CLINICAL PROTOCOL

IND No. **18850**

Title: **Immunologic Efficacy of Heplisav B Vaccine in Patients Undergoing Treatment with Immunosuppressive Medications**

Version 3: **July 17, 2019**

Sponsor: **Baylor Scott and White Research Institute**

Clinical Development Approval:

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July 17, 2019

Name
Title, Department

Date

INVESTIGATOR AGREEMENT PAGE

Company Name

Protocol Version No. 3

July 17, 2019

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

	July 17, 2019
Principal Investigator	**Date**

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1.0 TABLE OF CONTENTS

PAGES

2.0 STUDY SYNOPSIS

Title of Study:	**Immunologic Efficacy of Heplisav B Vaccine in Patients Undergoing Treatment with Immunosuppressive Medications**
Sponsor:	Baylor Scott and White Research Institute
Phase of Development:	Phase 1 (Medically immunosuppressed subjects)
Objectives:	Preliminary trial of Heplisav-B vaccine in medically immunosuppressed patients with co-primary objectives of vaccine immunogenicity and patient safety
Study Design:	This is an open label exploratory study of the immunologic efficacy and safety of an FDA licensed HBV vaccine that contains HsAg-1018 adjuvant which has TLR 9 agonist properties (Heplisav-B). It will be used in patients treated with long term immunosuppressive drug therapy. The patients will be given two doses of Heplisav-B, the first delivered at the baseline visit and the second at week 4. Anti-HBs titers will be determined at baseline and at weeks 4, 8, 12, 24 and 60. The proportion of those with seroprotective anti-HBs levels and the geometric mean titers of anti-HBs at each time interval will be compared with those observed in phase III trials of immunocompetent individuals receiving the same dosing schedule. Individuals who fail to demonstrate protective levels of anti-HBs at week 8 will be given a third booster dose at week 12.
Study Population:	A total of 18 patients will be entered into the study including 3 evenly sized groups of 6 as follows: Group A patients are taking tumor necrosis factor alpha or interleukin inhibitor therapy for underlying chronic inflammatory disorders; Group B patients are taking chemotherapy for solid organ malignancy; and Group C patients are either recipients of livers from anti-HBc positive donors or individuals transplanted for chronic HBV infection without recurrent hepatitis B at the time of enrollment. **Serologic Characteristics Per Group**: All patients in Groups A and B must be HBsAg negative but anti-HBc positive to qualify indicating that they have serologic evidence for resolved hepatitis B. Those with low titer (<20 mIU) antibody will not be specifically excluded permitting observation of a possible anamnestic anti-HBs response. Patients in Group C will have either a remote history of liver transplant for HBV or receipt of an anti-HBc positive donor liver. Eligibility requires HBsAg to be negative w/wo anti-HBc reactivity.

Safety Evaluation:	Yes
Efficacy Evaluation:	Yes
Schedule of Events:	In the absence of appropriate documentation, all patients will initially be screened for HBsAg, anti-HBc, and anti-HBs status by qualitative testing at a screening visit. Patients in Group A and B found to be anti-HBs positive will be tested for anti-HBs quant within one week to confirm final eligibility. Two doses of Heplisav-B will be administered at a baseline visit and 4 weeks later. Anti-HBs levels will be assessed at the baseline visit and again at weeks 4, 8, 12, 24 and 60. All patients who fail to respond with seroprotective anti-HBs levels (≥ 10 mIU/mL) at week 8 will be given a third dose of vaccine at week 12 and followed until week 60. Liver transplant patients (Group C) will be vaccinated and followed in the same manner as Groups A and B.

3.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
IRB	Institutional Review Board
µg	Microgram
MAAE	Medically attended adverse event
mL	Milliliter
PE	Physical examination
piMMCs	Potentially immune-mediated medical conditions
SAE	Serious Adverse Event
SGOT (AST)	Serum Glutamic Oxaloacetic Transaminase
SGPT (ALT)	Serum Glutamic Pyruvic Transaminase
NsCap	HBsAg negative, anti-HBc positive
ISDT	Immunosuppressive drug therapy
HBV	Hepatitis B virus
HBVr	Hepatitis B virus reactivation
HBIg	Hepatitis B immune globulin
HBsAg-1018	Vaccine adjuvant for Heplisav-B

4.0. BACKGROUND

Hepatitis B vaccination is recommended for all immunocompromised persons at risk for hepatitis B infection.[1] However, traditional recombinant HBV vaccines have limited efficacy in this situation even when given in higher dosage.[2,3] In addition, the relatively cumbersome 3 dose regimen with traditional HBV vaccines has been associated with disappointingly low rates of vaccine completion.[4]

Recently, the Food and Drug Administration has licensed a new HBV vaccine (Heplisav-B®) which incorporates HBsAg particles bound to 1018 immunostimulatory sequence which serves as a TLR 9 agonist. The incorporation of the HBsAg-1018 adjuvant makes the vaccine considerably more immunogenic than traditional HBV vaccines that contain a solid phase alum adjuvant. In addition, Heplisav-B offers the advantage of only requiring two doses given at 0 time and 4 weeks later. This vaccine stimulates a directed immune response to hepatitis B surface antigen (HBsAg) instead of the multi-pathway, broad immunostimulatory response induced by alum adjuvant. Two randomized controlled clinical trials in immunocompetent adults and a third randomized, controlled study in patients with chronic kidney failure have shown Heplisav-B to be considerably more immunogenic when compared to a traditional recombinant vaccine (Engerix®).[5-8] Heplisav-B given in two doses 4 weeks apart induced significantly higher seroprotection (anti-HBs ≥ than 10 miU/ml) rates when compared to Engerix given in a 3 dose regimen at 0, 4 weeks and 24 weeks. Increased immunogenicity was evident by 8 weeks after the second dose of Heplisav-B. Also, geometric mean titers of anti-HBs were significantly greater with Heplisav-B doses starting at week 12. In a randomized, controlled trial in patients with chronic kidney failure, a group that demonstrates attenuated responses to traditional vaccine, patients were randomized to 3 injections of Heplisav-B or to Engerix given in a double dosage at four intervals. While seroprotection rates were only slightly higher in the Heplisav-B group (89% vs 81.9%), geometric mean titers of anti-HBs were significantly higher in the Heplisav-B group (587 miU/ml versus 156 miU/mL) by week 28.

It is important to note that adverse event profiles did not differ between the vaccines used in these studies.[5-8] One case of granulomatosis with polyangitis was reported 170 days after the second dose in the Heplisav B group but the collective data from these trials demonstrated that the vaccine did not induce autoimmune disorders at a higher than expected frequency (Dynavax Technologies, data on file) Moreover, the frequencies and titers of ANA and anti-dsDNA were comparable in the two vaccine treatment groups in these studies.

Potential Clinical Utility of a More Immunogenic HBV Vaccine

The development of a more immunogenic vaccine that induces rapid protection against HBV has particular relevance in situations where timely induction of neutralizing anti-HBs is desirable and

whenever attenuated responses to traditional HBV vaccine may otherwise be anticipated. Both of these issues are relevant in patients who are immunosuppressed due to medication. This is especially relevant in patients with resolved hepatitis B due to long term persistence of the genomic template for viral transcription in liver tissue and an inherent risk that hepatitis B viral reactivation may occur when immunosuppressed (see 1, below).

