Informed Consent to participate in a Phase 1 clinical trial of a therapeutic HSV-2 vaccine

Individuals who suffer with symptoms of recurrent HSV-1 or HSV-2 genital herpes lesions and/or HSV-induced neuralgia are being invited to participate in a Phase 1 clinical trial of an investigational therapeutic HSV-2 vaccine, *Theravax*$^{HSV-2}$. Participants will be asked to (1) donate a small volume of blood on 3 occasions, (2) receive a therapeutic HSV-2 vaccine on 3 occasions, and (3) answer questionnaires before and for 12 months after vaccination. This HSV-2 vaccine may help reduce your genital herpes symptoms. Donated blood samples and your responses to questionnaires will be used by researchers to measure the body's immune response to the HSV-2 vaccine, and to assess its safety and tolerability as a human vaccine.

If you agree to participate in this study, you will be asked to read and sign this informed consent document. Informed consent is a written agreement indicating your willingness to participate. This document will tell you about the purpose as well as risks and benefits of participating in this study. You should consent only after you understand all of the information in this document and have had enough time to decide whether or not you wish to participate.

Your signature on this form is voluntary and does not waive any of your legal rights or make any institutions or persons involved in this study any less responsible for your well-being.

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Phase 1 clinical trial of the *Theravax*$^{HSV-2}$ vaccine

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1. Who is responsible for the *Theravax*$^{HSV-2}$ vaccine trial?

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2. Significance of the Theravax^{HSV-2} vaccine trial

More than 500 million people between the ages of 14 and 49 (>10% of adults) are infected with herpes simplex virus type 2 (HSV-2), which is one of the viruses that causes genital herpes. Approximately 20% of infected persons experience chronic HSV-2 infections that compromise their quality of life. Symptoms may include ***1.*** recurrences of painful clinical lesions, ***2.*** neuralgia which may range from nerve tingling to a chronic burning pain, and ***3.*** distress about the possibility of transmitting HSV-2 infection to others during sex. The current standard of medical care does not adequately address these problems.

The goal of the proposed Phase 1 clinical trial is to explore the possibility that an investigational new treatment, the *Theravax*$^{HSV-2}$ vaccine, is safe and well tolerated and may offer HSV-1 and/or HSV-2 genital herpes sufferers a higher standard of care. This HSV-2 vaccine candidate has been developed by a team of researchers led by Dr. William Halford of Southern Illinois University. The vaccine candidate is a live-attenuated mutant of HSV-2. In pre-clinical animal studies in mice and guinea pigs, the mutant HSV-2 virus, known as HSV-2 0ΔNLS, establishes a self-limited infection in vaccine recipients, but does not cause disease or adverse effects after vaccination.

This clinical trial is being conducted to determine if three intradermal shots of HSV-2 0ΔNLS administered to individuals with pre-existing HSV-1 and/or HSV-2 infection (1) are safe and well tolerated and (2) elicit a therapeutic effect that reduces a participant's burden of genital herpes symptoms including epithelial lesions and/or neuralgia.

Following vaccination with the HSV-2 mutant virus, a recipient's immune system is exposed to nearly all of HSV-2's proteins, which serves as the stimulus that activates and expands the body's population of HSV-2-specific B- and T-cells. Because the HSV-2 mutant virus encodes 99% of HSV-2's proteins, it may engage nearly all of the body's B- and T-cells that are available to confer protection against HSV-2 and to a lesser extent against HSV-1. The 1% of HSV-2's proteins that have been removed from the live HSV-2 vaccine come from HSV-2's "ICP0 protein," and this genetic modification eliminates HSV-2's capacity to cause disease. Individuals vaccinated with the HSV-2 mutant virus may acquire a more protective immune response against wild-type HSV-2, and to a lesser extent against wild-type HSV-1, and this may be associated with fewer symptoms of genital herpes. Extensive pre-clinical studies of the HSV-2 *ICP0*$^{-}$ mutant vaccine strain have been published and are freely available online through PubMed:

- **Halford, W.P.**, R. Püschel, and B. Rakowski. 2010. HSV-2 *ICP0*$^{-}$ mutants are avirulent and immunogenic: implications for a genital herpes vaccine. *PLoS ONE* 5: e12251. PMID: 20808928.
- **Halford W.P.**, Püschel R., Gershburg E., Wilber A., Gershburg S., Rakowski B. 2011. A live-attenuated HSV-2 ICP0 virus elicits 10 to 100 times greater protection against genital herpes than a glycoprotein D subunit vaccine. *PLoS ONE* 6:e17748. PMID: 21412438.
- **Halford, W.P.**, J. Geltz, and E. Gershburg. 2013. Pan-HSV-2 IgG antibody in vaccinated mice and guinea pigs correlates with protection against HSV-2. *PLoS ONE*. 8:e65523. PMID: 23755244.
- **Halford, W.P.** 2014. Antigenic breadth: a missing ingredient in HSV-2 subunit vaccines? *Expert Rev Vaccines* 13: 691–710. PMID: 24837838.
- Geltz, J., E. Gershburg, and **Halford, W.P.** 2015. HSV-2 infected cell proteins are among the most dominant antigens of a live-attenuated HSV-2 vaccine. *PLoS ONE*: 10(1): e116091. PMID: 25658852.
- **Halford, W.P.,** J. Geltz, R.J. Messer, and K.J. Hasenkrug. 2015. Antibodies are required for complete vaccine-induced protection against HSV-2. *PLoS ONE* 10(12): e145228. PMID: 26670699.

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3. Introduction

You are invited to take part in a Phase 1 clinical trial, a type of research study, because you have a history of recurrent HSV-1 and/or HSV-2 genital herpes, which may not be adequately controlled by antiviral drugs such as valacyclovir, famciclovir, or acyclovir. Research is a way of gaining new knowledge. A person who participates in a research study is called a "participant" rather than a patient. This research study is evaluating the *Theravax*$^{HSV-2}$ vaccine being developed by an American company, Rational Vaccines, Inc (RVx).

At least 10 people will take part in this research study. This research consent form explains why this research study is being done, what is involved in participating, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research participant.

The decision to participate is yours and is strictly voluntary. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. We encourage you to take some time to think this over, to discuss it with other people and your doctor, and to ask questions now and at any time in the future.

4. Why is this research study being done?

This research study is a Phase 1 clinical trial. Phase 1 clinical trials test the safety of an investigational new treatment, such as the *Theravax*$^{HSV-2}$ vaccine. "Investigational" means that the *Theravax*$^{HSV-2}$ vaccine is still being studied and that research doctors are trying to find out more about it. It also means that the FDA (U.S. Food and Drug Administration) has not approved the *Theravax*$^{HSV-2}$ vaccine for sale and use in patients, including people with recurrent HSV-2 genital herpes. In the current Phase 1 clinical trial, researchers and doctors are investigating the *Theravax*$^{HSV-2}$ vaccine for its safety, potential to cause toxicity or side-effects, and its capacity to stimulate a therapeutic immune response against HSV-2. This is the first study in which the *Theravax*$^{HSV-2}$ vaccine is being given to humans. The *Theravax*$^{HSV-2}$ vaccine is a genetically modified, and highly attenuated, or weakened, form of HSV-2.

HSV-2 is a virus that usually causes recurrent genital herpes lesions and/or recurring neuralgia (nerve pain) in the nervous tissue emanating from the lower spine. In rare circumstances, HSV-2 can cause severe infections in immunocompromised individuals or may spread to newborns causing an infection of the brain (herpes encephalitis) that is often fatal. The *Theravax*$^{HSV-2}$ vaccine was developed from a HSV-2 virus that encodes a mutated "ICP0 protein," which eliminates HSV-2's ability to cause disease in all species studied to date (mice, guinea pigs, and rabbits).

Injection of vaccine recipients with the live HSV-2 *ICP0*$^{-}$ mutant virus in the *Theravax*$^{HSV-2}$ vaccine is not without risk, but the risks posed by this live HSV-2 *ICP0*$^{-}$ mutant virus are several thousand-fold lower than the risks posed by an infection with the naturally-occurring (wild-type) form of HSV-2. All participants in the *Theravax*$^{HSV-2}$ vaccine trial will have a pre-existing infection with wild-type HSV-1 or HSV-2. The risks posed by the *Theravax*$^{HSV-2}$ vaccine should be many thousand-fold smaller than the risks posed by each participant's pre-existing HSV-1 or HSV-2 infection.

