Pivotal	STATISTICAL ANALYSIS PLAN

Study Code:	ALT-301-202
Protocol Version:	Version 5.0 (Amendment 04)
Protocol Date:	24-Jul-2022

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)

Investigational Product	HepTcell (Adjuvanted FP-02.2)
Indication studied	Inactive Chronic Hepatitis B (CHB)
EudraCT No	2020-002118-42
Phase of study	Phase 2
Sponsor (company and address)	Altimmune, Inc. 910 Clopper Road, Suite 201 S Gaithersburg, MD 20878 - USA
Sponsor representative: (name, title and company)	Jay Yang, VP of Biostatistics and Data Management; Altimmune, Inc
Lead investigator	Mark Thursz, MD, Professor of Hepatology, Imperial College London

Pages Nº	51
SAP Author	Tania San José, Lead Biostatistician; Pivotal S.L.U.
SAP Version	V2.0 Draft A1
SAP Date	22 Apr-2024

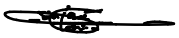
STATEMENT

By signing this document, I acknowledge that I have read the Statistical Analysis Plan and approve of the planned statistical analysis described herein.

I agree that the planned statistical analyses are appropriate for the objective of the study and are consistent with the methodology described in the protocol, clinical development plan, and all regulatory guidelines.

I also understand that any subsequent changes to the statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

APPROVALS

Developed by:	*Tania San José* *Lead BS; Pivotal S.L.U.*		*Electronically signed by: Tania San Jose* *Reason: I am the author* *Date: May 2, 2024 21:28 GMT+2*
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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

CHANGES COMPARED TO PREVIOUS STATISTICAL ANALYSIS PLAN (SAP) VERSIONS

STATISTICAL ANALYSIS PLAN HISTORY

Author	Version	Date	Comments
Elisabel García Ioulietta Mulligan	1.0	24-Nov-2023	Original SAP
Tania San José	2.0	22-Apr-2024	Inclusion of Non-parametric model in the analysis and minor issues have been changed. Modified TFLs according the document 'Addendum to the Statistical Analysis Plan' including in Appendix 2.

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1. LIST OF ABBREVIATIONS

Abbreviations

AE	Adverse event(s)
ALT	Alanine aminotransferase
anti-HBs	Antibodies to hepatitis B surface antigen
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CHB	Chronic hepatitis B
CHMP	Committee on Human Medicinal Products
CI	Confidence Interval
cm	Centimeters
CRF	Case Report Form
CSR	Clinical Study Report
DAAs	Direct acting antiviral agents
DBP	Diastolic Blood Pressure
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ELISpot	Enzyme-linked immunosorbent spot
EMA	European Medicine Agency
ET	Early termination
GGT	Gamma glutamyl transferase
HBcrAg	Hepatitis B core-related antigen
HBeAg	Hepatitis B e antigen
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IFN-α	Interferon-alpha
IFN-γ	Interferon gamma
IM	Intramuscular
IMC	immune-mediated medical condition
INR	international normalized ratio
LFT	liver function tests
LLOQ	lower limit of quantitation
LOCF	Last Observation Carried Forward
MAE	Medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
mRNA	Messenger RNA
n	Number of observations
NCI	New-onset chronic illness
NUC	Nucleos(t)ide analogs
PBMC	Peripheral blood mononuclear cells
PE	Physical Examination

PEP	Primary EndPoint
pg-RNA	Pre-genomic RNA
PP	Per Protocol
PT	Preferred Term
Q1	Quartile 1
Q3	Quartile 3
qHBsAg	Qualitative HBsAg
ReML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SOC	System Organ Class
SFC	Spot Forming Cell
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures and Listings
UA	Urinalysis
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

An interim analysis was conducted at Week 24 that demonstrated that the primary and secondary endpoints of the study were not met. HepTcell was well-tolerated, with no significant safety events.

Per protocol Section 7.2, the Sponsor is terminating the study for lack of efficacy. The IND and respective CTAs will be inactivated, and the investigational product will not undergo further clinical testing. As there were no ongoing MAEs, NCIs or IMCs at the time of termination, safety follow-up will end as of this date. Any accrued efficacy or safety information prior to study termination will be provided in tables and listings only up through the date of study termination.

2.2. Study Objectives

2.2.1 Primary Objective

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

2.2.2 Secondary Objectives

- To assess the 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.

2.3 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, except for 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), antibodies to hepatitis B surface antigen (anti-HBs), HBV DNA, HBV pre-genomic RNA (pg-RNA), hepatitis B core-related antigen (HBcrAg), and interferon gamma (IFN-γ) ELISpot assay in peripheral blood mononuclear cells (PBMCs). Patients will record any reactogenicity events (see section 5.3.3.7) for 7 days after

administration of each dose of study medication. A visit consisting of a targeted physical examination and safety laboratory tests, including liver panels, will be conducted 7±2 days after each administration of study medication. These visits, per the schedule of events (see Protocol), 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 it has been 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.

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.

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

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).

2.3.1 Eligibility and 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. 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 5.3.6.1) 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.

2.3.2. Eligibility criteria

2.3.2.1 Inclusion Criteria

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.

2.3.2.2 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.

2.3.2 Withdrawals

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 (described in the protocol) 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.

2.3.3 Study treatment

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). All study administration data collected at patient level will be presented in patient level listings as well as by visit. This will include missed doses or dose delays information.

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. Also, from the second dose, 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.

2.3.4 Replacement of Patients

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.

3. STUDY(ANALYSIS) POPULATIONS

3.1 Modified Intent-to-treat population (mITT)

The modified Intent-to-Treat (mITT) population includes all randomized patients who receive any amount of study medication, have a baseline and at least one post-baseline efficacy assessment (i.e., at least one post-baseline measurement for one of the following parameters: qHBsAg, HBV DNA, HBcrAg and pg-RNA).

3.2 Safety population

The Safety Analysis population includes all patients who receive any study medication. Patients will be analyzed according to the treatment that they receive.

3.3 Per Protocol Population

The Per Protocol population includes all randomized patients who receive the full designated amount of study medication according to the correct treatment assignment, who have results from HBV serology and viral markers at baseline and Day 85.

3.5 Screening Failures

Screen failure patients will be defined and a listing, including number identification, demography and why considered a screening failure will be created. In addition, the listing will provide information for re-screening patients.

4. STUDY ENDPOINTS AND DERIVED VARIABLES

This section is intended to outline the way to build the variables needed to assess all study endpoints and state definitions properly. For the statistical methods that will be used, refer to section 5.

4.1 Baseline and demographics characteristics

Baseline was defined as the most recent, non-missing value prior to or on the first study treatment dose date. Demographic data and baseline characteristics will be recorded during Screening. Patients can be re-screened and, in this case, these data at re-screening will be recorded and reassessed.

Specific disease variables are the following: Fibroscan, hepatitis B genotype, HCV, HDV, and HIV tests and HBV serology and viral markers including HBsAg, anti-HBs, HBV DNA, pg-RNA, HBcrAg, HBeAg, HBeAg antibody.

4.2 Efficacy endpoints

4.2.1 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.

A patient is considered to have achieved the virologic response if one of the following occurs:

1.- Log reduction in qHBsAg of at least 1.0, where

Log reduction = log_{10} (A/B), where A= qHBsAg at Baseline and B= qHBsAg to Day 169

2.- Serologic clearance of HBsAg is achieved on Day 169:

HBsAg to Day 169 is below the limit of quantitation (defined as 0.05 IU/mL).

Please refer to section 5.3.2 for details on the handling of intercurrent events and missing data.

4.2.2 Secondary Efficacy Endpoint

- **Proportion of patients achieving serologic clearance of HBsAg on Day 169**

  A patient is considered to have achieved serologic clearance of HBsAg on Day 169, if HBsAg on Day 169 is below the limit of quantitation (defined as 0.05 IU/mL).