Thus, this protocol is an exploratory trial to assess the safety and effectiveness of Heplisav-B in three common clinical situations where patients are medically immunosuppressed: (1) in patients given tumor necrosis factor (TNF) or interleukin inhibitor therapy for chronic inflammatory disorders; (2) in patients placed on cancer chemotherapy for solid organ malignancy; and (3) in patients who are immunosuppressed after liver transplantation either done for a) chronic hepatitis B or for b) the same or other indications during which they receive a liver from an anti-HBc positive donor.

1. Hepatitis B reactivation. Hepatitis B reactivation (HBVr) is defined by a sudden increase in HBV DNA and ALT/AST level, and is most frequently caused by immunosuppressive drug therapy (ISDT) where it is thought to occur because of a loss of immunologic control over HBV replication. Many cases of HBVr are subclinical or mild, but it also can be severe enough to cause liver failure. Hepatitis B reactivation during ISDT not only occurs in HBsAg-positive patients but also in those who are HBsAg negative yet anti-HBc positive.[9] This is a serologic profile that is typically observed in cases of resolved hepatitis B. As many as 60 to 80% of anti-HBc positive persons have detectable anti-HBs and this has been associated with a reduced rate of HBVr in several observational studies of HBsAg negative, anti-HBc patients treated with ISDT.[9]

Current management recommendations to reduce the risk of HBVr in HBsAg negative/anti-HBc positive patients during ISDT vary depending on the immunologic potency of the drug(s) used and the serologic profile of the patient. It is currently recommended that persons with resolved hepatitis B who are taking tumor necrosis factor or interleukin inhibitor either receive prophylactic antiviral therapy *or* close monitoring of aminotransferase and HBV DNA levels. This dichotomous recommendation Is based on data collected from large observational studies showing a relatively low rate (0 to 5%) of HBVr when anti-HBc positive patients take these biologic agents without anti-HBV prophylaxis.[12] In contrast, anti-HBc positive patients undergoing cancer chemotherapy are considerably more likely to reactivate (10 to 20%), and standard recommendations call for antiviral prophylaxis during chemotherapy and for as long as 12 months after discontinuation if rituximab or other B cell depleting agents are used.[10,11]

The protective role of neutralizing anti-HBs has not been well defined in patients receiving ISDT. However, there are indications that high titers of anti-HBs may be helpful in preventing reactivation during cancer chemotherapy. In one observational study it was found that patients with non Hodgkin's lymphoma who had anti-HBs titers >100 mIU failed to demonstrate HBV

reactivation during CHOP combined with B cell depletion therapy whereas those with lower anti-HBs titers frequently did.[13] Furthermore, a more recent meta-analysis of 20 studies of resolved hepatitis B patients with hematologic malignancy documented that anti-HBs positivity was associated with reduced HBVr risk (pooled odds ratio of 0.21) when compared to resolved cases who lacked anti-HBs. Unfortunately, qualitative rather than quantitative assessments of anti-HBs have been used in the vast majority of studies which makes it difficult to assess the relationship between anti-HBs concentration and protection against HBV reactivation or the protective benefit of periodic booster dosing in the transplant setting .[14] (See section 2, below).

2. De novo hepatitis B after liver transplantation. The use of cadaveric (or living) donors harvested from individuals found to be negative for HBsAg but positive for anti-HBc has become a standard practice due to the urgent need for an expanded donor pool. De novo HBV infection in HBV susceptible recipients of these organs occurs in more than of 50% of cases if not given antiviral prophylaxis.[15] Such patients are generally treated with long-term antiviral prophylaxis which is sometimes combined with peri-operative hepatitis B immune globulin.[15,16] The concentration of anti-HBs that would be partially protective against de novo hepatitis B in this setting has not been defined. However, recent studies using multiple booster doses of HBV vaccine have reported successful termination of HBIg and long term antiviral prophylaxis in recipients of anti-HBc-positive livers provided they develop sustained anti-HBs titers greater than 100 mIU/ml.[17]

3. Prevention of recurrent hepatitis B after liver transplantation. Patients transplanted for chronic HBV infection are treated with hepatitis B immune globulin (HBIg) for variable periods along with a third generation nucleoside analogue with anti-HBV potency to prevent recurrence of HBsAg, HBV DNA, and overt hepatitis B. The nucleoside analogue therapy must be given indefinitely. HBIg contains high titers of anti-HBs and serum anti-HBs concentrations of 100 miU/ml or greater were shown to be partially effective in the prevention of recurrent hepatitis B before nucleoside analogue therapy was developed. Attempts to vaccinate such patients in preparation for transplantation often fail due to the immune suppression effect of end stage liver disease, the requirement for a second or third dose in patients with short waiting times, and because transplant recipients are immunosuppressed after surgery with tacrolimus, mycophenolate, rapamycin or other anti-rejection therapies.

Why is this Study Being Done? Rationale/Significance of Proposed Study In Selected Patient Groups Receiving Immunosuppressive Drug Therapy

Chronic ISDT results in an attenuated antibody response to new and repeat antigen exposure. B cell depletion therapy further results in rapid attrition of pre-existing anti-HBs.[9] Weakened antibody responses to HBV vaccine during ISDT can be important factors when trying to protect a patient with resolved hepatitis B from HBVr or in preventing recurrent or de novo hepatitis B

after liver transplantation. The proposed study is the first known to the investigator in which patients are administered HBsAg-1018 containing vaccine immediately before or during ISDT. It is also the first to use this vaccine in persons with serologic evidence for resolved hepatitis B. However, vaccinating anti-HBc positive patients who are taking ISDT can be justified by previously published studies. First, as many as 40% of patients with the serologic profile of resolved hepatitis have seroprotective levels of anti-HBs due to the fact that exposure to HBV may have occurred remotely in the past. Second, an anamnestic boost in anti-HBs has been reported in a substantial minority of immunocompetent anti-HBc positive individuals after a single dose of traditional HBV vaccine.[18] In consideration of these findings, the current study will not exclude anti-HBc positive patients who have weak anti-HBs levels (<20 mIU/ml). Third, the medical literature supports a lower frequency of HBVr in anti-HBs positive individuals over a broad range of ISDTs.[9,14] Fourth, some studies using quantitative anti-HBs assays have reported greater protection against HBVr in persons having a high anti-HBs titer compared to individuals with low titer or no detectable anti-HBs.[13]

Heplisav-B vaccine has been shown to more quickly result in seroprotective levels of anti-HBs and higher geometric mean titers than traditional HBV vaccine in immunocompetent recipients including the elderly, persons with diabetes mellitus, and patients with chronic kidney failure. These are important groups to have studied because It can be anticipated that some recipients may have had age or disease-related subclinical immune deficiency.

Use of Heplisav-B in patients with prior hepatitis B (Groups A and B).

Prevention of HBVr.

