

## **PARTICIPANT INFORMATION SHEET**

### **Clinical trial to evaluate a new Hepatitis B vaccine (CONSTANT study)**

The Oxford Vaccine Group, University of Oxford would like to invite you to take part in a clinical research study of a vaccine against hepatitis B virus (HBV). Before deciding whether you want to take part, it is important for you to understand what the study will involve. Please take the time to read this participant information sheet carefully. If there is anything you do not understand, or if you would like more information, please contact the study team (contact details are on page 1). You may also wish to discuss the study with family members, friends, and your general practitioner (GP)/family doctor.

#### **What is Hepatitis B?**

Hepatitis B is a serious infection of the liver caused by a virus (HBV) that is spread through blood and other body fluids, and affects millions of people worldwide. Long-term (chronic) infection with HBV can lead to liver failure, cancer and even death. Once HBV infection has become chronic, treatment options are limited, therefore a better option is to prevent HBV infection by using vaccines. Vaccines are designed to defend against a particular infection by boosting the body's immune system defences against that infection. The stronger your immune system defences against HBV are, the better able you will be to protect yourself from hepatitis B infection.

#### **Why are we doing this study?**

This study is being performed to compare an "investigational" HBV vaccine against a "standard" HBV vaccine (Engerix-B®) that is already licensed in the United Kingdom (UK), to measure whether it is as good as the currently used vaccine. The study will also compare three lots of the study vaccine (produced at different times), to ensure that the vaccine quality is consistently good.

The study vaccine is classed as "investigational" because it is not currently approved for use by the regulatory authorities in the UK, United State (US), Canada or the European Union (EU). However, it has been used in Israel for almost 20 years, and has been approved for use in several other countries to provide protection for infants, children, and adults against hepatitis B disease.

Since its original development, the study vaccine has undergone changes in some ingredients used to prepare the study vaccine to make it more effective and safer. In addition, the company that makes study vaccine has changed. Previous studies suggest that the study vaccine has remained an effective vaccine against HBV throughout these changes; however, only a small number of clinical studies have been carried out with the current formulation of the study vaccine. The results of this study will be used to support an application for approval to use the study vaccine in the UK, US, Canada, and Europe.

#### **What happens during the study?**

Approximately 3,200 healthy people aged 18-45 years who have not previously been vaccinated against HBV will be enrolled in this study at up to 40 study sites in the UK, US, Canada, and the EU. The study will last for about a year, and will involve a screening visit and five study visits, plus four telephone check-ups. Participants will receive three doses of vaccine over the course of the study, and be asked to provide blood samples on 5 occasions. The table below provides an overview of what will happen at each visit.

<b>Visit</b>	<b>Screen</b>	<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3</b>	<b>Visit 4</b>	<b>Visit 5</b>
<b>Time point</b>	-1 month	Day 0	1 month	6 months	7 months	12 months
<b>Health Checks</b>	X	X	X	X	X	X
<b>Blood sample</b>	X	X		X	X	X
<b>Vaccination</b>		X	X	X		
<b>Diary Card</b>		X	X	X		
<b>Pregnancy test (women)</b>	X	X	X	X		

### Consent

Before any study procedures take place, a member of the study team will discuss the study with you and answer any questions you may have. You will then be asked to sign a consent form and given a copy of the consent form to keep.

### Health Checks

The purpose of the screening visit is to check that you are eligible and well enough to take part in the study. The nurse and/or doctor will ask you questions about your health and any medicines you are currently taking. They will carry out a physical exam and measure things like height, weight, blood pressure and pulse. A urine sample will also be collected from every participant at screening for standard laboratory tests.

Over the course of the study, the study team will continue to check your health regularly by asking you about any changes since the previous visit, and taking standard measurements (blood pressure, pulse etc). If there are any concerns, the study doctor may wish to carry out another physical exam. If your study doctor believes that you should have additional test(s) for your safety, for example, in the event of a new symptom or side effect, you may be asked to come for an additional visit.

The study team will inform your GP/family doctor that you are taking part in this study and may ask them to provide relevant medical information, if required.

### Blood samples

Blood samples will be taken at screening for standard laboratory tests to check that you are well enough to take part in the study. This includes testing for HIV, and hepatitis B and C. If your sample is positive, we may need to contact your GP/family doctor with your permission to arrange for you to be referred to a specialist. In the UK, all cases of viral hepatitis are routinely reported for public health purposes.

Blood samples will also be taken at visits 1, 3, 4, and 5 to look at your immune response (the level and type of antibodies that are created by your immune system against HBV). The total amount of blood taken at any one visit will not be more than approximately 15 mL (4 teaspoons). The total amount of blood taken over the entire study will be about 60 mL (16 teaspoons).