- **Proportion of patients achieving serologic clearance of HBV DNA on Day 169**

  A patient is considered to have achieved serologic clearance of HBV DNA (PCR) on Day 169, if HBV DNA (PCR) on Day 169 is below the limit of quantitation (defined as 10 IU/mL).

- **Changes in qHBsAg, HBV DNA, HBcrAg and pg-RNA levels, Baseline to Days 85 and 169**
  Changes in qHBsAg, HBV DNA, HBcrAg and pg-RNA levels from Baseline to Days 85 and 169 are defined as:

  Change of Test from Baseline to Day 85 = Test value [Day 85] – Test value [Baseline];
  Change of Test from Baseline to Day 169 = Test value [Day 169] – Test value [Baseline];

  where *Test* correspond to the following quantitative tests:
  qHBsAg, HBV DNA and HBV DNA log, HBcrAg (Log U/mL and kU/mL) and pg-RNA

- **Change in LPMIX9 IFN-γ Spot Forming Cells (SFC) by ELISpot assay in PBMCs, Baseline to Days 85 and 169**
  Change in LPMIX9 IFN-γ SFC by ELISpot assay in PBMCs, Baseline to Days 85 and 169 are defined as:

  Change of LPMIX9 IFN-γ SFC from Baseline to Day 85 =
  LPMIX9 IFN-γ SFC [Day 85] – LPMIX9 IFN-γ SFC [Baseline];
  Change of LPMIX9 IFN-γ SFC from Baseline to Day 169 = LPMIX9 IFN-γ SFC [Day 169] – LPMIX9 IFN-γ SFC [Baseline]

  Where LPMIX9 is a pool of the 9 peptides contained in FP-02.2. Values for analyses are LPMIX9 raw values corrected with the control.

- **Change in LPMIX9 IFN-γ Spot Forming Cells (SFC) by ELISpot assay in PBMCs:**
    - *Some replicates of some subjects and days, the -ve Control was higher than the analogous LPMIX9 value which led to negative values.*
    - *Given that the control does not correspond to the analogous LPMIX9 in each of the replicates since the corresponding wells are not linked, the calculation of the continuous parameter to be analyzed, will be revised as follows:*
        - *Mean (i=1,2,3) of ["Value for Peptide LPMIX9 (R#i)"] - Mean (i=1,2,3) of ["-ve Control for Peptide LPMIX9 (R#i)"] where R#i is replicate #i, i=1,2,3*
        - *Adding a new specification: If the result turns out negative, it will round up to "0"*

Please refer to section 5.3.2 for details on the handling of intercurrent events and missing data or all the secondary endpoints.

4.3 Safety Endpoints

- **Incidence and severity of AEs, medically-attended AEs (MAEs), new-onset chronic illnesses (NCIs), and immune-mediated medical conditions (IMCs)**

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

    - An NCI is an AE that is new (i.e., 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.

    - An IMCs is any AE appearing in the list of AEs detailed in Appendix 2 of the protocol. Any AE assessed by the Investigator as immune-mediated but not appearing in the list will also be reported as an IMC.

- **Incidence and severity of local and systemic reactogenicity events**

  Reactogenicity local or systemic events, and oral temperature will be recorded by the patient in a diary daily for 7 days after each dose. 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].

Reactogenicity events will be categorized separately from AEs unless they are assessed as serious, in which case they will be reported as SAEs. The solicited reactogenicity events are the following:

Local (injection site) reactogenicity events:

- Pain at injection site (without pressure)
- Redness
- Swelling or hardening
- Tenderness

Systemic reactogenicity events

- Fatigue
- Fever
- Chills
- Headache
- Muscle aches
- Joint aches
- Nausea
- Vomiting
- Diarrhoea

Unsolicited events reported by the patients outside of this 7-day reporting period will be recorded as AEs.

- **Incidence and duration of hepatitis flares;**

Hepatitis flares are defined as alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and > 100 U/L.

The incidence and duration of hepatitis flares will be estimated considering ALT values across all measurements taken (scheduled and repeated) during the treatment period, as follows:

- Incidence of hepatitis flares will be estimated with the number of episodes across measurements on the treatment period per patient.
  An episode of hepatitis flare will start when the patient experiences ALT ≥ 3 × ULN and > 100 U/L (hepatic flare definition) and will stop in the assessment that verifies one of the following:

  i) The definition for hepatitis flare is not verified and there were no missing ALT values in precedent assessments;
  ii) There is no data for ALT with subsequent assessments without data either (if the patient is still in the study);
  iii) EOT visit (if the patient ended the study for any reason) and criteria for hepatitis flares were meet until EOT;
  iv) There is no data for ALT in one or more consecutive visits but there is available data in a subsequent assessment:
    a. If the definition of hepatitis flare is verified in the assessment with ALT data available after several without data, the episode will continue until i), ii) or iii) occur.
    b. If the definition of hepatitis flares is not verified in the assessment with ALT data available after several without data, the episode is considered to have finished in the previous assessment where data is available again.

- The duration of an episode of hepatitis flare will be estimated as the difference, in days, between the serum chemistry sample assessment's dates in which the episode starts and the episode stops (according to the definition above) + 1. i.e.,

Duration of hepatitis flares episode =

Sample assessment Date (episode stops) – Sample assessment Date (episode starts) +1

In case there is no sample assessment date, but the visit was performed, the visit date will be taken.

Illustrative example for visits assessments Ass1 to Ass8 (Assessment including repeated assessments between visits):

ASS1	ASS 2	ASS 3	ASS 4	ASS 5	ASS 6	ASS 7	ASS 8	Start Episode 1	Stop Episode 1	Start Episode 2	Stop Episode 2
√	X	√	√	X				ASS1	ASS2	ASS3	ASS5
√	√	NA	NA	NA				ASS1	ASS3		
√	√	NA	NA	√	X			ASS 1	ASS6		
√	√	NA	NA	X				ASS 1	ASS4		

√	√	√ (EOT)						ASS 1	ASS3		

√ = Criteria for Hepatitis Flares met
X = Criteria for Hepatitis Flares not met
NA = Not data available (but visit has been performed)

- **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**

  Changes from baseline across visits in laboratory parameters.

Safety endpoints that are also measured during the Follow-Up period will be assessed separately for the 24-week Treatment Period and 52-week Follow-Up Period.

5. GENERAL STATISTICAL METHODS

This section describes the general statistical methods for the study, such as sample size estimation, reporting of patient's disposition and protocol deviations and the statistical methods to be applied in demographics and baseline characteristics, efficacy and safety analyses.

Interim analyses are planned for this study. Details can be found in section 5.3.5.

Safety Committee Meetings as well as DMC are planned for this study. Details can be found in section 5.3.6.

Data handling and missing data handling as well as reporting conventions are described in sections 5.3.8, 5.3.9 and 5.3.11 respectively.

5.1 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.

5.2 Patient disposition

5.2.1 Patient disposition and withdrawals

This section describes patient disposition.

Screened patients include all patients who signed the informed consent form and are entered into the clinical database.

Re-screened patients include all patients who were declared screening failures at their first screening but were screened in a subsequent requalification.

Randomized patients will include all patients who were provided a treatment assignment that was recorded in the interactive response technology database, regardless of whether the treatment kit was used.

For patients' study status, the total number and percentage of patients in each of the following categories will be presented in the CSR using a flowchart diagram or summary table:

- Screened patients
- Re-screening patients among screened patients.
- Screen failure patients.
- Nonrandomized but treated patients (if applicable).
- Randomized patients.
- Randomized but not treated patients (if applicable).
- Patients in the mITT Population.
- Patients in the Safety Population.
- Patients in the PP Population.
- Patients who discontinued study treatment early, including primary reason for discontinuation.
- Patients who discontinued study early, including primary reason for discontinuation.

For all categories of patients (except for the screened and nonrandomized categories) the summaries will be provided by randomized treatment arms, and percentages will be calculated using the number of randomized patients as the denominator.