It is the opinion of the investigator that the immunologic efficacy of Heplisav-B in patients with resolved hepatitis B is an extremely important clinical area to study because it offers the potential to change current management recommendations for the prevention of HBVr during ISDT.[19] This is very relevant in (a) persons undergoing immunosuppressive treatment for chronic inflammatory disorders which are considered to be autoimmune in nature and b) individuals who are undergoing treatment with cancer chemotherapy where the risk of HBVr is particularly high due to the higher level of immune suppression. Further insight into the clinical relevance of a more immunogenic vaccine to prevent HBVr during ISDT in these two groups is provided below.

1. Group A (chronic inflammatory disorders). A rapid and highly effective response to vaccination might supplant any concern about the need for antiviral therapy in patients treated with tumor necrosis factor or interleukin inhibitor therapy for chronic rheumatic, intestinal or dermatologic disorders. Taken together this is a large patient population with current estimates of use for TNF inhibitor therapy being 3 million people in the United States. Major quality of life improvement may occur using TNF inhibitor therapy but this often requires the

use of long-term ISDT. This indefinite exposure to ISDT can put the patient at prolonged risk of HBVr. At the current time routine antiviral prophylaxis is not recommended in this setting because HBVr rates are quite variable in the literature and anti-HBV prophylaxis would have to be given indefinitely. [19]

2. Group B (cancer chemotherapy). The rapid induction of high titer anti-HBs following vaccination with Heplisav-B either delivered prior to or soon after starting chemotherapy could prove helpful in preventing HBVr in resolved hepatitis B patients treated for solid organ malignancy.[13,14] Such patients have the highest risk for HBVr when compared with the other groups (A and C) proposed in this study. Reactivation frequency varies from 10 to 20% for anthracycline based chemotherapy and 20 to 50% for lymphoma therapy that includes rituximab. The demonstration of high titers of anti-HBs with Heplisav-B during cancer chemotherapy would be a significant breakthrough because anti-HBs levels ≥ 100 mIU/ml have been shown to be associated with significantly lower rates of HBVr during rituximab treatment.[9,13]

3. Group C: susceptible recipients of anti-HBc-positive livers. Until recently, HBV susceptible recipients of cadaveric liver donations were routinely vaccinated for hepatitis B at Baylor Scott and White and other programs throughout the United States. In part, this was done because of the possibility that a high MELD score recipient might acquire an organ from an anti-HBc positive donor. Vaccination completion was often not completed, however, prior to transplant and the use of HBIg and long term antiviral prophylaxis ultimately made de novo hepatitis B a treatable condition. To prevent de novo infection, however, requires indefinite antiviral prophylaxis, possibly life long. Should Heplisav-B induce high anti-HBs titers in these immune suppressed patients, it could limit antiviral drug exposure by deploying a periodic booster dose strategy.[17]

Group C: patients transplanted for chronic hepatitis B. These patients currently are treated with short duration HBIg and life-long antiviral prophylaxis. All continue to take anti-rejection therapy indefinitely. Hepatitis B vaccine is not used in these patients prior to transplant. Frequent double dose inoculations of HBV vaccine post transplant have been given in clinical trials in an attempt to eliminate antiviral therapy in highly selected patient groups. However, most studies have failed to reliably induce protective anti-HBs titers with a few notable exceptions.[20] Patients with successful prophylaxis remain HBsAg negative, anti-HBc positive, and HBV DNA negative (similar to resolved cases of hepatitis B), but anti-HBs is almost always non detectable after liver transplantation for hepatitis B. This suggests that patients without recurrent hepatitis B might be at continued risk for recurrence if antiviral therapy were to be withdrawn. It would be instructive to see if high levels (>100 mIU/ml) of protective anti-HBs could reliably be induced in these patients using a routine booster dose strategy and if this could lessen the requirement for life long antiviral treatment.

4.1. Investigational Agent

Heplisav B

4.2. Preclinical Data

Included in Investigator's Brochure [Feb, 2019, revision 16].

4.3. Risk/Benefits of Study

The risk benefit ratio for this study is considered to be low to moderate only. There are several reasons for this presumed level of risk. Acute myocardial infarction was reported in 19 patients, as compared with 3 patients taking the traditional vaccine. Additional evidence, however, considering the presence of risk factors does not support a clear cause and effect relationship. The risk of immune mediated events with Heplisav B appears to be very low. The results of multiple phase III studies which included more than 5,000 non-infected immune competent patients have shown that it is not associated with a disproportionate amount of immune events, including the origination of what are commonly considered to be autoimmune disorders or potentially immune-mediate medical conditions (piMMCs). In those few situations where immune mediated disorders appeared to arise after vaccination, an outside panel of experts did not attribute them to vaccination. Also, Heplisav-B vaccination was not associated with an unusual frequency of ANA or anti-ds-DNA antibodies. Certain relatively common immunologic disorders such as juvenile diabetes, hypo or hyperthyroidism, and rheumatoid arthritis were not more common when compared with those given traditional vaccine. One reason for this may be that the 1018-HBsAg adjuvant is not anticipated to promote innate immunity to host tissue proteins because TLR activation is primarily a defense mechanism against infecting microbes rather than host tissue antigens. Also, it has been proposed that the 1018 adjuvant stimulates a directed immune response to HBsAg instead of the multi-pathway, broad immunostimulatory response induced by alum adjuvant [Investigator's Brochure, February 2019, revision 16].

Patients receiving chemotherapy are not anticipated to have an unusual frequency of adverse effects to the vaccine. In this study it is anticipated that all HBsAg negative, anti-HBc positive cancer patients will be placed on the standard of care antiviral prophylaxis which greatly minimizes the chances for HBV reactivation (HBVr). Thus, HBVr is very unlikely to interrupt the study. Should the vaccine prove to be highly immunogenic in cancer patients, rapid induction of seroprotective anti-HBs could further reduce the risk of HBVr.

The risk for acute cellular rejection of the liver should be minimal because this requires an orchestrated T lymphocyte response to alloantigens expressed on the surface of liver cells. Moreover, transplanted patients will have had remote transplantation (> 3 years) and are much less likely to undergo acute cellular rejection. Should the vaccine be highly immunogenic in these patients, it might eliminate the need for the very costly hepatitis B immune globulin (HBIg) immunoprophylaxis and ultimately might decrease the need for life-long antiviral prophylaxis after transplantation for hepatitis B. As with anti-HBc-positive cancer patients, all patients transplanted for hepatitis B and those given an anti-HBc positive liver organ will receive the standard of care antiviral prophylaxis to recurrent hepatitis B and de novo infection, respectively.

A third dose of the vaccine is unlikely to result in adverse events. This has been given to several hundred hemodialysis patients in phase III studies and there were no disproportionate adverse event outcomes when compared to historical cohorts who were administered four doses of Engerix [Investigator's Brochure, Feb 2019, version 16].