### Pregnancy testing

Women who are pregnant or who intend to become pregnant during the study period will not be able to participate in the study. You will be asked to use appropriate and reliable contraception for the study duration. You should also not be breast-feeding an infant during the study.

If you are a woman who may be able to have children, you will have 4 urine pregnancy tests during the study: at screening and at visits 1, 2, and 3. If your urine pregnancy test is positive, you will have a blood test to confirm if you are pregnant. A negative result must be obtained before you can receive the vaccine. If the pregnancy test is positive we may need to contact your GP/family doctor with your permission to notify of positive test.

### Vaccination

To make the comparison between the different study vaccine lots and the standard vaccine as fair as possible, this study is “double-blinded”. This means that neither you nor the study doctor will know which vaccine you are receiving. If necessary, the study doctor can find out which vaccine you got.

The vaccine you are given will be decided at random by a computer. You will have an equal chance of being assigned to get either lot 1, lot 2 or lot 3 of the study vaccine or the standard vaccine. This means that approximately 75% (3 out of 4 people) will get the study vaccine (lot 1, 2 or 3) and approximately 25% (1 out of 4 people) will get the standard vaccine.

However, everyone who takes part will receive a vaccine designed to protect against HBV. During the study, you will receive 3 injections of the vaccine you were assigned (at visits 1, 2 and 3). These will be given in alternating arms, so if the first dose is given in the muscle of the upper left arm, the second is given in the right arm, and the final dose in the left arm again.

If you are likely to have other vaccinations during the study period, like flu or travel vaccines, please let the study team know, so that they can take this into account when scheduling visits. Other vaccines should not be given within 2-4 weeks of a study vaccination.

### Diary Cards

At visit 1, you will be given a 28-day diary card, a ruler, and an oral thermometer to take home with you. You will be shown how to measure the size of any redness or swelling you might see around the injection site during this period, using the ruler provided. You will be asked to take your temperature on the day of the vaccination and for the next 6 days, using the thermometer given to you. You will also be asked to record the maximum amount of pain, tenderness, and itching you may experience at the injection site on the day of the vaccination and for the next 6 days.

You will be shown how to complete the diary card, and will be asked to bring the completed diary card with you to the next visit, so that the study team can review it with you. You will be given a new diary card to complete when you receive a dose of vaccine (visit 2 and 3), which will be reviewed at the following visit (visit 3 and 4).

### Telephone check-ups

There are four scheduled telephone check-ups as part of the study, one about a week after visits 1, 2 and 3, and a further call 3 weeks after visit 2. You will also be able to contact the study team at any time during the study period if you have any concerns.

You will be provided with an identification card, which says that you are taking part in the study. Please carry this card with you at all times, and show it to any doctors or nurses treating you, for example if you need to see your GP/family doctor or go to A&E for any reason. If you have any signs or symptoms that you see as serious, or if you are hospitalised or suffer any serious illness during the study period, please let the study team know as soon as possible after seeking treatment.

**Do I have to take part in the study? What alternative treatments are there?**

No, it is entirely up to you to decide whether you want to take part or not. There are approved vaccines against HBV available if you would like to protect yourself against hepatitis B disease but don't want to take part in the study. These are currently only offered on the NHS to people at particular risk of contracting hepatitis B disease, but the study team can advise you if you need more information.

**Can I stop being in the study if I change my mind?**

If you decide to take part, you can change your mind at any time and stop being in the study. This will not affect your access to health care. You do not need to give a reason for withdrawing if you don't want to. The study doctor may also decide to withdraw you from the study at any time, if they feel this is in your best interest or if you cannot comply with study requirements. It is also possible that the Sponsor or regulatory authorities may decide to stop the study at any time; if this is the case, the reason(s) for doing so will be explained to you. If any new information becomes available which may influence your decision to continue in the study, you will be told in a timely manner.

If you stop taking part in the study, you will be asked to have the tests, examinations, and follow-up questions described above in relation to "Visit 5". You have the right to refuse these tests and examinations.

If you withdraw your consent for participating in this study, your study data that have already been collected may still be used. Once you have withdrawn, no further data will be collected about you for the purposes of the study unless you agree otherwise, for example, if you agree to have further tests and examinations, in which case these study data may also be used.

**Benefits**

If you take part in the study, you will be vaccinated against HBV (either with the standard or the study vaccine), which should provide protection against hepatitis B infection. Your response to the vaccine (antibodies against the virus) will be measured as part of the study, using the blood samples taken from you. Once the results of the blood tests have been analysed, the study team will contact you to let you know whether your antibody levels were adequate. If you received the study vaccine and your antibody levels are not high enough, you will be offered re-vaccination with the standard vaccine (Engerix-B) at no cost to you.

You may also receive information about your health from the physical exam(s) and other tests done in this study.

