol No. 1.0	May 23, 2014	
Version 1.1	Sept 17, 2014	• Study schedule: correction of typos • Vital Signs and Physical Exmination: Eye exam procedure modified to exclude irrelevant retinal exam • Inclusion/Exclusion Criteria for HCV, HIV-1/HIV-2 and CMV antibody has been amended to specify the kind of antibody • Inclusion Creterion BMI have been revised to increase the upper limit • Exclusion Criterion for ALT levels has been amended taking into account central lab normal ranges • Two more tests (part of regular medical care) added to the screening visit schedule by request of the investigators in order to eliminate over sampling.
Version 2.0	Oct 19, 2014	• HDAg+ is removed from the list of inclusion criteria. • Details of required blood pressure monitoring before and after REP 2139-Ca administration specified in Note 1 on tables from page 9 and 44. • Order of procedures during a patient visit is specified in section 16. • Allowance of unscheduled visits for the study is specified in section 15 • Clarification of acceptable rescheduling of dosing visit in case of patient conflict is provided in Section 15 (Selection and Timing of Dose for Each Subject). • Data protection and medical confidentiality revised to reflect the arrangements in the context of this study • Statistical Analysis section revised to specify data to be tabulated
Version 2.1	Jan 27, 2015	• HDAg testing and associated endpoint analysis is removed from the protocol • Add urine pregnancy test during follow-up
Version 2.2	June 04, 2015	• The hematologic growth factors are excluded from the list of concomitant treatment in the Section 14 • Dose reduction instructions in Table 2 have been revised to be more comprehensive.

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-301 dated 04 June 2015 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

JUNE 5 2015

Date

Andrew Vaillant
Chief Scientific Officer, REPLICor Inc.

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of the clinical protocol REP-301 dated 04 June 2015 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:
Dr. Victor Pântea
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V. Pântea — 15.06.2015

Signature of Principal Investigator — Date

1. SYNOPSIS

Clinical Protocol REP 301

Protocol Title: A study of the safety and efficacy of combination treatment with REP 2139-Ca and Pegasys™ in 12 patients with hepatitis B / hepatitis D co-infection.

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

REP 2139-Ca: 500 mg intravenously (IV) once weekly, with dose reduction to 250 mg weekly when given in combination with Pegasys™. Planned total REP 2139-Ca exposure scheduled to be 11.25 g per patient.

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

Study Phase: Phase IIa

Research Hypothesis:

Elimination of HbsAg with REP 2139-Ca will lead to:

Creation of a favourable immunological activation in the absence of HbsAg
Appearance of free anti-HBs
Clearance of HBV and HDV virions in the blood.
Synergistic immunostimulation with conventional dosing of Pegasys™ and the restoration of the immunological control of HBV and HDV infection.

Endpoint(s):

Primary objective:
To evaluatge the safety of REP 2139-Ca when given in patients with chronic HBV / HDV co-infection and with subsequent exposure to pegylated interferon-alfa-2a in combination.

Secondary objectives:
To evaluate the effect of REP 2139-Ca administration on the following:

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

Study Design:
Treatment Period:
REP 2139-Ca monotherapy (15 weeks @ 500mg / week) followed by

combination therapy with Pegasys (180 ug per week) and REP 2139-Ca (250mg / week) for 15 weeks followed by 33 weeks of Pegasys monotherapy (180 ug per week).

Planned REP 2139-Ca exposure not to exceed 11.25g.

Planned Pegasys exposure not to exceed 48 weeks.

Follow up:	Minimum of 24 weeks.
Dosing interval:	REP 2139-Ca: once weekly Pegasys™: once weekly
Dosing route:	REP 2139-Ca: IV, maximum speed of 250 mg/hour slow infusion Pegasys™: subcutaneous injection
Dose level:	REP 2139-Ca: 500mg (250mg when given with Pegasys™) Pegasys™: 180ug (not to exceed 48 weeks total exposure)
Number of patients:	12

Pre-treatment assessment:

During a one month period prior to treatment, candidate patients will have their serum 25OH vitamin D levels brought into the optimal range (> 150 nmol / L) by supplementation with vitamin D_3 (5,000 IU PO QD). The use of additional vitamin D_3 administration (200,000 IU IM once weekly) may be used in those patients with severe 25 OH vitamin D deficiency (< 50 nmol / L).

Candidate patients will also be asked to take mineral supplements (containing calcium, magnesium, zinc, copper, manganese, molybdenum, chromium, boron and vanadium) before, during and for 6 months after treatment and an iron supplement at any time during or after treatment if haematological blood tests suggest the development of an iron deficiency.

Dosing regimen:

All patients are to start once weekly REP 2139-Ca therapy (500mg/week).

Patients start add-on Pegasys™ therapy (180 ug / week) on the 16th week (with REP 2139-Ca dose reduction to 250mg / week).

Combination therapy with REP 2139-Ca and Pegasys™ will continue until week 30 at which point the patient will continue on Pegasys™ monotherapy for an additional 33 weeks (48 weeks Pegasys total).

Follow-up:

These patients will be seen on the 4th, 12th and 24th week after treatment has ended to monitor the durability of their antiviral response off treatment and to monitor their liver function.

Scheduled Screening, on-treatment and Follow Up Assessments:

Procedure / Test	Frequency
Inclusion and Exclusion Criteria	Screening visit
Medical History	Every visit
Vital Signs[1]	Every visit
Physical Examination	Every visit
Eye exam[2]	Screening visit every 4 weeks on treatment
Verification of prior / concomitant medications[3]	Every visit
Verification of mineral supplement compliance	Every visit
ECG	Screening, every four weeks on treatment, FW4, 12 and 24
Ultrasound	Screening and weeks 16, 31, 63(EOT) and FW24
Fibromax / Fibroscan	Screening and weeks 31, 63(EOT) and FW24
HBV DNA / HDV RNA viral load	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
HbsAg	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
Anti-HBs / Anti-HDAg	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
HbeAg / Anti-HbeAg	Weeks 1, 31, 63 (EOT) and FW24
anti HIV 1+2 / anti-CMV / anti-HCV	Screening visit
ALT / AST / Alkaline Phosphatase[4]	Every visit
GGT	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Total bilirubin[5]	Screening, every two weeks on treatment, FW 4, 12 and 24
Creatinine	Every visit
Biochemistry[6]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Urinalysis(Heme / Protein / Sugar)	Every visit
25 OH vitamin D	Screening, week 1 and every 8 weeks during treatment, FW 24
Heavy metal analysis[7]	Screening visit
Electrolytes[8]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Hematology[9]	Screening, every 4 weeks during REP 2139-Ca, every two weeks during Pegasys and FW4, 12, and 24
INR / PTT / aPTT[10]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Lipid profile[11]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
AFP[12]	Screening visit, week 63 (EOT) and FW2 4
ANA	Screening and weeks 16, 31, 63(EOT) and FW24
Serum pregnancy test[13]	24 hours prior to first drug administration
Urine pregnancy test	Every 4 weeks on treatment, FW 4, 12 and 24
AMA, LKM1[14]	Screening Visit
Frozen serum (4 X 1 cc aliquots) collected	Screening visit, weeks 1, 2, and then every 4 weeks during treatment, FW 4, 12 and 24

NOTES

1. Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at all study visits. Physical measurements including Height measurement will be performed at screening visit and weight measurement for calculation of BMI will be performed at each visit. Blood pressure must be measured before and after REP 2139-Ca administration.
2. An eye exam - will be done at Screening and every 4 weeks on treatment. If the subject has hypertension or a history of pre-existing eye disease detected during screening, the patient will be excluded from the trial.
3. Especially review of therapy with an immunomodulatory agent, cytotoxic agent, or systemic corticosteroids within 2 months of screening. Subjects receiving theophylline therapy should undergo frequent monitoring of serum theophylline levels due to the identified increase in theophylline levels with Peginterferon α-2a. Any hematopoietic growth factor medications with known or potential anti-HBV activity other than the assigned study treatment are prohibited.
4. Reflex to GGT if alkaline phosphatase ≥ 3X ULN
5. Reflex to direct bilirubin if abnormal; reflex to GGT if bilirubin ≥ 2X ULN
6. Albumin, Total Protein, LDH, BUN, Phosphate, Uric Acid, Glucose (fasting), HbA1c
7. Cadmium, Lead, Mercury in whole blood
8. Na, HCO3-, K, Cl, Mg, Ca
9. RBC, WBC (count with differential), Reticulocyte count, Hemoglobin, Hemtocrit, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Cell Distribution Width, Platelet Count, Mean Platelet Volume, Neutrophils, Lymphocytes, Monocytes, Eosinophiles, Basophils.
10. INR, PT (reflex to PTT if ≥ 2x PTT elevation), aPTT

11. Triglycerides (fasting), total cholestrol (fasting), HDL (fasting), LDL (fasting)
12. If AFP is ≥ 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.
13. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of the investigational product.
14. AMA, LKM1 are part of a patient's medical care and should be retained on the patient's medical record: these assessments are not required for study puprposes and will not be captured in eCRF.

Study Population:

Key Inclusion:

- Age between 18 and 55 years
- HBsAg > 1000 IU / ml
- HDV RNA +
- No detectable antibodies to HIV, HCV or CMV (IgM).
- Non cirrhotic
- Willingness to utilize adequate contraception while being treated with REP 213-Ca and for 6 months following the end of treatment
- Adequate venous access allowing weekly intravenous therapies and blood tests
- Body Mass Index (BMI) ≥ 18 kg/m2 and ≤ 30 kg/m2

Key Exclusion:

- Evidence of cardiovascular disease
- Autoimmune hepatitis
- Presence of Wilson's disease
- Presence of severe NAFLD
- Evidence of any other co-existent liver disease
- ANA (anti-nuclear antibody) positive
- Fibroscan and Fibromax showing evidence of advanced cirrhosis. Any history of ascites, hepatic encephalopathy or variceal hemorrhage
- Body weight > 100 kg
- Platelet count < 90,000, PMN count < 1,500 or HCT < 33%
- Evidence of significant heavy metal load in whole blood.
- AFP > 100 ng/ml or the presence of a hepatic mass suggestive of HCC
- Bilirubin above the normal range
- ALT > 10x ULN
- Creatinine > 1.5 mg/dl
- Serum albumin < 35 mg/ml
- The presence of diabetes (whether controlled or uncontrolled)
- Another serious medical disorder
- A serious psychiatric disorder
- Evidence of hypertension
- A history of alcohol abuse within the last year
- The use of illicit drugs within the past two years
- Inability to provide informed consent
- Inability or unwillingness to provide weekly blood samples
- Poor venous access making IV infusion too difficult
- Patiens not willing to come every week to receive therapy

Study Assessments:

Primary Endpoint

The primary endpoint is the safe completion of REP 2139-Ca / Pegasys therapy:
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 > 2mg/dL, chronic elevations in ALT or AST > 10X ULN > 8 weeks in duration)
- Proportion of subjects who develop renal impairment (as defined by serum creatinine > 1,5 mg/dl for > 4 weeks)
- Proportion of subjects with AEs, SAEs, dose reductions, and discontinuations due to AEs through end of 6 months of follow-up
- Proportion of subjects with treatment emergent laboratory abnormalities by toxicity grade

Key Secondary Endpoints

- Proportion of patients who achieve serum HBsAg < 50 IU/ml.
- Proportion of subjects who achieve anti-HBs titers above10 mIU/ml
- Proportion of patients who suppress serum HBV DNA
- Proportion of patients who suppress serum HDV RNA
- Proportion of subjects who maintain HBsAg suppression, HBV DNA and HDV RNA supression during follow-up.