Potential benefit. If seroprotective levels of anti-HBs are demonstrated in medically immunosuppressed individuals, the potential benefit to society could be very large. For example, there are more than 3 million people in the US who are taking long term biologic immunosuppressive therapy for chronic inflammatory disorders and with a population prevalence for anti-HBc alone of 5 percent, this could reduce the need to depend on potentially life-long antiviral prophylaxis in 100,000 to 150,000 cases. This same figure of 5% prevalence of anti-HBc in the general population can be applied to individuals undergoing chemotherapy for malignancy (estimated incidence of 68,760 anti-HBc positive cases undergo chemotherapy in the United States each year).[21] Long term antiviral prophylaxis may be associated with unanticipated adverse events and is economically costly. Taken together, approximately 5 to 8% of all adults transplanted require antiviral therapy either to prevent recurrent hepatitis B or to prevent de novo infection.

4.4. Dose Rationale

The standard 0.5 ml dose of Heplisav-B will be delivered at baseline (0 time) and 4 weeks later. Immunologic efficacy will be compared to historical cohorts in phase III trials of the vaccine. In the event that a seroprotective level of anti-HBs (< 10 mIU/ml) does not develop by week 8, a booster dose of Heplisav-B vaccine will be given at week 12.

4.5. Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

4.6. Population

This is an exploratory observational study of 18 individuals divided into 3 equal sized groups of six patients (Groups A, B, and C). Groups A (chronic inflammatory disorders) and B (patients on cancer chemotherapy for solid organ malignancy) will be limited to patients with resolved hepatitis B as defined by the absence of HBsAg and the presence of anti-HBc in serum. Patients who have low titer anti-HBs at baseline (< 20 mIU) will not be excluded. Group C (liver transplant) patients will be HBsAg negative and anti-HBc positive after transplantation for hepatitis B or seronegative for all HBV markers if a recipient of an anti-HBc positive donor organ.

4.7. Schedule of Events

The schedule of events can be seen in Table 1. Patients will be seen and consented at a screening visit to determine eligibility. It is anticipated that most if not all of the serologic data needed to qualify the patient will be available by review of electronic records at the screening visit. If not, one or more of the serologic HBV markers will be tested at screening. The serologic studies for HBV must have been done within the past year. Turnaround times are less than 5 days and so there should be no lagging data needed at the time the patients receive their first dose of vaccine 28-30 days later. There will also be a 28-30 day window between the first vaccine inoculation visit and the second vaccine inoculation visit. The 12, 24, and week 60 visits will have a one week ± window.

In the event of an intercurrent acute illness that either places the patient at added risk or makes vaccine adverse event relatedness difficult to interpret, every effort will be made to bring the patient back when the illness is resolved and preferably no longer than one week of the initially specified time.

Heplisav-B vaccine will be delivered at the baseline/enrollment visit (visit # 2 considered to be day 0) and again 4 weeks later. In the unlikely event that anti-HBs titer is ≥ 300 mIU/ml after a single dose of vaccine, patients will not be given a second dose. All individuals who do not have protective levels of anti-HBs (> 10 mIU/ml) after two doses at week 8 will be given a third identical dose of vaccine at the week 12 visit.

Adverse events (e.g, localized skin reactions, fever) that occur soon after vaccination will be assessed by weekly telephone assessments and patients will be asked to record changes in underlying disease activity on a Patient Related Outcome Measurement form. These will be distributed at the enrollment visit and subsequent visits. They will initially be completed by the patient and completed as needed by the investigator and coordinators at all study visits. Data on all AEs will be recorded on an Adverse Event Data Capture form (Appendix 1). These will be filled out by the study coordinator in conjunction with the investigator at each visit.

5.0. TRIAL OBJECTIVES

There are two co- primary objectives: (1.) To assess immunogenicity of Heplisav-B and (2.) to assess safety in medically immunosuppressed patients. The former will require assessing the proportion of patients who respond with seroprotective levels (>10 mIU/ml) of anti-HBs and who maintain this response until study completion at week 60. The second objective will require follow up of all patients for one year after the last dose of vaccine during which time all adverse events will be collected.

6.0. TRIAL DESIGN

The study is non blinded and exploratory only.

The clinical algorithm describing the study is depicted in Figure 1. Actions taken at clinic visits is depicted in Table 1.

6.1. Primary Study Endpoints/Secondary Endpoints

Primary endpoints: determination of (1) adequate safety and (2) immunologic efficacy of Heplisav-B in patients taking ISDT. Immunologic efficacy will be determined by the seroprotection rate (SPR) or percentage of patients who have anti-HBs titers greater than 10 mIU/ml at weeks 24 and 60. Secondary endpoints include (1) determination of the percentage of patients with anti-HBs titers ≥ 100 mIU/ml at weeks 24 and 60. Both (1) and (2) as well as geometric mean titer of anti-HBs at all study visit intervals will be will be compared to those observed with historical immune competent cohorts who received identical dosing with Heplisav-B. An additional secondary endpoint will to determine the proportion of patients on ISDT who require a third dose of vaccine to induce seroprotective level of anti-HBs.

6.2. Study Design/Type

This is an open label study of 18 patients taking long term immunosuppressive drug therapy.

6.3. Randomization—Not applicable

6.4. Maintenance – Not applicable

6.5. Trial Treatment

See Study Synopsis (2.0) and Figure 1

6.6. Duration

The protocol includes a 52 week observation period after two doses of vaccine.

6.7. Premature Drug Discontinuation

Further dosing of Heplisav-B will be withheld in the following situations:

1. For all groups: A grade 3 AE or SAE that is considered to be possibly or definitely related to Heplisav-B.

2. For Group A patients: A significant clinical worsening of their inflammatory disorder or development of a new onset pIMMC after one or two doses of vaccine regardless of relatedness.

3. If the patient requests not to continue with dosing or if is the opinion of the investigator that further dosing should be withheld.

4. If the patient develops transplant rejection that is possibly or definitely vaccine related.

Indications for participant withdrawal in are further outlined in sections 7.3.

6.8. Product Accountability

All vaccine will be kept in a locked refrigerator to which only the principal investigator and clinical coordinator have access. This refrigerator is immediately proximate to the clinic where patients will be seen. A log of doses dispensed and those remaining will be kept for each patient by the study coordinator and will be made available to the principal investigator and sponsor upon request.

6.9. Data Identification

CRFs will include: (a) patient age, sex, (b) Group (c) baseline serologic status, (d) results of anti-HBs quantification, CRP, and AST and ALT levels, (e) immunosuppressant medications, and (f) any potential short or long term adverse events with plan of management. Items (d), (e), and (f) will be recorded for each interval.

7.0. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

1.) Age 18 or older and agree to adhere to the requirements of the study
2.) Must be willing to provide informed consent
3.) Serologic profile consistent with resolved hepatitis B (HBsAg negative but anti-HBc positive*)
4.) Recipient of anti-HBc positive liver (Group C).
5.) Chronic inflammatory disease requiring TNF or interleukin inhibitor therapy (Group A)
6.) Solid organ malignancy that requires systemic cancer chemotherapy
7.) Post liver transplant for chronic HBV infection (Group C).
8.) Recipient of immunosuppressive drug medication as described above

7.2. Exclusion Criteria

1.) HBsAg positivity
2.) Anti-HBs titer $\geq$ 20 mIU/mL at baseline
3.) HIV infection**
4.) HCV infection**
5.) Prior hepatitis B vaccination
6.) Receipt of hepatitis B immune globulin during the past 4 months
7.) Hematologic malignancy

8.) Hepatocellular carcinoma
9.) Active alcohol use > 20 grams daily
10.) Unstable underlying inflammatory disorder
11.) Pregnancy or breast feeding
12.) History of severe depression or other severe psychiatric disorder
13.) Receipt of liver allograft < 3 years earlier
14.) Transplant rejection within the past year
15) Individuals having unstable or poorly responsive inflammatory disorders
16) All persons who are judged by the investigator to have an unreasonable risk of complications
17) Anticipated life expectancy less than one year

Footnotes to Inclusion/Exclusion Criteria *There must be evidence of anti-HBc positivity at the screening visit and if so, documentation that this is chronic in nature will be obtained from a review of the electronic record (for example, history of past exposure, past serology documentations). If documentation is lacking, however, then an IgM anti-HBc test will be at done at the screening visit to confirm that the patient has not recently acquired hepatitis B.