The number (%) of patients in each population will also be summarized by treatment. They will also be listed. The number of mis-stratified patients will be listed.

A listing of patients with population assignment including individual reasons of exclusion from the respective analysis populations will be provided. Data listing for early termination reasons will be also provided.

5.2.2 Protocol Deviations

Protocol deviations, including violations of inclusion/exclusion criteria, will be collected, and assessed as “minor” or “major” by the study team and the final version will be provided to the biostatistics contract research organization (Pivotal) prior to the database locks (1)- When all patients complete the Day 169 assessments or terminate the trial; (When all patients complete the Day 505 assessments or terminate the trial). Where it is programmatically possible deviations will be verified programmatically from the database. Statistically significant deviations will be identified by the sponsor and project team prior to each database lock. These are defined as deviations which have the potential to have a significant impact on the statistical analysis and interpretation of the study data.

All protocol deviations will be collected separately from the database and listed. The final listing of protocol deviations will be reviewed before each database lock to assist in the Per Protocol population selection and definition of the final study populations as well as a preliminary assessment of the quality of the trial data. All deviations will be summarized by deviation type and listed in the CSR.

5.3 Summary of Statistical Methods

This study is designed as a phase 2 study, exploratory in nature, to evaluate the response to HepTcell in treatment-naïve patients with inactive CHB. Comparisons will be performed between HepTcell and Placebo at a two-sided type I error rate of 0.05 which will not be adjusted for multiple testing.

The study will be considered to have achieved proof-of-concept when the 2-sided p-value is <0.05. Accordingly, the primary and key secondary efficacy endpoints will present 2-sided 95% Confidence Intervals (95%CIs) when applicable.

Unless otherwise specified, efficacy analyses will be performed using the mITT population, where patients will be in the treatment arm to which they received. As described in more detail elsewhere, patients will be analysed according to the treatment of the most treatment received. Moreover, supportive efficacy analyses will be performed in the PP population. Safety related analyses will use the safety population, where patients will be analyzed according to the treatment that they receive.

All applicable baseline data will be summarized by treatment arm (HepTcell, placebo), unless specified otherwise. Safety and efficacy data will also be summarized by treatment arm and additionally by time-point of assessment and/or follow-up, when appropriate.

Continuous variables will be summarized using the number of observations (n), mean (95%CI, if appropriate), standard deviation (SD), Standard error (SE, if appropriate), median, first quartile (Q1), third quartile (Q3), minimum, and maximum along with the total number of patients contributing values.

Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The denominator for all percentages will be the total number of patients in the treatment arm and dose number (if applicable) within the population of interest, unless stated otherwise in the table footnote.

Change from baseline is calculated only for patients with non-missing values for both the baseline and the time-point of interest and will be missing otherwise.

Statistical comparisons will be performed between HepTcell and placebo at a 5% confidence level.

All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings. The listings will be generally sorted by treatment arm and then Patient ID, unless specified otherwise.

5.3.1 Demographics, Other Baseline Characteristics and Medication

Summary statistics will be provided by treatment arm and overall (if applicable) for baseline characteristics and demographic variables; summaries will be provided on the mITT population. Prior and concomitant medications will be reported for the Safety population.

5.3.1.1 Demographic Characteristics

Descriptive statistics by treatment arm and overall (if applicable) will be performed for the demographic characteristics and disease history. Listings will also be presented for the demographic characteristics and disease history, respectively.

5.3.1.2 Fibroscan

A Fibroscan will be conducted at screening/re-screening visit if it was not performed within the prior 12 months of the corresponding visit. The Fibroscan is not required if no fibrosis was seen on liver biopsy within 2 years prior to screening/re-screening visit.

Result of Fibroscan (reported in kPa) will be summarized by treatment arm and overall. Summaries will be performed for all patients together regardless of the time that the Fibroscan was conducted (either within the prior 12 months of screening/re-screening or at the moment of screening/re-screening).

Number of patients with a liver biopsy performed within 2 years prior to screening will be summarized.

For re-screened patients, only information in the re-screening visit will be analyzed.

All data collected related to Fibroscan will be listed.

5.3.1.3 Hepatitis B Genotyping

HBV genotyping will be performed at screening/re-screening if it has not been documented in the prior medical record. HBV Genotype testing by means of PCR will be summarized by treatment arm and overall.

For re-screened patients, only information in the re-screening visit will be analyzed If the value in the re-screening visit is not valid (ie: "CANCELLED", "Not Detected", "Unknown") but the screening measurement has a valid result, this will be the one used in the summaries.

All data collected related to HBV genotyping will be listed.

5.3.1.4 HCV, HDV and HIV tests

The results of following tests will be summarized by treatment arm and overall:

- Human Immunodeficiency Virus-I antibodies (HIV-I);
- Human Immunodeficiency Virus-II antibodies (HIV-II);
- Hepatitis C virus antibodies (HCV);
- Hepatitis Delta virus antibodies (HDV)

For re-screened patients, only information in the re-screening visit will be analyzed.

All data collected related to HCV, HDV and HIV tests will be listed.

5.3.1.5 Medical History

Medical history abnormalities will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms. The version used will be specified in the data display footnote. Conditions will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment arm and overall. Listings will also be presented.

5.3.1.6 Physical Examination

Results of the complete physical examination assessment performed at Screening will be summarized by system class and by treatment arm and overall:

- Normal
- Abnormal Not Clinically Significant
- Abnormal Clinically Significant

For re-screened patients, only information in the re-screening visit will be analyzed.

The result of the baseline physical exam and the significant findings will be presented by listing.

5.3.1.7 Electrocardiogram (ECG)

Summaries of evaluation (normal; abnormal not clinically significant; abnormal clinically significant) will be provided by treatment arm and overall. Only available data will be used, and missing data at baseline will not be imputed.

For re-screened patients, only information in the re-screening visit will be analyzed.

All ECG results will be listed on a by-patient basis.

5.3.1.8 Vital Signs and Height, weight and BMI

Height, weight and Body Mass Index (BMI) as well as the vital signs at baseline will be described by treatment arm and overall. The variables to be included are:

- Blood Pressure:
  - Systolic (SBP)
  - Diastolic (DBP)
- Pulse rate
- Body temperature
- Respiration rate

Summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) for height, weight, BMI and all vital signs at baseline will be calculated by treatment arm and overall (if appropriate). Only available data will be used, and missing data at baseline will not be imputed.

For re-screened patients, only information in the re-screening visit will be analyzed.

Height, weight, BMI and all vital signs measurements will be listed.

5.3.1.9 Laboratory values at baseline

Laboratory assessments at baseline include hematology, serum chemistry and urinalysis.

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) of all quantitative laboratory variables at baseline will be calculated by treatment arm and overall (if appropriate). Only available data will be used, and missing data at baseline will not be imputed. Data will be listed by patient.

For re-screened patients, only information in the re-screening visit will be analyzed.

5.3.1.10 Prior and Concomitant Medications

Prior medications are those that the patient used prior to the date of first dose of study drug. Concomitant medications (including immunosuppressive medications, vaccines, and new HBV treatments) are defined as medications that continued or started on or after the date of first dose of study drug, recorded through Day 169. If start date is after Day 169, they will not be considered in the summaries of concomitant medications. 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. Prior and concomitant medications will be summarized by treatment arm according to the World Health Organization Drug Dictionary (WHO-DD), using the version in effect at the time of database lock (September 2021 or subsequent) and considering the first digit of the Anatomical Therapeutic Chemical

(ATC) classification system and the first 3 digits of the ATC classification system (therapeutic category). Patients will be counted once in each ATC category (anatomical or therapeutic).

Prior and concomitant medications will be summarized separately. Medications recorded after Day 169 will also be summarized separately as Post-Treatment medications.

Listings will also be presented.

5.3.1.11 Other Baseline Variables

Serum pregnancy test, Urine drug and alcohol screen and Eligibility criteria will be listed.

