Altimmune, Inc.
910 Clopper Road, Suite 201 S
Gaithersburg, MD 20878
USA

Clinical Study Protocol

DRUG:	HepTcell (Adjuvanted FP-02.2)
STUDY NUMBER:	ALT-301-202
PROTOCOL TITLE:	Phase 2, Double-blind, Randomized, Placebo-controlled Study of HepTcell (Adjuvanted FP-02.2) as an Immunotherapeutic Vaccine in Treatment-naïve Patients with Inactive Chronic Hepatitis B (CHB)
IND NUMBER	IND 20482
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SPONSOR:	Altimmune, Inc.

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Confidentiality Statement

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: Phase 2, Double-blind, Randomized, Placebo-controlled Study of HepTcell (Adjuvanted FP-02.2) as an Immunotherapeutic Vaccine in Treatment-naïve Patients with Inactive Chronic Hepatitis B (CHB)

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Protocol Version Date: 24 July 2022

This study protocol was subject to critical review and has been approved by the Sponsor representative.

M. Scott Harris
Chief Medical Officer
Altimmune, Inc.
910 Clopper Road
Suite 201S, Gaithersburg, MD 20878

M. Scott Harris, MD Digitally signed by MATTHEW SCOTT HARRIS Date: 2022-07-24 22:41:33-04:00

Signature and Date: _____

PROTOCOL ALT-301-202

Phase 2, Double-blind, Randomized, Placebo-controlled Study of HepTcell (Adjuvanted FP-02.2) as an Immunotherapeutic Vaccine in Treatment-naïve Patients with Inactive Chronic Hepatitis B (CHB)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to HepTcell are the confidential and proprietary information of Altimmune, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Altimmune, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Altimmune, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about HepTcell and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date (dd-mmm-yyyy) Site Number

STUDY SUMMARY

Sponsor: Altimmune, Inc.
Study Title: Phase 2, Double-blind, Randomized, Placebo-controlled Study of HepTcell (Adjuvanted FP-02.2) as an Immunotherapeutic Vaccine in Treatment-naïve Patients with Inactive Chronic Hepatitis B (CHB)
Study Number: ALT-301-202
Study Phase: 2
Study Centers: Approximately 35 study centers in North America, Europe, United Kingdom and Asia-Pacific
Number of Patients Planned: Approximately 80 patients with inactive CHB and low hepatitis B surface antigen (HBsAg) levels (10 to 200 IU/mL) randomized 1:1 to HepTcell or placebo and stratified by study center
Duration of Patient Participation: Each patient will participate in the study up to approximately 77 weeks (a 5-week Screening Period, a 24-week Treatment Period, and a 52-week Follow-Up Period commencing after the last dose of study medication at Week 20)
Enrollment Period: Approximately 24 months
Test Product: HepTcell (adjuvanted synthetic fluoropeptide hepatitis B immunotherapeutic vaccine) 150 µg of each fluoropeptide + IC31® (500/20 nmol KLK/ODN1a) administered by intramuscular (IM) injection at intervals of 4 weeks for 6 doses
Study Objectives: Primary Objective: To assess virologic response to HepTcell in treatment-naïve patients with inactive CHB Secondary Objectives: • To assess cellular immune response of HepTcell in treatment-naïve patients with inactive CHB • To assess the safety of HepTcell in treatment-naïve patients with inactive CHB
Study Design: This study is a Phase 2, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the antiviral effects, immunogenicity, and safety of HepTcell in treatment-naïve patients with inactive CHB and low HBsAg levels (10 to 200 IU/mL). After providing informed consent, patients will undergo a screening period of up to 35 days. A Fibroscan will be performed in all patients who have not had this examination within the previous 12 months before screening, with the exception of

patients with a prior history of liver biopsy within the past 2 years demonstrating no evidence of significant fibrosis.

Patients who meet inclusion and exclusion criteria will be randomized in a 1:1 ratio to receive 6 IM doses of HepTcell or placebo (normal saline) at study visits 4 weeks apart (Days 1, 29, 57, 85, 113, 141). Randomization may occur up to 3 working days before the first day of dosing to allow for the possible preparation of study medication by a central pharmacy and shipment to the study site. Adverse events (AEs) will be monitored, and blood samples will be collected for quantitative HBsAg (qHBsAg), anti-HBsAg antibodies (anti-HBs), hepatitis B virus (HBV) DNA, HBV pre-genomic RNA (pg-RNA), hepatitis B core-related antigen (HBcrAg), and interferon-gamma (IFN-γ) enzyme-linked immunosorbent spot (ELISpot) assay in peripheral blood mononuclear cells (PBMCs). Patients will record any reactogenicity events for 7 days after each administration of study medication in a diary. A visit consisting of a targeted physical examination and safety laboratory tests, including liver panels, will be conducted 7±2 days after administration of Doses 1 and 2 of study medication. These visits may be conducted at home or workplace or, in part, as a telemedicine visit, at the discretion of the Investigator.

If the patient has experienced an acute illness or temperature > 38°C in the 2 days prior to dosing, the administration of study medication and corresponding visit will be delayed until the illness or fever has resolved.

A Safety Committee will conduct regular blinded reviews of all AEs and reactogenicity events. The safety of study participants will also be overseen by an unblinded Data Monitoring Committee (DMC); its responsibilities will be laid out in a DMC charter.

A sentinel cohort of 12 patients (6 receiving HepTcell and 6 placebo) will undergo blinded safety review by the Safety Committee 7 to 10 days after all ongoing patients in the sentinel cohort have completed the respective dose of study medication and will determine the decision to continue at that dose to the expanded cohort. Safety will be assessed in the sentinel cohort before each dose is administered to the expanded cohort. If any of the Stopping Rules (below) are met in one or more patients and the event(s) is deemed possibly or probably related to HepTcell, dosing will be suspended pending DMC review. DMC recommendations may include instituting modifications to ensure the safety of continued dosing or discontinuing the study. If none of the Stopping Rules are met, randomization and dosing may continue in the expanded study cohort. Patients will be unblinded as necessary as to assess the relationship between the study medication and events that meet criteria for Stopping Rules.

Safety laboratory testing (Table 3), including liver panel, for Doses 1 and 2 will be obtained during the visits conducted 7±2 days after these doses of study medication. Safety laboratory testing following Doses 3, 4 and 5 will be obtained in the interval from 7 days after dose administration and before the next dose of study medication is administered. Safety labs after Dose 6 will be assessed at the Day 169 visit. Investigators will review the eligibility of all patients prior to dosing to determine if the next treatment is to be administered. Eligibility for the next treatment will include:

1) confirmation that patients did not meet a Stopping Rule (below); 2) confirmation that the pre-treatment liver parameters are within acceptable ranges for treatment (below); 3) confirmation that patients do not have a new confirmed or suspected immune-mediated medical condition (IMC) (Appendix 2). Patients not meeting these criteria will not be treated.

If abnormalities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, or international normalized ratio (INR) are reported after dosing is commenced, the following monitoring and dosing rules will be applied:

Toxicity	**Management**	**Discontinuation of Study Medication**
ALT or AST ≥ 5× but < 10× ULN, *and* Total and direct bili < 1.5× ULN, *and* INR < 1.3 × ULN	Continue dosing Monitor liver panel weekly If ALT/AST fall to <1.5× ULN, stop weekly monitoring	
ALT or AST ≥ 10× ULN, *and* Total and direct bili < 1.5× ULN, *and* INR < 1.3 × ULN	Interrupt dosing Monitor liver panel weekly If ALT/AST fall to <5× ULN, restart dosing; if ALT/AST fall to <1.5×, stop weekly monitoring	If the event does not resolve in 4 weeks or recurs, consult medical monitor about discontinuing study medication
ALT or AST ≥ 5× ULN, *and* Total or direct bili ≥ 1.5× ULN, *or* INR ≥ 1.3 × ULN		Discontinue study medication
ALT or AST < 5× ULN, *and* Total or direct bili ≥ 1.5× ULN, *or* INR ≥ 1.3 × ULN	Interrupt dosing Monitor liver panel weekly If total and direct bili fall to <1.5 × ULN and/or INR falls to < 1.3× on 2 consecutive tests, stop weekly monitoring and restart dosing	If the event does not resolve in 4 weeks or recurs, consult medical monitor about discontinuing study medication

For patients with Gilbert Syndrome, the 1.5 × ULN criteria for total and direct bilirubin will be replaced with a 1.5 × ULN for direct bilirubin and there will be no monitoring criteria for total bilirubin [Fontana 2020]. Other etiologies of ALT, AST, total and direct bilirubin, and INR elevations, such liver injury induced by other drugs and other viral infections, should be ruled out and treated accordingly.

If a patient prematurely discontinues study medication on or before Day 169, the Day 169/Early termination procedures will be performed. Patients who prematurely discontinue study medication will remain in the study for follow-on study assessments.

Patients will be followed for 52 weeks after the last dose of study medication (504 days beyond Day 1 for patients who complete the 24-week Treatment Period).

AEs and concomitant medications will be recorded from the signing of informed consent to Day 169, but only medically-attended adverse events (MAEs), new-onset chronic illnesses (NCIs), and IMCs, which will be categorized as AEs, will be followed subsequently. Likewise, concomitant medications will be recorded through Day 169, but only immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury will be recorded beyond this point. At the end of the clinical trial, the decision about follow-on treatments and medical care will be made by the patient's medical physician or medical team in accordance with the usual standard of care.

Patients will be required to limit their alcohol consumptions to no more than moderate intake (defined as 2 drinks/day for men and 1 drink/day for women) during their participation in the study.

Risk-factor appropriate surveillance for hepatocellular carcinoma (HCC) may be performed at the discretion of the investigator.

The measures to be taken at each investigative site to minimize the risks of COVID-19 will be communicated to the patient, along with any changes to the risks of study participation that occur as a result of changing local COVID-19 conditions. Study participants will not be prevented from receiving COVID-19 vaccines during their trial participation and will be advised accordingly. If an authorized COVID-19 vaccine has been administered in proximity to a scheduled investigational product (IP) administration, a ± 3 day window is allowed for IP dosing.

Stopping Rules:

In consultation with the DMC, the following Stopping Rules will be applied:

- ALT or AST ≥ 10 × upper limit of normal (ULN)
- INR ≥ 1.3
- Total bilirubin ≥ 1.5× ULN (excluding patients with Gilbert Syndrome)
- Direct bilirubin ≥ 1.5× ULN (for patients with Gilbert Syndrome)
- Serious adverse events (SAEs)
- Severe systemic reactogenicity event

Inclusion Criteria:

Patients who meet all of the following criteria may be included in the study.

1. Able and willing to provide informed consent
2. Men and women 18 to 65 years of age, inclusive
3. Body Mass Index (BMI) 18.0 to 34.9 kg/m^2, inclusive
4. Inactive, treatment-naïve CHB with documented HBsAg positivity for at least 12 months before Day 1. (The history of HBsAg positivity may be reduced to 6 months provided HBV anti-core IgM antibodies are negative).
5. qHBsAg ≥ 10 IU/mL but ≤ 200 IU/mL in the 12 months prior to screening or from informed consent to randomization

If a patient has more than one qHBsAg value within 12 months and prior to randomization, the patient will be deemed eligible if any one measurement is within the eligible range.

6. AST, ALT, INR, albumin, total bilirubin (excluding patients with Gilbert Syndrome, who will only be eligible for study participation if total bilirubin is ≤ 3.0 mg/dL) and direct bilirubin within normal limits at screening. Note: ALT and AST elevations up to 1.5 x ULN are allowed if evidence of hepatic steatosis, defined as one of the following criteria: 1) fatty liver on ultrasound, or other imaging modality or Fibroscan controlled attenuation parameter (CAP) ≥ 260 dB/m. To qualify under these conditions, HBV DNA must be <2,000 IU/mL, and there must be no history or signs of liver disease other than fatty liver and HBV.
7. Negative drug screen at screening unless prescribed by a medical practitioner for medical use (NB, recreational and prescription cannabis is allowed)
8. For women of childbearing potential (women who are not permanently sterile [documented hysterectomy, bilateral tubal ligation, salpingectomy, or oophorectomy] or postmenopausal [12 months with no menses without an alternative medical cause]):
    a. Negative pregnancy test on Day 1
    b. Willingness to practice a highly effective method of birth control with low user dependency from screening through one menstrual cycle after the last dose of study medication, which include:
        i. Abstinence
        ii. Sex only with persons of the same sex
        iii. Monogamous relationship with vasectomized partner
        iv. Intrauterine device
        v. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
        vi. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
        vii. Intrauterine hormone-releasing system

        Patients who practice true abstinence or who exclusively have same sex partners need not use contraception, provided it is in line with their preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Should any such patient stop practicing abstinence, they must use contraception as described above.
9. For men with sexual partners of childbearing potential, as defined above:
    a. Abstinence
    b. History of vasectomy or surgical sterilization

c. Monogamous relationship with a postmenopausal or surgically sterilized partner

d. Willingness to practice a highly effective method of contraception, as defined above, for 90 days after the last dose of study medication and to refrain from sperm donation for this time

The same criteria pertaining to abstinence and withdrawal methods in women of childbearing potential (Inclusion Criterion 8) apply to men with sexual partners of childbearing potential

10. Willingness to comply with all aspects of the study through the entire study period

Patients who fail to meet Inclusion Criteria 5 and/or 6 and otherwise meet the requirements for study participation will be permitted one additional blood draw during the same screening period to requalify. Patients who screen fail for other Inclusion Criteria may undergo rescreening at the discretion of the Investigator and Medical Monitor.

Exclusion Criteria:

Patients who do not meet any of the following exclusion criteria may be included in the study.

