PROTOCOL RESEARCH

Study promoter	**Foundation Institute for Science Studies Castilla y León Health (IECSCYL) - Salamanca Biomedical Research Institute (IBSAL)**
EUDRA CT number	2016-004991-23
Project Code	IBS-VACANTIB-1701
Qualification	VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES
Date	18-October-2018
Version	Version 2.0

STUDY SUMMARY

There are healthcare workers who are exposed to known biological hazards; among others, there is the risk of developing infection by the Hepatitis B virus, because of a biological accident when encountering fluids from a source patient with a situation of virus transmissibility.

The health worker population and non-sanitary of the NHS has a real risk of contracting this infection, especially the unvaccinated groups and those classified as "non-responders"; understood as such, those people who, having received the conventional vaccine for hepatitis B in a complete schedule (6 doses), do not present the antibody titers required to confirm their immunological protection against hepatitis B.

The need arises to provide a solution to health and non-health workers in our environment, in whom conventional vaccination has not worked and to offer them a vaccine alternative from which they can be beneficiaries, and which is already authorized. It is an adjuvanted hepatitis B vaccine (rDNA), but whose marketing authorization restricts its use to the immunization of patients with an immune response lower than that of healthy individuals.

A preliminary study has been carried out at the University Hospital of Salamanca based on investigations carried out with healthy individuals, which support the efficacy of this vaccine in an adult population that has not responded to the standard vaccine. Despite these promising results, the sample is still insufficient to extract definitive data, so we need to carry out the vaccination study involving more hospitals within the NHS.

SIGNATURE OF APPROVAL OFPROTOCOL

Promoter's Signature:

TITLE OF THE PROTOCOL: VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES

Project: IBS-VACANTIB-1701

EudraCT Number: 2016-004991-23

Representative from the promoter: Rogelio González Sarmiento

Signature Date

Signature of the Coordinating Investigator:

TITLE OF THE PROTOCOL: VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES

Project: IBS-VACANTIB-1701

EudraCT Number: 2016-004991-23

Coordinating Researcher of the Firm: José Lorenzo Bravo Grande

Signature Date

CONFIDENTIALITYAND GCP DECLARATION OF CONFORMITY

I have read the protocol of the previous clinical study entitled: " VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES" and I agree that it contains all the information necessary to carry out the study.

I hereby confirm that I have carefully read and understood this clinical study protocol, and I agree that my staff and I will conduct the study in accordance with the protocol and comply with its requirements, including safety and ethical considerations.
I understand that if The Promoter decides to terminate or suspend the study prematurely for any reason, said decision will be communicated to me in writing. On the contrary, if I decide to withdraw from the execution of the study, I will immediately communicate this decision to the Promoter.
I agree not to publish any part of the results of the study conducted under this clinical study protocol without the prior written consent of the Sponsor.

Principal investigator_____

Hospital Center_____

_____

Firm

_____

Date

Castilla y León Institute of Health Sciences Studies Foundation (IECSCYL) - Salamanca Biomedical Research Institute (IBSAL)

Salamanca University Hospital Virgen de la Vega, 10th floor

Pº San Vicente, 55-182. 37007 Salamanca

Acronyms

SAE	Serious Adverse Event
AcAnti HBs	Hepatitis B antigen antibody
DNAr	Recombinant DNA
AEMPS	Spanish Agency of Medicine sand Sanitary Products
Anti-HB	Hepatitis B antibodies
CAUSA	Salamanca University Assistance Complex
CEIm	Ethics Committee for Drug Research
CIOMS	advice of International Organizations of Medical Sciences
ECRF	Notebook data collection
ES	End of study
GRS	Regional Management of health
HBsAg	Hepatitis B surface antigen
ICH	International Conference Harmonization
IEC	Clinical study report
IECSCYL-IBSAL	Foundation of the Institute of Health Sciences Studies of Castilla y León- Institute of Biomedical Research of Salamanca
MIR	Hospital resident
MPL	Monophosphoryl lipid
ORP	Occupational Risk Prevention
NHS	National system of health
HBV	Hepatitis B virus

1. Summary

- **Study promoter: Fundación Institute of Health Sciences Studies of Castilla y León (IECSCYL) -Institute of Biomedical Research of Salamanca (IBSAL). IECSCYL-IBSAL Foundation**

- **Study title:** VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES.

- **Protocol code: IBS-VACANTIB-1701**

- **EudraCT number:**2016-004991-23

- **Study coordinator and direction:**
  Dr. José Lorenzo Bravo Grande
  Head of the Occupational Risk Prevention Service

  Salamanca University Hospital Pº San
  Vicente, 58-182.
  ZIP: 37007 Salamanca

- **Telephone fax:**0034 92329 12 00. Ext. 55605

- **Direction of e-mail:** jlbravo@saludcastillayleon.es

- **Participating centers**
  - University Clinical Hospital from Valladolid.
  - Healthcare Complex of Zamora.
  - University Healthcare Complex of Lion.
  - University Healthcare Complex of Palencia.
  - University Healthcare Complex of Salamanca. (Coordinating Center)

- **CEIm evaluating the study:**
  - CEIm Salamanca Health Area (Healthcare University Complex of Salamanca).