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The primary purpose of this research study is to determine the safety of the *Theravax*$^{HSV-2}$ vaccine in participants who are already infected with wild-type HSV-1 or HSV-2. Participants will receive three intradermal vaccinations containing a live HSV-2 *ICP0*$^{-}$ mutant virus, which is known as HSV-2 0ΔNLS in the published research literature. We are also looking to evaluate (1) your body's antibody response to the *Theravax*$^{HSV-2}$ vaccine and (2) whether you note a reduction in the frequency and/or duration of outbreaks of HSV-1 or HSV-2 genital herpes and any associated symptoms of neuralgia.

If you choose to participate, we will request you complete (1) a *Pre-Vaccination Genital Herpes Symptoms* questionnaire at the outset of the trial, (2) three *Tolerability & Adverse Events* questionnaire about 10 to 14 days after each vaccination, and (3) 12 monthly *Post-Vaccination Genital Herpes Symptoms* questionnaires for a year after the first vaccination. It is anticipated that each of these questionnaires will require 5 to 15 minutes to complete. Because Rational Vaccines (RVx) values your time, we will be offering a $500 compensation payment to all participants who complete 12 of 12 of the *Post-Vaccination Genital Herpes Symptoms* questionnaires.

5. What other options are there?

Taking part in this research study is voluntary. Instead of being in this research study, you have other treatment options which may include the following:

- Do not seek therapy for your HSV-2 genital herpes.
- Take daily antiviral drugs including valacyclovir, famciclovir, or acyclovir.
- Participate in another research study of a therapeutic HSV-2 vaccine.

You may wish to consult with your physician who has helped you manage your HSV-2 genital herpes symptoms in the past, and consider all of your options before you decide whether or not you wish to participate in this research study.

6. What are the potential benefits of participating in the Theravax^{HSV-2} *vaccine trial?*

The primary goal of this Phase 1 clinical trial will be to determine if HSV-seropositive participants, who are already infected with HSV-1 and/or HSV-2, find that three intradermal vaccinations with *Theravax*$^{HSV-2}$ are safe and well tolerated. The second goal of this study will be to determine, based on several blood draws, if the vaccine elicits a significant increase in HSV-2-specific antibody titers, which may (1) correlate with improved host immune control of HSV-2 and (2) which may correlate with improved host immune control of an immunologically cross-reactive virus, HSV-1. The final goal of this study will be to determine if participants note any change in the frequency and/or duration of HSV-1 and/or HSV-2 genital herpes symptoms after receiving the *Theravax*$^{HSV-2}$ vaccine.

Participating in this study may be of medical benefit to you. Information obtained from this study may advance understanding of immune responses to the *Theravax*$^{HSV-2}$ vaccine, and may help advance an effective HSV-2 vaccine into clinical usage around the world. You will not be notified of any results of the research conducted on your blood samples, or the results obtained from other participants in this trial.

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We hope that the *Theravax*$^{HSV-2}$ vaccine series will benefit participants by reducing their genital herpes symptoms. In addition, valuable information will be learned from this study, which may benefit millions of HSV-2 genital herpes sufferers in the future.

7. What are the potential risks of participating in the Theravax^{HSV-2} vaccine trial?

Injection of vaccine recipients with the live HSV-2 *ICP0*$^{-}$ mutant virus in *Theravax*$^{HSV-2}$ is not without risk. However, in pre-clinical animal studies, the risks posed by this live HSV-2 *ICP0*$^{-}$ mutant virus are several thousand-fold lower than the risks posed by a natural infection with wild-type HSV-2. Because all participants in the *Theravax*$^{HSV-2}$ vaccine trial will be HSV-1 and/or HSV-2 seropositive (and thus previously infected with wild-type HSV-1 and/or HSV-2), the risks posed by the *Theravax*$^{HSV-2}$ vaccine should be much lower than the risks associated with being a carrier of wild-type HSV-1 and/or HSV-2. The risks to participants in the *Theravax*$^{HSV-2}$ vaccine trial are summarized:

- **Blood draw -** Risks to participants of the blood draw include pain, bruising and swelling, and infection at the needle insertion site.
- **Privacy and confidentiality -** There is a small risk of loss of confidentiality, but procedures have been planned to ensure the privacy and confidentiality of participants in the *Theravax*$^{HSV-2}$ vaccine trial. Blood samples will be coded with each participant's initials, and participant records will be securely stored on a password protected online server that is only accessible to study personnel.
- **Vaccination:**
  Anticipated side effects after receiving the *Theravax*$^{HSV-2}$ vaccine include (1) replication of the live HSV-2 0ΔNLS virus at the injection site for 2 to 4 days; (2) redness at the injection site lasting up to 7 days; (3) local tenderness and pain at the injection site lasting up to 5 days; (4) malaise and elevated temperature lasting up to 6 days and not to exceed 39 ºC (102.2 ºF); (5) a HSV-2 genital herpes outbreak within 3 to 6 days after immunization triggered by any fever that accompanies the vaccination; (6) local lymph node swelling and tenderness in the groin lasting up to 7 days; and/or (7) neuralgia (nerve pain) similar to what HSV-2 sufferers call "prodrome," but potentially more intense and lasting for up to 7 days post-vaccination.

  Unanticipated or adverse events after receiving the *Theravax*$^{HSV-2}$ vaccine include (1) viral replication at the injection site lasting >10 days; (2) local tenderness and pain at the injection site lasting >10 days; (3) elevation in body temperature lasting >7 days; (4) elevated body temperature exceeding 39.5 ºC (103.1 ºF) within the first 7 days post-vaccination; (5) local lymph node swelling and tenderness in the groin lasting >7 days; (6) generalized, constitutional illness within two weeks post-vaccination; and/or (7) reactivation of the *Theravax*$^{HSV-2}$ vaccine strain that produces a recurrent red lesion at the injection site weeks or months later.

  Relative risk of wild-type HSV versus Theravax^{HSV-2}: In pre-clinical studies, hundreds of animals have been vaccinated with the live HSV-2 0ΔNLS virus in the *Theravax*$^{HSV-2}$ vaccine, and this mutant virus (1) fails to produce symptoms in vaccine recipients and (2) is incapable of reactivating to cause recurrent disease like wild-type HSV-2. Therefore,

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the risk of uncontrolled disease caused by the live HSV-2 0ΔNLS mutant virus in the *Theravax*$^{HSV-2}$ vaccine is several thousand-fold smaller than the risk posed by a pre-existing infections with HSV-1 and/or HSV-2, as will be carried by all participants in this clinical trial.

8. Theravax^{HSV-2} vaccine quality control

The *Theravax*$^{HSV-2}$ vaccine is not an FDA-approved treatment, nor has the *Theravax*$^{HSV-2}$ vaccine been manufactured per the GMP criteria required to initiate an Investigational New Drug application with the FDA (http://www.ispe.org/gmp-resources). While the FDA continues to play a vital role in protecting U.S. consumer safety, the Founders of Rational Vaccines feel the FDA's one-size-fits-all approach to drug approval does not address the needs of millions of HSV-2 genital herpes sufferers.

For example, Rational Vaccines anticipates that >10 years will be required for the *Theravax*$^{HSV-2}$ vaccine to gain FDA approval to proceed to clinical trials in the U.S. During that time, (1) tens of millions of people will continue to suffer with recurrent HSV-2 genital herpes and (2) 100 million people will be newly infected with HSV-2. The *Theravax*$^{HSV-2}$ vaccine represents a potential functional cure for HSV-2 genital herpes sufferers and their seronegative sexual partners who are at high risk for contracting a HSV-2 infection. The current clinical trial seeks to address this possibility immediately rather than letting millions of people suffer while RVx is navigating lengthier, regulatory approval processes.

To ensure that each dose of the *Theravax*$^{HSV-2}$ vaccine is safe and pure, Rational Vaccines has instituted its own strict quality control guidelines which are defined, as follows. Each 0.2-ml dose of the *Theravax*$^{HSV-2}$ vaccine will:

1. be resuspended in a pH-balanced and isotonic solution.
2. be free of bacterial and fungal contaminants.
3. be free of *Mycoplasma* species as defined by polymerase chain reaction.
4. contain less than 0.1% fetal bovine serum.
5. contain less than 0.001% wild-type HSV-2 revertants.
6. contain ~100 million infectious units of the live HSV-2 0ΔNLS vaccine strain.