1. Pregnant or lactating women
2. Positive hepatitis B e antigen (HBeAg) at screening
3. History of a hepatitis B flare or 1-log increase in HBV DNA or HBsAg in the prior 6 months
4. Prior or current history of active or untreated human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis delta virus (HDV)
5. Acute COVID-19, a positive test result for SARS-CoV2 infection, or exposure within 14 days to an individual with acute COVID-19
6. Febrile illness (temperature ≥ 38.0 °C) within the past 14 days
7. Prior or current history of any underlying liver disease not related to HBV (NB, steatosis, as documented by imaging or Fibroscan CAP, is permitted if ALT and AST are <1.5 x ULN and HBV DNA <2,000 IU/mL and there is no history or signs of liver disease other than fatty liver and HBV)
8. Fibroscan > 8.5 kPA at screening, or history of hepatic fibrosis or cirrhosis (NB, a Fibroscan is not required if an examination is performed within 12 months before screening, or a liver biopsy was performed within 2 years before screening and no fibrosis [F1 or greater] was identified.)
9. History of cirrhosis or signs of hepatic decompensation, including but not limited to variceal bleeding, ascites, or hepatic encephalopathy
10. White blood cell count < 3,500/µL, neutrophils < 1,000/µL, hemoglobin < 11 g/dL, or platelets < 125,000/µL

    Note: Individuals of African descent with a white blood cell count <3,500/ µL will not be excluded for this reason if white blood cell count is ≥ 2,500/µL,

provided that the neutrophil count is ≥ 1,000/μL and there is no other identified cause of leukopenia.

11. Prior treatment with an approved or investigational agent for HBV.
12. History of conditions associated with immunocompromise
13. History of conditions associated with altered immune response, such as anaphylaxis, angioedema, or autoimmune disease
14. Treatments known to affect the immune system, such as corticosteroids (other than topical or inhaled preparations), alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics, allergy injections, immunoglobulins, interferons or other immunomodulating therapies, within 30 days of screening
15. Uncontrolled diabetes mellitus, defined as Hemoglobin A_1C (HbA_1C) ≥ 10% at screening
16. Receipt of live-attenuated replicating vaccines within 30 days or receipt of any other licensed or authorized vaccines (including vaccines intended to prevent COVID-19) within 14 days prior to Day 1
17. Change in any chronically administered medication or treatment within 14 days of screening or inability to maintain these medications at the same dose through Day 169 (NB, patients chronically using aspirin, non-steroidal anti-inflammatory agents, antacids, vitamins, probiotics, and over-the-counter medications will maintain their level of intake throughout the study)
18. Malignancy within 3 years of screening, excluding non-melanoma skin cancers and carcinoma *in situ* cervical cancer (NB, patients who have undergone prior screening for HCC by imaging or alpha-fetoprotein levels will have negative test results)
19. Untreated alcohol or drug abuse
20. Planned elective surgery or hospitalization during the study period
21. Participation in a prior trial involving HepTcell or FP-02.2
22. Known allergy to any of the ingredients in HepTcell
23. Receipt of any investigational drug or treatment within 30 days before Day 1 or planned use during the study period
24. Any medical, psychiatric, or social condition or occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including reactogenicity), or a patient's ability to give informed consent

Patients who are excluded by Exclusion Criterion 10 but otherwise meet the requirements for study participation will be permitted one additional blood draw to requalify. Patients who screen fail for other Exclusion Criteria may undergo rescreening at the discretion of the Investigator and Medical Monitor.

Efficacy Endpoints:

Primary Efficacy Endpoint:

The proportion of patients achieving virologic response, defined as a 1.0-log reduction in qHBsAg or serologic clearance of HBsAg, Baseline to Day 169

Secondary Efficacy Endpoints:

- Proportion of patients achieving serologic clearance of HBsAg on Day 169
- Proportion of patients achieving serologic clearance of HBV DNA on Day 169
- Changes in qHBsAg, HBV DNA, HBcrAg, and pg-RNA levels, Baseline to Days 85 and 169
- Change in IFN-γ frequency by ELISpot in PBMCs, Baseline to Days 85 and 169

Exploratory Efficacy Endpoints:

- Proportions of patients achieving serologic clearance of HBsAg on Day 505
- Proportions of patients achieving serologic clearance of HBV DNA on Day 505
- Proportion of patients with anti-HBs on Day 505
- Changes in qHBsAg, HBV DNA, HBcrAg, and pg-RNA levels, Baseline to Days 323 and 505
- Change in IFN-γ frequency by ELISpot in PBMCs, Baseline to Days 323 and 505

Safety Endpoints

- Incidence and severity of AEs, MAEs, NCIs, and IMCs
- Incidence and severity of local and systemic reactogenicity events
- Incidence and duration of hepatitis flares, defined as ALT ≥ 3 × ULN and > 100 U/L
- Changes in ALT, AST, alkaline phosphatase [AP], gamma glutamyl transferase [GGT], bilirubin total and direct, and INR and other laboratory parameters

Safety endpoints will be assessed separately for the 24-week Treatment Period and 52-week Follow-Up Period

Statistical Methods:

Power and Sample Size Assumptions:

A study of interferon-α2 in a population with inactive CHB reported a mean incremental decrease of 1.3 log-qHBsAg at 24 weeks in those patients completing interferon-α2 treatment compared to non-treatment. Mean decrease would translate to approximately 50% of patients completing treatment achieving 1.3 log-qHBsAg

response (reduction). To estimate treatment effect in the current study, the proportion of patients achieving a 1.0-log reduction in qHBsAg is estimated as one-half (25% of patients) who achieve this response. Assuming a response rate of 3% on placebo and 25% on HepTcell, 40 patients will be randomized per treatment group to detect a difference in the proportion of patients treated with HepTcell achieving the primary endpoint compared to patient treated with placebo at a 0.05 level of significance (two-sided) with approximately 80% power.

Statistical Analysis:

Population definitions:

Safety Analysis Set: All patients who receive any study medication.

Modified intent to treat (mITT): All randomized patients who receive any amount of study medication, have a baseline and at least one post-baseline efficacy assessment. Patients will be analyzed according to the treatment that they receive. This analysis set will be used for primary and secondary analyses.

Per Protocol (PP): All randomized patients who receive the full designated amount of study medication according to the correct treatment assignment and who have results from HBV serology and viral markers at Day 85.

General:

Baseline is defined as data collected closest to randomization prior to any study medication dosing. All analyses and summary statistics will be presented by treatment group (HepTcell, placebo).

Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided by treatment.

Patients will be randomized 1:1 to HepTcell or placebo and stratified by study center to minimize imbalances between treatment groups. To assure a 1:1 distribution of HepTcell and placebo (6 patients each of 12 patients) in the sentinel cohort, randomization in this group will not be stratified.

An interim analysis will be performed after all patients complete 24 weeks (6 doses) of treatment or discontinue study medications.

Efficacy Analyses:

Descriptive statistics will be used to evaluate differences in demographic and baseline characteristics.

For the primary analysis, proportions of patients with virologic response, defined as a 1.0-log reduction in HBsAg or serologic clearance of HBsAg, will be compared between HepTcell and placebo groups using Fisher's Exact Test at a 0.05% two-sided level of significance. The same approach will be applied for secondary or exploratory endpoints that are categorical in nature. Patients who discontinue prematurely or have missing data will be considered non-responders for that endpoint. Linear and logistic regression will be employed to examine the effects of baseline factors, such as qHBsAg level, HBV DNA levels, hepatitis B genotype on response.

Changes from baseline in PBMC ELISpot, HBsAg, HBcrAg, pg-RNA and HBV DNA will be analyzed using a mixed model for repeated measures (MMRM) model. The model will include the fixed effects of treatment, stratification factor, week, and treatment-by-visit interaction as well as the continuous, covariate of baseline level. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood (ReML) estimation method.

A Kaplan-Meier model will be developed to compare changes between treatment groups in HBsAg clearance and a 1-log reduction in HBsAg over time.

Relationships between hepatitis flares and HBsAg loss and/or decline will be evaluated logistic and linear regression.

No multiplicity adjustments will be made for secondary or exploratory endpoints.

Safety and Tolerability:

Quantitative safety data will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment arms. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Concomitant medications will be coded using World Health Organization (WHO) drug dictionary.

Laboratory evaluations, vital signs assessments and electrocardiogram (ECG) parameters will be summarized by treatment group and protocol specified collection time point. A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented.

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AE	adverse event
ALT	alanine aminotransferase
anti-HBs	antibodies to hepatitis B surface antigen
AST	aspartate aminotransferase
Bili	bilirubin
CAP	controlled attenuation parameter
CHB	chronic hepatitis B
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
ELISpot	enzyme-linked immunosorbent spot
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBcrAg	hepatitis B core-related antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IM	intramuscular

IMC	immune-mediated medical condition
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KLK	KLKLLLLLKLK (peptide component of IC31)
MAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NAFLD	nonalcoholic fatty liver disease
NB	nota bene
NCI	new-onset chronic illness
PBMC	peripheral blood mononuclear cells
pg-RNA	pre-genomic RNA
qHBsAg	quantitative hepatitis B surface antigen
SAE	serious adverse event
SAP	statistical analysis plan
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION AND RATIONALE

1.1. Background

1.1.1. Chronic Hepatitis B

Chronic hepatitis B (CHB) affects 292 million people worldwide (3.9% of the world's population), of which 887,000 die annually of complications of the disease [Razavi-Shearer 2018, WHO 2019]. Universal childhood vaccination has significantly reduced new incidence of hepatitis B [WHO 2019]. Globally the most common cause of CHB is mother-to-child transmission at birth or close childhood contact with infected body fluids of a CHB carrier in endemic areas with incomplete vaccination programs. Most adults newly infected with hepatitis B virus (HBV) achieve spontaneous serologic clearance mediated by HBV-specific CD4+ and CD8+ T cells [Gehring 2019]; those that do not clear hepatitis B surface antigen (HBsAg) within 6 months are considered chronically infected. Individuals with CHB have profound defects in strength and quality of anti-HBV T cell immune responses as a result of immune tolerance or exhaustion [Ye 2015]. Immune tolerance may be the result of persistently elevated levels of HBV antigens including HBsAg secreted by infected hepatocytes. Overcoming immune tolerance by eliciting stronger and more functional cellular immunity is a cornerstone of novel CHB treatment strategies to achieve functional cure.

Current standard of care involves therapy with nucleos(t)ide HBV polymerase inhibitors (NUCs) or interferon-alpha (IFN-α) to suppress HBV replication, and reduce hepatic necroinflammation and risk of end-stage liver disease [Terrault 2018; EASL 2017]. Nucleos(t)ide treatments only rarely achieve functional cure because of their inability to restore anti-HBV immunity [Tang 2014] and achieve HBsAg loss. Lifelong treatment is required for most patients because of viral rebound that occurs when treatment is discontinued. Although NUC therapy is well tolerated, long-term costs are substantial [Stahmeyer 2017; Tadrous 2018] and risks of hepatocellular carcinoma, cirrhosis, and liver failure are not eliminated [Block 2015; Wong 2018]. These complications have also been reported to occur in individuals with inactive CHB who might not otherwise be deemed candidates for NUC therapy [Chen 2010]. Interferon-based therapies have been associated with high variability of response and unfavorable safety profile that severely limit their use, and the use of interferon therapies is not recommended in patients with normal liver transaminases and low HBV DNA levels [EASL 2017].

Inactive CHB represents a condition of low-level viral replication and low or absent hepatic inflammation. Current society guidelines do not recommend treatment for these patients, because interferon, the only potential therapy for these patients, has toxicity, and the benefit risk ratio is low. However, the risk of hepatocellular carcinoma and cirrhosis in these patients remains real, and they continue to bear the lifelong stigmata of infectivity, including infecting sexual partners. They also are expected to endure the inconvenience of lifelong monitoring, including physician visits and blood tests every 6 to 12 months, and pass these costs onto the healthcare system. As a result, these patients are seeking access to effective and better tolerated treatments for their condition.

Should an effective therapy emerge that would also be well-tolerated by patients, the benefit-risk ratio would favor benefit. The specificity of HepTcell for hepatitis B epitopes, the lack of homology with human proteins and expected absence of off-target effects, and the safety and tolerability of the immunotherapeutic in the prior Phase 1 trial suggest a favorable risk-benefit ratio for subjects who participate in this trial.

1.1.2. HepTCell

Altimmune is developing HepTcell (adjuvanted FP-02.2), an immunotherapeutic vaccine for treatment of CHB, to address the substantial unmet medical need of this patient population.

HepTcell (adjuvanted FP-02.2) is the final reconstituted product for administration, that consists of a lyophilized mixture of 9 fluoropeptides and mannitol (FP-02.2 drug product), L-histidine buffer, normal saline (to achieve an isotonic, neutral pH), and IC31® (developed by Valneva SE). The 9 synthetic peptides (designated P877, P151, P113, P856(K), P753(K), P376, P797(K), P277(K), and P1266(K)) are each covalently linked to a fluorocarbon moiety on the N-terminus under a controlled process and formulated in mannitol. The peptides vary in length from 32 to 40 amino acids and correspond to a conserved region of HBV polymerase, core, or surface protein and contains CD4+ and CD8+ T cell epitopes. IC31 is a synthetic, 2-component adjuvant solution comprised of 40 nmol/mL ODN1a, a single stranded oligodeoxynucleotide consisting of dimeric repeats of deoxy-inosine/deoxy-cytosine linked by an unmodified phosphodiester backboned and of 1000 nmol/mL KLKLLLLLKLK (KLK), comprising an 11 amino acid artificial cationic antimicrobial peptide.

HepTcell is an immunotherapeutic vaccine specifically designed to enhance T cell immunity in patients with CHB and achieve durable control of the virus. With this aim, HepTcell has been designed to redirect CD4+ and CD8+ T cell immunity against multiple HBV targets, considering both human leukocyte antigen (HLA) and viral genetic diversity. It is intended to focus the immune system on discrete conserved and immunodominant regions of the HBV proteome presumably less subject to immune escape. It is envisioned that HepTcell can either be used alone or as an adjunct to one of the emerging and newer direct-acting agents, such as a small interfering RNA (siRNA) or capsid assembly modulator (CAM) that are designed to suppress HBV antigens to levels that allow restoration of T cell immune functions and the response to the vaccine.