Statistical Analysis:

Enrolled subjects are those who signed an informed consent form and were assigned a Patient Identification number (PID).

Treated subjects are subjects who received at least 1 dose of study therapy.

Categorical variables will be summarized with counts and percents. Confidence intervals for difference in proportions will be based on the normal approximation with unpooled proportions used in the computation of the standard error of the difference. Continuous variables will be summarized with univariate statistics (eg, mean, median, standard error).

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.

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.

Baseline demography, HBV disease characteristics, and other baseline laboratory values will be tabulated by treatment regimen, including:

- Demographics: age, race, gender, ethnicity
- Disease characteristics at screening: HBsAg level, HBV DNA / HDV RNA level, anti-HBs /anti-HDAg leveland cirrhosis status
- Physical measurements at baseline: height, weight, BMI
- Laboratory tests at baseline
- Prior medications.

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

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.

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.

2. LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
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
CHB	Chronic Hepatitis B
CI	Confidence interval
CMV	Cytomegalovirus
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
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
ECG	Electrocardiogram
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
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCO3	Bicarbonate
Hct	Hematocrit
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HDAg	Helatitis D antigen
HDV	Hepatitis D virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNα	Interferon α
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
IU	International units

Kg	Kilogram
LDH	Lactate dehydrogenase
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
NUCs	Nucleoside analogs
PBMCs	Peripheral blood mononuclear cells
PID	Patient identification number
PMN	Polymorphonuclear
PRO	Patient reported outcomes
PT	Prothrombin time
PPT	Partial prothrombin time
QD	Every day
RBC	Red blood cell
RGT	Response-guided therapy
RNA	Ribonucleic acid
RVR	Rapid virologic response
SAE	Serious adverse event
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	Standard of care
SVR	Sustained virologic response
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of normal
WBC	White blood cell
WOCBP	Women of child-bearing potential

3. ADRESSES/LIABILITY

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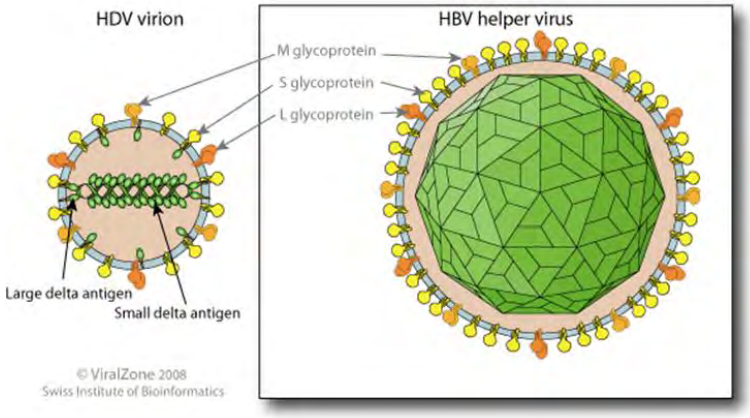
4. INTRODUCTION

Theoretical and clinical background

Chronic hepatitis D infection (HDV) affects between 15 to 20 million patients worldwide. For comparison, 35 millions patients are affected with HIV. The natural evolution of the disease is that 80% of untreated patients with HDV will develop cirrhosis within 10 years of getting infected. The only treatment that has shown any degree of efficacy is interferon. Unfortunately, interferon rarely cure the disease. It has been shown that long term administration of interferon can prevent or delay the progression to liver cirrhosis. However, in most cases, the HDV infection will return within 2 to 6 months after interferon therapy is stopped. This is important because most patients will not accept to tolerate the side effects associated with long term administration of interferon over years when the chance for a cure is so low. In addition, the cost of interferon for an extended period of time is hard to justify in the absence of a significant probability of cure. There is therefore a clear and urgent need to develop new effective therapies for this condition.

HDV infection is always associated with chronic hepatitis B infection (HBV) since the HDV virus needs the surface membrane proteins of the HBV virus (HBsAg) to complete the formation of the HDV virus.



The requirement for the presence of HBV surface antigen (HBsAg), explains why HDV cannot exist without HBV and why patients immunized against HBV are also protected against HDV. It also explains why polymerase inhibitors used against HBV are useless in HDV infections since they can only lower titers of HBV virions but have no impact on the levels of HBsAg produced in infected cells.

Rationale for proposed therapy

HBsAg is an abundant viral protein found in the blood of patients with chronic hepatitis B or chronic hepatitis B / hepatitis D co-infection 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.

Our drug called REP 2139-Ca (or REP 9AC') 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 immunotherapeutic agents such as interferon (Pegasys, Roche) and thymosin alpha 1 (Zadaxin) and is associated with the production of high levels of antibodies against HBsAg called anti-HBs. This results in a high rate of sustained virological responses in HBV (see effects in human patients below). An important part of the life cycle of the HDV virus is that it uses HBsAg (obtained from HBV) on its surface for cell entry into hepatocytes the same way than the HBV virus enters cells. The HBsAg present on the surface of the HDV virus can be targeted by anti-HBs to help remove the virus from the circulation and specifically block the entry of the virus into hepatocytes. This would prevent the replenishment of the virus in the hepatocyte over time and should lower viral HDV titers in the blood. Patients with HBV infections treated with our drug and interferon have been able to generate high antibodies titers that could effectively block HDV entry into hepatocytes and directly reduce HDV blood titers.

It is expected that the persistence of HBsAg in patients with chronic HDV infection prevents an optimal response to interferon like is the case for patients with chronic HBV infection. The removal of HBsAg with our drug could therefore result in a significant improvement in the response to interferon for these patients.

Nucleic acid-based polymers (NAPs) have been shown to block the entry of duck HBV virus into primary hepatocytes by virtue of their chemical similarity to sulfated polysaccharides like heparin sulfate (Noordeen et al., 2013 AAC 57: 5291-5298) and as such will also be expected to block the entry of HDV as well since HDV uses the same entry mechanism as HBV.

5. STUDY RATIONALE

The rationale for conducting this study with Peginterferon alfa-2a and REP 2139-Ca is based on the efficacy and safety data observed in recent proof of concept clinical trials. NAPs are a new class of broad-spectrum antiviral compounds which 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.

REP 2139-Ca 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 < 116 copies/ml. Short term combination treatment with pegylated interferon alfa-2a (Pegasys™) 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 experiencing 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. Six of these patients are still experiencing a SVR 20-28 weeks post treatment.

Treatment Duration Rationale

The REPLICor Study will evaluate the efficacy and safety of the combination of REP 2139-Ca and peginterferon alfa-2a (Pegasys™) as an add-on therapy after 15 weeks of REP 2139-Ca monotherapy given in a weekly regimen scheduled to not exceed 11.25 g of total REP 2139-Ca exposure, followed by an additional Pegasys™ monotherapy exposure such that the total Pegasys™ exposure does not exceed 48 weeks. Interim analysis of data from previous proof of concept studies has shown that 8 of 9 patients with HBV monoinfection experienced HBsAg clearance, appearance of free-anti-HBs, synergistic amplification of anti-HBs within 6-10 weeks of Pegasys therapy and achieved a SVR off treatment in the absence of NUC therapy. Due ot the critical role of HBsAg in the lifecycle of HDV and the previously demonstrated antiviral inpact of REP 2139-Ca / Pegasys therapy on HBV infection, this combination regimen may have profound antiviral effects in patietns with HBV / HDV co-infection.

Rationale to Support the Inclusion of non-Responders

Previous non-responders to interferon theapy may experience a significantly improved response to immunotherapy when used in combination with REP 2139-Ca due to the clearance of serum HBsAg achieved by REP 2139-Ca. Therefore, prior interferon non-responders can be included in this trial following a washout period of at least 6 months

Rationale to Support Open-Label Study

This study will be open label due to: 1) it is a pilot phase; 2) the efficacy and safety of REP 2139-Ca has not been fully evaluated; 3) registration of AE which makes true-blinding unrealistic; 4) the small amount of patient enrollment.

6. Research Hypothesis

Clearance of serum HBsAg with REP 2139-Ca will lead to:

a) the appearance of anti-HBs, which will in turn clear serum HBV and HDV.
b) the appearance of anti-HBs, which will prevent the entry of HBV and HDV viruses into hepatocytes.
c) the creation of a permissive environment in which host immunity can begin to control HBV and HDV infection.
d) a synergistic effect on the immunostimulatory action of Pegasys which may further increase the chance of patients achieving control of their HBV / HDV infection off treatment.
e) entry inhibition of both HBV and HDV may also have an additional therapeutic benefit in achieving control of HBV / HDV co-infection.

Objectives

Primary Objective

To demonstrate that REP 2139-Ca in monotherapy and in combination with Pegasys is well tolerated when given intravenously to patients with HBV / HDV co-infection.