9. Who is eligible to participate?

The eligible study population will consist of persons who:

- are between the ages of 18 and 64, and who have a valid passport that allows them to travel to the Federation of St Kitts and Nevis.
- are not pregnant.
- are willing to travel to St Kitts on three occasions over a 3- to 4-month period of time.
- are seropositive for HSV-1 and/or HSV-2, as proven by a small blood sample (0.01 - 0.1 ml) submitted to RVx Diagnostic Laboratory.
- self-report experiencing 4 to 30 symptoms per year that are typical of recurrent genital herpes, and which may include visible genital lesions and/or neuralgia (nerve pain) localized to the tailbone.
- are healthy enough to travel and participate in a clinical trial of a live-attenuated viral vaccine. Serious health conditions that would preclude an individual's participation include, but are not limited to, advanced diabetes, AIDS, cancer, chronic hepatitis,

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organ transplant recipient, or any condition that might compromise an individual's immune system.

- are comfortable working with computers, the internet, and who will be able to complete sixteen online questionnaires, which will be integral to this research study.

Should a participant choose to withdraw from the study or fail to return to the clinical trial site for their second or third vaccine doses, an alternate will be recruited to fill the participant's spot. Any participant who fails to timely return for their second or third vaccine shot will be notified by the Principal Investigator that they have been withdrawn from the study and that they may not re-enroll at a later point in time. Assuming that no adverse events are noted, the clinical trial will continue until at least n=10 participants have completed the 3-shot *Theravax*$^{HSV-2}$ vaccination series.

10. Where will the blood draw and vaccination be performed?

Travel to St Kitts

- Rational Vaccines (USA) is, in partnership with a Caribbean Clinical Trial Management firm (Minerva Laboratories, Dominican Republic), conducting a Phase 1 clinical trial of the *Theravax*$^{HSV-2}$ vaccine in St Kitts.
- Participants will fly to the Robert L. Bradshaw airport (RLB) in Bassetere, St Kitts, and will be met by a driver who will transport them from the airport to their hotel and to appointments with the Administering Physician, Dr. Luisa Veloz, at Minerva Laboratories' St Kitts facility.

Why is this clinical trial being conducted in St Kitts?

- The Principal Investigator and company sponsoring this clinical trial, Rational Vaccines, are American-based. Although there exists a regulatory process to gain approval to start U.S. clinical trials of the *Theravax*$^{HSV-2}$ vaccine, this process will likely take >10 years to complete. During that time, over 100 million people will be newly infected with HSV-2. The Founders of Rational Vaccines are committed to curbing the incidence of HSV-2 genital herpes before 2020, and this is not an attainable goal via the U.S. FDA's lengthy approval process. By conducting a Phase 1 clinical trial of the *Theravax*$^{HSV-2}$ vaccine in St Kitts and other Caribbean islands, Rational Vaccines will be able to make a new line of safe and effective HSV-2 vaccines available to HSV-2 sufferers and discordant couples starting in 2017.

Initial Appointment with Administering Physician: Day 0

- Participants will be brought to the Medical Office in Minerva Laboratories St Kitts facility where they will meet with the Administering Physician, Dr. Luisa Veloz
- Before each blood draw and vaccination, participants will be reminded by the Administering Physician that their participation in the *Theravax*$^{HSV-2}$ vaccine trial is strictly voluntary, and they will be asked if they wish to continue participating.
- Participants who wish to proceed will be interviewed about their genital herpes history.
- About 20 ml (about 1 tablespoon) of blood will be drawn from participants.
- Participants will receive an intradermal shot of 0.2 ml of the *Theravax*$^{HSV-2}$ vaccine. The injected liquid will contain the live HSV-2 0ΔNLS virus, and will form a small bubble within the dermis of the skin.

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- Participants will be vaccinated in the skin of the left or right calf such that they may easily observe and/or photograph the injection site in the days following vaccination. This will be important for the participant's ability to assist in the assessment of the tolerability of local symptoms such as the size of the inflamed (red) area and the degree of local tenderness in the days after receiving the vaccine.
- Vaccine shot 1 will be delivered in the skin of the left calf.
- Vaccine shot 2 will be delivered in the skin of the right calf.
- Vaccine shot 3 will be delivered in the skin of the left calf.
- Participants will be instructed to not apply pressure to the injection site (by hand or by tight clothing) for at least one hour post-vaccination.