The manufacturing of the 9 fluoropeptides included in HepTcell relies on a well-established solid-phase protein synthesis using FMOC (fluorenylmethoxycarbonyl protecting group) chemistry and conventional reversed-phase high-performance liquid chromatography (RP-HPLC) purification systems for the production of fully characterizable drug substances.

Each of the 9 peptides included in HepTcell is conjugated to a fluorocarbon moiety as part of the solid phase synthesis. Fluorocarbon conjugation results in the formation of a short-term antigen depot at the site of injection that prolongs the exposure of the antigens

to the immune system [Francis 2015a]. The time course for local degradation at the site of injection has not been determined.

HepTcell was designed to bypass HLA restriction; each peptide sequence has been selected from the HBV proteome using a bioinformatics platform so that each peptide contains high-density clusters of HLA class I- and class II-binding epitopes that can be recognized by a broad patient population irrespective of their genetic background. In addition, these peptides have been selected to direct the immune system to target the most conserved regions of the virus, have the potential to induce immune responses against all known HBV genotypes, and impose high viral fitness costs that limit immune escape. Collectively, these peptides representing 18.7% of the HBV proteome can stimulate peripheral blood mononuclear cells (PBMCs) in patients with CHB with diverse HLA backgrounds. By redirecting the immune system toward the conserved sequences, HepTcell has the potential to be more efficient than other vaccine strategies comprising full-length antigens, which are associated with poorly directed immune response.

Perfluorocarbon emulsions have been evaluated as artificial oxygen carriers and shown to be safe and well tolerated in animal and human studies [Spahn 1999; Noveck 2000]. The perfluorocarbon tested in these studies shares strong homology with the fluoropeptides in HepTcell. The dose of fluoropeptides in a single dose of HepTcell (2.25 µg fluorocarbon/kg) is several log-fold lower than the dose of fluorocarbon (1.8 g/kg) employed in these studies.

A 6-fluoropeptide influenza vaccine (FP-01.1) using the same fluorocarbon moiety was also evaluated in 222 healthy volunteers at doses equivalent of 30 to 300 µg of fluorocarbon per injection [NCT01701752, NCT01677676, NCT02071329, NCT01265914 and Francis 2015b]. Administration of FP-01.1 resulted in an acceptable safety profile and induced robust antiviral T cell responses in a high proportion of subjects tested. Clinical studies of perfluorocarbon emulsions with related structure to the fluorocarbon moiety used in FP-02.2 have shown these compounds to be well tolerated at doses much higher than the fluorocarbon dose in HepTcell.

1.1.3. IC31

IC31 is a synthetic, 2-component adjuvant comprised of ODN1a, a phosphodiester backboned single-stranded oligonucleotide with alternating sequences of the nucleic acids inosine and cytidine, and KLKLLLLLKLK (KLK), a cationic antimicrobial peptide.

During nonclinical development, the fluoropeptides (FP-02.1 and FP-02.2) were administered by intramuscular (IM) injection over a range of doses, both with and without adjuvant IC31. Nonclinical immunogenicity was studied in BALB/c mice and the addition of IC31 increased the magnitude and breadth of the immune response and prolonged its duration. Additionally, IC31 has been used as an adjuvant combined to different vaccines in at least 20 Phase 1 and 2 clinical studies and more than 1221 subjects with an acceptable safety profile and demonstrated adjuvanticity. Details of these studies can be found in the Investigator's Brochure.

1.2. Nonclinical Studies

Altimmune evaluated the functional properties of individual HBV peptides in human PBMCs to select the peptides to be included in HepTcell and subsequently evaluated the immunogenicity of FP-02.2 in the presence or absence of IC31 and earlier formulations in mice. The toxicity of FP-02.2 in the presence or absence of IC31 was also assessed in in vitro and in vivo studies.

Immunogenicity studies in mice demonstrated a robust CD8-dominated T cell response, with both phenotypic and functional cytotoxic T cell profiles. The addition of IC31 increased the magnitude and breadth of this response and prolonged its duration in these studies.

Sequence homology analysis showed no significant similarity between the 9 peptides in FP-02.2 and human protein sequences, including those related to autoimmune manifestations.

Intramuscular administration of FP-02.2 + IC31 to mice in 4 doses over 6 weeks (Days 1, 15, 29, and 43) was well tolerated with no test article-related deaths and only minor changes in clinical pathology that were likely attributable to immune stimulation. Administration of FP-02.2 only, IC31 only, or FP-02.2 + IC31 was associated with a number of histopathological changes at the injection sites, particularly evident in females. Additionally, increased cellularity within the splenic white pulp was seen in animals administered IC31 only and FP-02.2 + IC31 and in female animals administered FP-02.2 only. All the changes observed were considered to represent the expected local and systemic response to injection of a potent immunostimulatory product and were not considered to be adverse. Partial or complete reversibility was seen for all changes after a 4-week recovery period.

Assessment of mutagenicity of FP-02.2, the fluorocarbon vector, and IC31 by Ames testing showed no mutagenic activity. In vitro genotoxic studies of the FP-02.2 and IC31 showed no induction of chromosomal aberration.

In a local tolerance study in New Zealand White rabbits, IM injection of FP-02.2 with or without IC31 was well tolerated with no evidence of systemic toxicity or local dermal intolerance.

Nonclinical toxicology data provided by Valneva demonstrate a general lack of toxicity for IC31 alone or in combination with vaccine antigens.

Further details of the non-clinical studies can be found in the Investigator's Brochure.

1.3. Previous Clinical Study of FP-02.2

Study FP-02.2_CS_01 was a Phase 1, randomized, double-blind, placebo-controlled clinical study of the safety, tolerability, and immunogenicity of FP-02.2 with and without IC31 conducted in the United Kingdom and South Korea. Sixty-one adult hepatitis B e antigen (HBeAg)-negative patients with CHB who were on chronic nucleoside analogue therapy were randomized to receive one of the following treatments as 3 IM

administrations in 4-week intervals over 12 weeks: low dose FP-02.2 (150 µg/peptide), low dose FP-02.2 + IC31, high dose FP-02.2 (500 µg/peptide), high dose FP-02.2 + IC31, IC31 alone, or placebo. Immunogenicity was assessed by an interferon-gamma (IFN-γ) enzyme-linked immune absorbent spot (ELISpot) assay in PBMCs.

A robust immunogenicity response was observed in patients treated with FP-02.2 in combination with IC31, with the low dose showing responses comparable to high dose responses. The magnitude of response increased with each successive dose of FP-02.2 and suggested that additional doses would result in an even more robust immunologic response.

All dose regimens were generally safe and well tolerated, with no effect of dose level, number of doses, or adjuvant was observed for any of the safety parameters. The incidences of injection reactions and adverse events (AEs) were similar in the FP-02.2-treated and placebo groups. A trend to higher incidences of patient-reported injection site reactions were noted in the high dose + IC31 group but no severe reactions were reported, and reactions resolved by the next day in approximately half the subjects. There were no hepatitis flares or drug related serious AEs (SAEs). Laboratory results and vital signs measurements in the placebo group were similar to those in the FP-02.2 groups.

Further details of the prior clinical study can be found in the Investigator's Brochure.

1.4. Study Rationale

This Phase 2 study will evaluate the antiviral effects, immunogenicity, and safety of HepTcell in treatment-naïve patients with inactive CHB and low HBsAg levels (10 to 200 IU/mL).

The findings of Study FP-02.2_CS_01 establish the ability of HepTcell to induce cell-mediated responses in HBeAg-negative patients under NUC treatment, which is known to be characterized by weak and dysfunctional circulating HBV-specific T cells. It also supports the superior immunological characteristics of FP-02.2, designed around highly selected conserved and immunodominant HBV-derived peptides, compared with other products from other companies in the HBV pipeline of full-length antigens.

HepTcell was also safe and well-tolerated, with incidences of local injection site reactions and TEAEs similar to placebo. The results were consistent with the findings of nonclinical toxicology studies and the outcomes of other investigational vaccines adjuvanted with IC31. The safety of the current study will be enhanced by the use of a sentinel cohort and the use of the lower dose of FP-02.2 from Study FP-02.2_CS_01.

While FP-02.2 did not show any significant impact on HBsAg levels (decline or loss), this likely reflects the short duration of the vaccine regimen and the unfavorable immunological status of NUC-treated HBeAg-negative patients enrolled in the study. With each successive dose of FP-02.2, a trend toward an increase of the immune responses was observed in this trial, so it is anticipated that longer treatment will further improve the anti-HBV immune response over time, and treatment has thus been extended from 3 to 6 doses. Furthermore, the patients in Study FP-02.2_CS_01 achieved low

circulating HBV DNA and HBsAg levels as the result of NUC therapy rather than spontaneous (intrinsic) immune control. HBeAg-negative patients with CHB on long-term NUC therapy often have relatively high and stable levels of serum HBsAg with little or no decline on therapy, and rarely achieving treatment induced HBsAg loss.

High HBV antigen levels are a known cause of T cell exhaustion during chronic viral infection, and experts in the field have expressed the viewpoint of targeting HBV mRNA with nucleic acid-based products or using capsid assembly as a way to limit the HBV antigen production and serum levels and consequently improve HBV-specific T cell immune reconstitution in patients with CHB [Fanning 2019]. In this context, HepTcell is eventually anticipated to be beneficial in combination with novel direct acting antiviral agents (DAAs) to reduce HBsAg expression.

In Study FP-02.2_CS_01, HepTcell tended to promote T cell responses primarily targeting the HBV polymerase antigen. This would indicate that in HBeAg-negative patients under NUC treatment, polymerase is less tolerizing than other HBV antigens, a hypothesis that is in line with other observations in the field [Rivino 2018; Loggi 2013]. Increasing the breadth of the response to other FP-02.2 antigens can be potentially achieved with longer treatment duration, combination with novel DAAs, and the selection of patients including those with spontaneous decline in HBsAg who tend to show better T cell responses [Loggi 2013]. Therefore, the composition of FP-02.2 will not be altered until further clinical evaluations are completed.

2. STUDY OBJECTIVES

2.1. Primary

The primary objective of the study is to assess virologic response to HepTcell in treatment-naïve patients with inactive CHB.

2.2. Secondary

The secondary objectives of the study are to assess:

- Cellular immune response of HepTcell in treatment-naïve patients with inactive CHB
- Safety of HepTcell in treatment-naïve patients with inactive CHB

3. STUDY ENDPOINTS

3.1. Primary Efficacy Endpoint

The proportion of patients achieving virologic response, defined as a 1.0-log reduction in quantitative HBsAg (qHBsAg) or serologic clearance of HBsAg, Baseline to Day 169.

3.2. Secondary Efficacy Endpoints

- Proportion of patients achieving serologic clearance of HBsAg on Day 169
- Proportion of patients achieving serologic clearance of HBV DNA on Day 169
- Changes in qHBsAg, HBV DNA, hepatitis B core-related antigen (HBcrAg) and pre-genomic RNA (pg-RNA) levels, Baseline to Days 85 and 169
- Change in IFN-γ frequency by ELISpot assay in PBMCs, Baseline to Days 85 and 169

3.3. Exploratory Efficacy Endpoints

- Proportion of patients achieving serologic clearance of HBsAg on Day 505
- Proportion of patients achieving serologic clearance of HBV DNA on Day 505
- Proportion of patients with anti-HBsAg antibodies (anti-HBs) on Day 505
- Changes in qHBsAg, HBV DNA, HBcrAg, and pg-RNA levels, Baseline to Days 323 and 505
- Change in IFN-γ frequency by ELISpot assay in PBMCs, Baseline to Days 323 and 505

3.4. Safety Endpoints

- Incidence and severity of AEs, medically-attended AEs (MAEs), new-onset chronic illnesses (NCIs), and immune-mediated medical conditions (IMCs)
- Incidence and severity of local and systemic reactogenicity events
- Incidence and duration of hepatitis flares, defined as alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and > 100 U/L
- Changes in ALT, aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), bilirubin total and direct, international normalized ratio (INR) and other laboratory parameters

Safety endpoints will be assessed separately for the 24-week Treatment Period and 52-week Follow-Up Period.

4. STUDY PLAN

4.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the antiviral effects, immunogenicity, and safety of HepTcell in treatment-naïve patients with inactive CHB and low HBsAg levels (10 to 200 IU/mL).

After providing written informed consent, patients will undergo a screening period of up to 35 days. A Fibroscan will be performed in all patients who have not had this examination within the previous 12 months before Screening with the exception of patients with a prior history of liver biopsy within the past 2 years demonstrating no evidence of significant fibrosis.

Patients who meet inclusion and exclusion criteria will be randomized in a 1:1 ratio to receive 6 IM doses of HepTcell or placebo (normal saline) at study visits 4 weeks apart (Days 1, 29, 57, 85, 113, 141). Randomization may occur up to 3 working days before the first day of dosing to allow for the possible preparation of study medication by a central pharmacy and shipment to the study site. Adverse events (AEs) will be monitored, and blood samples will be collected for qHBsAg, anti-HBs, HBV DNA, HBV pg-RNA, HBcrAg, and IFN-γ ELISpot assay in PBMCs. Patients will record any reactogenicity events (see Appendix 1) for 7 days after each administration of study medication in a diary. A visit consisting of a targeted physical examination and safety laboratory tests, including liver panels, will be conducted 7±2 days after administration of Doses 1 and 2 of study medication. These visits, per the Schedule of Events (Table 1 and Table 2), may be conducted at home or workplace or, in part, as a telemedicine visit, at the discretion of the Investigator.

If the patient has experienced an acute illness or temperature > 38°C in the 2 days prior to dosing, the administration of study medication and corresponding visit will be delayed until the illness or fever has resolved.