Key Secondary Objectives

To demonstrate the efficacy of REP-Ca 2139 in achieving the following outcomes in patients with HBV / HDV co-infection:

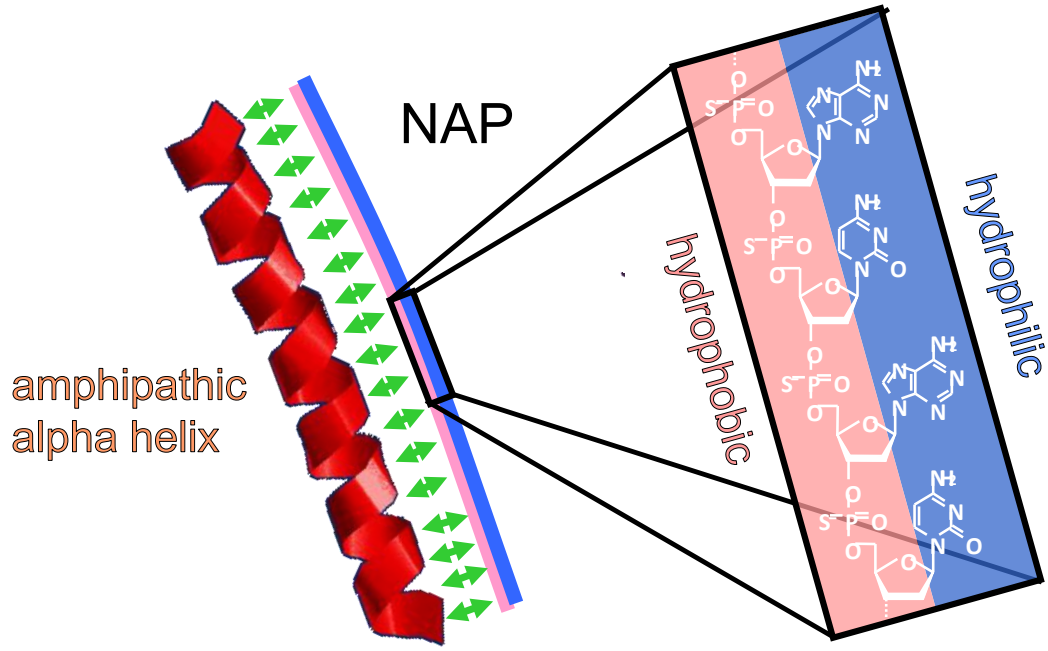
a) to reduce or clear serum HBsAg
b) to reduce or clear serum HBV DNA and/or serum HDV RNA
c) to produce a synergistic effect with Pegasys (as measured by anti-HBs production) with clearance of serum HBsAg.
d) to establish control of HBV / HDV co-infection off treatment.

7. Product Development Background

Background of NAPs (Nucleic Acid Polymers)

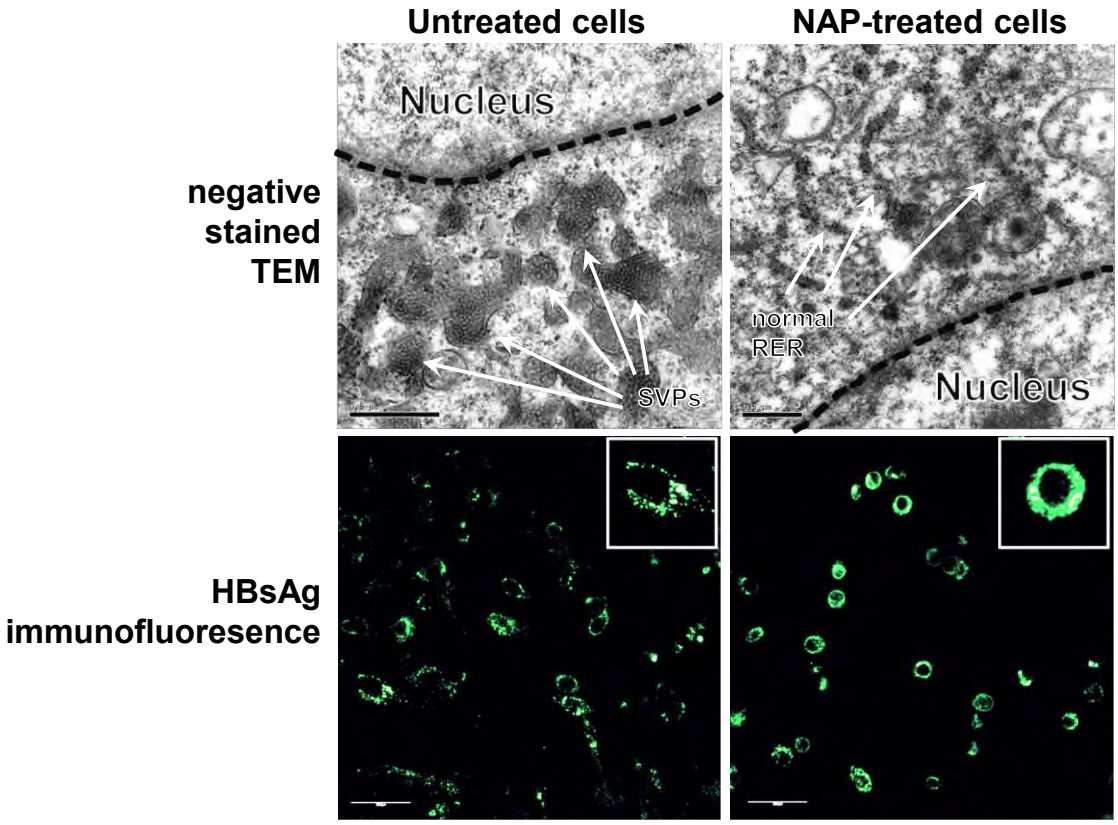
IN VITRO MECHANISM OF ACTION OF NAPs

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 the infected hepatocyte.

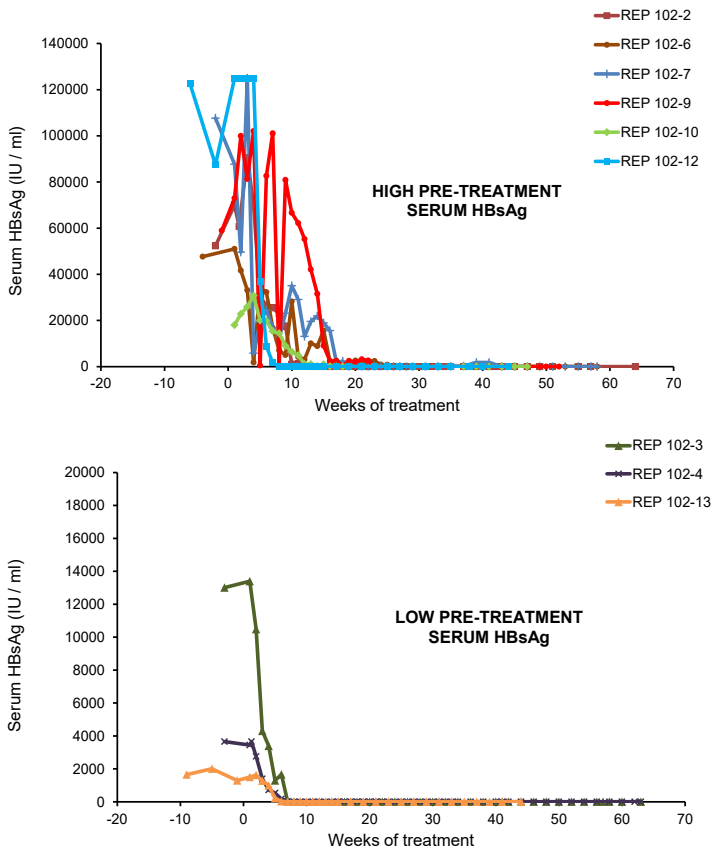


NAP EFFECT ON SUBVIRAL PARTICLE MORPHOGENESIS HBsAg TRANSIT
Formation of subviral particles (SVPs, see upper left panel) in cells expressing HBsAg is absent with NAP treatment (upper right panel). Concurrent with the inhibition of SVP assembly, normal HBsAg transit through the constitutive secretory pathway (bottom left panel) is blocked, resulting in the retention of HBsAg in the perinuclear space (bottom right panel).

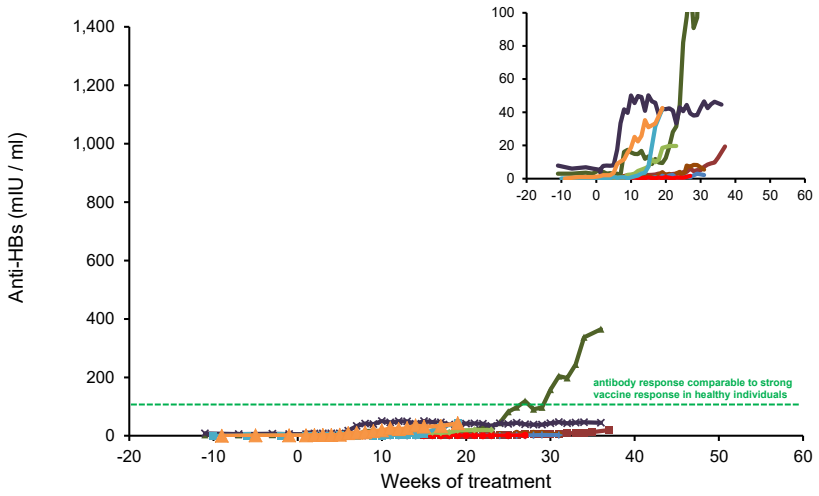
CLINICAL EFFECT OF NAP THERAPY IN PATIENTS WITH CHRONIC HBV

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).