Follow-Up Appointment with Administering Physician: Day 2

- Each participant will return to the Minerva Laboratories St Kitts facility for a follow-up appointment with Dr. Veloz two days after each vaccine shot.
- Upon this return visit, the Administering Physician will (1) record the participant's temperature and vital signs, (2) discuss any potential side-effects such as fever, local tenderness, and any other symptoms experienced post-vaccination; and will (3) photograph the participant's vaccination site to record the scope of local swelling.
- If the Administering Physician deems that the response to the vaccine is within normal limits, then the participant will be cleared to travel. If the Administering Physician deems that a participant's response to the vaccine constitutes an Adverse Event, then the participant will be asked to remain in St Kitts for two more days at Rational Vaccines' expense, and follow up appointments will be scheduled with the Administering Physician on Days 3 and 4 post-vaccination.

11. Use of antiviral drugs during the Theravax^{HSV-2} vaccine trial

- Participants will need to discontinue anti-herpesviral drugs (e.g., acylcovir, valacyclovir, or famciclovir) at least 72 hours before vaccination and should discontinue these antiviral drugs for at least 7 days after vaccination.
- The *Theravax*$^{HSV-2}$ vaccine contains a live-attenuated virus that needs to complete its growth cycle and engage the body's immune system to achieve the desired therapeutic effect. Antiviral drugs taken during the 10-day window surrounding the vaccination will likely negate the therapeutic effects of the vaccine.
- Avoidance of antiviral drugs throughout the entire 3-shot *Theravax*$^{HSV-2}$ vaccination series will increase the odds that the host immune system may be re-trained to better recognize and control a participant's HSV-2 infection.
- Participants may continue taking other medications including, but not limited to, prescription drugs, herbal supplements, vitamins, etc. The only drugs that are contraindicated and will interfere with the vaccine are the antiviral drugs acylcovir, valacyclovir, or famciclovir, which participants will be advised to avoid if they wish to maximize the opportunity to reprogram their body's immune system to better recognize and control their pre-existing HSV-2 infection.

12. What information will be collected if you participate?

If you choose to participate in this research study, the following information will be collected from you over the 12-month duration of this study.

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A. Personal information and medical history. Information that will be collected from each study participant will include:

- Name, address, age, gender, height, weight, race, citizenship
- Medical history to verify lack of potential complicating factors including, but not limited to, being an organ transplant recipient, being pregnant, or having cancer, HIV infection, or infection with hepatitis B virus or hepatitis C virus.
- Participant's herpes history in terms of (1) duration of infection with HSV-1 and/or HSV-2 and (2) history of herpes antibody testing including HerpeSelect ELISA and/or Herpes Western Blot within the past 7 years.
  - Frequency and average duration of outbreaks of recurrent genital herpes
  - Relative frequency of genital herpes lesions versus neuralgia or other symptoms
  - Past and current use of antiviral drugs such as valacyclovir (valtrex)

B. Online questionnaires. Participants who meet the eligibility criteria and provide their Informed Consent to participate will be enrolled in this research study, and will be asked to complete sixteen 5- to 15-minute questionnaires over the 12-month duration of this study. Specifically, participants will be asked to complete the following questionnaires by logging onto a secure online website.

- *Pre-Vaccination Genital Herpes Symptoms* questionnaire. Participants will be required to complete a questionnaire before their first vaccination appointment is scheduled. This questionnaire will ask participants to report the frequency, duration, and nature of their genital herpes symptoms and/or outbreaks prior to enrolling in this research study.

- *Tolerability & Adverse Events* questionnaire. Participants will be required to complete a questionnaire between 10 to 14 days post-vaccination following their first, second, and third *Theravax*$^{HSV-2}$ vaccine shots. This questionnaire will ask participants about the duration of redness at the vaccination site in the days following vaccination as well as other potential vaccine-induced symptoms such as fever or lymph node (groin) swelling. In particular, participants will be asked if they found those symptoms to be acceptable and well-tolerated, or rather if the level of discomfort after vaccination exceeded a participant's expectation for what was tolerable. Completion of these questionnaires will be required before a participant's second or third vaccination will be scheduled, and completion of these questionnaires will be required for a participant to be eligible for a $500 compensation payment at the conclusion of the trial.

- *Post-Vaccination Genital Herpes Symptoms* questionnaire. Participants will be asked to complete a *Post-Vaccination Genital Herpes Symptoms* questionnaire via a secure online website once per month for 12 months after starting the *Theravax*$^{HSV-2}$ vaccination series. This questionnaire will ask participants to report any changes (or lack thereof) in the frequency, duration, or nature of their genital herpes symptoms and/or outbreaks. In particular, the questionnaire will prompt participants to note (1) whether they have observed an increase or decrease in the duration or frequency of genital herpes symptoms and (2) whether they have engaged in activities that typically trigger an outbreak of genital herpes symptoms, such as consumption of alcohol or certain foods, sunburn, severe cold, menstrual cycle, etc.