A Safety Committee will conduct regular blinded reviews of all AEs and reactogenicity events. The safety of study participants will also be overseen by an unblinded Data Monitoring Committee (DMC); its responsibilities will be laid out in a DMC charter.

A sentinel cohort of 12 patients (6 receiving HepTcell and 6 placebo) will undergo blinded safety review by the Safety Committee 7 to 10 days after all ongoing patients in the sentinel cohort have completed the respective dose of study medication and will determine the decision to continue at that dose to the expanded cohort. Safety will be assessed in the sentinel cohort before each dose is administered to the expanded cohort. If any of the Stopping Rules in Section 7.1.1 are met in one or more patients and the event(s) is deemed possibly or probably related to HepTcell, dosing will be suspended pending DMC review. DMC recommendations may include instituting modifications to ensure the safety of continued dosing or discontinuing the study. If none of the Stopping Rules are met, randomization and dosing may continue in the expanded study cohort. Patients will be unblinded as necessary to assess the relationship between the study medication and events that meet criteria for Stopping Rules.

Safety laboratory testing (Table 3), including liver panel, for Doses 1 and 2 will be obtained during the visits conducted 7±2 days after these doses of study medication. Safety laboratory testing following Doses 3, 4 and 5 will be obtained in the interval from 7 days after dose administration and before the next dose of study medication is administered. Safety labs after Dose 6 will be assessed at the Day 169 visit. Investigators will review the eligibility of all patients prior to dosing to determine if the next treatment is to be administered. Eligibility for the next treatment will include: 1) confirmation that patients did not meet a Stopping Rule (Section 7.1.1); 2) confirmation that the pre-treatment liver parameters are within acceptable ranges for treatment (below); 3) confirmation that patients do not have a new confirmed or suspected IMC (Appendix 2). Patients not meeting these criteria will not be treated.

If abnormalities of ALT, AST, total bilirubin, direct bilirubin, or international normalized ratio (INR) are reported after dosing is commenced, the following monitoring and dosing rules will be applied:

Toxicity	**Management**	**Discontinuation of Study Medication**
ALT or AST ≥ 5×but < 10 × ULN, *and* Total and direct bili < 1.5×ULN, *and* INR < 1.3 ×ULN	Continue dosing Monitor liver panel weekly If ALT/AST fall to <1.5×ULN, stop weekly monitoring	
ALT or AST ≥ 10×ULN, *and* Total and direct bili < 1.5×ULN, *and* INR < 1.3 ×ULN	Interrupt dosing Monitor liver panel weekly If ALT/AST fall to <5×ULN, restart dosing; if ALT/AST fall to <1.5×, stop weekly monitoring	If the event does not resolve in 4 weeks or recurs, consult medical monitor about discontinuing study medication
ALT or AST ≥ 5×ULN, *and* Total or direct bili ≥ 1.5×ULN, *or* INR ≥ 1.3 ×ULN		Discontinue study medication
ALT or AST < 5×ULN, *and* Total or direct bili ≥ 1.5×ULN, *or* INR ≥ 1.3 ×ULN	Interrupt dosing Monitor liver panel weekly If total and direct bili fall to <1.5 ×ULN and/or INR falls to < 1.3× on 2 consecutive tests, stop weekly monitoring and restart dosing	If the event does not resolve in 4 weeks or recurs, consult medical monitor about discontinuing study medication

For patients with Gilbert Syndrome, the 1.5 × ULN criteria for total and direct bilirubin will be replaced with a 1.5 × ULN for direct bilirubin and there will be no monitoring criteria for total bilirubin [Fontana 2020]. Other etiologies of ALT, AST, total and direct bilirubin, and INR elevations, such liver injury induced by other drugs and other viral infections, should be ruled out and treated accordingly.

If a patient prematurely discontinues study medication on or before Day 169, the Day 169/Early termination procedures will be performed. Patients who prematurely discontinue study medication will remain in the study for follow-on study assessments.

Patients will be followed for 52 weeks after the last dose of study medication (504 days beyond Day 1 for patients who complete the 24-week Treatment Period). AEs and concomitant medications will be recorded from the signing of informed consent to Day 169, but only MAEs, NCIs, and IMCs, which will be categorized as AEs, will be followed subsequently. Likewise, concomitant medications will be recorded through Day 169, but only immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury will be recorded beyond this point. At the end of the clinical trial, the decision about follow-on treatments and medical care will be made by the patient's medical physician or medical team in accordance with the usual standard of care.

Patients will be required to limit their alcohol consumptions to no more than moderate intake (defined as 2 drinks/day for men and 1 drink/day for women) during their participation in the study.

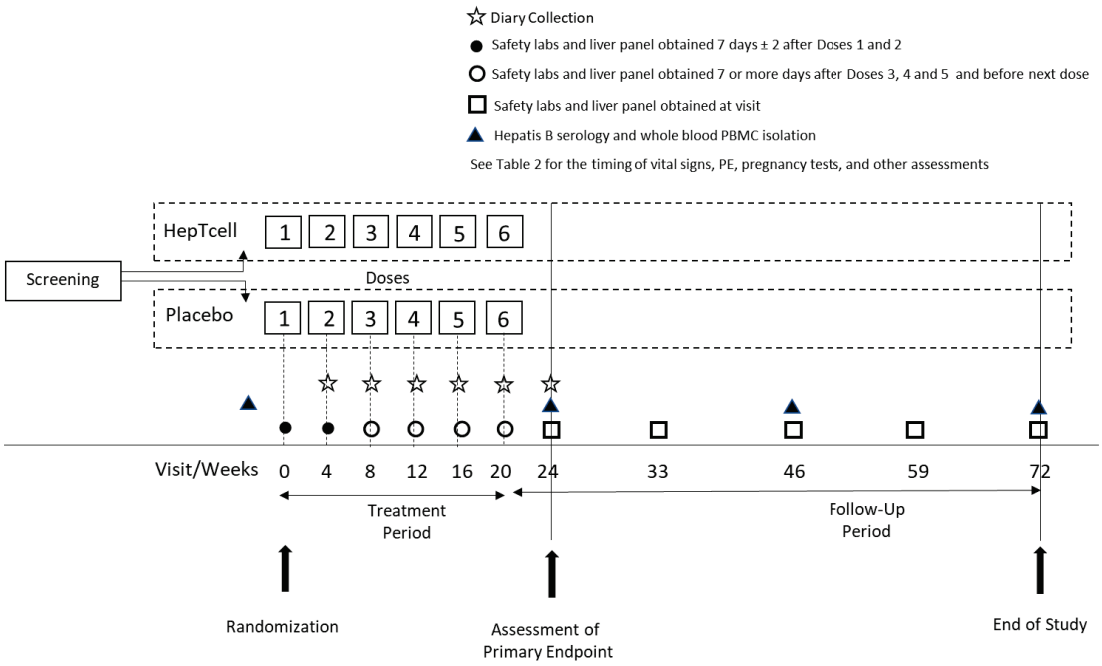
Risk-factor analysis and appropriate surveillance for hepatocellular carcinoma (HCC) may be performed at the discretion of the investigator.

The measures to be taken at each investigative site to minimize the risks of COVID-19 will be communicated to the patient, along with any changes to the risks of study participation that occur as a result of changing local COVID-19 conditions. Study participants will not be prevented from receiving COVID-19 vaccines during their trial participation and will be advised accordingly. If an authorized COVID-19 vaccine has been administered in proximity to a scheduled investigational product (IP) administration, a ± 3-day window is allowed for IP dosing (Table 1).

4.2. Study Schematic

Each patient will participate in the study up to approximately 77 weeks (a 5--week Screening Period, a 24-week Treatment Period, and a 52-week Follow-up Period commencing after the last dose of study medication at Week 20).

Figure 1: Study Visits and Treatments



4.3. Rationale for Study Design

The study design replicates the general design of the prior Phase 1 study but extends treatment from 3 to 6 doses and the follow-up after the last dose of study medication from 30 to 52 weeks. These modifications will enhance the effects of study medication and provide a more extended follow-up to assess the durability of immunogenicity and AEs. Diaries will be collected for reactogenicity events at visits on Days 8 and 36, which correspond to 7±2 days after the first and second dose of study medication. A visit consisting of a targeted physical examination will be conducted 7±2 days after administration of Doses 1 and 2 of study medication. Safety laboratory testing (Table 3), including liver panel, for Doses 1 and 2 will be obtained during the visits conducted 7±2 after these doses of study medication. Safety laboratory for Doses 3, 4 and 5 will be obtained in the pre-treatment interval from 7 days after dose administration through the time that the next dose of study medication is administered. Safety labs after Dose 6 will be assessed at the Day 169 visit. Investigators will review the eligibility of all patients prior to dosing to determine if the next treatment is to be administered. Eligibility for the next treatment will include: 1) confirmation that patients did not meet a Stopping Rule (Section 7.1.1); 2) confirmation that the pre-treatment liver parameters are within acceptable ranges for treatment (Section 4.1); 3) confirmation that patients do not have a new confirmed or suspected IMC (Appendix 2). If abnormalities of ALT, AST, total bilirubin, direct bilirubin, or INR are reported after dosing is commenced, the monitoring and dosing rules of Section 4.1 will be applied. These procedures are considered sufficient to evaluate reactogenicity events, particularly after Doses 1 and 2, and guard

against hepatitis flares and liver function abnormalities that would preclude the scheduled administration of the next dose of study medication.

For most vaccines, reactogenicity is typically experienced within 3 days of vaccination, commensurate with the innate immune response. Because distinct and separate antigens are targeted, no specific interactions or immunological interferences between COVID-19 vaccines and HepTcell are otherwise anticipated. Therefore, if an authorized COVID-19 vaccine has been administered in proximity to a scheduled investigational product (IP) administration, a ± 3 day window is allowed for IP dosing (Table 1). A COVID-19 vaccine given to a trial subject will be considered as a simple concomitant medication.

The grading of AE severity is described in Section 9.3.1. The US Food and Drug Administration Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [United States Food and Drug Administration 2007] will be the primary scale used to grade AE severity. This scale is being employed because the study population is anticipated to be relatively healthy and the proposed scale is felt to be better reflective of a healthy population that participates in vaccine trials. This scale also offers more detailed grading criteria for local reactogenicity events, particularly those for which measurement offers better characterization of the event

The study design adheres to the 2020 US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada and Medicines Health products Regulatory Agency (MHRA) guidances on the conduct of clinical trials during the COVID-19 pandemic [United States Food and Drug Administration 2020, European Medicines Agency 2020, Health Canada 2020, Medicines and Healthcare products Regulatory Agency 2021]. To that end, the minimal number of in-person clinic assessments deemed necessary for the safety and protection of patients are being undertaken, with home, work and telemedicine visits being conducted whenever possible. The risks and methods to minimize the risks of COVID-19 will be discussed with each patient, and changes in the risks of clinical trial tasks that occur as a result of changes in local circumstances will be assessed during the trial and communicated to patients on an ongoing basis. Study participants will not be prevented from receiving COVID-19 vaccines during their trial participation and will be advised accordingly.

4.4. Rationale for Study Population

Patients with inactive CHB and low HBsAg are likely to represent a population of patients more likely to benefit from immunotherapy than the population in Study FP02.2_CS_01, who could only achieve viral suppression through the use of nucleoside analogues. Inactive CHB patients have relatively low circulating levels of HBV DNA and are already demonstrating intrinsic immune control, albeit incomplete, over the virus. T cell responses against HBV antigens have also been shown to be inversely associated with serum HBsAg level, with lower levels leading to higher rates of spontaneous HBsAg serologic clearance [Loggi 2013]. In two studies of patients with inactive CHB treated with IFN-α therapy, the HBsAg cutoffs predicting HBsAg serologic clearance were 71 and 200 IU/mL, respectively [Lim 2019, Cao 2017]. In a metanalysis

of effects of patients treated with IFN-α, baseline qHBsAg levels predicted functional cure [Song 2021]. After 48 weeks of therapy, the HBsAg clearance rates were 92% (95% CI: 79% - 99%) for HBsAg <10 IU/mL, 88% (95% CI: 77% -95%) for <20 IU/mL, 73% (95% CI: 62% - 83%) for <100 IU/mL, 60% (95% CI: 48% - 71%) for <500 IU/mL, and 39% (95% CI: 25% - 53%) for <1000 IU/mL. While it is clear that clearance of HBsAg is predicted by baseline levels in these studies, there is minimal change in levels between 100 and 500 IU/mL (13%), and the most significant drop-off in HBsAg clearance is in those with qHBsAg >1000 IU/mL (34%). These observations support the recruitment of a well-defined subpopulation of inactive CHB patients with low qHBsAg levels to enhance anti-HBV immune responses and increase HBsAg loss rates. The provision for allowing the participation of patients with any one HBsAg level within the eligible range (qHBsAg ≥ 10 IU/mL but ≤ 200 IU/mL) within the past 12 months is to account for the variability in the quantitative HBsAg assay.

Patients with inactive CHB and over the age of 65 have also been excluded, as they would not be candidates for treatment of their condition in routine clinical practice. There is a global epidemic of obesity and those with hepatitis B are at risk for hepatic steatosis from nonalcoholic fatty liver disease (NAFLD). The risk and prevalence of NAFLD amongst those with HBV appears to be similar as the general population, ranging 17-30% [Shi 2021]. Inclusion of these subjects in the current study is allowed provided there is radiologic evidence of fatty liver or a Fibroscan consistent with hepatic steatosis and no evidence of active CHB (i.e., HBV DNA ≥2000 IU/mL) or other forms of liver disease.