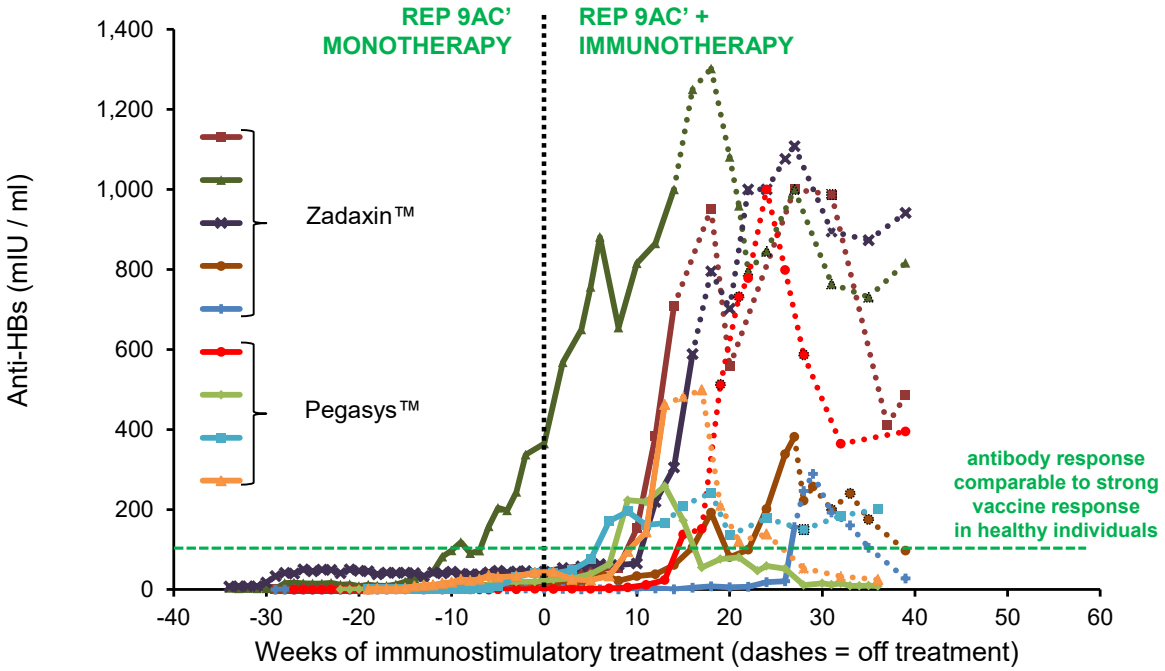
Weekly treatment with REP 2139-Ca rapidly resulted in the elimination of serum HBsAg in patients regardless of their pre-treatment HBsAg setpoints (see below).



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 4 years 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 α1 – 1.6mg SC twice weekly) or Pegasys™ (pegylated interferon α-2a – 90-180 µg SC once weekly).



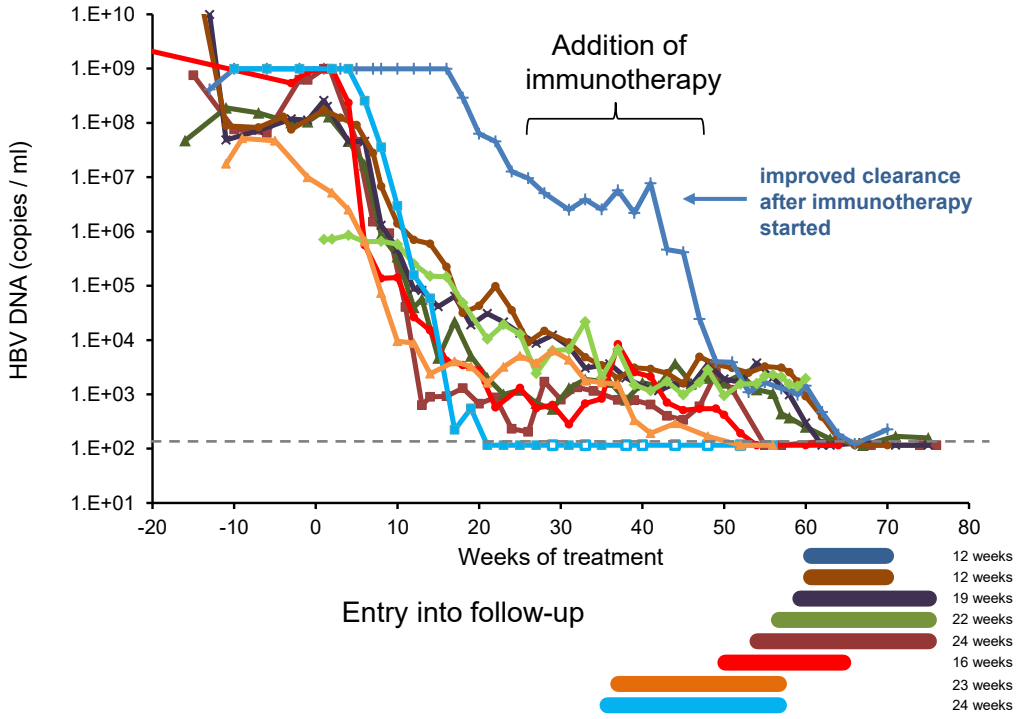
Improvement in anti-HBs titers with short term exposure to immunotherapy. Dashes represent antibody production after cessation of all treatment. Note antibody responses in all patients have been synchronized to the start of add-on immunotherapy (week 0) in the continuing presence of REP 2139-Ca.

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 all 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 durable 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.

Packaging

The REP 2139-Ca drug product container is a 3cc polyethylene syringe with a polyethylene luer lock cap closure packed in a plastic bag containing 5 syringes. Each syringe contains 2.1cc of 25 mg/ml REP 2139-Ca calcium chelate complex (7.5 mg/ml CaCl2-2H20) in normal saline which is sterilized by filtration through a 22 µm filter. The drug product is certified sterile and its pyrogen content meets or exceeds the criteria for allowable pyrogen content for injectable medications.

Storage and drug infusion

Before infusion the luer lock is removed and replaced with a suitable needle for loading the drug into IV bottle. For a typical 500 mg dose, contents of 10 syringes will be loaded into a 200cc glass bottle of normal saline which will then be infused over 2 hours. The drug product is stored between 4 and 30 °C.

8. Background of Peginterferon α-2a

Peginterferon α-2a 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, Peginterferon α-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. Peginterferon α-2a is the only available therapy for chronic hepatitis B or D 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 Peginterferon α-2a because of the risks of severe side effects.

9. Non-Clinical Safety Studies

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

10. Clinical Experience with REP 2139-Ca and Peginterferon α-2a

To date 19 human patients have been exposed to NAPs (8 with REP 2055 (REP 9AC) and 12 with REP 2139-Ca (REP 9AC') where one patient in the REP 2139-Ca group transitioned from REP 2055 to REP 2139-Ca therapy after failing to control his viremia in follow-up) monotherapy with regular weekly administration in the 400-500mg range in regimens lasting 20-62 continuous weeks. Detailed information on the toxicological effects of REP 2139-Ca treatment can be found in the REP 2139-Ca IB.

The novel 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 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. Overall Risk/Benefit Assessment

Key Risks Associated with the Use of REP 2139-Ca

19 patients have been treated with NAPs (8 with REP 2055 and 12 with REP 2139-Ca) in clinical trials (please refer to 1.4.6). Reviewing the safety data from those clinical studies did not reveal any major safety concerns (please see the REP 2139-Ca Investigational Brochure for additional information) but indicated the importance of mineral supplementation in patients receiving REP 2139-Ca 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 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 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 othe 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. 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 exposure to NAPs. All patients receiving REP 2139-Ca 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 19 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-Ca 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.

Risks Associated with the Use of Peginterferon α-2a

Peginterferon α-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 α-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 α-2a, 9% of subjects with HCV developed binding antibodies to Peginterferon α-2a, and 3% of subjects developed low-titer neutralizing antibodies.2

12. Potential Benefits of REP 2139-Ca Treatment

Patients undergoing combination treatment with REP 2139-Ca and Pegasys™ are expected to have a high likelihood of achieving an effective immunological recovery capable of permanent control or eventual elimination of their HBV / HDV co-infection.

13. ETHICAL CONSIDERATIONS

Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (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 (eg, 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 (eg, 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 or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative 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 are 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 or the subject's legally acceptable representative or legal guardian, 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 (eg, subjects with severe 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.

14. INVESTIGATIONAL PLAN

Study Design and Duration

12 chronic HBV / HDV co-infected subjects will be enrolled in this open- label trial. This is a pilot study in order to assess safety and efficacy of the proposed combination theapy in patients with HBV / HDV co-infection. .

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 should comply with the protocol-specified follow-up procedures as outlined in Section 15. 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.
Subjects who withdraw from the study will not be replaced.

Duration of Study Participation

The total duration of this study for each subject is a maximum 93 weeks (6 weeks from screening to first treatment, 63 weeks on-treatment plus 24 weeks post-treatment follow-up).

An analysis of primary endpoints will be conducted after all subjects reach the week 15, week 30 and first post-treatment follow-up visit. An additional analysis will be conducted when all subjects complete the Week 24 post-treatment follow-up visit.

Post Study Access to Therapy

At the end of the study, REPLICor Inc. will not continue to supply study drug to subjects/investigators.

Study Population

For entry into the study, the following criteria MUST be met. Participants will be chosen based on the duration of their HBV / HDV infection, treatment status and HBV / HDV-serology. Goal is to enroll 12 subjects. There will be no randomization as this is a pilot study (proof of principle).

Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Patients chronically infected with HBV and HDV as documented by positive serum HBsAgand HDV RNA at screening and either:
b) Seronegative for HIV, HCV and CMV (IgM).
c) Absence of advanced cirrhosis based on fibroscan evaluation.
d) Body Mass Index (BMI) $\geq$ 18 kg/m^2 and $\leq$ 30 kg/m^2 at screening.

3) Age and Reproductive Status

Males or females 18-55 years of age

Women of childbearing potential (WOCBP) must use an effective methods of birth control throughout the duration of the ontreatment study period to minimize the risk of pregnancy. Women of childbearing potential must follow instructions for birth control for the entire duration of the study.

Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of the investigational product.

Women must not be breastfeeding.

Sexually active men must use an effective method of birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration of the study.

Sexually active men must use an effective method of birth control if their partners are women of childbearing potential (WOCP). Men that are sexually active with WOCP must follow instructions for birth control 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).

Exclusion Criteria

1) Target Disease Exceptions

Positive HCV antibody,or HIV-1/HIV-2 or CMV antibody (IgM) test at screening
Evidence of chronic liver disease caused by diseases other than chronic HBV infection (such as but not limited to: hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, biliary disease, nonalcoholic hepatic steatosis and toxin exposure).

2) Medical History and Concurrent Diseases

a) Current evidence of or history of variceal bleeding, 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) 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)
j) 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.)
k) Presence of diabetes (controlled or uncontrolled).
l) Prior or current history of clinically significant hemoglobinopathy or hemolytic anemia
m) Subjects with pre-existing ophthalmologic disorders considered clinically significant on eye exam.
n) Prior or current history of severe chronic obstructive pulmonary disease, interstitial lung disease or sarcoidosis
o) 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)
p) 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
q) 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
r) 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
s) Current evidence or known history of decompensated cirrhosis based on radiologic criteria or biopsy results and clinical criteria
t) Poor venous access
u) Current use of heparin or coumadin
v) Received blood products within 30 days prior to study enrollment
w) Use of hematologic growth factors within 90 days prior to study enrollment
x) Use of any investigational product within 1 year prior to study enrollment
y) Systemic antibiotics, antifungals, or antivirals for treatment of active infection within 14 days of enrollment.