5.3.2 Efficacy Analyses

Analyses of efficacy endpoints will be performed in the mITT population. In addition, sensitivity analyses will be performed in the PP population and will be considered supportive.

All parameters involved in any of the primary, secondary, or exploratory efficacy endpoints will be summarized according to their nature by treatment arm and overall. The original value for these parameters will be listed.

5.3.2.1 Primary endpoint

The primary endpoint will be considered as described in section 4.2.1.

Patients who discontinue early or have missing HBsAg values on Day 169 but who achieve virologic response or serologic clearance of HBsAg on the last available assessment prior to Day 169 will be treated as responders for the primary endpoint; otherwise, patients with early discontinuation or missing HBsAg values on Day 169 will be treated as non-responders.

The proportion of patients achieving virologic response (defined as a 1.0-log reduction in HBsAg or serologic clearance of HBsAg) on Day 169 will be estimated as follows:

(Number of patients having achieved virologic response or serologic clearance of HBsAg to Day 169) / (Number of patients in the corresponding treatment (or overall)) x 100%

This proportion will be compared between treatment groups using Chi-Square Test or Fisher's Exact Test at a 0.05% two-sided level of significance. Fisher's Exact Test will be used if the expected values of at least the 80% of the cells in the contingency table created for estimating proportions are lower than 5.

This proportion will be analyzed using logistic regression models with treatment arm and baseline qHBsAg level as covariate. The analysis of maximum likelihood and odds ratio estimates for patients predicting a 'Yes' in achieving virologic response will be shown.

5.3.2.2 Secondary endpoints

The secondary efficacy endpoints are related to the evolution of serologic and viral markers as well as the PBMC ELISpot by days 85 and 169.

The secondary endpoints will be considered as described in section 4.2.2. Analyses to be performed are described in the following subsections.

No multiplicity adjustments will be made for secondary endpoints.

5.3.2.2.1 Proportion of patients achieving serologic clearance of HBsAg on Day 169

Patients who discontinue early or have missing HBsAg values on Day 169 but who achieve serologic clearance of HBsAg on the last available assessment prior to Day 169 will be treated as responders for this endpoint; otherwise, patients with early discontinuation or missing HBsAg values on Day 169 will be treated as non-responders.

The proportion of patients achieving serologic clearance of HBsAg on Day 169 will be estimated as follows:

(Number of patients having achieved serologic clearance of HBsAg on Day 169) / (Number of patients in the corresponding treatment (or overall)) x 100%

This proportion will be compared between treatment groups using Chi-Squared Test or Fisher's Exact Test at a 0.05% two-sided level of significance. Fisher's Exact Test will be used if the expected values of at least the 80% of the cells in the contingency table created for estimating proportions are lower than 5.

This proportion will be analyzed using logistic regression models with treatment group and baseline qHBsAg level as covariate. The analysis of maximum likelihood and odds ratio estimates for patients predicting a 'Yes' in achieving serologic clearance of HBsAg on Day 169 will be shown.

5.3.2.2.2 Proportion of patients achieving serologic clearance of HBV DNA on Day 169

Patients who discontinue early or have missing HBV DNA values on Day 169 but who achieve serologic clearance of HBV DNA on the last available assessment prior to Day 169 will be treated as responders for this endpoint; otherwise, patients with early discontinuation or missing HBV DNA values on Day 169 will be treated as non-responders.

The proportion of patients achieving serologic clearance of HBV DNA on Day 169 will be estimated as follows:

(Number of patients having achieved serologic clearance of HBV DNA on Day 169) / (Number of patients in the corresponding treatment (or overall)) x 100%

This proportion will be compared between treatment groups using Chi-Squared Test or Fisher's Exact Test at a 0.05% two-sided level of significance. Fisher's Exact Test will be used if the expected values of at least the 80% of the cells in the contingency table created for estimating proportions are lower than 5.

This proportion will be analyzed using logistic regression models with treatment group and baseline HBV DNA levels as covariate. The analysis of maximum likelihood and odds ratio estimates for patients predicting a 'Yes' in achieving serologic clearance of HBV DNA on Day 169 will be shown.

5.3.2.2.3 Changes in qHBsAg, HBV DNA, HBcrAg and pg-RNA levels, Baseline to Days 85 and 169

Changes from baseline to days 85 and 169 in qHBsAg, HBV DNA (and HBV DNA log), HBcrAg (Log U/mL and kU/mL) and pg-RNA will be summarized by means of descriptive statistics including mean, standard deviation, median, Q1 and Q3, minimum and maximum by treatment arm.

Changes from baseline for qHBsAg levels will be analyzed fitting a mixed model for repeated measures (MMRM) including treatment group, visits days (Day 1 through Day 169), and baseline values as a covariate. Interactions between visit days and treatment group will also be included. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood (ReML) estimation method. In addition, HBV DNA, HBcrAg and pg-RNA will be analyzed in the same manner. The data distribution will be tested for normality and appropriate transformations will be applied, as needed. Any transformation, if applied, will be reported.

Change from baseline is calculated only for patients with non-missing values for both the baseline and the time-point of interest and will be missing otherwise.

5.3.2.2.4 Change in IFN-γ frequency by ELISpot assay in PBMCs, Baseline to Days 85 and 169

Changes from Day 1 to days 85 and 169 in IFN-γ frequency by ELISpot assay in PBMCs (including LPMIX9 IFN-γ SFC and will be summarized by means of descriptive statistics including mean, standard deviation, median, Q1 and Q3, minimum and maximum by treatment arm.

Changes from baseline for IFN-γ frequency by ELISpot assay in PBMCs levels (including LPMIX9 IFN-γ SFC a) will also be analyzed fitting a mixed model for repeated measures (MMRM) including treatment group, visits days (Day 1 through Day 169), and baseline values as a covariate. Interactions between visit days and treatment group will also be included. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood (ReML) estimation method. The data distribution will be tested for normality and appropriate transformations will be applied, as needed. Any transformation, if applied, will be reported.

Change from baseline is calculated only for patients with non-missing values for both the baseline and the time-point of interest and will be missing otherwise.

- **The LPMIX9 variable is not normally distributed, and none of the transformations we have attempted are valid.**
    - Upon examining the data, highly right-skewed distribution was observed, with a significant number of subjects reporting a value of 0.
    - Given these challenges we cannot proceed the Mixed model proposed the previous version of SAP because the data do not fit the assumptions of normality. Therefore, the Wilcoxon-Mann Whitney test to compare these differences between treatments will be used instead.

5.3.3 Safety Analyses

Summary statistics will be provided by treatment arm and overall (if applicable) for the safety endpoints; summaries will be provided on the Safety population. Listings will also be presented.

The safety endpoints will be considered as described in section 4.3. Analyses to be performed are described in the following subsections.

5.3.3.1 Treatment exposure

Patients are initially planned to receive 6 doses of HepTcell or placebo at study visits 4 weeks apart (Days 1, 29, 57, 85, 113, 141). 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.

Exposure to the investigational product (HepTcell or placebo) will be summarized by descriptive statistics by treatment arm and dose (expressing cumulative data with previous doses) number as follows:

- Number of patients under each dose number
- Total number of doses administered
- Duration of exposure (defined as “last dose date of study drug – first dose date of study drug + 1”, regardless of temporary interruptions in study drug administration and will be expressed in days)

A listing of investigational product administration data by day of administration will be provided.
Randomization number assignment along with data related as well as cohort of assignment will be listed.

5.3.3.2 Adverse events

AEs will be coded using MedDRA v25.1 or subsequent.

Summary of AEs:

The primary focus of AE reporting will be on Treatment-Emergent Adverse Events (TEAEs). A TEAE is defined as an AE that starts or worsens on or after the date and time of the first administration of the study drug.

All reported AEs (regardless of TEAE or not) will be included in a by-patient AE listing, identifying which is treatment emergent and which it not.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as treatment-emergent or not. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of AEs with missing or partial-onset dates are provided in Section 5.3.9.