The level of effectiveness and timeframes for contraception use for study eligibility comply with the guidelines of the Clinical Trial Facilitations Group recommendation related to contraception and pregnancy testing in clinical trials [Clinical Trial Facilitation Group 2014]. The fluoropeptides and IC31 of HepTcell are designed to form a local depot at the site of injection, and the magnitude and period of systemic exposure are anticipated to be limited. The high molecular weight peptides that comprise HepTcell present a low risk of passive transmembrane penetration and/or systemic exposure and it is unlikely that they will be absorbed vaginally or placentally. Peptides are expected to be degraded into smaller peptides and individual amino acids by the protein degradation pathways that are well understood. Even if systemic exposure to HepTcell were to occur, the fluoropeptides and IC31 adjuvant components would be rapidly metabolized and their appearance in semen would be limited, as would their appearance in plasma from semen. Any T cells stimulated by HepTcell would also be HBV specific and unable to cross the placenta. Therefore, one-month period of pregnancy testing after the last dose of study medication is considered sufficient to protect patients or their sexual partners who become pregnant after the 6 doses of study medication are administered.

4.5. Dose Rationale

The lower dose of FP-02.2 fluoropeptides from the Phase 1 study was chosen for this study. The immunogenicity of this dose was equal to or greater than the immunogenicity of the higher dose in the prior Phase 1 study. The selection of the lower dose is expected to further improve on the safety profile of treatment. Furthermore, with each successive

dose of FP-02.2, a trend toward an increase of the immune responses was observed in this trial. Consequently, treatment has been extended from 3 to 6 doses. It is anticipated that longer treatment will further improve the anti-HBV immune response over time.

4.6. Schedule of Events

The schedule for study activities is presented in Table 1 for the Screening and Treatment Periods and in Table 2 for the Follow-up Period.

Table 1 Schedule of Events – Screening and Treatment Periods

Study Day	Screening Period		Treatment Period							
	Day -35 to Day -4	Telephone Visit (if needed) [a]	Day 1	Day 8, 36	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169 or ET[b]
Week (s)	**-4 to -1**		**0**	**7 days after prior visit**	**4**	**8**	**12**	**16**	**20**	**24**
Window (days)	—	**Up to 3 working days before Day 1**	—	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2days**	**±2 days**	**±2 days**
Dose of study medication			1		2	3	4	5	6	
Visit may be conducted at home or work or in part as a telemedicine visit [c]				X						
Informed consent	X									
Eligibility criteria check	X	X	X							
Demographics	X									
Medical history	X									
Concomitant medications (including immunosuppressive medications, vaccines, and new HBV treatments) [d]	X	X	X	X	X	X	X	X	X	X
Complete PE	X									X
Targeted and symptom-driven PE			X	X	X	X	X	X	X	
Height, weight, and BMI	X									X
Vital signs [e]	X		X	X	X	X	X	X	X	X
Fibroscan [f]	X									
ECG [e]	X									X
Urine pregnancy test [g]	X		X		X	X	X	X	X	X
Drug and alcohol screen	X									
Hepatitis B genotype [h]	X									
HCV, HDV, and HIV tests	X									
Safety labs [o]	X		X	X	X	X	X	X	X	X
Liver panel [o]	X		X	X	X	X	X	X	X	X
HBV serology and viral markers [i]	X		X				X			X
Whole blood for PBMC isolation			X				X			X
Randomization		X[a]	X							
Study medication administration (number)			**1**		**2** [j,k,l]	**3** [j,k,l]	**4** [j,k,l]	**5** [j,k,l]	**6** [j,k,l]	
Diary distribution (D) review (R) [p]			D	R	D	D	RD	RD	RD	R

Study Day	Screening Period		Treatment Period							
	Day -35 to Day -4	Telephone Visit (if needed) [a]	Day 1	Day 8, 36	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169 or ET[b]
AEs, including MAEs, NCIs and IMCs, and reactogenicity (systemic and local) [m]	X	X	X	X	X	X	X	X	X	X
Stored blood sample for future analyses[n]			X							X

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; MAE = medically-attended adverse event; NCI = new-onset chronic illness; IMC = immune-mediated medical condition; PBMC = peripheral blood nonnuclear cell; PE = physical examination; UA = urinalysis

[a] Randomization may occur up to 3 working days before Day 1 (the day of first dosing) to allow for the possible preparation of study medication by a central pharmacy and shipment to the study site. If the patient is to be randomized before Day 1, the eligibility of the patient will be confirmed by a telephone visit prior to randomization. Concomitant medications AEs will also be assessed.

[b] If a patient prematurely discontinues study medication before Day 169, Day 169/Early termination procedures will be performed. Patients who prematurely discontinue study medication will remain in the study for Follow-Up Period study assessments, the dates of visits adjusted to correspond to 13, 26, 39 and 52 weeks after the last dose of study medication.

[c] A telemedicine visit would include a home visit by appropriate trained personnel to perform a target and symptom-driven physical and obtain vital signs and safety laboratories. The remaining portions of the visit may be conducted virtually by the study investigator.

[d] After Day 169 or ET, only immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury will be recorded.

[e] Measured before any blood sample collection.

[f] Not required if performed within 12 months or if no fibrosis seen on liver biopsy within 2 years before screening.

[g] For women of childbearing potential only. A serum pregnancy test will be obtained in lieu of a urine pregnancy test at screening.

[h] Hepatitis B genotyping will be performed at screening if it has not been documented in the prior medical record.

[i] Serology and viral markers = HBsAg, anti-HBs, HBVDNA, pg-RNA, HBcAg, HBeAg, HBeAg antibody.

[j] If the patient has experienced an acute illness or temperature > 38°C in the 2 days prior to dosing, the administration of study medication and corresponding visit will be delayed until the illness or fever has resolved.

[k] Investigators will review the eligibility of all patients to determine if the next treatment is to be administered. Eligibility for the next treatment will include 1) confirmation that patients did not meet a Stopping Rule (Section 7.1.1); 2) confirmation that the pre-treatment liver parameters are within acceptable ranges for treatment (Section 4.1); 3) confirmation that patients do not have a new confirmed or suspected IMC (Appendix 2). Patients not meeting these criteria will not be treated.

[l] If an authorized COVID-19 vaccine has been administered in proximity to a scheduled IP administration, a ± 3 day window is allowed for IP dosing.

[m] After Day 169 or ET, only MAEs, NCIs and IMCs will be recorded.

[n] A single blood sample will be collected for biobanking at the beginning of the study (prior to dosing on Day 1) and end of the study. This sample will be used for future analyses not specified in the protocol. Analysis will be limited to HBV serologic and HBV-specific DNA and RNA and patients' DNA will not be analyzed.

[o] Safety laboratory testing, including liver panel, for Doses 1 and 2 will be obtained during the visits conducted 7±2 days after these doses of study medication. Safety laboratory testing following Doses 3, 4 and 5 will be obtained in the interval from 7 days after dose administration and before the next dose of study medication is administered. Safety labs after Dose 6 will be assessed at the Day 169 visit.

[p] Diaries will also be reviewed at the Day 85, Day 113, Day 141 and Day 169 visits

Table 2 Schedule of Events – Follow-up Period

Study Visit	Follow-Up Period			
	Day 232	**Day 323**	**Day 414**	**Day 505 or ET[a]**
Completion of Week (number)	**33**	**46**	**59**	**72**
Window (days)	**±10 days**	**±10 days**	**±10 days**	**±10 days**
Visit may be conducted at home or work or in part as a telemedicine visit[b]	X		X	
Immunosuppressive medications, vaccines, and new HBV treatments (only)[c]	X	X	X	X
Targeted and symptom-driven PE	X	X	X	X
Height and weight				X
Vital signs[d]	X	X	X	X
ECG[d]				X
Hematology and serum chemistry	X	X	X	X
Liver panel	X	X	X	X
HBV serology and viral markers[e]		X		X
Whole blood for PBMC isolation		X		X
MAEs, NCIs and IMCs (only)[f]	X	X	X	X

AE = adverse event; ECG = electrocardiogram; ET = early termination; HBV = hepatitis B virus; HIV = human immunodeficiency virus; MAE = medically-attended adverse event; NCI = new-onset chronic illness; IMC = immune-mediated medical condition; PBMC = peripheral blood nonnuclear cell; PE = physical examination.

[a] If a patient prematurely discontinues study medication before Day 505, Day 505/Early termination procedures will be performed.

[b] A telemedicine visit would include a home visit by appropriate trained personnel to perform a target and symptom-driven physical and obtain vital signs and safety laboratories. The remaining portions of the visit may be conducted virtually by the study investigator.

[c] After Day 169 or ET, only immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury will be recorded.

[d] Measured before any blood sample collection.

[e] Serology and viral markers = HBsAg, anti-HBs, HBVDNA, pg-RNA, HBcAg, HBeAg, HBeAg antibody.

[f] After Day 169 or ET, only MAEs, NCIs and IMCs will be recorded.

5. POPULATION

5.1. Number of Patients

Approximately 80 patients are planned for enrollment over approximately 24 months at approximately 35 study centers in North America, Europe, UK and Asia-Pacific.

5.2. Inclusion Criteria

Patients who meet all of the following inclusion criteria may be included in the study.

1. Able and willing to provide informed consent
2. Men and women 18 to 65 years of age, inclusive
3. Body Mass Index (BMI) 18.0 to 34.9 kg/m^2, inclusive
4. Inactive, treatment-naïve CHB with documented HBsAg positivity for at least 12 months before Day 1. (The history of HBsAg positivity may be reduced to 6 months provided HBV anti-core IgM antibodies are negative).
5. qHBsAg ≥ 10 IU/mL but ≤ 200 IU/mL in the 12 months prior to Screening or from informed consent to randomization

   If a patient has more than one qHBsAg value within 12 months and prior to randomization, the patient will be deemed eligible if <u>any</u> one measurement is within the eligible range.
6. AST, ALT, INR, albumin, total bilirubin (excluding patients with Gilbert Syndrome, who will only be eligible for study participation if total bilirubin is ≤ 3.0 mg/dL) and direct bilirubin within normal limits at screening. Note: ALT and AST elevations up to 1.5 x ULN are allowed if evidence of hepatic steatosis, defined as one of the following criteria: 1) fatty liver on ultrasound, or other imaging modality or Fibroscan controlled attenuation parameter (CAP) ≥ 260 dB/m. To qualify under these conditions, HBV DNA must be <2,000 IU/mL, and there must be no history or signs of liver disease other than fatty liver and HBV.
7. Negative drug screen at Screening unless prescribed by a medical practitioner for medical use (NB, recreational and prescription cannabis is allowed)
8. For women of childbearing potential (women who are not permanently sterile [documented hysterectomy, bilateral tubal ligation, salpingectomy, or oophorectomy] or postmenopausal [12 months with no menses without an alternative medical cause]):
   a. Negative pregnancy test on Day 1
   b. Willingness to practice a highly effective method of birth control with low user dependency from screening through one menstrual cycle after the last dose of study medication, which include:
      i. Abstinence

ii. Sex only with persons of the same sex
iii. Monogamous relationship with vasectomized partner
iv. Intrauterine device
v. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
vi. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
vii. Intrauterine hormone-releasing system

Patients who practice true abstinence or who exclusively have same sex partners need not use contraception, provided it is in line with their preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Should any such patient stop practicing abstinence, they must use contraception as described above.

9. For men with sexual partners of childbearing potential, as defined above:

    a. Abstinence
    b. History of vasectomy or surgical sterilization
    c. Monogamous relationship with a postmenopausal or surgically sterilized partner
    d. Willingness to practice a highly effective method of contraception, as defined above, for 90 days after the last dose of study medication and to refrain from sperm donation during this time

    The same criteria pertaining to abstinence and withdrawal methods in women of childbearing potential (Inclusion Criterion 8) apply to men with sexual partners of childbearing potential

10. Willingness to comply with all aspects of the study through the entire study period

Patients who fail to meet Inclusion Criteria 5 and/or 6 and otherwise meet the requirements for study participation will be permitted one additional blood draw during the same screening period to requalify. Patients who screen fail for other Inclusion Criteria may undergo rescreening at the discretion of the Investigator and Medical Monitor.

5.3. Exclusion Criteria

Patients who do not meet any of the following exclusion criteria may be included in the study.

1. Pregnant or lactating women
2. Positive HBeAg at Screening
3. History of a hepatitis B flare or 1-log increase in HBV DNA or HBsAg in the prior 6 months

4. Prior or current history of active or untreated human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis delta virus (HDV)
5. Acute COVID-19, a positive test result for SARS-CoV2 infection, or exposure within 14 days to an individual with acute COVID-19
6. Febrile illness ($T \geq 38.0^{o}C$) within the past 14 days
7. Prior or current history of any underlying liver disease not related to HBV (NB, steatosis, as documented by imaging or Fibroscan CAP, is permitted if ALT and AST are <1.5 x ULN and HBV DNA <2,000 IU/mL and there is no history or signs of liver disease other than fatty liver and HBV)
8. Fibroscan > 8.5 kPA at Screening or history of hepatic fibrosis or cirrhosis (NB, a Fibroscan is not required if an examination is performed within 12 months before Screening, or a liver biopsy was performed within 2 years before Screening and no fibrosis [F1 or greater] was identified.)
9. History of cirrhosis or signs of hepatic decompensation, including but not limited to variceal bleeding, ascites, or hepatic encephalopathy
10. White blood cell count < 3,500/µL, neutrophils < 1,000/µL, hemoglobin < 11 g/dL, or platelets < 125,000/µL

    Note: Individuals of African descent with a white blood cell count <3,500/ µL will not be excluded for this reason if white blood cell count is ≥ 2,500/µL, provided that the neutrophil count is ≥ 1,000/µL and there is no other identified cause of leukopenia.
11. Prior treatment with an approved or investigational agent for HBV
12. History of conditions associated with immunocompromise
13. History of conditions associated with altered immune response, such as anaphylaxis, angioedema, or autoimmune disease
14. Treatments known to affect the immune system, such as corticosteroids (other than topical or inhaled preparations), alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics, allergy injections, immunoglobulins, interferons, or other immunomodulating therapies within 30 days of Screening
15. Uncontrolled diabetes mellitus, defined as hemoglobin A_1C (HBA_1C) ≥ 10% at Screening
16. Receipt of live-attenuated replicating vaccines within 30 days or receipt of any other licensed or authorized vaccines (including vaccines intended to prevent COVID-19) within 14 days prior to Day 1
17. Change in any chronically administered medication or treatment within 14 days of Screening, or inability to maintain these medications at the same dose through Day 169 (NB, patients chronically using aspirin, non-steroidal anti-inflammatory

agents, antacids, vitamins, probiotics, and over-the-counter medications will maintain their level of intake throughout the study)

18. Malignancy within 3 years of Screening, excluding non-melanoma skin cancers and *in situ* cervical cancer (NB, patients who have undergone prior screening for HCC by imaging or alpha-fetoprotein levels will have negative test results)
19. Untreated alcohol or drug abuse
20. Planned elective surgery or hospitalization during the study period
21. Participation in a prior trial involving HepTcell or FP.02-2
22. Known allergy to any of the ingredients in HepTcell
23. Receipt of any investigational drug or treatment within 30 days before Day 1 or planned use during the study period
24. Any medical, psychiatric, or social condition or occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including reactogenicity), or a patient's ability to give informed consent

Patients who are excluded by Exclusion Criterion 10 but otherwise meet the requirements for study participation will be permitted one additional blood draw to requalify. Patients who screen fail for other Exclusion Criteria may undergo rescreening at the discretion of the Investigator and Medical Monitor.