- **Main goal:**
  - Benefit and equip NHS staff with an additional protection tool against hepatitis B infection.

- To evaluate the efficacy of the adjuvanted vaccine in healthy subjects not responding to the conventional hepatitis B vaccine.

- **Design:** Open, multicenter, low-level clinical trial.

- **Pathology or study disorder:** NHS workers, including university students who carry out their internships in health centers of the National Health System (inclusion of students is subject to and limited by the specific instructions on occupational prevention in each autonomous community) with biological risk in their tasks, which have been classified as non-responders to vaccination against Hepatitis B.

- **Facts about study medication:** Fendrix®is a hepatitis B vaccine containing HBsAg adjuvanted by 3-O-desacyl-4'-monophosphoryl lipid A and with aluminum phosphate. This adjuvant system is called AS04C and increases the immunogenicity of the vaccine. An anti-HB antibody titer ≥10 mIU / mL correlates with protection against HBV infection.

- **Population study and total number of patients:** Workers from the health field of the NHS, with biological risk in their tasks, who have been classified as non-responders to vaccination against Hepatitis B. Initial estimate of up to 80 subjects in total included in the study among all centers.

- **Key dates of the study**

  Start of study (PVPP)- April 2018

  The end Inclusion (PVUP) - May 2019

  The end study (UVUP) - December 2019

  Ending of the Clinical Study Report (IEC) - February 2020

  Date Publication - April 2020

- **Sources financing**

  Projects research. Castilla and leon meeting. Ministry of Health. GRS 1360 / A / 16.
  Sponsor's own funds dedicated to promoting Clinical Research.

2. Index

3. General information

- **Protocol code:** IBS-VACANTIB-1701

- **Tittle:** VACCINATION ADJUVED AGAINST HEPATITIS B IN SNS WORKERS TYPED AS NO RESPONDERS TO CONVENTIONAL VACCINES

- **Study promoter**: IECSCYL-IBSAL Foundation

- **Telephone fax:**0034 923 21 09 60/0034 92329 04 72

- **Direction of e-mail:** ensayosclinicos@ibsal.es

- **Principal investigator:**
  Dr. José Lorenzo Bravo Grande
  Head of the Occupational Risk Prevention Service at the
  Salamanca University Assistance Complex

- **Participating centers**
  - University Clinical Healthcare from Valladolid.
  Address: Avda. Ramón y Cajal, 7
  Town: Valladolid CP: 47005

  - Healthcare Complex of Zamora.
  Address: Avda Hernán Cortés, 40 Town:
  Zamora Zip Code: 49021

  - University Healthcare Complex of Lion.
  Address: AC / Altos de Nava, s / n
  Town: León ZIP: 24071

  - University Healthcare Complex of Palencia.
  Address: Avda. Donantes de Sangre, s / n
  Town: Palencia CP: 34004

  - University Healthcare Complex of Salamanca. (Coordinating center)
  Unit: Salamanca Healthcare Complex
  Address: Pº San Vicente, 55-182. ZIP: 37007

- **Trial duration:** 2 years

4. Study justification: Review criticism of literature

Currently there is no effective solution for health workers who have not responded to two complete guidelines for hepatitis B vaccine and are exposed to developing Hepatitis B virus infection, because of a biological accident (due to needle stick, splashing, etc ...) when encountering fluids from a source patient with a situation of virus transmissibility.

The probability of contagion after a puncture, it is estimated between 7 - 30% in the presence of a positive source of hepatitis B virus (HBV). It is the most contagious hepatitis and is fulminant in 1-2% of cases, with a mortality between 63-93%. It progresses to chronicity in 10% of acute infections and can lead to occupational disease / disability.

The health and non-health worker population of the NHS has a real risk of contracting this infection, especially the unvaccinated groups and those classified as "non-responders"; understood as such, those people who have received two complete schedules of three doses of conventional vaccine (trade name Engerix®) for hepatitis B at doses of 20 µg / mL (total six doses). The percentage of non-response for this traditional vaccine is between 5-10% of those vaccinated, with titers of Ab Anti HBs less than 10 mIU / ml. The lack of response to standard vaccination is influenced by the following characteristics:

- Age: over 40 years old
- Gender: Male
- BMI> 30
- Smokers
- Chronic illness
- Immunodeficiency
- Some HLA haplotypes.

Although there is the possibility of applying specific anti-hepatitis B Gamma Globulin in the case of a biological accident, as a remedy indicated in 'unvaccinated' and likewise in 'non-responding' workers, it seems logical that a vaccine alternative could be offered these workers from which they may be beneficiaries.