**Serologic testing for HCV and HIV must be within 4 months of potential eligibility. If this is not the case, the testing will be repeated at the screening visit.

7.3 Vaccine Withdrawal

Need for vaccine withdrawal and subject withdrawal (see Section 7.4 below) will be assessed by application of the grading criteria for adverse events as described in the Common Terminology Criteria for Adverse Events as published by the US Department of Health and Human Services/National Institutes of Health, and the National Cancer Institute (version 5.0, November 2017). A three point scale will be used to judge relatedness: unrelated, possibly related, and definitely related. *Possibly related* will be defined as any AE in which there is a reasonable time sequence to vaccination but the AE could be explained by another potential cause such as other drugs or events, patient noncompliance with immune suppression medication, or recent switch in immune suppression medication. Definitely related will require a plausible time relationship to vaccine administration that cannot be explainable by other events and condition as described above. Also, it will be further considered to be definitely related if there is a response to withholding further vaccination.

1. Any patient in Group A who is deemed to have significant clinical worsening of their inflammatory disorder or develop a new onset pIMMC after one or two doses of vaccine will be withdrawn from further dosing regardless of relatedness to the vaccine. However, the subject will be followed until week 60 to collect additional safety data. During this time, additional immunogenicity data may be obtained if the patient had received at least two doses of vaccine

before clinical worsening became apparent and if seroprotective levels were observed when last tested.

2. Regardless of which group a patient belongs to, any subject who has a Grade 3 AE or SAE will not receive further vaccination if the adverse event is considered to be possibly or definitely related to Heplisav-B. Each of these patients will continue to be seen at the visits specified in the protocol until the end of the study (week 60) so that additional safety data may be collected.

Additional immunogenicity data may be obtained if the patient had received two doses of vaccine before the AE became apparent and if seroprotective levels of anti-HBs were evident when last tested.

3. Transplant rejection suspected by unexplainable increase in liver enzymes *and* proven by liver biopsy will be considered as a Grade 3 AE that requires medical intervention (MAAE). Each patient with rejection will be withdrawn from further vaccination if the rejection is considered to be possibly or definitely related to the vaccine. Such patients will be followed until the end of the study (week 60) so that additional safety data may be collected. Additional immunogenicity data may be obtained if the patient had received at least two doses of vaccine before allograft rejection became apparent and if seroprotective levels were evident when last tested.

7.4 Clinical Hold on Further Group Enrollment

1**.** If at any time a Grade 3 AE or SAE develops that is considered to be definitely related to vaccination, then an immediate hold on further enrollment will be placed on the group the patient belongs to. Also, neither the affected individual nor other participants in that group will be given further vaccine inoculations. This applies to all groups.

2. If transplant rejection develops that is considered to be definitely related to vaccination, this will be considered as an SAE that is medically attended (MAAE) and a clinical hold on further enrollment will be enacted for the group (C) the patient belongs to. In addition, no further vaccination will be given to the affected individual.

3. Should 2 patients in any group have a grade 3 AE or SAE considered to be *possibly* related to vaccine, then an immediate hold on both further enrollment and repeat inoculations in that group will be enacted.

7.5. Subject Withdrawal

1. Patients with a Grade 4 adverse event that is possibly or definitely related will immediately be withdrawn from the study and followed clinically until resolution of the event occurs. Every effort will be made to have the patient continue with the study visits to collect additional safety data up to 52 weeks after the last dose of vaccine.

2. Patients will be withdrawn from the study if (a) it is the opinion of the investigator that further dosing or follow up should be withheld because of poor study compliance or (b) if the patient

wishes to end participation. Patients who are excluded from further vaccine for reasons of safety will continue to meet study visit requirements to obtain additional safety data.

8.0. TREATMENT OF SUBJECTS

Patients will be given 0.5 ml of Heplisav-B in the clinic office on the 8th floor of the Sammons Cancer Center by skilled nursing staff. It will be delivered by IM injection in the deltoid region.

8.1. Medication

The patient will continue to take all prescription drugs and may be on prophylactic nucleoside analogue therapy for HBV infection.

8.2 Timing of Vaccine Initiation in Relation to Time of Initiation of Immune Suppressive Medication.

Patients in Group A will be taking ISDT when seen at the screening visit. They must have stable underlying disease to be eligible for the study. Provided they are eligible, the first vaccine inoculation will be 4 weeks after screening. Patients with malignancy (Group B) will either be given vaccination prior to chemotherapy (depending on the planned schedule for initiation of chemotherapy) or alternatively as shortly as possible after chemotherapy has already begun. Patients who have been transplanted (Group C) will be receiving ISDT at the time they are first seen. Those transplanted for hepatitis B will have been taking ISDT for three or more years when first vaccinated. The same post-transplant interval will also apply to recipients of anti-HBc positive organs.

8.3 Monitoring for Subject Compliance

Patients will be called 24-48 hours before each visit to remind them. A failure to appear will result in a call back by the principal investigator's coordinator during work hours or at times by the principal investigator after work hours. The patient will be offered a suitable time for reappearance within 3 to 5 working days of the initially scheduled visit. This has proven to be successful in the investigator's previous clinical research studies. At each visit, the principal investigator will provide continuous education about the importance of continued participation to minimize noncompliance.

9.0 ASSESSMENT OF EFFICACY

9.1 Efficacy Parameters

- Assessment of proportion of subjects with anti-HBs titers ≥ 10 mIU/ml at each study interval.
- Assessment of percentage of subjects with anti-HBs titers ≥ 100 mIU/ml at each study interval.

- Assessment of geometric mean titers for all subjects at each study interval.

- Assessment of reasonable safety in patients who are medically immunosuppressed

9.2 Method and Timing

Assessment of efficacy will require quantitative anti-HBs assessments at each of the visits that are specified in Table 1. This includes week 4,8,12, 24 and 60 week visits.

10. 0. ASSESSMENT OF SAFETY

10.1 Safety Endpoints

Patient safety is a co-primary objective of the study and the following endpoints will be considered and used for future reporting:

1. Proportion of subjects with unsolicited AEs after inoculation. All adverse events including those that are unsolicited will be recorded for a period of 28 days after vaccine administration, and at each visit changes in the patient's state of health will be recorded on the Appendix 1 (AE capture form) and as needed on the Appendix 2 form. To facilitate accurate reporting in real time, patients will be questioned at a weekly telephone assessment and seen by the principal investigator should this appear warranted. Photographic evidence by the patient may be requested between visits for certain AEs.