6. STUDY MEDICATION

6.1. Description

6.1.1. Formulation

6.1.1.1. HepTcell

HepTcell (adjuvanted FP-02.2) is the final reconstituted product for administration, that consists of a lyophilized mixture of 9 fluoropeptides and mannitol (FP-02.2 drug product), L-histidine buffer, normal saline (to achieve an isotonic, neutral pH), and IC31 (developed by Valneva SE). The 9 synthetic peptides (designated P877, P151, P113, P856(K), P753(K), P376, P797(K), P277(K), and P1266(K)) are each covalently linked to a fluorocarbon moiety on the N-terminus under a controlled process and formulated in mannitol. Each peptide is 32 to 40 amino acids in length and corresponds to a conserved region of HBV polymerase, core, or surface protein and contains CD4+ and CD8+ T cell epitopes. IC31 is a synthetic, 2-component adjuvant solution comprised of 40 nmol/mL ODN1a, a single stranded oligodeoxynucleotide consisting of dimeric repeats of deoxy-inosine/deoxy-cytosine linked by an unmodified phosphodiester backboned and of 1000 nmol/mL KLK, comprising an 11 amino acid artificial cationic antimicrobial peptide.

HepTcell is administered by IM injection.

6.1.1.2. Placebo

Normal saline for IM injection will be supplied by the site pharmacy.

6.1.2. Packaging, Storage, and Handling

All supplies are labelled as investigational products (IPs) in accordance with applicable legal and regulatory requirements. All IPs will be stored in a secure place under appropriate storage conditions.

FP-02.2 (0.36 mg per vial or each peptide) supplied in 2 mL single-use glass vials is stored at -20°C ± 5°C.

28 mM L-histidine diluent (1.2 mL) supplied in 2 mL single-use glass vials is stored at 2-8°C.

IC31 (1000 nmol/mL KLK; 40 nmol/mL ODN1a) (1.6 mL) supplied in 2 mL single-use glass vials is stored at 2-8°C.

All components will be brought to room temperature before dose preparation.

In the US, Canada, Spain, Thailand, and Italy reconstitution of IP will be performed by unblinded staff at the site. In the UK and Germany, reconstitution of IP will be done at a centralized location. Please refer to the ALT-301-202 Pharmacy Manual for more information.

Use of gloves is recommended when removing material from vials or cleaning up spills. Broken, damaged, or leaking vials should be handled with protective gloves as is done for sharps and infectious material. Take precautions to avoid accidental injection, contamination of wounds or skin abrasions, and contact with sharp materials or needles contaminated with IPs.

Full preparation instructions are detailed in a separate pharmacy manual.

6.2. Randomization

Following completion of the Screening activities, patients who meet the all the inclusion and none of the exclusion criteria will be registered by the Interactive Web Response System (IWRS). Eligible patients will be randomly assigned in a 1:1 ratio to HepTcell or placebo treatment groups. Randomization will be stratified by study center to minimize imbalances between treatment groups.

The first 12 patients (6 HepTcell, 6 placebo) will form the sentinel cohort. To assure a 1:1 distribution of HepTcell and placebo in the sentinel cohort, randomization in this group will not be stratified.

If none of the Stopping Rules (see Section 7.1.1) are met in one or more patients in the sentinel cohort, randomization may continue in the expanded study cohort.

The randomization list will be drawn up by an independent statistician.

6.3. Dose and Administration

HepTcell or normal saline placebo will be administered by IM injection at intervals of 4 weeks for 6 doses. Doses will be administered on Days 1, 29, 57, 85, 113, and 141 (±2 days for each dose). The 1.0 mL HepTcell injection contains 0.150 mg of each FP-02.2 peptide and IC31 at 500 nmol KLK and 20 nmol ODN1a.

Each dose of HepTcell or placebo will be administered as an IM injection (1.0 mL) in the deltoid muscle, where possible, of the non-dominant arm by appropriately trained clinical staff members. Patients will stay in the unit for at least 2 hours following administration of the first and second doses. Vital signs will be assessed before dosing and every 15 minutes post dosing over 2 hours at these two visits, and medications and qualified medical personnel will be available in case a patient experiences a severe acute allergic reaction during the immediate post-vaccination period.

Refer to ALT-301-202 Pharmacy Manual for specific preparation information and country specific procedures (if applicable).

If an authorized COVID-19 vaccine has been administered in proximity to a scheduled IP administration, a ±3 day window is allowed for IP dosing.

6.4. Dosing Modifications

The sentinel cohort of 12 patients will undergo blinded safety review by the Safety Committee 7 to 10 days after all ongoing patients in the sentinel cohort have completed

the respective dose of study medication and will determine the decision to continue at that dose into the expanded cohort. Safety will be assessed in the sentinel cohort before each dose is administered to the expanded cohort. If any of the Stopping Rules in Section 7.1.1 are met in one or more patients in the sentinel cohort and the event(s) is deemed possibly or probably related to HepTcell, dosing will be suspended pending DMC review. DMC recommendations may include instituting modifications to ensure the safety of continued dosing or discontinuing the study. If none of the Stopping Rules (below) are met, randomization and dosing may continue in the expanded study cohort. Patients will be unblinded as necessary to assess the relationship between the study medication and events that meet criteria for Stopping Rules. Patients who experience events that meet criteria for Stopping Rules will permanently terminate dosing.

Monitoring and dosing rules for patients who experience liver abnormalities is described in Section 4.1.

6.5. Blinding and Unblinding

The Pharmacy staff at the central or site pharmacy will be unblinded for the purpose of final drug preparation. The pharmacist will consult the IWRS for dose allocation and the Pharmacy staff will prepare each dose in compliance with the randomization list.

Due to the fact that formulations cannot be made to look identical, a blinded syringe will be used for administration.

Knowledge of the randomization list will be limited to the persons responsible for creation of the randomization list, pharmacy staff who prepare the study medications, unblinded site staff who administer the study medication and any unblinded study monitors or auditors, until all data has been entered in the electronic Case Report Form (eCRF), quality control and verification of the eCRF and assignment of patients to the analysis populations has been completed, the database has been locked, and the study formally unblinded.

Data provided to the Safety Committee will be blinded.

If unblinding is required in the interest of the safety of a patient, an Investigator will discuss the matter with the Sponsor before unblinding. In a medical emergency, the Investigator or delegate may unblind via the IWRS for that patient without prior consultation with the Sponsor. In that event, the Investigator or delegate will notify the Sponsor as soon as possible that the randomization code has been broken for the patient. If the blind is broken, the date, time, and reason must be recorded.

Patients may also be unblinded for the processing of SAEs, expedited safety reports, and the emergency unblinding of patients, as detailed in a separate Safety Management Plan.

6.6. Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of each study medication as shipped by the Sponsor (or designee), including the date received. In

addition, an accurate study medication disposition record will be kept, specifying the amount dispensed for each patient and the dates of dispensation and any returns.

Sponsor approval is required for on-site destruction of all used study medication and shipment of all unused study medication back to the Sponsor at the completion of the study and once all reconciliation has occurred.

6.7. Prior and Concomitant Therapy

In the interests of patient safety and acceptable standards of medical care, the Investigator will be permitted to prescribe additional treatment(s) at his/her discretion. However, as noted below, changes in any chronically administered medications or treatments should be avoided during the Treatment Period (through Day 169).

All medications must be recorded in the patients' eCRFs from 30 days before the first dose through Day 169 or early termination (ET) from the Treatment Period, but only immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury will be recorded beyond this point through the end of the Follow-up Period (Day 505 or ET from Follow-up).

6.7.1. Prohibited Prior and Concomitant Medications

Prohibited prior and concomitant medications are as follows:

- Any prior treatment with an approved or investigational agent for HBV.
- Treatments known to affect the immune system, such as corticosteroids (other than topical preparations), alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics, allergy injections, immunoglobulins, interferons or other immunomodulating therapies are prohibited within 30 days of Screening and through the course of the trial.
- Live vaccines (such as live influenza vaccinations or live travel vaccinations) are also not permitted with 30 days of Screening and through the course of the trial.
- Receipt of any investigational drug or treatment within 30 days before Day 1 or planned use during the study period
- Change in any chronically administered medication or treatment within 30 days of Screening or inability to maintain these medications at the same dose through Day 169

In case of worsening or disease progression, study medication will be discontinued, and the above medications prohibited will be allowed, at the discretion of the investigator and Sponsor, if it is in the patient's best interest to initiate any treatment prohibited in the study.

Preventive COVID-19 vaccines that have regulatory approval or emergency use authorization will be allowed prior to IP dosing on Day 1, provided that their administration adheres to Exclusion Criterion 16. COVID-19 vaccination is also permitted during study participation. A ± 3 day window is allowed for IP dosing if a COVID-19 vaccine is administered in proximity to a scheduled IP administration after Day 1. These vaccines will be captured as a concomitant medication.

6.8. Contraception

All female patients of childbearing potential must practice a highly effective method of birth control with low user dependency, as defined in Section 5.2, from Screening through one menstrual cycle after the last dose of study medication. Male patients with partners of childbearing potential must practice a highly effective method of contraception for 90 days after the last dose of study medication and refrain from sperm donation during this time.

6.9. Compliance

The injections will be administered by study personnel and therefore compliance with study medication dosing is not a concern. The study personnel will be appropriately trained on study medication administration procedures and documentation requirements prior to study start.

Non-compliance with study procedures will be reported to the Sponsor who will decide if persistent non-compliant patients should be withdrawn from continued study treatment.

7. PREMATURE DISCONTINUATION

7.1. Individual Patients

Patients can choose to discontinue study medication or participation in the study at any time, for any reason, without prejudice to their future medical care. Patients could be discontinued for any of the following reasons:

- Patient request/withdrawal of consent
- Noncompliance with study requirements
- Loss to follow-up
- Investigator discretion
- Sponsor request, including termination of the study by the Sponsor

In case of worsening or disease progression, study medication will be discontinued, and the medications prohibited in Section 6.7.1 will be allowed, at the discretion of the investigator and Sponsor, if it is in the patient's best interest to initiate any treatment prohibited in the study.

If a patient prematurely discontinues study medication before Day 169, Day 169/ET procedures will be performed. Patients who prematurely discontinue study medication will remain in the study for Follow-up Period study assessments, with the dates of visits adjusted to correspond to 13, 26, 39 and 52 weeks after the last dose of study medication.

Eligible patients who are randomized and withdrawn before their second dose of study medication will be replaced. Patients who have received two doses of study medication who are subsequently withdrawn from the study will not be replaced.

In consultation with the DMC, patients in the Sentinel Cohort may be replaced at any time to assure that the reliability and integrity of the data from this cohort remains intact.

7.1.1. Stopping Rules

In consultation with the DMC, the following Stopping Rules will be applied:

- ALT or AST ≥ 10 × ULN
- INR ≥ 1.3
- Total bilirubin ≥ 1.5 × ULN (excluding patients with Gilbert Syndrome)
- Direct bilirubin ≥ 1.5 × ULN (for patients with Gilbert Syndrome)
- SAEs
- Severe systemic reactogenicity event (see Appendix 1)

If any of the Stopping Rules are met in one or more patients in the sentinel cohort (ie, the first 12 patients dosed) and the event(s) is deemed possibly or probably related to study medication, dosing will be suspended pending DMC review. Similar procedures will be

applied if 2 or more patients in the sentinel or expanded study cohort together experience Stopping Rules deemed possibly or probably related to study medication at any time during the 24-week Treatment Period. DMC recommendations may include instituting modifications to ensure the safety of continued dosing or discontinuing the study.

If the study is halted based on a DMC decision or safety concern, the trial will only be restarted after notification of the competent authority via a substantial amendment.

7.1.2. Disease Progression / Need for Active Treatment

At the end of the clinical trial, either due to premature discontinuation or study completion, the decision about follow-on treatments and medical care will be made by the patient's physician or medical team in accordance with the usual standard of care. This will assure that patients have access to appropriate therapies in case of progression or other need for active treatment. Patients in need of active treatment will receive treatment based on the recommendations of American Association for the Study of Liver Disease [Terrault 2018], the Canadian Association for the Study of the Liver and Association of Medical Microbiology and Infectious Disease Canada [Coffin 2018], and European Association for the Study of the Liver guidelines [EASL 2017].