Currently, there is a solution for workers and university students who do their internships in the NHS exposed to contagion of hepatitis B. It is a vaccine for hepatitis B, with HBsAg, the surface antigen of the hepatitis B virus (Ac AntiHBs - Antibody against hepatitis B antigen -) obtained by genetic recombination (like current hepatitis B vaccines), but with an adjuvant: AS04 (lipid A) and adsorbed on aluminum phosphate (Thoelen, 2001, Desombere). Its trade name is Fendrix®, it is indicated for the immunization of patients with kidney failure (Technical Data Sheet, AEMPS; ChiewTong, 2005). The adjuvant system increases the immunogenicity of HBsAg, making it effective in this group of patients, which is characterized by presenting a lower immune response than that of healthy individuals. AS04C,

Immunization of other groups of patients not included in the population with renal insufficiency is not contemplated in the Fendrix® technical data sheet. However, it should be noted that there are data that support the efficacy of this vaccine in the

adult population that has not responded to the standard vaccine, with success rates of 98% (Jacques, 2002; Hoebe, 2012; Walayat, 2015).

Dr. Bravo, principal investigator and coordinator of the study proposed in this application, has carried out a previous study with this adjuvanted hepatitis B vaccine at the University Hospital of Salamanca, based on the work of P. Jacques (2002). The study was conducted through compassionate use and was carried out between 2009-2011 with:

1. Approval unanimously by the Pharmacy Commission of the Salamanca University Hospital, in March 2009), with the approval of the Center's Management.
2. Authorization of the Spanish Agency for Medicines and Health Products in April 2009.
3. Participated 20 working subjects of the Salamanca Hospital.
4. Results:
    - The Mean values, prior to vaccination, of Anti HBsAc titers were 1.05 mIU / mL (9.03 - 0.00)
    - Average age: 49.1 years
    - All received the full 40 µg regimen, in months 0 - 1 - 6, in two injections: one in each deltoid in the same vaccination act, except for one person who became pregnant after the second dose and did not want to receive the third. (still answered).
    - Only one person did not achieve protection titers two months after finishing the vaccination (7.06 mIU / mL), three had negative titers one year after vaccination (1.7, 1.1, and 8.0)
    - Two could not be followed up at one year, but they were responders at two months.
    - Average at two months:
    - 575.23 mIU / mLof respondents (95%) (n = 19)
    - Between> 1000 and 25.67
    - Average per year:
    - 175.18 mIU / mLof respondents (75%) (n = 15)
    - Between> 1000 and 14.22
    - Adverse Effects: General malaise and fatigue with the first dose, and the rest well (2 people), no data: 7 people, like any vaccine (1 person), local pain, which subsided in a few days (10 people)
    - Non Responders: one person

The Conclusions of this preliminary study of vaccination with adjuvanted hepatitis B vaccine (rDNA) is that it is well tolerated clinically, its conversion values are excellent, although the sample is still insufficient to extract definitive data and the behavior in healthy individuals seems to be different from other with pathologies that are

compromised with the immune response.

In relation to the inclusion of the population of university students who carry out their practices in health centers of the National Health System, Even though the trainees have no employment relationship of any kind with the NHS Managements in which they carry out their training activities, they may be subject to the same or similar risks as the workers with whom they carry out their training practices.
Royal Decree 1707/2011, of November 18, which regulates the external academic practices of university students, establishes a series of rights and duties of the student and the collaborating entity in matters of risk prevention and occupational health.
Among them is the student's right to receive, from the collaborating entity, information on the safety regulations and prevention of occupational risks (art. 9 1.f), as well as the duty to (...) respect the rules of operation, safety and prevention of occupational hazards (art.9 2.d).
In relation to the tutor of the collaborating entity, it determines that he / she will have the duty to inform the student of the organization and operation of the entity and of the regulations of interest, especially those related to safety and occupational risks (art. 11 lc).
For its part, Directive 2010/32 / EU of May 10, 2010, which applies the Framework Agreement for the prevention of injuries caused by sharp instruments in the hospital and health sector and article 6 of Order ESS / 1451/2013, of July 29, which transposes the previous Directive, establishes that "vaccination must be offered free of charge to all workers and students who carry out health and related activities in the workplace": In the case of not acceptance of the offered vaccination must be recorded in writing of this decision.
The inclusion of this population of university students will be subject to the specific instructions on occupational prevention in each autonomous community. In the case of centers located in the Community of Castilla y León, their inclusion will be made based on the document "Instructions of the Ministry of Health of the Junta de Castilla y León of October 11, 2013" (link: http: // www.sanidad.ccoo.es/comunes/recursos/15617/doc287408_Instruccion_de_la_gerencia_regional_de_Salud_sobre_adopcion_de_medidas_de_prevencion_de_riesgos_y_salud_laboral_para_los_estudiantes_que_realizan_sus_practicas_df_que_realizan_sus_practicas_df

Therefore, it is proposed to carry out a broader study involving as collaborators several hospitals belonging to the NHS and the expansion of the target population.

5. goals

- **Main goal**

1. Benefit and equip NHS staff with an additional protection tool against hepatitis B infection.
2. To evaluate the efficacy of the adjuvanted vaccine in healthy subjects NON-responders to the conventional hepatitis B vaccine.

- **Secondary objectives**

1. Analyze results of anti-HBs antibody titers to see the immune response to the adjuvanted vaccine.
2. Evaluate safety results and clinical tolerance of the adjuvanted vaccine.