2. Proportion of subjects with SAEs. The study will capture all SAEs (and Grade 3 AEs) that occur through one year after the last dose of vaccine. To facilitate accurate reporting, all patients with these events will be seen within 48 to 72 hours and acted upon if needed. Follow up will continue until at least 52 weeks after the last dose of vaccination Data will be collected on the Appendix 1 safety form and in the case of Group A, Appendix 2 as well.

3. Proportion of subjects with MAAEs. All MAAEs that occur within one year of the last vaccine dose will be captured. Patients will be handled as in 2 Above.

4. Proportion of subjects with pIMMCs. This will be captured for a period of 52 weeks after the last dose of vaccine. Patients will be handled as in 2 and 3 above. Data will be reported on both the Appendix 1 and Appendix 2 safety forms.

5. Proportion needing an increase in immune suppressive medication. All concomitant medications used during the 28 day period following vaccination and those used to treat MMAEs or SAEs during a 12 month period after the last dose of vaccine will be recorded. Special attention will be given to new or dose adjusted immune suppressive medications that are needed to treat adverse events. Data will be captured in Appendix 1 (adverse event capture form) under the header "Type Intervention."

10.2 Further Safety Considerations:

a. C-reactive protein blood testing will be used to assess augmentation of inflammatory disease activity in Group A.

b. Clinical assessment by principal investigator at each study visit. A focused physical exam will be part of the safety data base. Photographic evidence of underlying disorder in Group A patients may be obtained as needed for documentation.

c. After vaccine administration, patients will be monitored for any immediate or unusual injection site reactions. After leaving the clinic, reactions and AEs will be delineated by weekly post inoculation telephone assessment at which point photographic evidence of an underlying dermatologic disorder may be requested if deemed necessary.

10.3 Pregnancy Assessments. Potentially child bearing females will have a serum pregnancy test at the screening visit. If positive, they will be ineligible for the study. A urine pregnancy test will be taken prior to vaccination at the visits in which vaccine administration is anticipated, including the visit for the week 12 dose. Vaccine will be withheld if the test is positive at any time. A urine pregnancy test will also be repeated at week 24. Patients who are found to be pregnant after one or more doses have been given will be asked to continue with the per protocol visit schedule until week 60 so that additional safety data on pregnancy outcome can be collected

10.4 Method and Timing.
Each patient will be asked to report adverse events at the time of weekly telephone assessments or as needed after each dose of vaccine. At each study visit, all relevant safety data will be captured and kept in a patient binder. Data will be collected at each visit in regard to safety outcomes (AE Capture Form, Appendix 1, and Patient Related Outcome Assessment form, Appendix 2).

10.5 Adverse Event Reporting

All grade 3 or 4 adverse events will be reported simultaneously to the IRB and sponsor within one week and 72 hours, respectively. Should a death occur, notification of the IRB will be within 24 -48 hours of receipt of this information. Events will be conveyed to the IRB and if needed to the sponsor in both electronic and hard copy form along with whether or not the event was considered to be related to administration of the study drug. All relevant lab studies will be included in the correspondence. All Grade 1 and 2 AEs (for example, such as those related to reactogenicity of the vaccine) will be collected at each visit and reported to the sponsor in a yearly report.

10.6 Definitions

An adverse event will be considered as "unexpected" if not included in the Investigator's Drug Brochure (Feb, 2019) or not listed at the specificity or severity observed in the study (Code of Federal Regulations Title 21, April 1, 2018). Definitions of grade severity of adverse events will be considered as follows:

Grade 1: mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not needed.
Grade 2: Moderate; minimal local or noninvasive intervention indicated.
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care
Grade 4: Life threatening; urgent intervention needed
Grade 5: Death related to AE.

Adverse event: any untoward medical occurrence associated with the use of the vaccine

Serious adverse event: resulting in any of the following: death, potentially life-threatening, resulting in hospitalization, prolongation of hospitalization, persistent incapacity, substantial disruption of the ability to conduct normal life functions, or a congenital anomaly.

Medically attended adverse event (MAAE): any adverse event that leads to an evaluation by a healthcare professional.

Potentially immune mediated medical conditions (pIMMC): A list of these provided by the FDA is included in Appendix 4.

Grading of AEs will be according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 27, 2017 by the U.S. Department of Health and Human Services/National Institute of Health/National Cancer Institute.

10.7 Adverse Event Follow-up

Patients with grade 3 or greater AEs and all with SAEs including MAAEs will be seen no later than 48-72 hours of the time the event occurred. The patient will be followed by the principal investigator and/or referring specialist until resolution has been documented (regardless of relatedness consideration). Additional safety data will be included until at least week 52 after the last dose of vaccine.

11.0. STATISTICAL PLAN

11.1. Statistical Methods

The study is exploratory and as such descriptive statistics will be used. Continuous variables will be expressed as median values, range of values, and mean ± standard deviation while categorical variables will be expressed as number (percentage). Qualitative and quantitative differences between subgroups will be analyzed by Chi-square or Fisher's Exact tests for categorical parameters and Student's t test or Mann Whitney test for continuous parameters as appropriate. Statistical significance will be taken as $p < 0.05$.

11.2. Subject Population(s) for Analysis

18 patients will be enrolled into 3 equally sized groups of 6. This is deemed adequate to delineate whether further studies are warranted based on safety and efficacy observations made.

11.3. Significance

See above section 11.1

11.4. Termination Criteria

Termination of the study requires an assessment of the grade and number of SAEs, as well as their relatedness to the drug. A three point scale will be used for relatedness: unrelated, possibly related, and definitely related. Both sets of parameters are defined in Section 7.3, page 18. Definitely related will be assessed both temporally in relation to vaccine administration and will require the absence of other possible explaining factor(s).

1. The study will be terminated if a Grade 4 AE or death occurs that is considered possibly or definitely related to vaccine.

2. As previously mentioned in Section 7.4, page 19, a hold will be placed on further enrollment into a group if a patient develops a Grade 3 or SAE that is considered to be definitely related to vaccine. If this occurs, the study will be terminated if a *second patient in a different group subsequently develops* a grade 3 AE or SAE that is considered to be definitely related. All patients will continue to be followed for at least 52 weeks after the last dose of vaccine to collect additional safety data.

3. In the absence of a previous clinical hold on enrollment in any group, the study will be terminated if at any time *two patients*, *one each from different groups*, *concurrently develop* a Grade 3 AE or SAE both of which are considered definitely related. Such patients will continue to be followed for at least 52 weeks after the last dose of vaccine to collect additional safety data.

11.5. Accountability Procedure

All vaccine vials will be accountable in hard copy listings by the clinical coordinator using standardized good clinical practice procedures.

11.6. Deviation Reporting

Not applicable due to exploratory nature of the study

12.0. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Periodic audits by vaccine manufacturer will be allowed if this is thought to be needed. This will be formalized in a written agreement between Baylor Scott and White and Dynavax Technologies.