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In the event that a participant is unable to complete the electronic questionnaires that they receive by email in the necessary time period, the Principal Investigator, Dr. Halford, will offer participants the opportunity to schedule a phone call to review the questionnaire, and Dr. Halford will record the participant's verbal responses.

C. Blood draws. Participants in this research study will have a small volume of blood (20 ml; about a tablespoon) drawn immediately prior to vaccination. Each participant's blood will be analyzed before and after vaccination for changes in their antibody response to the HSV-2 virus, which may correlate with a therapeutic reduction in HSV-2 genital herpes symptoms. The two tests to be used for this analysis are the (1) HSV Type-Specific ABVIC test developed in Dr. Halford's lab which measures the total antibody response to HSV-2, and (2) a modified Herpes Western blot that assesses the antibody response to several, specific HSV-2 proteins (e.g., gD, RR-1, ICP8, and VP5). It is anticipated that the 3-shot *Theravax*$^{HSV-2}$ vaccination series will elicit an increase in antibody titers against one or more of these dominant protein antigens of the HSV-2 0ΔNLS vaccine.

13. What will happen to your blood samples and information?

Your blood will be drawn at Minerva Laboratories St Kitts facility immediately prior to receiving each shot of the *Theravax*$^{HSV-2}$ vaccination series. Your blood will be processed on-site in a clinical laboratory to obtain 4 aliquots of cell-free serum that will be frozen at -80ºC until shipment. Once your full panel of three serum samples have been collected from your visits to the trial site, ¼ of your serum samples will be shipped to RVx's Diagnostic Laboratory in Springfield, IL (USA) where it will be analyzed in two herpes serology tests (ABVIC and Western blot). Minerva Laboratories will store the remaining ¾ of your serum samples until RVx confirms receipt of the first batch of serum samples to safeguard against loss of serum samples during shipment. Upon confirmation of receipt, the remaining ¾ of serum samples at Minerva Laboratories will be shipped to RVx Diagnostic Laboratories and stored until the *Theravax*$^{HSV-2}$ vaccine has completed its safety and efficacy evaluation testing in human clinical trials around the world.

Regarding your personal information and your answers to the questionnaires, these will be downloaded and removed from the secure online website at the conclusion of the research study, and will be retained on Rational Vaccines' password-protected computers until the *Theravax*$^{HSV-2}$ vaccine has completed safety and efficacy evaluation testing in human clinical trials around the world.

14. Who will pay for my travel and medical costs associated with the trial?

Participants will not have to pay for tests or procedures that are a part of this study. While participants are in the study, they may still require regular medical care. Participants and/or their health care providers will have to pay for the costs of regular medical care that is not a part of this study.

- **Travel costs**: For the first n=10 participants in the *Theravax*$^{HSV-2}$ vaccine trial, RVx will reimburse each participant up to $1,000 per round-trip flight to the RLB airport in Bassetere, St Kitts for a total of three visits; (2) up to 4 nights hotel stay at the Sugar Bay Club Suites & Hotel (http://www.sugarbayclub.com/); and (3) local

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transportation from the airport to the hotel and clinical trial site. In the event that more than n=10 individuals seek to be enrolled in the *Theravax*$^{HSV-2}$ vaccine trial, then those individuals will receive the vaccine as specified herein with the exception that RVx will not be obligated to cover the costs of (1) their airfare or (2) their hotel accommodations in St Kitts. If company funds allow it, RVx will attempt to at least partially defray these travel costs but the company is under no such obligation to anyone other than the first n=10 participants in the *Theravax*$^{HSV-2}$ vaccine trial.

- **Unforeseen medical costs**: Although unlikely, if any adverse events are noted upon a participant's return home, Rational Vaccines will pay for any unforeseen medical costs that may arise as a direct result of the *Theravax*$^{HSV-2}$ vaccination series and this obligation will be true for all up to n=20 trial participants.