AE summaries will include number (n) and percentage (%) of patients experiencing an AE within each treatment arm and overall if appropriate. The denominator for computation of percentages is the number of patients in the safety population within each treatment arm. The number of events will be included in some summaries as well whenever appropriate.

Unless otherwise specified, when applicable, sorting order will be by decreasing number of patients in PTs within SOCs based on total patients. When more than one PT has same number of patients, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same patient will be counted only once for patients counting in the tables within a treatment arm.

Summary of All TEAEs:

The following TEAE summaries will be generated for the safety population:

- An overview of TEAEs. Number (%) of patients will be provided by treatment arm, to include:
    - TEAEs.
    - MAEs.
    - Grade 3 (Severe), Grade 4 (Life-threatening), and Grade 5 (Fatal) TEAEs.
    - Serious TEAEs.
    - Treatment-related AEs (defined as those events other than ‘Unrelated/Unlikely related’ as assessed by the investigator).
    - TEAEs serious leading to death.
    - TEAEs leading to study drug permanent discontinuation.

- TEAEs leading to clinical management of the AE.

- All TEAEs by primary SOC and PT.
- All TEAEs presented by PT.
- All treatment-related AEs presented by primary SOC and PT.
- All treatment-related AEs Grade 3 or higher, presented by primary SOC and PT.
- All TEAEs by maximum severity (i.e., Grade 1, Grade 2, Grades 3 to 5), presented by primary SOC and PT.

Separate listings will be provided for TEAEs leading to premature study drug discontinuation~~/interruption~~ and Study-Drug-Related TEAEs

5.3.3.3 Serious adverse events

Summary of SAEs and TEAEs leading to treatment change:

- All treatment-emergent SAEs by primary SOC and PT.
- TEAEs leading to study drug permanently discontinued by primary SOC and PT, defined as those AEs with action taken of treatment 'drug withdrawn'.

5.3.3.4 Medically-Attended AEs (MAEs)

Number and percentage of patients with MAEs will be reported by primary SOC and PT by treatment arm. These will be assessed separately for the Day 169 Treatment Period and Day 505 Follow-Up Period.

5.3.3.5 New-onset Chronic Illnesses (NCIs)

Number and percentage of patients with NCIs will be reported by primary SOC and PT by treatment arm. These will be assessed separately for the Day 169 Treatment Period and Day 505 Follow-Up Period.

5.3.3.6 Immune-mediated Medical Conditions (IMCs)

IMCs will be analyzed as recorded on the eCRF. Number and percentage of patients with IMCs will be reported by primary SOC and PT by treatment arm.

These will be assessed separately for the Treatment Period up to Day 169 and the Follow-Up Period up to Day 505.

5.3.3.7 Reactogenicity Events

Each patient will record local events, systemic events, and oral temperature in a diary daily for 7 days after each dose. Incidence of reactogenicity events will be analyzed by treatment arm and dose number.

The number of patients with injection site reactogenicity events and each of the solicited events (Redness, Swelling or hardening, Pain at injection site (without pressure), tenderness) as well as with systemic reactogenicity events and each of the solicited events (fatigue, fever, chills, headache, muscle aches, joint aches, nausea, vomiting, diarrhoea) will be shown.

Also, number of events will be estimated for grouped injection site reactogenicity events (Redness, Swelling or hardening, Pain at injection site (without pressure), tenderness) and grouped systemic reactogenicity events (fatigue, fever, chills, headache, muscle aches, joint aches, nausea, vomiting, diarrhoea). Each event will be counted once by day of registration in the patient's diary card (i.e.: if the same event is registered for 3 different days in the diary card of a specific dose, 3 events will be counted for that dose).

Summaries will be performed for All events and also according to the grade Mild, Moderate and Severe. The size of reaction for Redness and Swelling (or hardening) will be assigned with the measurement in cm, being Mild from 2.5 to 5, Moderate larger than 5 to 10 and Severe larger than 10. Patients may have self reported events under 2.5 cm as an event, but following formal guidance these will not be reported as reactogenicity event in the statistical analysis.

A listing of all events recorded in the diary card will be included.

5.3.3.8 Hepatitis Flares

The number and proportion of patients having any episode of hepatitis flares across all study visits during the treatment period will be analyzed by treatment arm and overall.

The following analyses will also be reported by treatment arm and overall:

- Incidence of hepatitis flares per patient;
- Maximum and average of duration of hepatitis flares by patient. This will be analyzed by means of descriptive statistics including mean, standard deviation, median, Q1 and Q3, minimum and maximum.

A listing for hepatitis flares will be created.

5.3.3.9 Physical Exam

Physical examination after baseline maybe targeted and symptom-driven for all study visits and only at the end of the Treatment Period (Day 169 or ET) a complete examination will be performed.

Results of physical examination assessments will be summarized by treatment arm and overall for each visit and by system class (in case of complete examination), as follows:

- Normal

- Abnormal Not Clinically Significant
- Abnormal Clinically Significant

Targeted and symptom-driven physical examination data during the treatment period will be summarized in the current visits: Day 1, 8, 29, 36, 57, 85, 113, and 141. Visits Day 64, Day 92, Day 120 and Day 148 for collection of this data during the treatment period were removed in the protocol version for which this SAP version is planned.

For patients following previous versions of the protocol, data recorded on the legacy visits will be used for analyses if an additional abnormality was reported. Data will be used for analyses following the correspondence: Day 64 to Day 85; Day 92 to Day 113; Day 120 to Day 141.

Post-baseline physical exams and the significant findings will be listed on a by-patient basis.

5.3.3.10 Electrocardiogram (ECG)

Summaries of evaluation (normal; abnormal not clinically significant; abnormal clinically significant) will be provided by treatment arm and overall for post-baseline measurements (End of Treatment Period (Day 169 or ET) .

All ECG results will be listed on a by-patient basis.

5.3.3.11 Vital Signs and Height, weight, and BMI

A summary of vital signs (including systolic and diastolic blood pressure and body temperature (in °C), heart rate and respiratory rate) including change from baseline (where appropriate), presented by descriptive statistics, will be displayed by treatment arm and overall, for each visit day from baseline through Day 169. Particularly, for vital signs measured after first and second doses, the maximum value among all values recorded in the 2 hours post-dosing will be taken as the representative for that day in summaries by visit.

Vital Signs data during the treatment period will be summarized in the current visits: Day 1, 8, 29, 36, 57, 85, 113, 141 and 169. Visits Day 64, Day 92, Day 120 and Day 148 for collection of Vital Signs data during the treatment period were removed in the protocol version for which this SAP version is planned.

For patients following previous versions of the protocol, data recorded on the days of the current visits listed above will be used for analyses. Only if there is no data collected in these visits and these patients have additional values in visits previously collected, those data will be used for analyses following the correspondence: Day 64 to Day 85; Day 92 to Day 113; Day 120 to Day 141; Day 148 to Day 169.

In addition, a summary and change from pre-dose of the values measured in the 2 hours post-dose (at 15 minutes intervals) after the first and second doses will be presented using the maximum value among

all values recorded in the 2 hours post-dosing. Pre-dose will be the latest assessment prior to the dose being summarized.

Height, weight, and BMI and the corresponding change from baseline will be summarized for visits after baseline.

Only available data will be used, and missing data will not be imputed. Change from baseline and pre-dose will be calculated only for patients with non-missing values for both the baseline or pre-dose and the time-point of interest and will be missing otherwise.

Vital Signs (on dosing and no-dosing days) and height, weight and BMI after baseline will be listed.

5.3.3.12 Laboratory Evaluation

Hematology (including white blood cells (WBC), red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, WBC differential (absolute and %), neutrophils, lymphocytes, monocytes, eosinophils, basophils); Liver Panel (including total and direct bilirubin, AST, ALT, total protein, albumin, GGT, lactate dehydrogenase, AP, INR); Serum Chemistry (including sodium, potassium, urea, creatinine, calcium, phosphate, glucose, creatine kinase) will be evaluated at each scheduled visit day during treatment period, as well as the scheduled days during Treatment follow-up period.