13.0. QUALITY CONTROL AND QUALITY ASSURANCE

Yearly submission of the findings of the study relevant to patient safety and overall study progress is required by the IRB. Annual reports to the FDA, including any pertinent case summaries, will be submitted under this IND # 18850 as required by 21CFR312.33. The data on each participant will be recorded in separate patient binders to which only the principal investigator and study coordinator have access. Also, periodic data monitoring will be conducted by an independent department through Baylor Scott and White Research Institute.

14.0. ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

15.0. DATA HANDLING AND RECORD KEEPING

Study binders for each patient kept in locked coordinator office. Weekly review of all safety data by the principal investigator.

16.0. PUBLICATION PLAN

This will be specified in written form by Baylor Scott and White Research Institute.

17.0. LITERATURE

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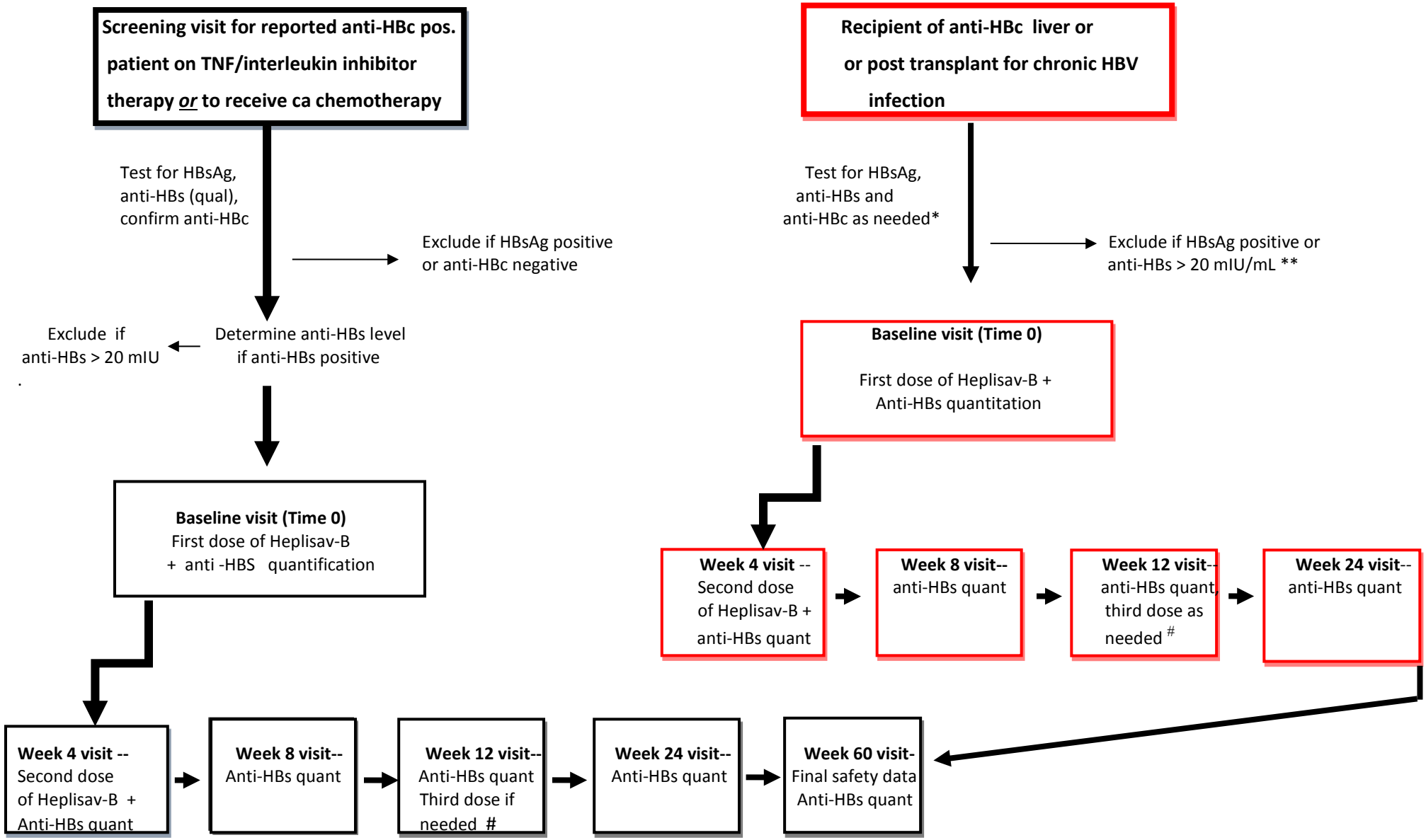
Figure 1. Flow Chart for Study of Immunologic Efficacy in Patients Undergoing Treatment with ISDT



*If not available in patient record

** 5% of recipients of anti-HBc donor liver are anticipated to be anti-HBc positive. These patients will be excluded if anti-HBs also > 20 mIU/ml. Patients transplanted for HBV infection are anticipated to be anti-HBc positive

If anti-HBs level remains < 10 mIU/ml

TABLE 1. Study Participation Table

	Visit 1: Screening	Visit 2 Enrollment/ Baseline	Visit 3 4 Week Follow up (+/- 3-5 d)	Visit 4 8 Week Follow up (+/- 3-5 d)	Visit 5: 12 Week Follow Up (+/- 3-5 d)	Visit 6: 24 Week Follow Up (+/- 1 week)	Visit 7: 60 Week Follow Up (+/- 1 week)
Read and Sign Informed Consent	X						
Medical History	X						X
Review of Immunosuppresants	X	X	X	X	X	X	X
Interview, brief physical	X	X	X	X	X	X	X
Vital Signs (heart rate, blood pressure, temperature)	X	X	X	X	X	X	X
Missing HBV blood testing*	X						
Quant anti-HBs	X≠	X	X	X	X	X	X
CRP**		X	X	X	X	X	X
Pregnancy test¥	X	X	X		X	X∞	
Hepatic function panel		X	X	X	X	X	X
Patient Related Outcome Form for Inflammatory Disorder		X	X	X	X	X	X
Repository Blood Sample (for repeat antibody test)		X	X	X	X	X	X
Vaccine Administration, with observation for reactions		X	X		X***		
Adverse effects form±			X	X	X	X	X

* Test for anti-HBs, anti-HBc, or HBsAg if not in the medical record or > one year previously. Test for HIV and HCV antibody is not within 4 months of screening.

≠ Only done at this visit if medical record indicates patient is anti-HBs positive by qualitative testing.

** This will only be done in patients taking TNF or interleukin inhibitor therapy for chronic inflammatory disorders.

¥ If potentially child bearing female. Patients who are positive will not be eligible.

*** A 3rd dose will be offered to those participants who lack seroprotection (>10 mIU/ml) at week 8.

± Observation for adverse events includes weekly telephone calls for 4 weeks after each vaccine dose.

∞ If patient requires third dose of vaccine as per protocol.