3) Physical and Laboratory Test Findings

a) Confirmed hemoglobin < 12.0 g/dL (males), < 10.0 g/dL (female)
b) Confirmed platelet count < 90,000/mm3

c) Evidence of significant heavy metal load in whole blood.
d) Confirmed creatinine clearance (CrCl) (as estimated by Cockcroft and Gault) ≤50 mL/min or confirmed creatinine >1.5 mg/dl
e) Confirmed total serum bilirubin is above the normal range.
f) Confirmed INR ≥ 2.0
g) PTT ≥ 2.0 x ULN
h) Confirmed serum albumin ≤ 3.5 g/dL (35 g/L)
i) ALT > 10x ULN
j) Confirmed ANC ≤ 1,500 cells/mm3
k) Diagnosed or suspected hepatocellular carcinoma as evidenced by screening alpha-fetoprotein (AFP) of ≥ 100 ng/mL. If AFP is ≥ 50 ng/mL and < 100 ng/mL, absence of a mass/findings suspicious for HCC must be demonstrated by ultrasound/CT/MRI within the screening period.
l) Poorly controlled diabetes mellitus as evidenced by HbA1C ≥ 8.5% at screening
m) Antinuclear antibody (ANA) titer ≥ 1:640 at screening and/or evidence of autoimmune hepatitis on liver biopsy
n) Evidence of hepatic decompensation in cirrhotic subjects: history of ascites, hepatic encephalopathy or bleeding esophageal varices, and/or screening laboratory results as detailed above
o) QTc interval > 500 msec.

4) Allergies and Adverse Drug Reaction

a) History of hypersensitivity to drugs with a similar biochemical structure to REP 2139-Ca (eg other phosphorothioate oligonucleotides) or Peginterferon α-2a (eg, other interferons).
b) Any other criteria or known contraindication that would exclude the subject from receiving REP 2139-CA or Peginterferon α-2a).

5) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

6) Concomitant Treatments

a) 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.

b) 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 α-2a.

The following restrictions apply at all times:

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 (≥ 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 is prohibited.

Assessment of concomitant medications will be performed at each on-treatment visit.

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 intercurrent 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 (eg, infectious disease) illness
e) Use of an investigational product other than study medication
f) Subjects who appear to have no reduction in serum HBsAg at the end of 30 weeks.
g) Evidence of confirmed hepatic decompensation
h) ALT > 2 x baseline and 10 x ULN for > 12 weeks, and total bilirubin > 2 x ULN
i) Platelets < 25,000/mm3
j) Any Grade 4 AE considered REP 2139-Ca-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 17 for reporting details). Potential DILI is defined as concurrent:

ALT ≥ 5 x baseline or nadir value, whichever is lower for > 12 weeks
AND
ALT ≥ 10 x ULN for > 12 weeks
AND
Total bilirubin ≥ 2 x 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 the REPLICor Inc. 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 (ie, ultrasound)
b) When etiology remains unclear, liver biopsy (if clinically feasible) with light and electron microscopic assessment.

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 in Section 16. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, 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.

7) Discontinuation of the clinical trial

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 the investigational drug (IP) is not beneficial for the condition under study/a solid evidence that the IP is not providing any benefit, OR

b) there is early evidence that the IP is, in contrary, harmful (the emergence of ADRs, SAEs, SUSARs, etc. in > 50% of patients within the first 8 weeks of treatment),

c) It is not feasible to reach the planned outcomes.

15. TREATMENTS

Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to study participation.

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

Study Treatments

Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per label)
REP 2139-Ca (IMP)	500 mg / 250mg (with Peginterferon α-2a)	2.1cc of 25mg/ml in a pre-filled 3cc syringe / open label	Plastic bags containing 5 syringes (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
Peginterferon α-2a (IMP)	180 µg/0,45 mL	0,45 mL pre-filled syringe/open label	Outer carton 1 syringe/open-label	Solution is clear and colorless to light yellow	Store at 2-8oC in the original package. Keep the prefilled syringes in the outer carton to protect from light. Do not freeze or shake.
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	< 25°C
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	< 25°C
Magnesium Caps (NIMP)	Magnesium - 500 mg (per capsule)	Sealed plastic bottle containing 100 capsules		white capsule	< 25°C
Vitamin D3 (NIMP)	5000 IU (per softgel)	Sealed plastic bottle containing 60 soft gels		pale yellow soft gel	< 25°C

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.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: REP 2139-Ca and Peginterferon α-2a. For additional information on REP 2139-Ca, please refer to the REP 2139-Ca IB. For additional information on Peginterferon α-2a, please refer to the package insert or Summary of Product Characteristics (SmPC)/reference label.

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)

Detailed information on these supplements are found in Appendix 3.

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

Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by REPLICor Inc. 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 (eg, required diluents, administration sets). Please refer to Section 19 for information on study drug record retention and information below for destruction and return instructions. **Method of Assigning Subject Identification**

Each subject participating in the study will be given an identification number by the Principal Investigator.

Selection and Timing of Dose for Each Subject

The pre-treatment assessment for this study is 6 weeks. This period will include several subject visit to perform screening assessment and may include unscheduled visits to perform re-testing, if required for safety reasons. Eligible subjects should be dosed within 42 days of the date they were screened.

On Day 1, after all Day 1 procedures have been performed, eligible subjects will start study drugs. On week 16, when combination therapy with REP 2139-Ca and Peginterferon α-2a is started, the first dose of Peginterferon α-2a should be administered after REP 2139-Ca infusion.

Subjects will be dosed as follows:

REP 2139-Ca: 500 mg i.v. once weekly in the clinic for 15 weeks with reduction to 250 mg i.v. weekly on week 16 when Peginterferon α-2a is started not exceeding a total of 30 weeks of REP 2139-Ca exposure.

Peginterferon α-2a: 180 µg s.c. once weekly (starting at week 16) for 48 weeks.

If a subject can not 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 the previous 3 dayes 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-testingcan be arranged, if required for safety reasons.

Dose Modifications

Dose modifications refers to dose adjustments necessary for the management of REP 2139-Ca or Peginterferon α-2a and SAEs. Investigators are encouraged to follow Tables 1, 2, and 3, respectively. These tables are based on recommendations from the Peginterferon α-2a 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 modifications may occur for medical reasons that 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 1: Dose Reductions of REP 2139-Ca and Peginterferon α-2a

Assigned Treatment	Starting Dose	1st Dose Reduction	2nd Dose Reduction
REP 2139-Ca	500 mg	450 mg	400 mg
Peginterferon α-2a	180 µg	135 µg	90 µg

Table 2: REP 2139-Ca and Peginterferon α-2a Dose Modification Guidelines

Toxicity	Dose Modifications	Additional Instructions
Adverse Events (see appendix 2)		
≥ Grade 3 AE considered related to study drug and clinically significant (excluding ALT / AST elevations when bilirubin is <2XULN)	Hold dose until ≤ Grade 1 or baseline value, and then restart at 1st dose reduction level.	Permanently discontinue if either of the following is true: 1) Event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level; 2) Event does not resolve within 14 days of the date that treatment was held (no more than 2 sequential doses can be held).
Hematological Abnormalities ANC		
≥750/mm3	Maintain dose	
≥ 500 to < 750/ mm3	Reduce to 1st dose reduction level.	Permanently discontinue if event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level.
< 500/ mm3	Hold dose until ANC > 1,000/mm3, and then restart pegIFN treatment at the 2nd dose reduction level.	Permanently discontinue and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level; 2) Event does not resolve within 14 days of the date that treatment was held (no more than 2 sequential doses can be held).
Platelets		
≥ 25,000 to < 50,000/ mm3	Reduce to 2nd dose reduction level.	Permanently discontinue if event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level.
< 25,000/ mm3	Permanently discontinue peg IFN.	
Liver Abnormalities		
ALT or AST:		
> 10 x ULN for > 4 weeks, regardless of baseline value when bilirubin > 2 x ULN	Hold dose until ALT or AST ≤ 5 x ULN or ≤ 3 x baseline value, whichever comes first, and then restart pegIFN at the 1st dose reduction level. If recurs, hold dose until ALT or AST ≤ 5 x ULN or ≤ 3 x baseline value, whichever comes first, and then restart pegIFN at the 2nd dose	Permanently discontinue and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level; 2) Event does not resolve within 14 days of the date that treatment was held (no more than 2 sequential doses can be

	reduction level.	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 dose until ALT or AST ≤ 5 x ULN or ≤ 3 x baseline value, whichever comes first, and then restart pegIFN at the 1st dose reduction level. If recurs, hold dose until ALT or AST ≤ 5 x ULN or ≤ 3 x baseline value, whichever comes first, and then restart pegIFN at the 2nd dose reduction level.	Permanently discontinue and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level; 2) Event does not resolve within 14 days of the date that treatment was held (no more than 2 sequential doses can be held); 3) There is evidence of liver decompensation.

Table 3: REP 2139-Ca and Peginterferon α-2a Dose Modification Guidelines

Toxicity	Dose Modifications	Additional Instructions
Bilirubin:		
Total bilirubin > 2.5 x ULN and direct bilirubin > 3 x ULN, regardless of ALT values	Hold dose until total bilirubin ≤ 1.5 x ULN and direct bilirubin ≤ 3 x ULN, and then restart pegIFN at the 1st dose reduction level. If recurs, hold dose until total bilirubin ≤ 1.5 x ULN and direct bilirubin ≤ 3 x ULN, and then restart pegIFN at the 2nd dose reduction level	Permanently discontinue and consult medical monitor if either of the following is true: 1) Event occurs or recurs when subject is receiving pegIFN at the 2nd dose reduction level; 2) Event does not resolve within 14 days of the date that treatment was held (no more than 2 sequential doses can be held); 3) There is evidence of liver decompensation.
Child-Pugh Score:		
≥ 6	Permanently discontinue pegIFN.	
Renal Impairment		
Creatinine Clearance:		
30-50 mL/min	Maintain dose.	
30 mL/min	Reduce to 1st dose reduction level.	
Hemodialysis	Reduce to 1st dose reduction level.	
New Ocular Symptom(s):		
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.
New or Worsening Neuropsychiatric Signs or Symptoms (including Depression b):		
Mild	No change	Evaluate weekly by visit or phone until symptoms improve.
Moderate	Reduce 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 pegIFN.	Psychiatric therapy necessary.

a Liver abnormalities:
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 17 for reporting details).