Urinalysis (including protein, bilirubin, urobilinogen, ketones, glucose, leukocyte esterase, red blood cells, pH, nitrites, specific gravity, microscopy) will only be evaluated in the same days during treatment period but not during the Treatment follow-up period.

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum, and maximum) of all quantitative laboratory variables (laboratory values and changes from baseline) will be calculated for each dose during the treatment period and for each visit during the follow-up period, by treatment arm.

Laboratory data will be analyzed at pre-doses of Dose 1 to 6. For all parameters, the last available measurement after last dose and before the current dose will be the representative value to be summarized for each dose (ie: for dose 2, last value taken from “Date of dose 1 + 1 day until Date of dose 2”).

For each visit during the follow-up period, the last of all measurements for the corresponding visit will be the representative value to be summarized.

The number (%) of patients with abnormal results (out of normal range) for each of the laboratory variables will be summarized at pre-dose of Doses 1 to 6 and in each visit during the follow-up period and treatment arm.

Shift tables for baseline versus each pre-dose for Doses 1 to 6 and follow-up visits will be presented for the hematology, urinalysis and chemistry laboratory parameters.

Data collected for Microscopy in Urinalysis (if clinically indicated or hemoglobin is detected on dipstick) will only be listed.

Data will be listed by patient.

Only available data will be used, and missing data will not be imputed.

5.3.3.13 Other

Serum pregnancy tests post-baseline will be listed.

5.3.3.14 Hepatitis flares and HBsAg

Relationships between hepatitis flares and HBsAg loss (defined as at least two consecutive negative HBsAg results) will be evaluated by comparing the proportion of patients with HbsAg loss in patients with and without hepatitis flares through Day 169.

The proportion of patients with HbsAg loss through Day 169 will be analyzed using logistic regression models with treatment group as factor and hepatitis flares and ALT at baseline as covariates. The analysis of maximum likelihood and odds ratio estimates for patients predicting a 'Yes' in verifying HBsAg loss will be shown.

5.3.8 Data Handling Conventions and Transformations

For HBV serology parameters and viral markers that are continuous in nature as well as HBV pre-genomic RNA, the following lower limit of quantitation (LLOQ) have been identified:

Test	LLOQ
HbsAg (IU/mL)	0.05
anti-HBs (mIU/mL)	5.00
quantitative HBV DNA(IU/ml)	10
HbcrAg (Log U/mL)	3
HbcrAg (kU/mL)	1
pg-RNA (log U/mL)	0.49

Also, some of the laboratory parameters could be reported in the form "< x" being "x" the LLOQ for that parameter.

For analyses, the values assigned to the lower limit of quantitation will be imputed as follows:

A value that is 1 unit less than the LLOQ will be used in statistical analyses if the datum is reported in the form of "< x" (where x is considered the LLOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used in statistical analyses.

5.3.9 Missing Data and Outliers

5.3.9.1 Missing data

A missing data point for a given study visit may be due to any one of the following reasons:

- The visit did not occur
- The visit occurred but data were not collected or were unusable
- The patient permanently discontinued from the study before reaching the window for the study visit

In general, missing baseline data will not be imputed. The following approaches are default methods for missing data handling in summary tables:

- Categorical data at baseline will be summarized for each treatment arm using counts (n) and percentages (%). Unless otherwise specified, denominators for all percentages will be the total number of patients in the corresponding treatment arm and dose number (if applicable) within the population of interest.
- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only. Only available data will be used.
- In general, change from baseline is calculated only for patients with non-missing values for both the baseline and the time-point of interest and will be missing otherwise.

Missing data commonly encountered during the study may comprise:

- Missing/Partial Dates: For incomplete days or months, an imputation will be done by assigning the first day of month or the first month of year, respectively. For incomplete years in dates for measurements after randomization, the year of first dose date will be assigned.
- Continuous variables: mixed models are robust to the presence of missing at random and conducts the analysis with all participants despite the presence of missingness. Of note, this method calculates the estimations based on the variance-covariance structure but without any formal imputations.

Missing data commonly encountered for safety and background variables may comprise:

- Missing/Partial Dates for AEs:

  Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE

period, the AE will be classified as treatment-emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

- Missing/Partial Dates for Concomitant Medications:

  No imputation for medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a both prior and concomitant.

  Only for immunosuppressive medications, vaccines, and new HBV treatments or medications associated with MAEs, NCIs, SAEs, hepatitis flares, or hepatic injury that can be recorded beyond Day 169, it will also be considered as post-treatment.

- Handling of Missing Assessment of Relationship of AEs to IP

  If the assessment of the relationship to IP is missing, then the relationship to IP in the frequency tables is considered as “possibly related”, but no imputation should be done at the data level.

- Handling of Missing Severity of AEs

  If the severity is missing for some of the treatment-emergent occurrences of an AE, the maximum severity on the registered occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

- Handling of Missing values in WBC differentials

  For abnormalities reported only for one in the pair “absolute counts or percentages” in any of the WBC differentials (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), the same level of abnormalities will be imputed for the other in the pair.

  If any of the WBC differentials in absolute count or percentage is missing, it will be imputed from the total WBC value following the rule “Absolute values are calculated by multiplying the total number of WBCs by the percentage of each type of while cell”.

5.3.9.2 Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes. All data will be included in the data analysis.

5.3.11 Reporting conventions

Vital signs, laboratory and biomarker parameters will be reported in International Units. The descriptive statistics will be reported to 2 decimal places, except for 1) those parameters with low measurements such as biomarkers or others, that will be reported to 3 or 4 decimal places, as appropriate; 2) those parameters not requiring decimal places, will be reported without any decimal place. Estimated parameters, such as regression coefficients will be reported to 3 decimal places. Percentages should be rounded to a single decimal place. P-values ≥0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001." All reported dates will be shown in YYYY-MM-DD format.

5.3.12 Study timelines

Each patient will participate in the study up to approximately 77 weeks (a 5-week Screening Period, a Day 169 Treatment Period, and a Day 505 Follow-Up Period commencing after the last dose of study medication at Week 20).

A Safety Committee with take place after 7 to 10 days of 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. The DMC scheduled meetings will take place after the 28-day observation period after the 3rd dose of study medication (Day 85) of the first 20 patients and at the conclusion of the trial.

5.3.13 Technical Details

The most updated study protocol has been used as a reference for this document. SAS programs, SAS Logs and SAS outputs generated during the creation of the Statistical Report will be archived in the PIVOTAL's File System.

5.3.14 Software

The statistical analysis will be performed using the scientific software SAS® V9.4 or later releases and SAS® Enterprise Guide V7.15 or later releases.

5.3.15 Database Standardization

Datasets for analyses will follow CDISC compliance. SDTM version will be detailed in the corresponding Specifications document.

5.3.16 Maintaining the Blind during the study

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.

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.

All statistical analysis will be performed by a blinded team of statisticians and statistical programmers, who will work in a secure area without any treatment identifying information. For the interim analysis the blinded team will handover all programs prepared using blinded information to the unblinded team who will then be able to prepare unblinded outputs required for the interim analysis as specified in Appendix 1.0 of this document.

No unblinded individual level data will be shared with anyone outside the unblinded team. The unblinded team will be defined in the Project Management Plan.

5.3.17 Changes to Protocol-planned Analyses

According to the protocol, ECG parameters will be summarized by treatment group and protocol specified collection time point and a summary of change from baseline at each protocol specified time point by treatment group will also be presented. However, ECG parameters have not been collected and they are not available for analyses.