7.2. Study as a Whole

Both the Sponsor and the Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, the Sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB/IEC of the same. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

Possible reasons for termination are:

- Safety reasons – the incidence of AEs in this or any other study using the same investigational product(s) indicates a potential health risk for the patients
- New scientific knowledge becomes known that makes the objectives of the study no longer feasible/valid
- Unsatisfactory enrollment of patients

8. DESCRIPTION OF STUDY PROCEDURES

See Section 4.6 for the Schedule of Events for the Screening and Treatment Periods (Table 1) and the Follow-up Period (Table 2).

8.1. Screening Assessments

8.1.1. Demographics

Demographic data and baseline characteristics will be recorded during Screening.

8.1.2. Medical History

A complete medical history will be obtained and recorded during Screening. Enquiries will be made regarding all body systems including allergies/drug sensitivities, past surgeries, substance abuse and any other diseases or disorders.

The medical history will include a history of hepatitis B flares, Fibroscan tests and measurements of qHBsAg, HBV DNA, and liver tests in the 24 months prior to Screening.

8.1.3. Fibroscan

A Fibroscan will be performed at Screening. The Fibroscan is not required if an examination was performed within 12 months before Screening, or if no fibrosis was seen on liver biopsy within 2 years before Screening.

8.1.4. Hepatitis B Genotyping

Hepatitis B genotyping will be performed at Screening if it has not been documented in the prior medical record.

8.2. Efficacy Assessments

8.2.1. Immunology

Whole blood samples will be collected and processed to isolate, cryopreserve and store PBMCs. This will be conducted at designated laboratory, which may include a central laboratory or laboratories at Investigator sites. Further details can be found in the laboratory manual.

Cryopreserved PBMC samples will be transferred to a designated laboratory for immunological analyses (IFN-γ ELISpot). The methods of ELISpot analysis will be detailed in the laboratory manual.

8.2.2. Virology

Blood samples will be collected for the assessment of virological parameters (qHBsAg, anti-HBsAg antibody, HBV DNA, HBV pg-RNA, HBcrAg, HBeAg, HBeAg antibody) at the times indicated in the Schedule of Events (Section 4.6). Isolation of serum or plasma

will be performed at the clinical site following methods detailed in the laboratory manual. Serum and plasma will be stored at the clinical site under appropriate conditions (as described in the laboratory manual) until shipment to a designated laboratory. The methods of virologic analysis will be detailed in the laboratory manual.

8.2.3. Stored Sample for Future Analyses

A single blood sample from patients will be collected for storage at the beginning of the study prior to dosing and at the end of the study, as indicated in Table 1. This sample will be used for future analyses not specified in the protocol. Analysis will be limited to HBV serologic and HBV-specific DNA and RNA; patients' DNA will not be analyzed.

8.3. Safety Assessments

8.3.1. Reactogenicity Assessments

Each patient will record local events, systemic events, and oral temperature in a diary daily for 7 days after each dose. Diaries will be distributed to patients at each dosing visit to record these events. Patients will also be provided thermometers for daily recording of temperatures and measuring devices for the recording the size of injection reactions. Events will be graded according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [United States Food and Drug Administration 2007]. Unsolicited events reported by the patients outside of this 7-day reporting period will be recorded as AEs.

Microscopic hematuria will be assessed by urinalyses performed at the visits 7±2 days after Doses 1 and 2 of study medication, and after Doses 3, 4, 5, and 6 as per the Schedule of Events (Table 1).

Reactogenicity events will be categorized separately from AEs unless they are assessed as serious, in which case they will be reported as SAEs. A list of solicited reactogenicity events is provided in Appendix 1.

8.3.2. Adverse Events

Adverse events will be assessed by direct observation and patient assessments/interviews from Screening through the end of study. All AEs will be recorded through the end of the Treatment Period (Day 169 or ET). After that time, only MAEs, NCIs, and IMCs, which will be categorized as AEs, will be recorded through the end of the Follow-up Period (Day 505 or ET). A list of IMCs is provided in Appendix 2.

Details on the definitions, reporting, and management of AEs are provided in Section 9.

8.3.3. Clinical Laboratory Tests

Blood samples for the safety laboratory tests listed in Table 3 will be collected according to the Schedule of Events (Section 4.6).

Table 3: Safety Laboratory Tests

Hematology	
White blood cells (WBC)	Platelets
Red blood cells	WBC differential (absolute and %)
Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Mean corpuscular volume	Monocytes
Mean corpuscular hemoglobin	Eosinophils
Mean corpuscular hemoglobin concentration	Basophils
Liver Panel	
Total and direct bilirubin	
Aspartate transaminase (AST)	
Alanine aminotransferase (ALT)	
Total protein	
Albumin	
Gamma-glutamyl transferase (GGT)	
Lactate dehydrogenase	
Alkaline phosphatase (AP)[a]	
International normalized ratio (INR)	
Serum Chemistry	
Sodium	
Potassium	
Urea	
Creatinine	
Calcium	
Phosphate	
Glucose	
Creatine kinase[b]	
Urinalysis	
Protein	Red blood cells
Bilirubin	pH
Urobilinogen	Nitrites
Ketones	Specific gravity
Glucose	Microscopy (if clinically indicated or hemoglobin is detected on dipstick)
Leukocyte esterase	For the purpose of reactogenicity reporting, hematuria is defined as 3 or more red blood cells per high powered field

Serology (at Screening only)	
HIV I and II	HDV antibodies
HCV antibodies	
Drugs of abuse and alcohol screen (at Screening only)[c]	
Amphetamine/ecstasy	Opiates
Ethanol	Benzodiazepines
Cannabinoids	Methadone and/or metabolites
Cocaine	Barbiturates
Pregnancy test[d]	
Beta human chorionic gonadotropin	

a Alkaline phosphatase iso-enzymes (liver-specific and bile duct specific) will be measured if original alkaline phosphatase test result is above the upper limit of normal.
b Creatine kinase MB or Troponin T will be measured where clinically indicated.
c Sites may use locally available drugs of abuse panels and alcohol tests. The specific drugs may vary from the outlined list.
d A serum pregnancy test will be performed in all women of childbearing potential at Screening. Urine pregnancy tests will be performed at other time points.

8.3.4. Height, Weight and BMI

Height and weight will be measured and BMI calculated and recorded at Screening. Weight and BMI will also be recorded at end of the Treatment Period (Day 169 or ET) and at the end of the Follow-up Period (Day 505 or ET).

8.3.5. Physical Examination

Physical examinations will be performed by trained medical personnel. A complete physical examination will be performed at Screening and the end of the Treatment Period (Day 169 or ET). Targeted and symptom-driven physical examinations will be performed at all other study visits. Any clinically relevant change in physical examination findings will be recorded as AEs.

8.3.6. Vital Signs

Vital signs, including sitting blood pressure, pulse rate (after at least 5 minutes rest), and body temperature, will be recorded at every study visit. Patients will stay in the unit for at least 2 hours following administration of the first and second doses. Vital signs will be assessed before dosing and every 15 minutes post dosing over 2 hours at these two visits. At visits with laboratory assessments, vital signs should be measured before any blood sample collection. Any clinically relevant change in vital signs will be recorded as AEs. Significant changes of vital signs, including the occurrence of tachycardia, bradycardia, hypertension, hypotension and fever will categorized and graded according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [United States Food and Drug Administration 2007].

8.3.7. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening, the end of the Treatment Period (Day 169 or ET), and at the end of the Follow-up Period (Day 505 or ET), as indicated in the Schedule of Events (Section 4.6). At visits with laboratory assessments, ECGs should be measured before any blood sample collection. Any clinically relevant change in physical examination findings will be recorded as AEs. Any clinically relevant change in ECG findings will be recorded as AEs.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product whether or not related to the investigational product. An AE can be any sign, symptom, or diagnosis that appears or changes in intensity during the course of the study.

Unchanged chronic conditions are not AEs and should not be recorded on the AE pages of the eCRF. These medical conditions should be adequately documented on the appropriate page of the eCRF (medical history or physical examination). However, medical conditions present on the first day of treatment that worsen in intensity or frequency during the treatment or post-treatment periods in a manner not consistent with natural disease progression should be reported and recorded as AEs. The Investigator will actively solicit this information and assess the event in terms of severity and relationship to the study treatment regimen.

The term AE is used to include any AE whether serious or not serious.

9.1.2. Adverse Drug Reaction

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

9.1.3. Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the reference safety information in the Investigator's Brochure.

For the purpose of expedited reporting of unexpected serious adverse drug reactions (ie, Suspected Unexpected Serious Adverse Reactions [SUSARs]), only possibly or probably related and unexpected SAEs (Section 9.3.2) will be considered serious adverse drug reactions.

9.1.4. Medically Attended Adverse Event

An MAE is an AE resulting in hospitalization, emergency room visit, or visit to or from medical personnel (other than routine health care visits).

9.1.5. New-Onset Chronic Illness

An NCI is an AE that is new (ie, not present at baseline) and typically chronic. Because of the significance of this designation for the patient's health and for evaluation of vaccine safety, NCIs are expected to be diagnoses, not symptoms, and the Investigator should record sufficient data in the source document to support the diagnosis.

9.1.6. Immune-Mediated Medical Conditions (IMC)

A list of IMCs is provided in Appendix 2.

9.1.7. Serious Adverse Event

An AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening (An AE is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Life-threatening means that the patient or subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe. Hospitalization does not include same day surgery, elective surgery, optional admission not associated with a precipitating AE (ie, elective cosmetic surgery), or hospitalization planned before the start of the study for a pre-existing condition that has not worsened. Persistent or significant disability or incapacity means that there is a substantial disruption of a person's ability to carry out normal life functions.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2. Reporting Responsibilities and Periods

It is the responsibility of the Investigator or Subinvestigator(s) to perform periodic assessment of AEs. AEs spontaneously reported by the patient or reported in response to an open question from the study personnel (eg, 'Have you had any health problems since the previous visit/you were last asked?') or revealed by observation will be recorded.

AEs and concomitant medications will be recorded from the signing of informed consent to Day 169, but only MAEs, NCIs, and IMCs, which will be categorized as AEs, will be followed subsequently through Day 505. Concomitant medication collection will align with AE collection. The AE term, date of AE onset, date of AE resolution (if applicable), severity, causality, action taken for the AE, outcome and whether or not the AE is an MAE, NCI, and or SAE will be recorded.

AEs must be monitored until they are resolved or stabilized, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), or follow-up is no longer possible. Data describing AEs will be recorded in the patient's medical record and as appropriate, an SAE report form. SAEs will be reported to the Sponsor as described in Section 9.7.

Any SAE that the Investigator considers to be possibly or probably related to study medication and occurs at any time after completion of the study must be reported to the Sponsor or designee. If at the time the Investigator initially reports an SAE, the event has not resolved, the Investigator must provide a follow-up report as soon as it resolves (or upon receipt of significant information if the event is still ongoing).

9.3. Assessment of Adverse Events

9.3.1. Severity

The Investigator should assess the severity of each AE. The AE will be recorded at its highest severity grade.

The severity of all AEs, both serious and non-serious, will be assessed by assigning a grade according to the FDA Guidance on the Toxicity Grading Scale for Preventive Vaccine Clinical Trials [United States Food and Drug Administration 2007]. NCI CTCAE, v 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic _applications/ctc.htm) will be used for AEs not described in this guidance.

When an AE cannot be graded by the aforementioned FDA guidance or CTCAE, the following severity grading may be used:

- Grade 1 (Mild): awareness of sign or symptom, but easily tolerated
- Grade 2 (Moderate): discomfort enough to cause interference with usual activity
- Grade 3 (Severe): incapacitating with inability to work or do usual activity

- Grade 4 (Life-Threatening): refers to an event in which the patient was, in the view of the Investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
- Grade 5 (Fatal): death related to AE

An AE that is assessed as severe should not be confused with an SAE. Severity is a category for rating the intensity of an event, and both non-serious AEs and SAEs can be assessed as severe. An event will be defined as serious when it meets one of the criteria described in Section 9.1.7.

9.3.2. Relatedness (Causality)

The assessment of causality will be based on the information available and may be changed upon receipt of additional information.

Causality should be assessed using the following categories:

- Unrelated/Unlikely Related: clinical event with an incompatible time relationship to investigational agent administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the investigational agent
- Possibly related: clinical event with a reasonable time relationship to investigational agent administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals
- Probably related: clinical event with plausible time relationship to investigational agent administration, and that cannot be explained by concurrent disease or other drugs or chemicals

9.4. Safety Laboratory, Physical Examination, Electrocardiogram, and Vital Sign Abnormalities

Any abnormal laboratory result, physical examination finding, ECG interpretation, or vital sign measurement considered clinically significant by the Investigator will be recorded as an AE. A clinically significant laboratory abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening/Baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (eg, anemia) will be recorded as the AE term. Repeated additional assessments required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

9.5. Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication. Pregnancy in a patient's partner is not considered an AE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy will be followed-up and documented even if the patient was withdrawn from the study. See Section 9.7.4 for further information on reporting of pregnancy.

An induced elective abortion to terminate a pregnancy without medical reason is not regarded as an AE. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion in a study patient is always considered an SAE.

9.6. Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved study medication must be communicated to the Sponsor or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

An overdose of study medication is not expected, as it is administered via IM injection. Should patients receive a higher dose than the allocated dose, this should be reported in the eCRF and the Sponsor should be informed. Any deviations from the assigned dose will be handled as a protocol deviation.

9.7. Procedures for Recording and Reporting Adverse Events

9.7.1. Recording Adverse Events

To improve the quality and precision of AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE page of the eCRF. Do not use colloquialisms, jargon, or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms on AE pages of the eCRF (e.g., record "congestive heart failure" rather than "dyspnea", "rales", and "cyanosis"). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the eCRF page. For example, if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE.
- Adverse events occurring secondary to other events (i.e., sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable,

generally represents the most accurate clinical term to record on the AE page of the eCRF. If a primary SAE is recorded on an AE eCRF page, events occurring secondary to the primary event should be described in the narrative description of the event.

- Laboratory abnormalities that are identified by the Investigator as clinically significant are to be considered AEs and recorded on the AE eCRF page.