Appendix 1. Form to Capture All Adverse Events

Participant Number _____ Date _____ Visit Number _____

System Involved	Description of Event	HHS* Grade	Unexpected** Yes No	Relatedness a. Unrelated b. Possibly c. Definitely	Time Relationship to Dose 1	Time Relationship to Dose 2	MAAE, pIMMC, and/or SAE (specify) Yes No	Type Intervention	Participant Withdrawal Needed Yes No	Time to Resolution	PI Initials & Date
Local reaction											
Vital Signs											
Systemic											
Lab Abnormality											
HEENT											
Cardiac											
Lung											
Abdomen											
Muscular/ skeletal											
Neuro											
Skin											
Other											

Footnotes to Appendix 1

*As defined in Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0, November 27, 2017). U.S. Department of Health and Human Services/National Institute of Health/National Cancer Institute

Grade 1: mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not needed.
Grade 2: Moderate; minimal local or noninvasive intervention indicated.
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care
Grade 4: Life threatening; urgent intervention needed
Grade 5: Death related to AE.

** Unexpected indicates that the adverse event if not listed in the investigator's brochure or is not listed at the specificity or severity observed as indicated in CFR 312.32. Revised as of April 1, 2018.

Appendix 2 A. **Psoriasis Patient Related Outcome Measurement [Data Collected at Each Study Visit]**

Patient Study Number _____Date _____ Visit Number _____ Visit in Between Those Specified?-- Yes No

Skin related						
Areas affected	Arms	Legs	Back	Neck	Scalp	Feet
New areas Since last visit	YES/NO	Arms Legs	Back	Neck	Scalp	Feet
Eye	Redness	Pain	Sensitivity to light	Blurred vision		
Joint related	YES/NO	If so, where? (see below)				
	Fingers	Back	Neck	Shoulder	Hips	Ankles
Systemic						
Fever or feeling feverish?	YES/NO	99-100 F	101-103 F	>103 F		
Fatigue	YES/NO	Minimal	Moderate	Severe		
Overall assessment*	No change	Feel slightly worse	Feel moderately worse	Feel much worse		

Comments_____

_____

_____

Appendix 2B. **Rheumatoid Arthritis/Ankylosing Spondylitis Patient Related Outcome Measurement [Data Collected at Each Study Visit]**

Patient Study Number _____ Date _____ Visit Number _____ Visit in Between Those Specified?-- Yes No

Joint related						
Number affected	< 2	≥2 , ≤ 5	≥ 5			
Location	Hands	Wrists	Elbows	Shoulder	Hips	Ankles
Joint Pain	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10
Stiffness	Mild	Moderate	Severe			
Swelling	None	Mild	Moderate	Severe		
New joint location	YES/NO	If so, where? (see below)				
	Hands	Wrists	Elbows	Shoulder	Hips	Ankles
Systemic						
Fever or feeling feverish?	YES/NO	99-101 F	> 101-103 F	>103 F		
Muscle aching	YES/NO	If so, where?				
Fatigue	YES/NO	Minimal	Moderate	Severe		
Overall assessment*	No change	Feel slightly worse	Feel moderately worse	Feel much worse		
Function related						
Difficulty with dressing	YES/NO	Minimal	Moderate	Severe		
Difficulty with driving	YES/NO	Minimal	Moderate	Severe		
Difficulty with grasping	YES/NO	Minimal	Moderate	Severe		
Difficulty with walking	YES/NO	Minimal	Moderate	Severe		

Appendix 2 C. **Inflammatory Bowel Disease Patient Related Outcome Measurement [Data Collected at Each Study Visit]**

Patient Study Number _____ Date _____ Visit Number _____ Visit in Between Those Specified?-- Yes No

Bowel related					
Number stools/ 24 hr	< 2	>2 but < 5	> 5		
Blood in stools	None	Occasional (1-3 times Weekly)	Most days (4-6)	Daily	
Amount of blood		Minimal (teaspoonful mixed with stool)	Moderate (More than teaspoonful, but less than cupful)	Severe (Cupful or more)	
Abdominal Pain	None	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	On a scale 1-10 (with 10 being the worst) 1 2 3 4 5 6 7 8 9 10	
Systemic					
Fever	YES/NO	99-101 F	> 101 to 103 F	> 103	
Fatigue	YES/NO	Minimal	Moderate	Severe	
Overall assessment*	No change	Feel slightly worse	Feel moderately worse	Feel much worse	
Social Function					
	Normal	Occasional limitation	Several times weekly	Absence from work	Home ridden
Food tolerability	No problem	Minimally affected	Moderately affected	Severely affected	

Comments_____

_____

_____

Appendix 3. Quick View Table of Criteria for Subject Withdrawal, Vaccine Withdrawal, and Study Termination

Adverse Event	Relatedness Not Poss Def	Subject withdrawal	Vaccine Withdrawal	Anticipated Follow up	Study Termination
Death	Not	-	-	-	No*
	Possibly	-	-	-	Yes
	Definitely	-	-	-	Yes
Grade 4	No	No	No	Until 52 weeks after last vaccine dose	No*
	Possibly	Yes	Yes	Until 52 weeks after last vaccine dose	Yes
	Definitely	Yes	Yes	Until 52 weeks after last vaccine dose	Yes
Worsened underlying disease in Group A patient	**Regardless of relatedness**	Yes	Yes	Until 52 weeks after last vaccine dose	No, but **hold** on further enrollment & vaccine in group A if AE is definitely related**
Grade 3 AE or SAE in *any* patient group	Not	No	No	Until 52 weeks after last vaccine dose	No
	Possibly	No***	Yes	Until 52 weeks after last vaccine dose	No
	Definitely	No***	Yes	Until 52 weeks after last vaccine dose	**Yes,** if a second patient in different group has a Grade 3 AE or SAE that is also definitely related to vaccine$^{\Omega}$ **If this does not occur**, a hold on further enrollment & vaccine in the group the patient belongs to
Liver allograft rejection	Possibly	No***	Yes	Until 52 weeks after last vaccine dose	No
	Definitely	No***	Yes	Until 52 weeks after last vaccine dose	**Yes,** if a second patient in different group has a Grade 3 AE or SAE that is also definitely related to vaccine$^{\Omega}$ **If this does not occur**, a hold on further enrollment & vaccine in group C will be enacted.

*The finding of a death or Grade 4 AE that is considered unrelated to vaccine will not be considered sufficient to terminate the study nor place a hold on further enrollment in that group.

**The finding of a Grade 3 AE or SAE that is considered definitely related to vaccine will place a hold on further enrollment in Group A and all other groups (B and C). Should two subjects in one group have the same or similar Grade 3 AE or SAE assessed as *possibly* related, then enrollment and vaccination in that group will also be put on hold.

*** If patient meets criteria for vaccine withdrawal they will still be followed for safety until week 60.

$^{\Omega}$ Study termination will occur if two patients, one each from two different groups, develop a Grade 3 AE or SAE considered to be definitely related to vaccine.

Appendix 4. List of Potentially Immune-Mediated Medical Conditions

Gastrointestinal disorders

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

Liver disorders

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

Metabolic diseases

- Addison's disease
- Autoimmune thyroiditis (including Hashimotothyroiditis)
- 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 (e.g., non- infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- Guillain-Barre 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
- Sjogren's syndrome
- Stevens-Johnson syndrome
- Uveitis