When subjects have clinical signs of liver abnormalities (eg, 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, 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 (ie, 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 17 for reporting details). Subjects who meet criteria for DILI should be strongly considered for liver biopsy, provided clinical parameters do not contraindicate this.

Dose Interruptions

Should drug interruption/suspension be necessary for any laboratory abnormality or AE, the following rules must be applied, and REPLICor Inc. (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-Ca or Peginterferon α-2a can be held, and if not reinitiated within 14 days 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).

Blinding/Unblinding

Not applicable.

Treatment Compliance

All investigational drug products used in this protocol will be administered under supervision.
Mineral supplement compliance will be checked at regular intervals

Destruction and Return of Study Drug

Destruction of Study Drug

For this study, 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 (eg, cytotoxics 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 drug.

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.

Partially used and empty syringes of Peginterferon α-2a are to be disposed of by the site according to local regulations.

Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by REPLICor Inc. must be returned to REPLICor Inc. The return of study drug will be arranged by the responsible Study Monitor.

Retained Samples for Bioavailability/Bioequivalence

Not applicable.

16. STUDY ASSESSMENTS AND PROCEDURES

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

Procedure / Test	Frequency
Inclusion and Exclusion Criteria	Screening visit
Medical History	Every visit
Vital Signs[1]	Every visit
Physical Examination	Every visit
Eye exam[2]	Screening visit, every 4 weeks on treatment.
Verification of prior / concomitant medications[3]	Every visit
Verification of mineral supplement compliance	Every visit
ECG	Screening, every four weeks on treatment, FW4, 12 and 24
Ultrasound	Screening and weeks 16, 31, 63(EOT) and FW24
Fibromax / Fibroscan	Screening and weeks 31, 63(EOT) and FW24
HBV DNA / HDV RNA viral load	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
HBsAg	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
Anti-HBs / Anti-HDAg	Screening, weeks 1, 2 and then every two weeks during treatment, FW 4, 12, and 24
HBeAg / Anti-HBeAg	Weeks 1, 31, 63 (EOT) and FW24
anti HIV 1+2 / anti-CMV / anti-HCV	Screening visit
ALT / AST / Alkaline Phosphatase[4]	Every visit
GGT	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Total bilirubin[5]	Screening, every two weeks on treatment, FW 4, 12 and 24
Creatinine	Every visit
Biochemistry[6]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Urinalysis(Heme / Protein / Sugar)	Every visit
25 OH vitamin D	Screening, week 1 and every 8 weeks during treatment, FW 24
Heavy metal analysis[7]	Screening visit
Electrolytes[8]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Hematology[9]	Screening, every 4 weeks during REP 2139-Ca, every two weeks during Pegasys and FW4, 12, and 24
INR / PTT / aPTT[10]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
Lipid profile[11]	Screening visit, every 4 weeks on treatment, FW 4, 12 and 24
AFP[12]	Screening visit, week 63 (EOT) and FW2 4
ANA	Screening and weeks 16, 31, 63(EOT) and FW24
Serum pregnancy test[13]	24 hours prior to first drug administration
Urine pregnancy test	Every 4 weeks on treatment, FW 4, FW 12, FW 24
AMA, LKM1[14]	Screening Visit
Frozen serum (4 X 1 cc aliquots) collected	Screening visit, weeks 1, 2, and then every 4 weeks during treatment, FW 4, 12 and 24

NOTES

1. Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at all study visits. Physical measurements including Height measurement will be performed at screening visit and weight measurement for calculation of BMI will be performed at each visit. Blood pressure must be measured before and after REP 2139-Ca administration.
2. An eye exam will be done at screening visit and every 4 weeks on treatment. If the subject has hypertension or a history of pre-existing eye disease detected during screening, the patient will be excluded from trial.
3. Especially review of therapy with an immunomodulatory agent, cytotoxic agent, or systemic corticosteroids within 2 months of screening. Subjects receiving theophylline therapy should undergo frequent monitoring of serum theophylline levels due to the identified increase in theophylline levels with Peginterferon α-2a. Any hematopoietic growth factor medications with known or potential anti-HBV activity other than the assigned study treatment are prohibited.
4. Reflex to GGT if alkaline phosphatase ≥ 3X ULN
5. Reflex to direct bilirubin if abnormal; reflex to GGT if bilirubin ≥ 2X ULN
6. Albumin, Total Protein, LDH, BUN, Phosphate, Uric Acid, Glucose (fasting), HbA1c
7. Cadmium, Lead, Mercury in whole blood
8. Na, HCO3-, K, Cl, Mg, Ca
9. RBC, WBC (count with differential), Reticulocyte count, Hemoglobin, Hemtocrit, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Cell Distribution Width, Platelet Count, Mean Platelet Volume, Neutrophils, Lymphocytes, Monocytes, Eosinophiles, Basophils.
10. INR, PT (reflex to PTT if ≥ 2x PTT elevation), aPTT
11. Triglycerides (fasting), total cholestrol (fasting), HDL (fasting), LDL (fasting)
12. If AFP is ≥ 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.
13. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of the investigational product.

14. AMA, LKM1 are part of a patient's medical care and should be retained on the patient's medical record: these assessments are not required for study puprposes and will not be captured in eCRF.

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. The last day of this study is the day the last patient finishes his follow-up.

Data evaluation will proceed real time as safety and efficacy data become available. After the last patient has finished his follow up, the data analysis in 3 months and final report will be submitted.

Safety Assessments

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.

Laboratory Assessments

The assessments listed above will be analyzed by a central laboratory. 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. (eg, provided electronically). If the units of a test result differ from those printed 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.

The Abbott Architect assay for HBsAg is a chemiluminescent microparticle immunoassay approved in Europe for the detection and quantitation of HBsAg. It is internally calibrated using the World Health Organization standard for HBsAg, and measures HBsAg concentrations within the range of 0.05 to 250 IU/mL. The manufacturer recommends a 1:500 dilution of the test samples. Samples with HBsAg levels above or below this range require a lower or greater dilution in the manufacturer's diluent to bring them into the range of the calibration curve. The lower limit of detection of this assay is 0.05 IU/mL.

The Abbott Architect Anti-HBs assay determines the concentration of antibody to Hepatitis B surface antigen (anti-HBs) present in human serum and plasma. Samples with anti-HBs concentration less than 10.0 mIU/mL are considered non-protective by the Anti-HBs assay. Samples with anti-HBs concentrations greater than or equal to 10.0 mIU/mL are considered protective.

Adverse Events Assessments

Subjects will be closely monitored throughout the study for AEs. 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.

Vital Signs and Physical Examinations

Vital signs (seated blood pressure and heart rate), weight, and physical measurements and examinations must be performed at all study visits outlined. Height measurement will be performed at screening and weight measurement for calculation of BMI will be performed at each visit.

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

A full physical examination will be performed at the Screening visit, whereas a targeted physical exam will occur at Day 1 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.

An eye exam will be done at Screening. If the subject has hypertension or a history of pre-existing eye disease the patient will be excluded from the trial. Eye exams will continue to be performed every 4 weeks during treatment. The routine eye exam is should be limited to:

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

Liver assessment will include scheduled ultrasound, FibroMax and Fibroscan evaluations scheduled as described above.

Electrocardiogram

An ECG performed while the subject is resting in a supine position will be recorded at study visits outlined above. The ECG should be recorded after the subject has been supine for at least 5 minutes.

Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to REPLICor Inc. on a CRF. Additional procedures and assessments may be performed as part of the subject's standard medical care; however data for these assessments should remain in the subject's medical record.

Primary Safety Assessment

Analysis of laboratory results and AEs / SAEs at treatement Weeks 16, 31 and 63 will be used to assess safety.

Key Secondary Efficacy Assessments

Analysis of all HBV / HDV serum virology results will be use to assess key efficacy endpoints.

Specified Order of Procedures during Study Visits

The following order of procedures (when scheduled) should be followed for every patient visit:

1. Serum pregnancy test (WOCBP)
2. Assess vital signs prior to administration of treatment (including blood pressure)
3. Measure weigh and calculateBMI using height value obtained at screening
4. Physical Exam
5. Eye Exam
6. Symptoms experiences during the previous week
7. Urine sample for urinalysis.
8. Blood samples for virology / chemistry sampling / frozen sample (THIS MUST BE DONE BEFORE REP 2139-Ca ADMINISTRATION)
9. REP 2139-Ca administration
10. Symptoms during REP 2139-Ca infusion
11. BP post REP 2139-Ca infusion.
12. Pegasys administration (when scheduled)
13. Verification of mineral supplementation
14. Verification of any concurrent medication
15. Recording of any adverse events.

17. 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 [eg, 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 (eg, 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 (eg, 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 (eg, 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
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 (eg, Investigator Brochure for the investigational product)

Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see above). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious 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 nonserious 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 (eg, 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).

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.

18. STASTICAL CONSIDERATIONS

Enrolled subjects are those who signed an informed consent form and were assigned a Patient Identification number (PID).

Treated subjects are subjects who received at least 1 dose of study therapy.

Categorical variables will be summarized with counts and percents. Confidence intervals for difference in proportions will be based on the normal approximation with unpooled proportions used in the computation of the standard error of the difference. Continuous variables will be summarized with univariate statistics (eg, mean, median, standard error).

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.

Baseline demography, HBV disease characteristics, and other baseline laboratory values will be tabulated by treatment regimen, including:

- Demographics: age, race, gender, ethnicity

- Disease characteristics at baseline: HBsAg level, HBV DNA / HDV RNA level, anti-HBs /anti-HDAg level, and cirrhosis status
- Physical measurements at screening: height, weight, BMI
- Laboratory tests at baseline
- Prior medications.

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

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.

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.

19. 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 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 productand

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 (eg, relocation, retirement) the records shall be transferred to a mutually agreed upon designee (eg, 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
- nonstudy disposition (eg, 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

ThePrincipal Investigator will be a Signatory Investigator 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).

20. 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 is 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 numerized 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 complementations, 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 19.

21. REFERENCES

1. Hoffman La Roche. PEGASYS - pegInterferon alfa-2a injection, solution (prescribing information).
2. ICH Harmonised 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.
3. ICH Harmonised 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.
4. ICH Harmonised 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..
5. ICH Harmonised 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.
6. ICH Harmonised 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.