6. REFERENCES

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Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

7. APPENDIXES

Appendix 1.- Tables, Figures, and Listings

Appendix 1.- Index of Tables, Figures, and Listings

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
Table Number				
14.1 Demographic Data Summary Tables				
14.1.1 Patient Disposition				
14.1.1.1	Patient Enrollment and Disposition	All Screened Patients	Yes	√
14.1.1.2	Patient Study Status	All Screened Patients	Yes	
14.1.1.3	Analysis Populations	Randomized Patients	Yes	
14.1.1.4	Protocol Deviations	mITT Population	Yes	
14.1.2 Demographic and Baseline Characteristics				
14.1.2.1	Demographic Characteristics	mITT Population	Only mITT	√
14.1.2.2	Baseline Characteristics	mITT Population	Only mITT	√
14.1.2.3	Specific Disease Characteristics: Fibroscan, Hepatitis B genotype, HCV, HDV and HIV tests and HBV serology and viral markers	mITT Population	Only mITT	
14.1.2.4	Medical History by System Organ Class and Preferred Term	mITT Population	Yes	
14.1.2.5	Baseline Physical Examination	mITT Population	Yes	
14.1.3 Prior and Concomitant Medications				
14.1.3.1	Prior Medication by ATC 1st and 2nd level	Safety Population	Yes	
14.1.3.2	Concomitant Medication by ATC 1st and 2nd level	Safety Population	Yes	
14.1.4 Extent of Exposure for Investigational Products				
14.1.4.1	Treatment Exposure	Safety Population	Yes	
14.2 Efficacy Data Summary Tables and Figures				

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
14.2.1 Primary Efficacy Endpoint				
14.2.1.1	Summary of patients achieving Virologic Response on Day 169	mITT Population	Only mITT	√
14.2.1.2	Logistic Regression Analysis for Virologic Response on Day 169	mITT Population	Only mITT	√
14.2.2 Secondary Efficacy Endpoint				
14.2.2.1.1	Summary of patients achieving Serologic Clearance of HBsAg on Day 169	mITT Population	Yes	
14.2.2.1.2	Logistic Regression Analysis for Serologic Clearance of HBsAg on Day 169	mITT Population	Yes	√
14.2.2.2.1	Summary of patients achieving Serologic Clearance of HBV DNA on Day 169	mITT Population	Yes	
14.2.2.2.2	Logistic Regression Analysis for Serologic Clearance of HBV DNA on Day 169	mITT Population	Yes	√
14.2.2.3.1	Summary and change from baseline of qHBsAg, HBV DNA, HBcrAg and pg-RNA levels: Days 85 and 169	mITT Population	Yes	
14.2.2.3.2	Repeated Measured Mixed Model for qHBsAg, HBV DNA, HBcrAg and pg-RNA levels: Days 85 and 169	mITT Population	Yes	√
14.2.2.4.1	Summary and change from baseline of IFN-γ frequency by ELISpot assay in PBMCs: Days 85 and 169	mITT Population	Yes	
14.2.2.4.2	Non-Parametric Model for IFN-γ frequency by ELISpot assay in PBMCs: Days 85 and 169	mITT Population	Yes	√
14.3. Safety Data Summary Tables				
14.3.1. Adverse Events				

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety Population	Yes	√
14.3.1.2	TEAEs by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.1.3	TEAEs by Preferred Term	Safety Population	Yes	
14.3.1.4	TEAEs related to study drug by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.1.5	TEAEs related to study drug Grade 3 or higher by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.1.6	TEAEs by maximum severity by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.2 Serious Adverse Events				
14.3.2.1	Serious TEAEs by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.2.2	TEAEs leading to study drug permanently discontinued by System Organ Class and Preferred Term	Safety Population	Yes	
14.3.3 Other Adverse Events				
14.3.3.1.1	Medically-Attended AEs (MAEs) by System Organ Class and Preferred Term. Treatment Period	Safety Population	Yes	
14.3.3.1.2	Medically-Attended AEs (MAEs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population	Yes	
14.3.3.2.1	New-onset Chronic Illnesses (NCIs) by System Organ Class and Preferred Term. Treatment Period	Safety Population	Yes	
14.3.3.2.2	New-onset Chronic Illnesses (NCIs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population	Yes	

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
14.3.3.3.1	Immune-mediated Medical Conditions (IMCs) by System Organ Class and Preferred Term. Treatment Period	Safety Population	Yes	
14.3.3.3.2	Immune-mediated Medical Conditions (IMCs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population	Yes	
14.3.4 Clinical Laboratory Tests				
14.3.4.1.1	Summary of pre-dose Values and Change from baseline for Clinical Laboratory Hematology Results	Safety Population	Yes (Through D169)	
14.3.4.1.2	Summary of Abnormalities for Clinical Laboratory Hematology Results	Safety Population	Yes (Through D169)	
14.3.4.1.3	Summary of Clinical Laboratory Hematology Results: Shift from baseline vs post-baseline category	Safety Population	Yes (Through D169)	
14.3.4.2.1	Summary of pre-dose Values and Change from baseline for Clinical Laboratory Biochemistry Results	Safety Population	Yes (Through D169)	
14.3.4.2.2	Summary of Abnormalities for Clinical Laboratory Biochemistry Results	Safety Population	Yes (Through D169)	
14.3.4.2.3	Summary of Clinical Laboratory Biochemistry Results: Shift from baseline vs post-baseline category	Safety Population	Yes (Through D169)	
14.3.4.3.1	Summary of pre-dose Values for Continuous Urinalysis Results	Safety Population	Yes	
14.3.4.3.2	Summary of Values for Categorical Urinalysis Results	Safety Population	Yes	

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
14.3.4.3.3	Summary of Abnormalities for Clinical Laboratory Urinalysis Results	Safety Population	Yes	
14.3.4.3.4	Summary of Clinical Laboratory Urinalysis Results: Shift from baseline vs post-baseline category	Safety Population	Yes	
14.3.5 Reactogenicity Events				
14.3.5.1	Incidence of Reactogenicity Events	Safety Population	Yes	
14.3.6 Hepatitis Flares				
14.3.6.1	Incidence of Hepatitis Flares	Safety Population	Yes	
14.3.6.2	Summary of patients achieving HBsAg loss by Hepatitis Flares	Safety Population	Yes	
14.3.6.3	Logistic Regression Analysis for HBsAg loss by Hepatitis Flares at Day 169	Safety Population	Yes	
14.3.7 Vital Signs				
14.3.7.1	Summary of Values and Change from baseline for Vital Signs: Results by Visit	Safety Population	Yes (Through D169)	
14.3.7.2	Summary of Values and Change from pre-dose for Vital Signs: Results after first and second dose	Safety Population	Yes (Through D169)	
14.3.7.3	Summary of Height, weight, and BMI change from baseline	Safety Population	Yes (Through D169)	
14.3.8 Electrocardiogram Measurements (12-Lead ECG)				
14.3.8.1	Summary of Evaluation for 12-Lead ECG Results	Safety Population	Yes (Through D169)	
14.3.9 Physical Examination				
14.3.9.1.1	Complete Physical Examination after Baseline (Day 169/ET)	Safety Population	Yes	
14.3.9.1.2	Targeted and symptom-driven Physical Examination after Baseline	Safety Population	Yes (Through D169)	
Listing Number				
16.2.1 Patient's Disposition				