6. Source and information field

The source and field of information will be the electronic data collection notebook (ECRFe) that the researcher will fill in based on the patient's medical history.

7. Trial Design

- **Design:** open, multicenter clinical trial with use of off-label medication.
- **Duration:** 2 years
- **Ambit study:** Services of Prevention of Occupational Risks of the public hospitals of the NHS

The multicenter trial will be carried out in the following hospital centers:

- University Clinical Hospital from Valladolid. (Dr. Fernando Rescalvo Santiago)
- Healthcare Complex of Zamora. (Dr. José Manuel de la Fuente Martín)
- University Healthcare Complex of Lion. (Dr. José Manuel De la Torre Robles)
- University Healthcare Complex of Palencia (Dra. Marina Hervella Ordoñez)
- University Healthcare Complex from Salamanca (Dr. José Lorenzo Bravo Grande, (Coordinating Researcher)

The trial features one investigator coordinating the project and one principal investigator per hospital, who in turn will have the collaboration of teams belonging to the Occupational Risk Prevention Service.

- **Population study: selection criteria**

University workers and students from the health field of the NHS, with biological risk in their tasks, who have been classified as non-responders to vaccination against Hepatitis B. Initial estimate of a maximum of 80 subjects in total included in the trial among all centers.

Criteria inclusion:

- Workers of the NHS -including university students who carry out their practices in health centers dependent on the National Health System (inclusion of students is subject and limited by the specific instructions on occupational prevention in each autonomous community).
- In working age.
- No diseases that would contraindicate vaccination with Fendrix®.
- Criteria that define them as NOT responders to the conventional hepatitis

B vaccine: anti-HBs Ab titers <10 mIU / ml after the application of six doses of conventional vaccine at doses of 20 µg (two complete regimens)

- Subjects signing informed consent

Criteria of exclusion:

- Known allergy the active ingredient or any of the other ingredients of the medicine (included in section 6 of the product's technical sheet).
- If you have ever had an allergic reaction to any hepatitis B vaccine
- If you have a severe infection with a fever.
- Subjects of which informed consent is not obtained
- Subjects that have not revoked the initially signed consent.

- **Informed consent:**

Prior to the administration of the vaccination schedule, the worker will be informed of the purpose of said vaccination indication, its possible benefits and risks derived from its use, requesting the completion of a specific informed consent.

- **Withdrawal criteria and scheduled analysis of withdrawals and dropouts**

The patients they can leave the trial at any time and for any reason, without this having any negative effect on their aftercare.

Although the patient is not obliged to provide any explanation for leaving the trial prematurely, the investigator will reasonably attempt to determine the patient's motives, always respecting their rights. If a patient leaves the trial prematurely, the final visit data will be recorded in the ECRF.

The doctor may suspend the treatment at any time during the follow-up and replace it with another drug that he considers more beneficial for the patient, immediately informing the promoter of the trial.

- **Treatment description and definition of exposure**

Product description:

Fendrix® is a hepatitis B vaccine that contains HBsAg adjuvated by 3-O-desacyl-4'-monophosphoryl lipid A and with aluminum phosphate. This adjuvant system is called AS04C and increases the immunogenicity of the vaccine.

- Generic name: Vaccine of Hepatitis B adsorbed and adjuvanted by AS04C
- Trade name: Fendrix®
- Laboratory: Glaxo Smithkline
- ATC therapeutic group: J07BC (Hepatitis Vaccines)
- Form of presentation: 20 µg pre-filled syringes

Fendrix® is a hepatitis B vaccine that contains HBsAg adjuvanted by 3- O-desacyl-4'-monophosphoryl lipid A and with aluminum phosphate. This adjuvant system is called AS04C and increases the immunogenicity of the vaccine. An anti-HB antibody titer ≥10 mIU / mL correlates with protection against HBV infection. It is indicated for active immunization against infection by all known subtypes of Hepatitis B virus in patients with renal failure (including pre-hemodialysis and hemodialysis patients) older than 15 years. However, it is intended to take advantage of the greater immunogenic capacity

of this vaccine in non-responders, understood as those who have received two complete vaccination schedules without reaching an antibody titer greater than 10 mIU / mL.

Terms of administration:
Immunization will consist of a maximum of 4 doses of 0.5 ml administered according to the following schedule: 1 month, 2 months and 6 months from the date of the first dose, with an intramuscular vial in the deltoid muscle at the dose of 20µg, as stated in the Fendrix technical data sheet. After the administration of each of the doses, a serological analysis will be carried out (approximately 30 days after the administration of each dose), making it clear that if seroprotection is achieved (anti-HB ≥10 mIU / ml, the administration will be suspended. of successive doses.
The precautionary measures regarding contraindications and warnings of the product, recommended by the manufacturer and in accordance with the recommendations of the AEMPS for its use outside the technical data sheet, will be observed.