The study results could lead to approval by the regulatory authorities for use of the study vaccine in the UK, US, Canada, and the EU. This would mean that there would be a choice of vaccines available for use against HBV.

**Risks**

Blood samples

The taking of a blood sample may cause some discomfort and bruising, and sometimes dizziness or fainting.

### Vaccination

With all vaccines, there is a small chance of an allergic reaction. Symptoms can include swelling of the lips, mouth, throat (which may cause difficulty in swallowing or breathing), rash, swelling of the hands, feet and ankles, dizziness, and fainting. Each time you receive a dose of vaccine, the study staff will observe you for at least 30 minutes afterwards in case of any immediate reaction. You may be asked to stay longer, if necessary, to continue the observation. The study staff are specifically trained and equipped to deal with an allergic reaction, in the unlikely event that it occurs.

Known potential side effects reported so far for each vaccine are discussed below. In addition, there is a possibility that some people might experience other currently unknown side effects that are not listed below.

### Study vaccine

*Common or very common (occurs in 1 in 100 doses or more):* pain, tenderness, itching, redness, bruising, warmth, hard lump and swelling at the injection site; fatigue/weakness; headache; fever or generally feeling unwell; nausea; diarrhoea; sore throat / upper respiratory infection; sensation of warmth / flushing; light headedness / dizziness.

*Uncommon to rare (occurs in less than 1 in 100 doses):* sweating, chills; aching muscles, joints, back, neck or shoulder pain, neck stiffness; vomiting, abdominal pains/cramps, indigestion, diminished appetite; viral infection of the respiratory passages, cough; abnormal sensation of the skin; itching, rash, hives, swelling related to hives (often around your face and lips); lymphadenopathy (a disease affecting the lymph nodes); disturbed sleep; earache; difficulty urinating; low blood pressure.

### Standard vaccine (Engerix-B®)

While serious side effects and long-term illnesses have been reported after vaccination with the standard vaccine (Engerix-B®), no studies have found that these are actually caused by the vaccination. These serious side effects include chronic fatigue syndrome and rheumatoid arthritis, and two diseases that involve destruction of the linings of nerve cells, multiple sclerosis and Guillain-Barré syndrome.

*Common to very common (occurs in 1 in 100 doses or more):* pain, redness, hard lump and swelling at the injection site; irritability; tiredness; headache; drowsiness; dizziness; nausea, vomiting, diarrhoea, abdominal pain, abdominal cramps, constipation; fever, generally feeling unwell.

*Uncommon to rare (occurs in less than 1 in 100 doses):* aching muscles; flu-like symptoms (high temperature, sore throat, runny nose, cough and chills); abnormal sensation of the skin; swollen lymph nodes; loss of appetite; flushing, low blood pressure; rash, itching, hives; allergic reaction; pain in the joints; abnormal liver function tests; low platelets (a type of blood cell); inflammation of the nervous system; seizures; loss of consciousness; inflammation of the eyes; earache, ringing in the ears, vertigo; palpitations, fast heart rate; inflammation of blood vessels; shortness-of-breath, asthma-like symptoms.

### Potential harm to an unborn child

If you are or become pregnant, there may be unknown risks to the baby. If your pregnancy test at screening is positive, you will not be able to take part in the study. During the study, you will have a pregnancy test before each of the 3 vaccine injections.

If you are a woman of childbearing potential, you must use an adequate birth control method throughout the study (from the screening visit until your final visit). Effective birth control includes: hormone-based contraceptive (oral, implant, vaginal, or skin); diaphragm with spermicide; condom (with or without spermicide); intra-uterine devices (IUDs) or coil; vasectomy (sterilisation) of male partner; abstinence from penile-vaginal intercourse (if this is your preferred and usual lifestyle). The study doctor will discuss appropriate methods of birth control with you if relevant.

If you become pregnant or think you may be pregnant during the study, please contact the study team *immediately*. You will be withdrawn from the study. The study team must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you become pregnant during the study, the study team will ask to contact you and your GP/family doctor for information about the pregnancy and the child until 6-8 weeks after the birth.

#### **Who is organising and funding the research? Will I be paid?**

This study is being funded by VBI Vaccines Inc. (the Sponsor) who will pay the Oxford Vaccine Group, University of Oxford for their work on this study.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. This study has been reviewed and given a favourable opinion by North West - Greater Manchester Central Research Ethics Committee.

You will receive £50 per completed visit to compensate you for your time and inconvenience. Reasonable travel expenses associated with taking part in this study, for example to attend visits, will be reimbursed.

#### **What will happen to my samples after the study?**

Unused blood samples will be stored for up to 5 years after the study has been completed, after which they will be destroyed. The samples will be stored at a secure facility in the United States. If, for some reason, the samples must be relocated, they will be moved to another facility in the United States, Canada or Europe.