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
16.2.1.1	Listing of Patient's Disposition and Status	All Patients in DB	Yes	
16.2.1.2.1	Listing of Eligibility Criteria	All Patients in DB	Yes	
16.2.1.2.2	Listing of Eligibility Criteria for Next Dose	All Patients in DB	Yes	
16.2.1.3	Listing of Screen Failure Patients	Screening Failure Patients	Yes	
16.2.1.4	Listing of Analysis Populations	All Patients in DB	Yes	
16.2.2 Protocol Deviations				
16.2.2.1	Listing of Protocol Deviations	Randomized Patients	Yes	
16.2.3 Patients excluded from Efficacy Analyses				
16.2.3.1	Listings of Patients excluded from Efficacy analyses	mITT Population	Yes	
16.2.4 Demographic and Baseline Characteristics				
16.2.4.1	Listing of Demographic Characteristics	All Patients in DB	Yes	
16.2.4.2	Listing of Liver Biopsy and Fibroscan	All Patients in DB	Yes	
16.2.4.3	Listing of Hepatitis B Genotyping, HCV, HDV and HIV tests	All Patients in DB	Yes	
16.2.4.4	Listing of Medical History by Patient and MedDRA System Organ Class and Preferred Term	All Patients in DB	Yes	
16.2.4.5	Listing of Prior and Concomitant (and Post-Treatment) Medication	All Patients in DB	Yes	
16.2.5 Study Drug Exposure for Investigational Products				
16.2.5.1	Study Treatment Completion	All Patients in DB	Yes	
16.2.5.2	Listing of Study Drug Administration	All Patients in DB	Yes	
16.2.5.3	Listing of Study Drug Dispensation	All Patients in DB	Yes	
16.2.5.4	Patient Randomization Listing	Randomized Patients	Yes	
16.2.6 Efficacy Data				
16.2.6.1	Listing of Serology and Viral markers	Randomized Patients	Yes	

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
16.2.6.2	Listing of IFN-γ frequency by ELISpot assay	Randomized Patients	Yes	
16.2.7 Adverse Events				
16.2.7.1	Listing of Adverse Events	All Patients in DB	Yes	
16.2.7.2	Listing of Serious Adverse Events	All Patients in DB	Yes	
16.2.7.3	Listing of TEAEs leading to Study Drug Discontinuation or Study Discontinuation	All Patients in DB	Yes	
16.2.7.4	Listing of Study-Drug Related TEAEs	All Patients in DB	Yes	
16.2.7.5	Listing of Medically-Attended AEs (MAEs)	All Patients in DB	Yes	
16.2.7.6	Listing of New-onset Chronic Illnessess (NCIs)	All Patients in DB	Yes	
16.2.7.7	Listing of Immune-mediated Medical Conditions (IMCs)	All Patients in DB	Yes	
16.2.8 Clinical Laboratory Tests				
16.2.8.1	Listing of Clinical Laboratory Hematology Results	All Patients in DB	Yes	
16.2.8.2	Listing of Clinical Laboratory Biochemistry Results	All Patients in DB	Yes	
16.2.8.3	Listing of Clinical Laboratory Urinalysis Results	All Patients in DB	Yes	
16.2.8.4	Listing of Clinical Laboratory tests: Pregnancy Test Results	All Patients in DB	Yes	
16.2.8.5	Listing of Clinical Laboratory tests: Urine drug and alcohol screen	All Patients in DB	Yes	
16.2.9 Reactogenecity Events				
16.2.9.1	Listing of Diary Card and Reactogenicity Events	All Patients in DB	Yes	
16.2.10 Hepatitis Flares				
16.2.10.1	Listing of Hepatitis Flares	All Patients in DB	Yes	
16.2.11 Vital Signs				
16.2.11.1	Listing of Vital Signs and Height, weight, and BMI	All Patients in DB	Yes	
16.2.12 Electrocardiogram Measurements (12-Lead ECG)				
16.2.12.1	Listing of 12-Lead ECG measurements	All Patients in DB	Yes	

TFL Number	Title	Analysis Set	Included in Final report	TOP LINE TABLES
16.2.13 Physical Examinations				
16.2.13.1	Listing of Physical Examinations	All Patients in DB	Yes	

Addendum to the Statistical Analysis Plan

Study ALT-301-201, 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

An interim analysis was conducted at Week 24 that demonstrated that the primary and secondary endpoints of the study were not met. HepTcell was well-tolerated, with no significant safety events.

Per protocol Section 7.2, the Sponsor is terminating the study for lack of efficacy. The IND and respective CTAs will be inactivated, and the investigational product will not undergo further clinical testing. As there were no ongoing MAEs, NCIs or IMCs at the time of termination, safety follow-up will end as of this date. Any accrued efficacy or safety information prior to study termination will be provided in tables and listings only up through the date of study termination.

The following tables and listings will be generated to supplement those that were produced for the Week 24 interim analysis:

14.3.3 Other Adverse Events		
14.3.3.1.2	Medically-Attended AEs (MAEs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population
14.3.3.2.2	New-onset Chronic Illnesses (NCIs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population
14.3.3.3.2	Immune-mediated Medical Conditions (IMCs) by System Organ Class and Preferred Term. Follow-Up Period	Safety Population

Listing Number		
16.2.1 Patient's Disposition		
16.2.1.1	Listing of Patient's Disposition and Status	All Patients in DB
16.2.1.2.1	Listing of Eligibility Criteria	All Patients in DB
16.2.1.2.2	Listing of Eligibility Criteria for Next Dose	All Patients in DB
16.2.1.3	Listing of Screen Failure Patients	Screening Failure Patients
16.2.1.4	Listing of Analysis Populations	All Patients in DB
16.2.2 Protocol Deviations		
16.2.2.1	Listing of Protocol Deviations	Randomized Patients
16.2.3 Patients excluded from Efficacy Analyses		

TFL Number	**Title**	**Analysis Set**
16.2.3.1	Listings of Patients excluded from Efficacy analyses	mITT Population

16.2.4.1	Listing of Demographic Characteristics	All Patients in DB
16.2.4.2	Listing of Liver Biopsy and Fibroscan	All Patients in DB
16.2.4.3	Listing of Hepatitis B Genotyping, HCV, HDV and HIV tests	All Patients in DB
16.2.4.4	Listing of Medical History by Patient and MedDRA System Organ Class and Preferred Term	All Patients in DB
16.2.4.5	Listing of Prior and Concomitant (and Post- Treatment) Medication	All Patients in DB
16.2.5.1	Study Treatment Completion	All Patients in DB
16.2.5.2	Listing of Study Drug Administration	All Patients in DB
16.2.5.3	Listing of Study Drug Dispensation	All Patients in DB
16.2.5.4	Patient Randomization Listing	Randomized Patients
16.2.6.1	Listing of Serology and Viral markers	All Patients in DB
16.2.6.2	Listing of IFN-γ frequency by ELISpot assay	All Patients in DB
16.2.7.1	Listing of Adverse Events	All Patients in DB
16.2.7.2	Listing of Serious Adverse Events	All Patients in DB
16.2.7.3	Listing of TEAEs leading to Study Drug Discontinuation or Study Discontinuation	All Patients in DB
16.2.7.4	Listing of Study-Drug Related TEAEs	All Patients in DB
16.2.7.5	Listing of Medically-Attended AEs (MAEs)	All Patients in DB
16.2.7.6	Listing of New-onset Chronic Illnessess (NCIs)	All Patients in DB
TFL Number	**Title**	**Analysis Set**
16.2.7.7	Listing of Immune-mediated Medical Conditions (IMCs)	All Patients in DB
16.2.8 Clinical Laboratory Tests		
16.2.8.1	Listing of Clinical Laboratory Hematology Results	All Patients in DB
16.2.8.2	Listing of Clinical Laboratory Biochemistry Results	All Patients in DB
16.2.8.3	Listing of Clinical Laboratory Urinalysis Results	All Patients in DB
16.2.8.4	Listing of Clinical Laboratory tests: Pregnancy Test Results	All Patients in DB
16.2.8.5	Listing of Clinical Laboratory tests: Urine drug and alcohol screen	All Patients in DB
16.2.9 Reactogenicity Events		
16.2.9.1	Listing of Diary Card and Reactogenicity Events	All Patients in DB
16.2.10 Hepatitis Flares		
16.2.10.1	Listing of Hepatitis Flares	All Patients in DB
16.2.11 Vital Signs		
16.2.11.1	Listing of Vital Signs and Height, weight, and BMI	All Patients in DB
16.2.12 Electrocardiogram Measurements (12-Lead ECG)		
16.2.12.1	Listing of 12-Lead ECG measurements	All Patients in DB

16.2.13 Physical Examinations		
16.2.13.1	Listing of Physical Examinations	All Patients in DB

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