- **Stages developmental**

Stage 1:

- Start up:
  - Elaboration of the documentation of the final trial: latest version of the Protocol, Electronic Data Collection Notebook (ECRFe), Informed consent for the subject, etc.
  - Request to the AEMPS classification of clinical trial and recommendations for the use of the drug outside of the technical data sheet.
  - Obtaining of CEIms authorizations and necessary contracts with the centers: carried out by the Salamanca Hospital and the IBSAL (Technical Management Unit of the Salamanca Biomedical Research Institute-clinical trials area).
- Preselection of candidates (8 weeks) in the collaborating centers of:
  - Valladolid University Clinical Hospital.
  - Zamora Healthcare Complex.
  - León University Healthcare Complex.
  - Palencia University Healthcare Complex.
  - Salamanca University Healthcare Complex.

Pre-select the workers described in the target population based on the records obtained from their clinical-working histories, which have received 6 doses of conventional hepatitis B vaccine and have not exceeded 10 mIU / mL. Detection of new cases at the University Hospital of Salamanca.

Stage 2:

- Purchase of medication: coordinated from the IBSAL-Hospital de Salamanca.

- Transport of medication to the collaborating centers: from a commercial provider to the Occupational Risk Prevention Services of the participating centers.

Stage 3:

- Inclusion of participating subjects: recruitment in each center. Select the workers described in the target population based on the records obtained from their clinical-working histories, who have received 6 doses of conventional hepatitis B vaccine and have not exceeded 10 mIU / mL.
- Dosage administration, evolution monitoring and safety: Once the consent of the participant has been obtained, Fendrix® will be prescribed at a dose of 20 micrograms up to a maximum of 4 doses. The antibody titer per month of each dose of vaccine administered will be subsequently analyzed locally at each center. Possible events and adverse reactions will be detected, subsequently monitoring the applicable Pharmacovigilance.

Visits calendar from the patients:

Visits	**Selection Visit**	**Visit1**	**Visittwo**	**Visit3**	**Visit4**	**Final visit**
Time		**Month0**	**Month1**	**Month 2**	**Month6**	**Month7**
Procedures and tests						
Pick up of data and tests required for the test	**X**					
Analytics	**X**		**X**	**X**	**X**	**X**
Drug administration		**X**	**X**	**X**	**X**	
Pick up of data related to other medications and adverse events		**X**	**X**	**X**	**X**	**X**
Completion sheet						**X**

Stage 4:

- Compilation of the analyzes and ECRFs from the collaborating centers to the coordinating center.
- Treatment of data and statistical analysis: coordinating center-IBSAL.

Stage 5:

- **Publication:** from the coordinating center.

- **Schedule. Plan of work**

Activity:	People involved	From (mm / yyyy)	Until (mm / yyyy)
Stage 1	8	Jan-2017	Dec-2018
Stage 2	6	May-2017	Feb-2019
Stage 3	8	Jun-2017	Jun-2019
Stage 4	7	Dec-2018	Dec-2019
Stage 5	6	Jan-2019	Apr-2020

- **Available media to carry out the test.**

The infrastructure where it will be carried out resides in the prevention services of the hospitals involved. In addition to the management support for its development by IBSAL in its Technical Management Unit (HU Salamanca). In these services there are adequate facilities, material means to carry out all the processes required for the development of the test (refrigerators, determinations of Ab, etc.)

The personnel involved in the trial are NHS personnel with extensive experience in Occupational Risk Prevention in the health field, in addition the trial will receive the necessary administrative management support from the Clinical Trials Area of the IBSAL Technical Management Unit

- **Limitations of the trial**

The main limitation of the trial will be to find new cases of non-responding workers and overcoming the difficulties of the lack of standardized records of non-responding workers from the different prevention services of the collaborating hospitals.

8. Valuation criteria and measurement instruments

8.1. Driving of the samples

The samples will be stored in the laboratories of each center and will remain there until the end of the test. The handling of samples will be carried out according to the usual clinical practice of each center where the test is carried out.

Terms for the shipment of medication

The coordinating center will be responsible for sending the medication to the different centers participating in the trial. Special precautions for storage will be maintained to maintain optimal conditions and preserve the stability of the medication, as stated in the technical data sheet.

8.2. Variables to study

- Measurement of the anti-HBs antibody titer: before the first dose and one month after the administration of each dose.
- Pickup of adverse effects during administration and all those that could be

related to the vaccine and that appear within 30 days after each dose.

9. Statistical analysis

A statistical analysis of the data will be carried out, assisted by the IBSAL Biostatistics Research Group

- **Sample size justification**

The sample size is based on the recruitment carried out from the previous study carried out at the Salamanca University Healthcare Complex. Considering the number of subjects susceptible to study in the different centers, a sample size of up to 80 subjects is estimated.

- **Statistical methodology**

The results of the present trial and the clinical-biological data of the patients will be registered in a database.

Statistical significance: The results will be analyzed using SPSS software (version 15.0) for Windows.

An initial descriptive analysis of the quantitative variables will be carried out, which will include measures of central tendency (mean, median), measures of dispersion (range, standard deviation) and box plots, with possible extreme values. For qualitative variables, frequencies will be presented.

The level of significance will be set at $p < 0.05$.

10. Ethical aspects and legal

The researcher will carry out the study in compliance with the ethical principles of the Declaration of Helsinki.