22. 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.

23. APPENDIX 2 DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs
The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> **Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies
For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5
For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table
In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1
Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges
In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic)				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection. Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection. Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9/L – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9/L – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9/L – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9/L – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9/L – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9/L – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9/L – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9/L – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9/L – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9/L – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9/L – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9/L – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

*Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin)

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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Comment: Added ULN to Grade 1 parameter					
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*

[1] Values are for term infants. Preterm infants should be assessed using local normal ranges.

[2] Use age and sex appropriate values (e.g., bilirubin).

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DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

[1] Values are for term infants. Preterm infants should be assessed using local normal ranges.

[2] Use age and sex appropriate values (e.g., bilirubin).

24. APPENDIX 3: NON-INVESTIGATIONAL PRODUCTS

LifeExtension®

http://www.lef.org/

Bone Restore
120 capsules
Item Catalog Number: 01726

Throughout life, cells known as osteoblasts construct bone matrix and fill it with calcium. At the same time, osteoclasts work just as busily to tear down and resorb bone. This fine balance is regulated by many factors, including systemic hormones and cytokines. Bone mass reaches its peak by the middle of the third decade of life and plateaus for about ten years, during which time bone turnover is constant, with bone formation approximately equaling bone resorption.[1,2]

As our bodies age, this fine balance is lost. As the relative hormone levels shift in midlife — more drastically in women than in men — the osteoclasts gain the upper hand and bone mass begins to dwindle. Some bone is already being lost by the time women reach menopause, but the rate of loss can increase up to tenfold during the first five years after menopause.[2-4]

Bone density loss is not just associated with calcium deficiency, but also with an insufficient intake of a host of other nutrients[5-12] including **magnesium**[11,12] and **vitamin D3**.[13,14] In order for calcium to help maintain healthy bones, adequate amounts of vitamin D3, zinc,[15,16] magnesium,[17] manganese,[9] and other nutrients should be available so that calcium and phosphorus can be incorporated into the bone matrix. Additionally, many forms of calcium are not particularly well absorbed.[18-20]

While loss of bone mineral density is more commonly experienced by women, aging men can also have this issue.[21] Both men and women may experience significant deficits of magnesium if they do not supplement. Bone Restore now contains 300 mg of magnesium. Magnesium is not only needed to maintain strong bones, but it is critical to promoting a healthy vascular system.[22,23] In fact, magnesium is critical for facilitating hundreds of enzymatic reactions that our bodies require to maintain optimal health.[24,25]

To overcome the impediments that preclude aging adults from achieving optimal calcium status, Life Extension offers a proprietary comprehensive mineral formula called **Bone Restore** which has been designed to support healthy bone density and strength. Bone Restore provides **700 milligrams** of **elemental calcium** from three different forms, along with the critically important nutrients magnesium,[17] boron,[5,26,27] zinc,[8,15,16] silicon,[28-30] manganese[9] and vitamin D3[13,14] needed for healthy bones.

In fact, the boron in this formula, called **FruiteX B® OsteoBoron®**, is a calcium/carbohydrate/boron complex, similar to what is found in fruits and vegetables and is more bioavailable than boron citrate. Scientific research has established the beneficial effects of boron on the strength of bones and joints.[5,31-34]

One reason why aging people experience bone mineral density loss even though they are taking calcium supplements is that they may not be **absorbing** enough elemental **calcium**. Bone Restore provides calcium in capsule form to ensure that it breaks down fully in the digestive tract.

Calcium and other minerals are best not taken with fiber, because fiber can interfere with their absorption.[35-37] There is evidence that calcium from supplements and dairy foods may inhibit iron absorption, although it has been very difficult to distinguish between the effects of calcium on iron absorption versus other inhibitory factors, such as phytate.[38-40] Although current understanding of this suggests that the inhibition of calcium on absorption of iron is of short duration and the body has adaptive mechanisms.[41]

Calcium supplements are best taken with meals. They should always be taken with a full glass of water, juice, or other liquid to enhance solubility.[42] If calcium-containing formulas are taken only once daily, they may be best taken in the evening.[43]

References

1. *Acta Obstet Gynecol Scand.* 1993 Apr;72(3):148-56.

2. *Rheum Dis Clin N Am* 33 (2007) 149-176
3. *Eur J Clin Invest*. 1988 Oct;18(5):529-34.
4. *Bone*. 2001 Mar;28(3):327-31.
5. *Magnes Trace Elem*. 1990;9(2):61-9.
6. *Curr Pharm Des*.2003;9(32):2687-704.
7. *Ann Nutr Metab. 2002;46(6):249-53.*
8. *J Int Med Res*. 2007 Sep-Oct;35(5):692-5.
9. *J Nutr*. 1994 Jul;124(7):1060-4.
10. *Crit Rev Food Sci Nutr*. 2006;46(8):621-8.
11. *Magnes Res*. 1993 Jun;6(2):155-63.
12. *J Reprod Med*. 1990 May;35(5):503-7.
13. *J Clin Endocrinol Metab*. 2010 Jun;95(6):2630-3.
14. *Am J Clin Nutr*. 1995 Mar;61(3 Suppl):638S-45S.
15. *Ann Nutr Metab*. 2009;54(3):218-26
16. *Toxic Sci*. 2006 Jul;92(1):286-94
17. *PDR for Nutritional Supplements*, 1st ed. Montvale, NJ: Medical Economics Co.; 2001:288-95.
18. *J Nutr Sci Vitaminol* (Tokyo). 1999 Oct;45(5):509-17.
19. *Methods Find Exp Clin Pharmacol*. 1995 Sep;17(7):437-42.
20. *Scand J Gastroenterol. 2010;45(2):133-8.*
21. *Osteoporos Int*. 2009 Jul;20(7):1175-82.
22. *Congest Heart Fail*. 2006 Jan-Feb;12(1):9-13.
23. *Br J Sports Med*. 2006 Sep;40(9): 773-8.
24. *Front Biosci*. 2004 May 1;9:1278-93.
25. *South Med J*. 2001 Dec;94(12):1195-201.
26. *PDR for Nutritional Supplements*, 1st ed. Montvale, NJ: Medical Economics Co.; 2001:60-3.
27. *Environ Health Perspect. 1994 Nov;102 Suppl 7:59-63.*
28. *Bone*. 2003 Feb;32(2):127-35.
29. *Magnes Res*. 1993 Sep;6(3):247-9.
30. *Biol Trace Elem Res*. 2009 Jun;128(3):239-47.
31. *Environ Health Perspect*. 1994 Nov;102 Suppl 7:83-5.
32. *Crit Rev Food Sci Nutr*. 2003;43(2):219-31.
33. *Prog Food Nutr Sci*. 1993 Oct-Dec;17(4):331-49.
34. *Nutr Rev*. 2008 Apr;66(4):183-91.
35. *Am J Clin Nutr*. 2010 May;91(5):1461S-1467S.
36. *Diabetes Care*. 2009 Jun;32(6):990-5.
37. *Am J Clin Nutr*. 2010 May;91(5):1430S-1432S.
38. Institute of Medicine Washington, DC: National Academy Press, 2001. http://www.nap.edu/openbook.php?record_id=10026&page=292
39. *Am J Clin Nutr*. 1991 Jan;53(1):106-11.
40. *Am J Clin Nutr*. 1998 Jul;68(1):96-102.
41. *Int J Vitam Nutr Res*. 2010 Oct;80(4-5):293-9.
42. *Osteoporos Int*. 1991 Feb;1(2):65-71.
43. *J Clin Endocrinol Metab*. 1994 Sep;79(3):730-5.

Supplement Facts

Serving Size 4 capsules
Servings Per Container 30

Amount Per Serving	
Vitamin D3 (as cholecalciferol)	1000 IU
Calcium (as DimaCal® dicalcium malate, TRAACS® calcium bisglycinate chelate, calcium fructoborate)	700 mg
Magnesium (as magnesium oxide)	300 mg
Zinc (as zinc amino acid chelate)	2 mg
Manganese (as manganese amino acid chelate)	1 mg
Silicon [from horsetail (*Equisetum arvense*) extract (herb)]	5 mg
Boron (calcium fructoborate as patented Fruitex B® OsteoBoron®)	3 mg

Other ingredients: vegetable cellulose (capsule), vegetable stearate, maltodextrin, corn starch.

Fruitex B® and OsteoBoron® are registered trademarks of VDF Futureceuticals, Inc. U.S. Patent No. 5,962,049. DimaCal® and TRAACS® are registered trademarks of Albion Laboratories, Inc. Malate is covered by U.S. Patent 6,706,904 and patents pending.

Dosage and Use

- Take four capsules daily, or as recommended by a healthcare practitioner.

- Scientific studies suggest calcium supplementation in divided doses with food in the morning and evening may yield the best results.
- Maintaining an optimal vitamin D blood level also helps maximize calcium absorption.

Warnings

- **KEEP OUT OF REACH OF CHILDREN.**
- **DO NOT EXCEED RECOMMENDED DOSE.**
- **Do not purchase if outer seal is broken or damaged.**
- **When using nutritional supplements, please consult with your physician if you are undergoing treatment for a medical condition or if you are pregnant or lactating.**

To report a serious adverse event or obtain product information, contact 1-866-280-2852.

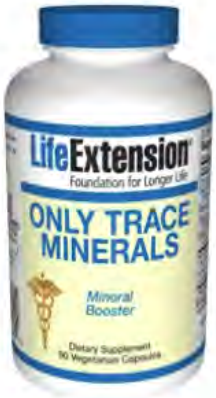
These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.