15. Will you receive payment for participating in the Theravax^{HSV-2} *vaccine trial?*

Participants who (1) complete the 3-shot *Theravax*$^{HSV-2}$ vaccine series and (2) timely complete all three *Tolerability & Adverse Events* questionnaires will be eligible to receive a $500 compensation payment from Rational Vaccines at the conclusion of the 12-month trial period. The amount of this compensation payment will be proportional to the (3) number of complete responses that participants provide to the 12 monthly *Post-Vaccination Genital Herpes Symptoms* questionnaires associated with this clinical trial. Participants who complete only a fraction of the *Post-Vaccination Genital Herpes Symptoms* questionnaires will receive a corresponding fractional payment. For example, a participant who provides complete responses to 6 of the 12 *Post-Vaccination Genital Herpes Symptoms* questionnaires will receive a compensation payment of $250.

16. How will your privacy be protected?

All of your blood samples will be coded with your initials, and will not bear your name or data that could identify you directly. The purpose of this code is to ensure your confidentiality. It is necessary to maintain a link between your blood samples and your (1) identifying information in the secure online database and (2) your completed questionnaires in the secure online database. Only Dr. Halford (Principal Investigator), Dr. Luisa Veloz (Administering Physician), and essential personnel at Minerva Laboratories will have direct access to your full name, which will be required to enroll you in the trial and make your hotel arrangements in St Kitts. Any information obtained that may identify you will remain confidential. Should public presentations result from this research, your identity will never be revealed.

17. What are your rights as a participant?

Taking part in this research study is voluntary. Should you at any time during the administration of the 3-shot *Theravax*$^{HSV-2}$ vaccination series decide you no longer wish to participate in this research study, you may withdraw your consent to further participate in the study. In such an event, your personal information and blood samples will be discarded.

Participant Initials

You should understand that once you have completed the 3-shot *Theravax*$^{HSV-2}$ vaccination series, any research performed with the information and blood samples you have already provided cannot be withdrawn. If you choose to withdraw your consent to participate in this research study prior to or during the administration of the 3-shot *Theravax*$^{HSV-2}$ vaccination series, then you should submit this request in writing to the Principal Investigator, William Halford, Ph.D., to inform him of your decision. Written requests should be sent via e-mail to halford@rationalvaccines.com.

Should a participant choose to withdraw from the study or fail to return to the clinical trial site for their second or third vaccine doses, an alternate will be recruited to fill the participant's spot. Any participant who withdraws or who fails to timely return for their second or third vaccine shot will be notified by the Principal Investigator that they have been withdrawn from the study, and are no longer eligible to re-enroll in the study at a future point in time. Assuming that no adverse events are noted, the clinical trial will continue until at least n=10 participants have completed the 3-shot *Theravax*$^{HSV-2}$ vaccination series.

If you choose to sign this consent form, you agree to allow the Principal Investigator and Administering Physician to use and/or disclose your protected health information described above with the sponsor of this research study, Rational Vaccines, Inc, and the company managing the clinical trial, Minerva Laboratories.

18. Whom do you call if you have questions or problems?

For questions about this research study, please contact the Principal Investigator, *William Halford, PhD at 217.299.9109 or halford@rationalvaccines.com*. You should also contact Dr. Halford with any inquiries you may have concerning your blood samples, experiences with the *Theravax*$^{HSV-2}$ vaccination series, or to find out more about how to withdraw your consent to participate in this research study.

Participant Initials

AFTER YOUR SIGNATURE IS GIVEN BELOW, A SIGNED COPY OF THIS CONSENT FORM WILL BE PROVIDED TO YOU.

You are voluntarily making a decision to participate in a research study to investigate the safety and tolerability of the 3-shot *Theravax*$^{HSV-2}$ vaccination series described above. Your signature on this form means that you have read and understood the information presented above and have made the decision to participate. Your signature also means that the information on this consent form has been fully explained to you and all your questions have been answered to your satisfaction. If you think of any additional questions you should contact the Principal Investigator.

I agree to take part in this research study.

_____ _____
Signature of Participant **Date**

_____
Printed Name

I certify that all the elements of informed consent described on this consent form have been explained fully to the participant. In my judgment, the participant has voluntarily and knowingly given informed consent and possesses the legal capacity to give informed consent to participate in this research study.

_____ _____
Signature of Principal Investigator **Date**

William P. Halford, Ph.D.
Printed Name

Person Authorized to Obtain Informed Consent from Participants
Principal Investigator, William Halford, PhD, 217-299-9109

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Participant Initials