The trial must adhere to the protocol, which guarantees compliance with Good Clinical Practices, described in the Harmonized Tripartite Guidelines of the ICH on Good Clinical Practices.

This trial will be submitted for evaluation by a Drug Research Ethics Committee and the Spanish Agency for Medicines and Health Products (AEMPS) will be notified.

The pertinent authorizations will be obtained in accordance with current regulations for clinical trials.

- **Information sheet and consent form**

The researcher will explain to each patient (witness or legal representative) the nature of the trial and the purposes, procedures, estimated duration, possible risks and benefits of participating in the trial and possible inconveniences that it may cause. All patients will be informed of the voluntary nature of their participation and that they may withdraw at any time, without affecting their future medical care or their relationship with the doctor responsible for their treatment.

The patient will have sufficient time to read and understand the explanations included in the patient information sheet (Annex 2) before giving their informed consent (Annex 2). No patient may be included in the trial before having obtained their

informed consent.

- **Protection of personal data**

The confidentiality of individual patient data will be always respected. The original data will be kept in the corresponding Service and only the trial researchers or inspectors will have access to them, in the event of inspection by the Spanish Health Authorities.

The patients will be identified by a patient code. The researcher will inform the patients that the data obtained during the trial will be stored and analyzed by computer, in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016, regarding the protection of natural persons about the processing of personal data and the free circulation of these data and to LO 15/1999, of December 13 on Protection of Personal Data.

The researcher is the only person who can and should know the origin of the data obtained and who can associate them with the patient.

Personal data (full name, address, place of work, NIF) of the researchers will be recorded in a computerized file, with the sole purpose of facilitating the organizational and logistical aspects necessary for the development of the trial.

In compliance with the afore mentioned regulations, the data file will be treated confidentially, and the researchers may exercise their rights of access, rectification, cancellation, and opposition regarding the registered personal data, if they request it by writing to the Delegate of Data Protection of the promoter at comunicacion@ibsal.es

- **Interference with the doctor's prescription habits.**

Patients included the trial must meet the inclusion and exclusion criteria detailed in the protocol. Based on the trial inclusion and exclusion criteria, researchers will only include patients for whom the study drug prescription is appropriate. As specified in Section 7, the doctor may suspend the treatment at any time during the follow-up and replace it with another drug that he considers more beneficial for the patient.

- **Responsibilities of all trial participants**

Investigator

The investigator must meet the following requirements:

- Engage to carry out the test as stipulated in the protocol.
- Report to trial patients and obtain their consent.
- Get, register, and report the data correctly, responding, if applicable, to its validity and quality in the audits.
- Facilitate audits and inspections by health authorities. Therefore, after submitting the final report, you should keep the trial documentation for at least 5 years.
- Know how to explain the objectives, the basic methodology and the meaning of

the test results to the scientific and professional community.

- Notify your participation in the test to those responsible for the management of your center.
- Make sure that the information recorded in the ECRF is accurate and correct, and that it has been obtained as indicated in the protocol.
- The researcher is the only person who can and should know the origin of the data obtained and associate them with the patient, ensuring that no extra (unsolicited) information appears in the ECRF that could identify the patient (name, PASSPORT NUMBER, SOCIAL SECURITY AFFILIATION NUMBER, address, telephone, etc.).
- Specifically, the researcher must guarantee the best possible care for the patient, always putting their well-being and safety first.

Coordinating researcher

The coordinating investigator must meet all the investigator requirements of the trial and sign the protocol and possible amendments, together with the sponsor; will be jointly responsible, together with the promoter, for the drafting of the final reports; help to disseminate the results of the trial in collaboration with the sponsor; undertake not to sign any contract that contains confidentiality clauses on future trial results and not to disclose the results of the trial, avoiding at all times jeopardizing the integrity of the trial (for example, by publishing partial results of an investigator or a center).

Monitor

Will does the functions contained in Royal Decree 1090/2015. From December 4, which regulates the clinical trials with drugs, the Ethics Committees for Drug Research and the Spanish Registry of Clinical Studies. The Sponsor has delegated the monitoring functions of the trial to the SCReN platform of the Carlos III Health Institute.

Head of the Pharmacovigilance Node

The Sponsor has delegated the monitoring functions of the trial to the SCReN platform of the Carlos III Health Institute.

Following SCReN's SOP-PFV 2, 3, 4, 5, 6, 7 procedures, your responsibilities will be:

- Receive by Fax or email from the researchers, and sign the information received. Check that AGA / pregnancy meets severity criteria, reflects intensity, investigational drug, causality assessment, and investigator signature. In the case of any blank data, the person in charge of Pharmacovigilance or person delegated, will immediately contact the center for immediate correction.
- Give a number to the notification of SAE / pregnancy and send it to the investigator (only in the first communication of the case)
- Review the information on the SAE / pregnancy received. It must be completely and medically consistent. Additional information may be required (queries or discrepancies).
- Send a copy (fax or email) of the receipt form or the queries / discrepancies to the CRA or the project manager or the Promoter.

- Register the cases individually in a database.
- Determine the predictability of the AGA / pregnancy received.
- Contact the promoter or coordinating researcher to report the AGA / pregnancy received and the causal relationship made by the notifier.
- Request from the promoter the confirmation of the causality and predictability of the AGA / pregnancy carried out by the Pharmacovigilance Node.
- Notify the researchers, Health Authorities (AEMPS and CCAA), the RAGIS received.
- Archive all generated documents. *

* Only AAs notified as serious and unexpected, and related to medication (RAGI), are sent to the competent authority. For this, the official form will be used. The RAGI will notify the AEMPs at Fax: +34 918 225 076 and the Autonomous Communities via mail electronic, but not to the CEIm.

Promoter

The promoter:

- It will be responsible for ensuring compliance with the relevant legislation.
- He will sign the protocol and possible amendments, together with the coordinating researcher.
- Will present the protocol to the CEIm.
- Will present the trial protocol and the final report within the established deadlines and, if necessary, will communicate the interruption of the trial and the reasons that have motivated it.
- Identify sources funding for the trial.

- Ethics Committee for Drug Research **(CEIm)**

The Ethics Committee for Drug Research (CEIm) will review the protocol, the proposed informed consent form and other information for patients. Any modification of the protocol, apart from administrative changes, will require an amendment to the protocol that must be approved by said Committee. Changes in the direction of the trial that are not accompanied by an amendment will be considered deviations. Deviations may lead to disqualification of the center from continuing to participate in the trial.

11. Practical considerations

- **Study plan and inclusion of patients**

The patients will be selected and, once informed consent has been obtained and verified that the patient meets the selection criteria, the information will be recorded in the ECRF and the samples provided will be analyzed.

- **Procedures for the communication of adverse reactions**

An adverse event is the appearance of signs, symptoms, or an undesirable medical pathology (or the worsening of the pre-existing ones) that occurs after the signing of the informed consent, even if the event is not considered related to the treatment.

An adverse drug reaction is the appearance of signs, symptoms, or an undesirable medical condition in a patient receiving a drug that is considered drug related.

Serious adverse event

To ensure patient safety, any serious adverse event (SAE), regardless of suspected causation, that occurs after the patient has given informed consent and up to 4 weeks after treatment / patient participation has been discontinued. the trial, the researcher will send the completed SAE / pregnancy form (Annexes 4 and 5), in the first 24 hours from its knowledge to the Pharmacovigilance Node (UICEC Hospital Universitario de Canarias). Fax +34 922 67 7284 or by email to: maria.garcia@scren.es. ,. The original and duplicate copies of the SAE Form, and the fax confirmation sheet, will be kept at the trial site, along with the data collection notebooks.

ASAE is defined as an event that:

- Cause death or life threatening.
- Causes a disability/ persistent or significant disability.
- It constitutes a congenital anomaly / birth defect.
- Requires hospitalization or the prolongation of a pre-existing hospitalization, unless the hospitalization is due to:
    - to routine treatment or to the control of the studied indication, without deterioration of the pathology (specify what it includes)
    - elective or previously planned treatment of a pre-existing pathology not related to the indication studied and that has not worsened since the beginning of the administration of the drug of interest.
    - to social reasons or temporary care of the patient, in the absence of deterioration of the general condition of the patient
- It is medically significant, that is, it is defined as an event that compromises the patient or may require medical or surgical intervention to prevent any of the above-mentioned outcomes.
- Outpatient treatment emergency for an event that does not meet any of the above definitions of SAE and does not result in a hospital admission.

Serious adverse events occurring more than 4 weeks after study withdrawal will only be reported to the Sponsor according to the procedures established in this protocol for other serious adverse events, if the investigator suspects that there is a relationship with the study treatment.

To the extent possible, all SAEs will also be described by (but not only):

- its duration (start date = date of first signs or symptoms) and end date
- severity and intensity criteria, if applicable (mild, moderate, severe)

- their relationship with current investigational drug (suspected / not suspected, investigator judgment),
- the action or actions taken and the results of your investigation, if applicable
- details of concomitant medication
- outcome

The follow-ups of the SAE will follow the same form indicating follow-up and its shipment must be made within 7 days, (stating that it is the "follow-up" form). The follow-up report will indicate if the event has been resolved or is still active, if and how it has been treated and if the patient's participation in the trial has continued or ended. The trial site will keep the form and the fax confirmation sheet.

To ensure the safety of female patients, pregnancies in participating patients will be reported within 24 hours of knowledge. The pregnancy will be recorded in a Pregnancy Form and the researcher will notify the Pharmacovigilance Node (UICEC Hospital Universitario de Canarias). Fax +34 922 67 7284 or by email to: maria.garcia@scren.es .. Pregnancy monitoring will be recorded in the same form and will include an assessment of the possible relationship between the outcome of the pregnancy and the drug under study. Any SAE that occurs during a pregnancy will be reported using the SAE Notification Form.

Adverse event

Adverse Events must be included in the relevant section of the ECRF - Adverse Event- describing the following parameters:

- Description of the Adverse Event.
- Start date.
- Has treatment finished?
- Relationship with medication (possibility of adverse reaction)
- Action taken with the Investigational Drug.
- Intensity of the event - Grade CTCAE-.
- Concomitant treatment administered.
- Resolution.

- **Registry of data and preservation of documentation**

The researcher will fill in all the data in the ECRF following the guidelines indicated for said completion and will report all the data according to the procedures specified by the sponsor at the beginning of the trial.

Patient data collected in the ECRF during the trial should be documented anonymously; patients will only be identified by the patient code. All the information registered in the ECRFe must be verifiable from the original documents of the patient's medical history.

The researcher will keep the original documents necessary for possible inspections by the health authorities for a period in accordance with current legislation.

The ECRF data will be entered into a trial database, through simple entry. The

information entered will then be systematically verified.

- **Periodic safety reports (DSUR)**

Following the rules of good clinical practice, current regulations, and SCReN's SOP-PFV 11 procedure, the Pharmacovigilance Node will have a safety report prepared once a year (SOP-PFV 11 / 01.1 Format). This report will contain the safety evaluation of the drug in accordance with all the SAEs received by the person in charge of Pharmacovigilance of the Node.

The person in charge of the Pharmacovigilance Node will send the DSUR to the Project Manager for review, indicating the need to receive a response within a maximum period of 15 days and the deadline.

The person in charge of the Pharmacovigilance Node will then send the DSUR to the Promoter for approval, indicating the need to receive a response within a maximum period of 15 days and the deadline.

All modifications suggested by the GP or the promoter will be carried out by the Head of Pharmacovigilance.

The latest version of the DSUR will be signed by the Head of PV of the Node, then by the GP (as reviewer) and finally by the promoter granting their approval.

The annual safety report (DSUR) will be sent by the promoter to:

- AEMPS: via ECM portal using "E iv) Annual safety report (DSUR) [AEMPS only]"
- CEIm of the Salamanca Health Area: via ECM portal using "E ii) Report on the progress of the trial."
- Contact points in clinical trials of the Autonomous Communities via email. (Annex 3: Annex 2 of the AEMPS Instructions)

The Project Manager will send the Pharmacovigilance Node a copy of the acknowledgment of receipt from the AEMPS.

- **Reports follow-up and conclusion**

The Promoter, in accordance with the current regulations and instructions that regulate clinical trials by the AEMPS, will send the pertinent monitoring reports.

Three months after the completion of the inclusion of patients, a statistical report will be drawn up that will include all the results of the study. This report will be made known to the participating researcher. In addition, copies of the report will be sent to the CEIm that has evaluated the study and to the AEMPS.

Any report obtained from this study will be considered confidential, at least until the person responsible for the study has reviewed and analyzed it. The data set can be used for general publications, which should always refer to the study. The researcher agrees not to provide information related to the study or provide access to their data to third parties.

- **Disclosure of results**

Independently of the results of the study, the promoter agrees to present them to the

medical community through scientific publications, conferences, or other means.

Any formal presentation or publication of study results will be considered a joint publication of the investigator (s) and the sponsor.

12. Practical utility results in relation to health

Relevance of the projects for its impact

1) clinical, healthcare and / or technological development.

2) bibliometric.

1) Fendrix® is a hepatitis B vaccine that contains a new adjuvant that has a higher immunogenic capacity than the conventional vaccine. For this reason, although its use is only authorized in patients with renal failure, it is intended to initiate a protocol for use outside the technical data sheet for its use in health workers who have not responded to two complete vaccination guidelines.
There must be considered that post-exposure prophylaxis with specific immunoglobulin should be done in non-responders. The recommended guidelines according to the technical data sheet are:

- Single dose 12-20 IU / kg (administered as soon as possible).
- Two doses, one during the first 24 hours and another a month.

Its cost is much higher than that of the currently available vaccine. However, it must be considered that the number of patients to be treated would be small and that in the event that a non-responding worker were accidentally exposed to the hepatitis B virus, the cost of secondary prophylaxis with specific immunoglobulin would offset part of the cost. of the vaccine.

2) The project will have a bibliometric impact at the national level, and probably international impact, since there is no precedent for this study in Spain and studies by other authors collect retrospective data from populations with a low number of participants, the only study that has established doses and guideline determining the efficacy of Fendrix® against conventional hepatitis B vaccination is the study by Jacques (Jacques P, Moens G, Desombere I et al. The immunogenicity and reactogenicity profile of a candidate hepatitis B vaccine in an adult vaccine non -Reply population. Vaccine 2002; 20: 3644-9). In addition, a recent bibliographic review establishes the need to establish official guidelines to vaccinate the population that does not respond to the conventional vaccine against HBV (Walayat, 2015) and the study proposed in this application would contribute to establish an initial guideline for future studies of prevention of biological risks in health personnel.

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14.Annexes

Annexed 1. CEIm approval

Independent document

Annexed 2. Patient information sheet and consent form

Independent document

Annexed 3. Contact points for the health authorities of the Autonomous Communities (DSUR)

Independent document

Annexed 4. Serious adverse event form

Independent document

Annexed 5. Pregnancy form

Independent document

Annexed 6. Manual of electronic data collection notebook

Independent document

Annexed 7. Traceability and management of medication

Independent document