LifeExtension®

LifeExtension®

http://www.lef.org/



Only Trace Minerals

90 vegetarian capsules

Item Catalog Number: 01328

Zinc is a mineral that stimulates the activity of approximately 300 enzymes, which are substances that promote biochemical reactions in your body.[131,132] These reactions are essential for the formation of superoxide dismutase, one of the body's most important free radical scavengers. Zinc also promotes immune function,[133-136] taste sensitivity,[137-139] protein and DNA synthesis,[131,140,141] insulin production,[142,143] reproductive organ development and sperm motility.[144-146] Zinc also supports normal growth and development during pregnancy, childhood, and adolescence.[147-149] Age-related declines in immune function are associated with zinc deficiency, and the elderly represent a group that is vulnerable to mild zinc deficiency. Certain aspects of immune function in the elderly have been found to improve with zinc supplementation.[133-135,137,150,151]

Chromium plays an important role in maintaining healthy blood sugar levels in those within normal levels when used as part of a healthy diet.[123-125]

Boron is an essential nutrient for optimal calcium metabolism and healthy bones and joints.[34,53,58,61,168] Boron may affect human steroid hormone levels. Dietary boron intake may support a healthy prostate.[169-173]

Vanadyl sulfate is an effective form of the trace mineral vanadium. Research indicates vanadyl sulfate may improve tissue sensitivity and promote already healthy glucose metabolism for those within normal range.[174-178]

Individuals consuming over 50 mg of zinc daily and/or a high level of fructose are advised to supplement their diet with 2 mg copper several times per week.[179-183] Copper is required by the body to convert iron into hemoglobin[184] and is an essential constituent of many important body enzymes including a form of superoxide dismutase, a major cellular antioxidant.[185]

Only Trace Minerals provides bioavailable forms of minerals in a convenient, low-cost supplement.

References

Supplement Facts

Serving Size 1 vegetarian capsule
Servings Per Container 90

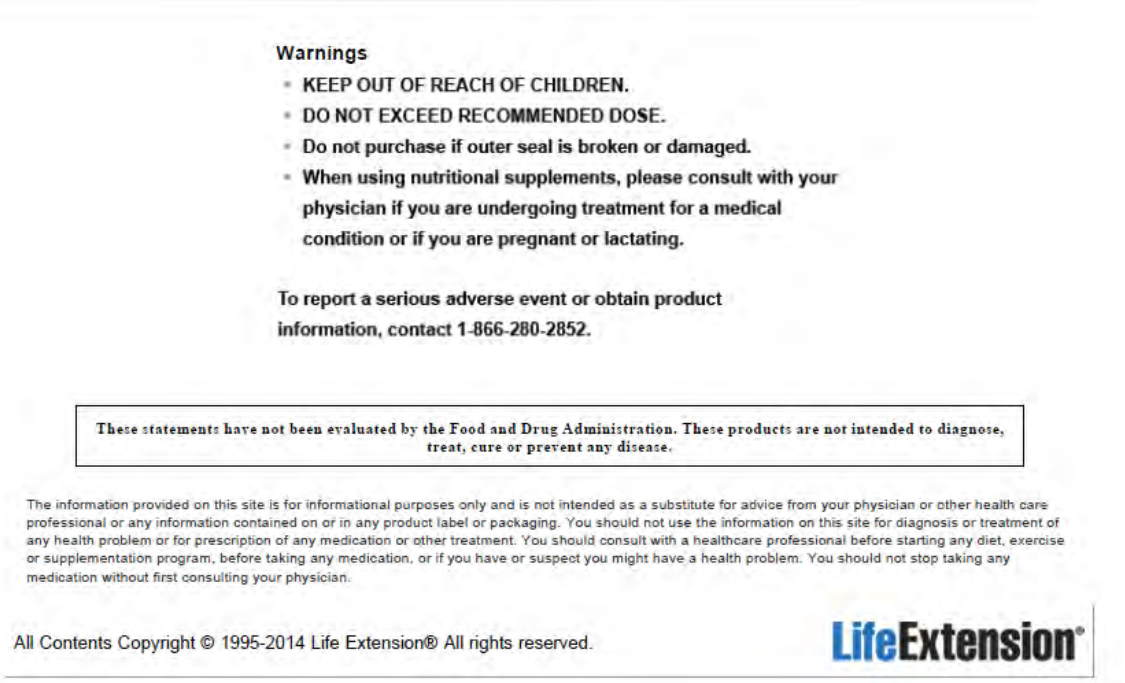
Amount Per Serving	
Zinc (as OptiZinc® zinc monomethionine)	20 mg
Copper (as TRAACS® copper bisglycinate chelate)	2 mg
Manganese (as manganese sulfate)	2 mg
Chromium (as TRAACS® chromium nicotinate glycinate chelate)	400 mcg
Molybdenum (as TRAACS® molybdenum glycinate chelate)	250 mcg
Boron (as boron citrate, aspartate glycinate complex)	3 mg
Vanadyl sulfate (providing 750 mcg vanadium)	3.75 mg

Other ingredients: microcrystalline cellulose, vegetable cellulose (capsule), vegetable stearate, maltodextrin.

OptiZinc® is a registered trademark of InterHealth Nutritionals, Inc.
TRAACS® is a registered trademark of Albion Laboratories, Inc.

Dosage and Use

- Take one capsule daily with food, or as recommended by a healthcare practitioner.



Warnings

- KEEP OUT OF REACH OF CHILDREN.
- DO NOT EXCEED RECOMMENDED DOSE.
- Do not purchase if outer seal is broken or damaged.
- When using nutritional supplements, please consult with your physician if you are undergoing treatment for a medical condition or if you are pregnant or lactating.

To report a serious adverse event or obtain product information, contact 1-866-280-2852.

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LifeExtension®

LifeExtension®

http://www.lef.org/

Magnesium Caps

500 mg 100 vegetarian capsules

Item Catalog Number: 01459

Many Americans do not obtain adequate amounts of magnesium in their diets.[83]

Magnesium is one of the body's most important minerals. It is required as a cofactor in hundreds of enzymatic processes within cells.[16] It helps maintain normal muscle and nerve function, keeps heart rhythm steady, promotes healthy cardiovascular function, supports a healthy immune system, and keeps bones strong. Magnesium also helps maintain blood sugar and blood pressure levels already within normal range, and it is known to be involved in energy metabolism and protein synthesis.[17,18]

Magnesium is a major factor in relaxing the smooth muscles within the blood vessels, thereby reducing peripheral vascular resistance and promoting a healthy cardiovascular system.[19-21] Magnesium also affects circulating levels of norepinephrine and the synthesis of serotonin and nitric oxide.[22-24]

Magnesium positively influences the bone mineral matrix and its ability to metabolize minerals needed for repair and rebuilding.[25,26] Scientific literature documents the need for a wide range of minerals, including calcium and magnesium, that are vital to maintaining strong, healthy bones.

Moreover, there is strong evidence that dietary magnesium intake and supplementation improves the metabolic profile.[86-88] Magnesium has been shown to beneficially impact insulin resistance, serum lipid profiles, inflammation, endothelial function, oxidative stress and platelet aggregability.[89]

Since magnesium is so inexpensive, everyone should consider supplementing with at least 500 mg of magnesium daily.

Magnesium Caps provides one of the highest concentrations of elemental magnesium per capsule available on the market.

References

Supplement Facts

Serving Size 1 vegetarian capsule
Servings Per Container 100

Amount Per Serving	
Magnesium (as magnesium oxide, citrate, succinate, TRAACS® magnesium lysyl glycinate chelate)	500 mg

Other ingredients: vegetable cellulose (capsule), microcrystalline cellulose, ascorbyl palmitate, medium chain triglycerides, silica, citric acid.

TRAACS® is a registered trademark of Albion Laboratories, Inc.

Dosage and Use

- Take one capsule one to three times daily with or without food, or as recommended by a healthcare practitioner.

Caution

If taken in high doses, magnesium may have a laxative effect. If this occurs, divide dosing, reduce intake, or discontinue product.

Warnings

- KEEP OUT OF REACH OF CHILDREN.
- DO NOT EXCEED RECOMMENDED DOSE.
- Do not purchase if outer seal is broken or damaged.
- When using nutritional supplements, please consult with your physician if you are undergoing treatment for a medical condition or if you are pregnant or lactating.

To report a serious adverse event or obtain product information, contact 1-866-280-2852.

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.

The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.

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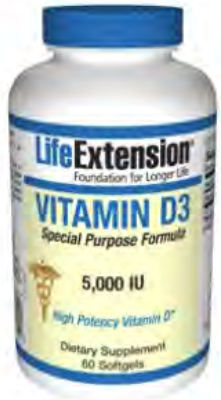

Vitamin D3
Special Purpose Formula
5,000 IU 60 softgels
Item Catalog Number: 01713

Vitamin D3 can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation from sunlight. But, due to the winter season, weather conditions, and sun block, the body's ability to produce optimal vitamin D levels may be inhibited.[87] These factors point to the value of taking a daily vitamin D supplement.

Vitamin D has long provided significant support for healthy bone density.[88-94] However, scientists have also validated the critical role that vitamin D plays in regulating healthy cell division and differentiation, and its profound effects on human immunity.[95-101] These findings link a deficiency of vitamin D to a host of common age-related problems.

The current RDA is only 600 IU. As a result of startling evidence of a widespread vitamin D deficiency, prominent nutritional scientists are calling on Americans to increase their vitamin D intake to 1,000 IU per day and higher. Currently, most experts in the field believe that intakes of between 1,000 and 10,000 IU for adults will lead to serum 25(OH)D levels above those indicative of vitamin D deficient levels, at approximately 80 nmol/L or 32 ng/mL.

Life Extension recommends that healthy adults supplement each day with at least 2,000 IU of vitamin D. Elderly adults may benefit from higher doses such as 5,000 IU daily up to 10,000 IU daily. The objective of taking a vitamin D supplement is to achieve an optimal 25-hydroxy vitamin D blood level of between 50-80 ng/mL.

Vitamin D in the amount of 2,000 IU is contained in the multi-nutrient Life Extension Mix™ and the multivitamin Two-Per-Day Tablets. A vitamin D blood test can help you determine the additional amount of vitamin D you may need to supplement to achieve an optimal level.

For those already obtaining 1,000-3,000 IU of vitamin D in their multinutrient formulas, this **5,000 IU** potency is what many need to achieve optimal vitamin D blood levels.

References

Supplement Facts

Serving Size 1 softgel
Servings Per Container 60

Amount Per Serving	
Vitamin D3 (as Cholecalciferol)	5,000 IU

Other ingredients: extra virgin olive oil, gelatin, glycerin, purified water, medium chain triglycerides oil.

Dosage and Use

- Take one softgel daily with food, or as recommended by a healthcare practitioner.

Caution

Individuals consuming more than 2,000 IU/day of vitamin D (from diet and supplements) should periodically obtain a serum 25-hydroxy vitamin D measurement. Do not exceed 10,000 IU per day unless recommended by your doctor. Vitamin D supplementation is not recommended for individuals

with high blood calcium levels.

Warnings

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