These samples will only be used if a study-related test needs to be repeated. Genetic testing will not be done. The samples may be destroyed earlier if the study vaccine is approved in the UK, US, Canada, and Europe.

If you withdraw your consent after a blood sample has been taken, the study doctor will arrange to have the samples destroyed. However, if the tests have already been performed, the sponsor is not obliged to destroy the results. In this case, only the sample will be destroyed.

#### **What will happen to the results of the research study?**

The results of this study may be published in a medical journal and presented at medical meetings. You will not be identified in any of these publications.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law, and on the European public website <https://www.clinicaltrialsregister.eu>. These Web sites will not include information that can

identify you. At most, the Web sites will include a summary of the results. You can search these Web sites at any time.

### **Will my participation be kept confidential?**

By signing the consent form you agree to the study team collecting and using your personal information for the study. This includes your year of birth, your gender, your ethnic origin, and information on your health. The sponsor and others working on this study will only use and disclose your information as described in this participant information sheet. All personal information from this study will be treated in accordance with national and local laws governing the protection of personal information and the protection of personal health information. If there any important findings from your medical examination or blood tests (including pregnancy, HIV, hepatitis B or C) then we will write to your GP/family doctor to organise appropriate follow up.

All medical and study records that identify you by name will be kept confidential as far as permitted by law. The study team will have direct access to these records in order to conduct the study; all paperwork will be securely stored for up to 15 years after the end of the study.

Auditors and monitors employed by the Sponsor, a company that has a contract with the sponsor, regulatory bodies such as the Medicines and Healthcare Products Regulatory Agency (MHRA), or the Oxford Vaccine Group may look at these records to check that the information is accurate and ensure the study is being run properly.

The information and samples collected from you during the study will be “pseudonymised”, which means it will be labelled with a unique number assigned to you, not your name. The sponsor and any laboratories testing the samples will only see this number and certain non-identifying information about you such as your gender and your age, but they will not know your name. The master list connecting your name to the number will be retained by the study doctor at the site. The pseudonymised information will be used to support an application for approval to use the study vaccine in Canada, the United States, and Europe.

The sponsor may transfer your (pseudonymised) personal medical and study data to countries outside of the UK for the purposes described in this participant information sheet. The laws in such countries may not provide the same level of protection of personal information as in the UK and may not stop your personal information from being shared with others. The study team, the regulatory authorities, and the sponsor may keep the (pseudonymised) study data indefinitely.

You have the right to request information about your personal information held by the study team and the sponsor, and to ask that any inaccuracies in your personal information are corrected. If you wish to make a request, please contact the study team, who can help you contact the sponsor if necessary. Any request for information must be submitted in writing.

Test results that are part of the study or information on which of the two vaccines you received may not be available to you until the study has been completed and all the results have been analysed. If there is a medical reason why you need this information sooner, the study doctor may be able to find this out earlier.

### **What do I do if there is a problem?**

In the unlikely event that you are harmed during the research you may have grounds for a legal action for compensation against the sponsor or the Oxford Vaccine Group. In both cases, appropriate insurance is in place.

The sponsor will provide compensation for any injury caused by taking part in this research study in accordance with the guidelines of the Association of the British Pharmaceutical Industry where the injury probably resulted from a drug being tested or administered as part of the trial protocol or any test or procedure you received as part of the trial. Any payment would be without legal commitment.

The sponsor is not bound by these guidelines to pay compensation where the injury resulted from a drug or procedure outside the trial protocol or the protocol was not followed.

### **Who can answer my questions about the study?**

If you have questions or concerns about any aspect of this study, you should contact the study team in the first instance (contact details are on page 1). If you are calling after hours or on a weekend, you may contact: the on-call doctor on 078722 969 411.

If you have questions about your rights as a research participant, or if you wish to make a complaint, please contact:

INVOLVE ([www.invo.org.uk](http://www.invo.org.uk)) which is a government funded national advisory group supporting those considering involvement in NHS, public health and social care research. Please feel free to discuss this study before deciding whether or not to participate.

Dr. Maheshi Ramasamy, Principal Investigator, (Tel: 01865 611400, Email: [info@ovg.ox.ac.uk](mailto:info@ovg.ox.ac.uk)) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email [ctrng@admin.ox.ac.uk](mailto:ctrng@admin.ox.ac.uk).

### **What do I need to do now?**

Thank you for taking the time to read this information. If you would like to take part in this study, please contact the study team (contact details are on page 1). If you do not want to take part, you do not need to do anything.

Best wishes,

A handwritten signature in black ink that reads "Maheshi Ramasamy". The signature is written in a cursive style and is underlined with a horizontal line.

Dr Maheshi Ramasamy, Principal Investigator  
**Study Doctor**