9.7.2. Reporting of Serious Adverse Events

Serious AEs require reporting to the Sponsor or designee within 24 hours, regardless of the relationship of the event to the study treatment regimen. Refer to Section 9.1.7 for the definition of an SAE. Procedures for recording and reporting SAEs will be detailed in a separate Safety Management Plan for processing SAEs, expedited safety reports, and the emergency unblinding of patients.

Within 24 hours of the Investigator's observation or learning of an SAE, the Investigator should notify Pivotal, S.L.U. (Pivotal Pharmacovigilance) by completing the SAE forms as thoroughly as possible with all available details of the event, including a determination of causality (even if preliminary), and signing them. The Investigator should communicate with Pivotal Pharmacovigilance if input is needed to complete the SAE assessment. Investigator causality determination and signature MUST be included for all SAEs. The completed SAE form and cover sheet should be sent by email or fax to Pivotal Pharmacovigilance.

Pivotal Pharmacovigilance

North America:	**(Fax) +1 877-853-3275**
	(Phone) +1 877-412-8673
Europe/UK/Asia-Pacific:	**(Fax) +34 913 076 047**
	(Phone) +34 619 085 538

e-mail: drugsafety@pivotalcr.com

If not all information regarding an SAE is initially available, the Investigator should not wait to receive additional information before completing the AE eCRF and SAE forms. For initial SAE reports, the Investigator should record all case details that can be garnered on the SAE form and the AE eCRF page. Relevant follow-up information is to be submitted on updated SAE forms as soon as it becomes available.

If there are questions regarding reporting an SAE or if information needs to be transmitted that cannot be recorded on the SAE forms (e.g., discharge summaries, laboratory reports), the Investigator should contact Pivotal Pharmacovigilance.

For unexpected serious adverse drug reactions (SUSARs), blinded reports will be disseminated and provided to Investigators at each study site.

When required and according to local law and regulations, unblinded SUSARs or other SAEs will be reported by an unblinded designee to the IRB/EC and regulatory authorities.

9.7.3. Special Reporting Situations

Death

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and the AE eCRF page.

Surgical or Diagnostic Procedures

The illness leading to a surgical or diagnostic procedure is to be recorded as an AE/SAE, not the procedure itself. The procedure is to be captured in the case narrative as part of the action taken in response to the illness.

9.7.4. Reporting Pregnancies

Pregnancy itself is not considered an AE. If a **patient becomes pregnant** during the study or **within 1 month of discontinuing** any study medication or the **partner of a patient** participating in the study becomes pregnant during the study or **within 3 months of discontinuing** any study medication, the Investigator should report the pregnancy on a separate pregnancy report form provided to the sites. Only pregnancies occurring from the time of first study medication dose administered to the patient through Day 505 will be reported and documented.

The patient/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy.

This pregnancy report form must be completed and submitted, either by e-mail or fax, immediately but no later than 24 hours of the Investigator's learning of the event to:

Pivotal Pharmacovigilance

North America: **(Fax) +1 877-853-3275**

Europe/UK/Asia-Pacific: **(Fax) +34 913 076 047**

e-mail: drugsafety@pivotalcr.com

However, any pregnancy complication, spontaneous or elective abortion, still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE, and reported, as applicable.

9.8. Safety Committee

A Safety Committee will conduct regular blinded reviews of all AEs and reactogenicity events. The Safety Committee will also review blinded safety data from a sentinel cohort

of 12 patients before dosing in the expanded cohort of patients. The responsibilities of the Safety Committee will be delineated in a Safety Analysis Plan.

9.9. Data Monitoring Committee

This study will be overseen by an independent DMC, which will have access to unblinded data, as needed, for the assessment of patient safety. A charter describing the roles, responsibilities, and operating procedures of the DMC will be implemented prior to study initiation.

9.10. Medical Monitor

A Medical Monitor will provide 24-hour/7-day coverage for medical issues pertaining to this study. The contact information for the Medical Monitor in the US and Canada is provided below:

Robert Hardi, MD
Altimmune, Inc.
910 Clopper Road, Suite 201S
Gaithersburg, MD 20878
Telephone: +1 301-461-1084

For issues arising in Europe/UK/Asia-Pacific, the contact information for the Medical Monitor in the EU is provided below:

Ernesto Estefania, MD
Pivotal, S.L.U.
Calle Gobelas 19, la Florida
28023 Madrid-Spain
Telephone: + 34 620 844 036
e-mail address: ernesto.estefania@pivotalcr.com

10. STATISTICS

10.1. General Procedures

Baseline is defined as data collected closest to randomization prior to any study medication dosing. All analyses and summary statistics will be presented by treatment group (HepTcell, placebo).

Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided by treatment.

10.2. Sample Size

A study of IFN-α2 in a population with inactive CHB reported a mean incremental decrease of 1.3 log-qHBsAg at 24 weeks in those patients completing IFN-α2 treatment compared to non-treatment. Mean decrease would translate to approximately 50% of patients completing treatment achieving 1.3 log-qHBsAg response (reduction). To estimate treatment effect in the current study, the proportion of patients achieving a 1.0-log reduction in qHBsAg is estimated as one-half (25% of patients) who achieve this response. Assuming a response rate of 3% on placebo and 25% on HepTcell, 40 patients will be randomized per treatment group to detect a difference in the proportion of patients treated with HepTcell achieving the primary endpoint compared to patient treated with placebo at a 0.05 level of significance (two-sided) with approximately 80% power.

10.3. Analysis Sets

Safety Analysis Set: All patients who receive any study medication. Patients will be analyzed according to the treatment that they receive.

Modified intent to treat (mITT) Analysis Set: All randomized patients who receive any amount of study medication, have a baseline and at least one post-baseline efficacy assessment. Patients will be analyzed according to the treatment that they receive. This analysis set will be used for primary and secondary analyses.

Per Protocol (PP) Set: All randomized patients who receive the full designated amount of study medication according to the correct treatment assignment and who have results from HBV serology and viral markers at Day 85.

10.4. Statistical Methods

10.4.1. Primary Efficacy Endpoint

For the primary analysis, proportions of patients with virologic response, defined as a 1.0-log reduction in HBsAg or serologic clearance of HBsAg, will be compared between HepTcell and placebo groups using Fisher's Exact Test at a 0.05% two-sided level of significance.

Patients who discontinue prematurely or have missing data will be considered nonresponders for that endpoint. Linear and logistic regression will be employed to examine the effects of baseline factors, such as qHBsAg level, HBV DNA levels, and hepatitis B genotype on response.

10.4.2. Secondary and Exploratory Efficacy Endpoints

The same approach as used for the primary efficacy endpoint will be applied for secondary and exploratory endpoints that are categorical in nature.

Changes from baseline in PBMC ELISpot, HBsAg, HBcrAg, pg-RNA, and quantitative HBV DNA will be analyzed using a mixed model for repeated measures (MMRM). The model will include the fixed effects of treatment, stratification factor, week, and treatment-by-visit interaction as well as the continuous, covariate of baseline level. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood (ReML) estimation method.

Relationships between hepatitis flares and HBsAg loss and/or decline will be evaluated logistic and linear regression.

A Kaplan-Meier model will be developed to compare changes between treatment groups in HBsAg clearance and a 1-log reduction in HBsAg over time.

No multiplicity adjustments will be made for secondary or exploratory endpoints.

10.4.3. Analysis of Safety

Quantitative safety data will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment arm. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and concomitant medications will be coded using WHO drug dictionary.

Laboratory evaluations, vital signs assessments and ECG parameters will be summarized by treatment group and protocol specified collection time point. A summary of change from baseline at each protocol specified time point by treatment group will also be presented.

10.4.4. Demographic and Baseline Characteristics

Descriptive statistics will be used to evaluate differences in demographic and baseline characteristics.

10.5. Interim Analysis

An interim analysis will be performed after all patients complete 24 weeks (6 doses) of treatment or discontinue study medication. The conduct of the interim analysis will be detailed in the statistical analysis plan (SAP).

The database will be locked when all patients complete the Day 169 assessments or terminate the trial; a second database lock will take place when all patients complete the Day 505 assessments or terminate the trial. Efficacy and safety endpoints (as applicable) will be reported on all data accrued through these times. With the exception of unblinding required to assess Stopping Rules or the relationship of SAEs to study medication for expedited safety reporting, patients will not be individually unblinded until the completion of the Day 505 database lock.

10.6. Statistical Analysis Plan

A formal statistical analysis plan (SAP) will be developed and finalized prior to the database lock and unblinding of treatment assignment. This plan will confirm the analysis sets used in the analysis, outline all data handling conventions, and specify all statistical methods to be used for all safety and efficacy analyses. The SAP will be formalized and signed-off on prior to the locking of the database and unblinding of the treatment codes. The SAP will supersede the protocol with respect to analyses specified, although the primary analysis will remain the same. It is anticipated that analyses other than those specified in the protocol may be pre-specified in the SAP.

11. DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. These are described in the following sections.

11.1. Data Handling

Data will be recorded at the site on source documents and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded in the eCRF system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

11.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.3. Data Entry

Data must be recorded using the eCRF system as the study is in progress. All study site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.4. Medical Information Coding

For medical information the following thesauri will be used:

- MedDRA v. 23.0 (or subsequent version) for AEs
- WHO Drug Dictionary June 2017 (or subsequent version) for concomitant medications

11.5. Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

11.6. Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP guidelines, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. Monitoring will include on-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by CRA signature and date on the study-specific monitoring log and the completion of a detailed monitoring report.

The CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications with the investigational site (monitoring visits, letter, telephone, email, and fax).

All unused study medication and other study materials are to be returned to the Sponsor or designee after the clinical phase of the study has been completed.

Regulatory authorities, the IRB/EC, and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

11.7. Source Document and Case Report Form Completion

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (i.e., original records or certified copies). Source documents and the eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/eCRF. The source document/eCRF should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents. A site-specific eCRF archive and audit trail will be provided at the close of the study to each Investigator. The Sponsor or designee will retain the eCRF archive and audit trail for all investigative sites.

11.8. Record Retention

Records of patients, source documents, monitoring visit logs, eCRFs, inventories of study product, regulatory documents, and other correspondence pertaining to the study must be kept in the appropriate study files at the site. The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

12. ETHICS

12.1. Good clinical practice

The study will be conducted in accordance with the protocol, GCP, the relevant ICH guidelines, the applicable regulatory requirements, and the ethical principles that have their origins in the Declaration of Helsinki. As required by US FDA (21 CFR 56) and the Declaration of Helsinki, the study protocol, amendments, and informed consent form will be reviewed and approved, according to 21 CFR Parts 50 and 56 (or similar local requirements, such as ICH E6, for ex-US sites), respectively, by each study center's IRB or EC.

12.2. Institutional Review Board / Independent Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of patients. Federal/local regulations and ICH GCP guidelines require that approval be obtained from an IRB/EC prior to participation of patients in research studies. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

No drug will be released to the site for dosing until written IRB/EC authorization has been received by the Sponsor.

12.3. Patient Information and Consent

The informed consent form and any changes to the informed consent form made during the course of the study must be agreed to by the Sponsor or their designee and the IRB/EC prior to its use and must be in compliance with ICH GCP guidelines, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient or proxy is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient or the patient's legally authorized representative before any study-specific activity is performed and will document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the informed consent form must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB/EC, and/or regulatory agencies. A copy of the signed informed consent form will be given to the study patient or proxy. Whenever possible, patients who participate based on proxy consent will be re-consented once deemed capable by the Investigator of providing consent on their own.

If significant new findings are developed during the course of research which may affect the willingness of patients to continue study participation, the Sponsor will notify each Investigator of the findings via letter or telephone.

12.4. Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study medication accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.5. Protocol compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, the approval/favorable opinion of the IRB/EC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/EC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/EC may provide, if applicable regulatory authority(ies) permits, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/EC. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation and reported to the appropriate study monitor or staff in a timely fashion.

13. COMPENSATION, INSURANCE AND INDEMNITY

The Sponsor has retained an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The patient will be appropriately treated or compensated, or both, for any health or other problems arising from participation in this study.

14. STEERING COMMITTEE

In addition to the DMC, a study Steering Committee will be appointed to advise the Sponsor on the conduct of the trial. The committee will comprise of the Principal Investigator, the Lead Investigators of the individual participating countries, the Sponsor's Chief Medical Officer, and managers from the Sponsor and the CRO overseeing study conduct. The committee will provide advice on study endpoints, compliance with protocol procedures, recruitment, safety signal detection, and issues that could impact data quality or safety. They will also advise on the acceptability of Investigators and sites that will participate in the trial. The Steering Committee will remain blinded throughout the trial. A charter describing the roles, responsibilities, and operating procedures of the Steering Committee will be developed prior to study initiation.

15. PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total, including articles in journals or newspapers, oral presentations, or abstracts, by the Investigator(s) or their representative(s), shall require prior approval, notification, and review within a reasonable time frame by the Sponsor and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprising the Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 60 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

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APPENDICES

Appendix 1 – Reactogenicity Events

The following reactogenicity events will be assessed by patients for 7 days after each dose of study medication and recorded in daily diaries.

Local (injection site) reactogenicity events

- Pain (pain on pressure)
- Pain (spontaneous pain without pressure)
- Erythema/Redness
- Swelling/hardening

Systemic reactogenicity events

- Headache
- Fatigue
- Myalgias (muscle aches)
- Nausea
- Vomiting
- Diarrhea
- Chills
- Fever
- Arthralgias (joint aches)

Note: Microscopic hematuria will be assessed by urinalyses performed at visits 7±2 days after each dose of study medication

Appendix 2 – Immune-Mediated Medical Conditions

Any AE assessed by the Investigator as immune-mediated but not appearing in the list below will also be reported as an IMC.

Gastrointestinal disorders

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis

Metabolic diseases

- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis

- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis, including site specific variants (eg, noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin disorders

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Rosacea
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis,

Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis