VIBLOK SAFE Trial Protocol

CLINICAL PROTOCOL
(Clinical Investigational Plan)
Study Number: 2015-01
Revision: Version 5.0
Date: 01/MAY/2017

Product name: VIBLOK

Investigation Sponsor: CLJI WORLDWIDE
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REVISION HISTORY			
Change #	**Version**	**Change Description**	**Date**
-----	1.1	Initial version	29-Jun-2016
1	1.2	Correction sample size estimates. Alignment swab instructions with materials. Clarification exploratory parameters. Added sentence on aim to enrol equal amount of men and women.	18-Jul-2016
2	1.3	Clarified project scope, improved swabbing instructions for men, aligned instructions with IFU.	20-Jul-2016
3	2.0	Rephrasing of study participant follow-up, sentence how to ensure equal enrolment of both sexes, and the exploratory objective with respect to HSV-2 and HSV-1 co-infection.	22-Jul-2016
4	3.0	Better alignment phrasing primary study endpoint throughout the protocol (28 days -> minimally 26 days). Improved specification of secondary endpoints (HSV -> HSV-2 DNA). Removed exploratory objective on HSV-1 as chances for simultaneous shedding in the external genital area are minimal. Rephrased inclusion criterion #3, to ensure proper understanding on what antiviral therapy is meant. Added inclusion criterion on willingness to use contraceptive throughout the study, to prevent any pregnancy after screening. Removed HIV serology measurement at screening to avoid any unnecessary ethical dilemmas. Added follow-up call with study participants 2-5 days after visit 1, to ensure proper understanding and execution of study procedures. Changed instructions for the 2nd swab from 15-60 to 5-60 minutes after applying the cream to better align with the intended use. Removed the redundant red circle indicating the swabbing area for men. Rephrased the section concerning the treatment in case of a recurrence, to clarify that participants will receive standard of care treatment via the usual health care channels. Changed instructions on storage of samples from in the refrigerator to at room temperature.	08-Sep-2016
5	4.0	Statistical sections concerning the primary and secondary endpoints have been improved upon EC (IRBN) questions. Risk evaluation concerning possible risks and mitigation associated with study procedures has been added upon EC questions. Additional instructions for study participants to wash hands (and to complete the diary) after taking the samples has been added.	18-Oct-2016

6	4.1	Typo statistical sections corrected	24-oct-2016
7	4.2	Adjustment VIBLOK package information (sachet instead of Easysnap).	02-Jan-2017
8	4.3	Adjustment VIBLOK package information (figure 1): change from 4.25 g to 5 ml due to different package. Changed wording in inclusion criteria from drug to device. Change address CLJI Worldwide.	01-Mar-2017
9	4.4	Added the study procedure external genital exam for unscheduled visit and added for women possible internal genital exam at V1, V2, V3 and unscheduled visit. Added sentence that pregnancy test and use of contraceptives is not applicable for women that are more than 1 year post-menopausal.	30-Mar-2017
10	5.0	Raised number to be enrolled from 48 to 84 due to high number of subjects enrolled turning out being HSV-2 negative.	01-May-2017

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Study Synopsis

Title	CLJI VIBLOK SAfety and perFormancE Trial (SAFE Trial)
Background	Genital herpes has a high prevalence in industrialized as well as developing countries. Genital herpes causes genital ulcers, increases risk for acquiring HIV infection, and may be transmitted mother to child during birth with possible serious consequences. Medical treatments and condoms only partially reduce the risk for transmission from/ to sexual partners. Genital herpes transmission despite use of condoms is thought to be due to transfer via skin-to-skin contact in unprotected areas, and HSV-2 transmission may be enhanced by current shaving habits in the genital area leading to micro lesions (lacerations) of the skin. VIBLOK™ is a cream designed to impede the passage of viruses, such as HSV-2, across the skin. Bench and animal experiments indicate that it can block virus transmission (HIV, HPV, HSV) up to 98%. The objective of this clinical trial is to assess the safety and performance of VIBLOK in adults with HSV-2 infection by comparing virus detection in the extra-genital area before and after application of the barrier cream.
Primary objective	To assess safety of VIBLOK in HSV-2 infected adults.
Secondary objective	To evaluate the performance of VIBLOK as a barrier for virus transmission in men and women.
Study design	The VIBLOK SAfety and perFormancE Trial is a prospective, non-randomized, comparative multi-center safety and performance study. Up to 84 adults with a suspected HSV-2 infection are planned to be enrolled at up to 6 participating investigational centers in The Netherlands and Germany. Participants with a confirmed HSV-2 infection are planned to be followed for 26-31 days, using VIBLOK for minimally 26 days in a row. Safety will be assessed by collecting all adverse events, and HSV will be measured from daily self-collected external genital swabs before and after application of VIBLOK.
Study device	VIBLOK cream
Study scope	Minimally 1 and maximally 6 sites in The Netherlands and Germany are

	planned to participate in this study.
Study duration	The study is anticipated to last 12 months from first-subject-in to last-subject-out. Study participants are planned to be followed for 26 to 31 days.
Study Population	Adults with recurrent genital HSV-2 infections that meet all the inclusion and none of the exclusion criteria.
Number of subjects	Up to 84 men and women are to be enrolled, ensuring 46 participants with confirmed eligibility applying VIBLOK.
Inclusion Criteria	1. Participant is male or female and at least 18 years of age 2. HSV-2 seropositive by the UW Western blot or Alegria assay 3. History of recurrent genital herpes with at least 3 recurrences in the last year or, if currently on suppressive/ prophylactic therapy, prior to starting the therapy (antiviral therapy has to be stopped at least 7 days prior to initiation of the trial product). 4. General good health at the discretion of the investigator. 5. Willing to not use any topical genital therapy aside from the study device for the duration of the trial. 6. Willing to not use any systemic anti HSV therapy during the entire study starting 7 days prior to baseline. 7. Willing to obtain 2 swabs from external-genital areas once daily for the duration of the trial. 8. Willing to keep a daily trial diary during the treatment period. 9. Negative pregnancy test for women at screening. 10. Willing to use contraceptives for the duration of the study. 11. Subject must be willing and able (in the opinion of the investigator) to understand the patient information and informed consent form and to comply with the clinical trial protocol and procedures. 12. Subject must be willing to give written informed consent.
Exclusion Criteria	1. Serious medical conditions, such as diabetes, significant autoimmune disease, cancer or immunosuppression, etc. that at the discretion of the investigator will likely affect study outcomes 2. Treatment with systemic steroids or other immune-modulating agents 3. Participation in any investigational drug or device trial within 30 days prior to screening. 4. Pregnancy or breastfeeding, in case of women. 5. Any other conditions that in the judgment of the investigator would preclude successful completion of the clinical trial.
Primary Endpoint	Serious Adverse Device Effect incidence during the period using VIBLOK cream.
Secondary	• Comparison of HSV-2 DNA detection rate on days with asymptomatic

Endpoints

shedding prior and after applying VIBLOK

- Comparison of HSV-2 DNA copy number on days with asymptomatic shedding prior and after applying VIBLOK
- Safety (Nature, frequency, duration, severity, seriousness and causality of adverse events)

Exploratory Parameters

- Sub-analyses to explore relation of device performance to
  - Gender
  - Time between VIBLOK application and sampling
  - Shaving and waxing habits
  - HSV symptoms
- Participant satisfaction using VIBLOK as assessed on the participant questionnaire

Assessments

	Treatment Period				
Activity	**Screening**	**Visit 1**	**FUP call**	**Visit 2**	**Visit 3**
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Medical History (including HSV history)	X				
Interim History (including HSV history)		X		X	X
Targeted Physical Exam (including external genital exam)	X	X*		X*	X*
HSV serology	X				
Urine pregnancy test	X				
Provide Study Device and/or training		X	X	X	
Review device use adherence				X	X
AE assessment		→			
User Questionnaire					X
Daily Swab Collection & Diary		→			

* for women possibly including internal genital exam if symptomatic

Subject visits

Visit	Exams	Visit window
0	Screening	Subject information and consent
1	Day 1	<21 days after ICF sign off
N/A	Day 3	2-5 days following visit 1
2	Day 14	12-16 days following Visit 1
3	Day 28	26-31 days following Visit 1

Statistical analyses	With a sample size of 36, an exact two-sided 95.0% confidence interval for a single proportion will show that the SADE incidence is below 10% at an expected incidence of 0.1%. Taking into account a drop-out rate of 15%, the estimated sample size needed is 42 study participants applying the VIBLOK cream. Comparing HSV-2 detection within participants before and after applying VIBLOK using Wilcoxon signed rank testing, with an 8% anticipated asymptomatic shedding rate, 80% power and type I error of 5%, 40 participants are needed to show a 50% reduction post-intervention (VIBLOK). Taking into account a drop-out rate of 15%, up to 46 adults applying VIBLOK cream are needed. Taking into account a screenfailure rate of 45% due to absence of an HSV-2 infection, up to 84 subjects will need to be enrolled.
Study Steering Committee members	Prof. C. Boucher, Prof. A. Wald, Dr A. Wensing, Dr A. Muetstege, and Dr C. Lichtblau.
Coordinating Investigator	Dr V. van de Walle, MD, PhD, CPI. PT&R, Elsstraat 47, 6191 JW Beek The Netherlands
Study Sponsor	CLJI Worldwide, 1141 Kane Concourse, Suite 203, Bay Harbor Islands, Florida 33154

1. Introduction

1.1. Study Purpose

The purpose of this trial is to assess the safety and performance of the CLJI VIBLOK cream in HSV-2 infected adults. Clinical safety and performance data will be submitted for the purposes of obtaining CE marking approval. Following CE mark approval, the subsequent clinical follow-up will continue to fulfill the post-market safety and surveillance reporting commitments.

1.2. Clinical Background

Sexually transmitted viral infections (viral STIs) have a high prevalence in industrialized as well as developing countries. They are associated with substantial morbidity and mortality, as well as a high risk for transmission from mother to child during birth. Genital lesions due to herpes are often painful, and can lead to substantial psychological morbidity [1]. The virus can also be passed from mother to child during birth, and neonatal infection can be very serious [2]. Without treatment, 80% of infants with disseminated disease die, and those who do survive are often brain damaged [3].

In addition, genital herpes is associated with an increased risk of HIV acquisition by two- to threefold, HIV transmission on a per-sexual act basis by up to fivefold, and may account for 40–60% of new HIV infections in high HSV-2 prevalence populations [4–9]. Indeed, the impact of suppressing HSV-2 shedding and associated disease on the rate of HIV acquisition has been tested in clinical trials using suppressive antiviral therapy, with disappointing results [10].

The most common STI encountered in practice are herpes simplex virus (HSV), type 1 and 2. Despite increased strategies to enhance patient awareness regarding safer sex practices and the liberal prescription of various antiviral medications like valacyclovir and acyclovir, the incidence of HSV infections has not decreased significantly in the last 2 decades.

Virologists have long known that the HSV may well gain entrance to the host by fissures and lacerations in the skin [11]. These lesions oftentimes are imperceptible to the host. The defects in the intact skin may be produced during common grooming practices or, as a result of friction during sexual intercourse. Condoms have been shown to reduce the risk of transmitting HSV; however, significant transmission occurs from skin to skin contact not shielded by the condom [12].

1.2.1. Disease Process

HSV-2 infection is acquired through direct contact with an active lesion or body fluid of an infected person principally through sexual activity. Herpes transmission occurs between discordant partners; a person with a history of infection (HSV seropositive) transmits the virus to an HSV seronegative person, the virus travels retrograde in the sensory nerves to establish a latent infection primarily in the sacral ganglia. Data suggest that the virus may reach ganglia far removed from the site of primary infection. The molecular mechanisms underlying HSV latency are incompletely understood [13].

1.2.2. Alternative Therapies/Techniques

No method eradicates the herpes virus from the body, and disease management focusses on symptom relief, healing of the lesions, reducing recurrent episodes, and reducing viral transmission. Episodic treatment with antiviral medications, such as valacyclovir and acyclovir, has shown to reduce the duration, and severity of outbreaks. Acyclovir and valacyclovir therapy has shown to reduce the duration of viral shedding, and time to healing of the lesions with days [4, 14-15].

Treatment of HSV is complicated by the fact that many people infected by HSV may not be aware they are shedding: Asymptomatic viral shedding rates have been reported to occur on up to 25% of days in HSV-2 seropositive patients [16]. Antiviral medication also reduces the frequency of asymptomatic shedding of HSV in the genital tract when used as suppressive therapy up to 80% [17-18].

Several clinical trials have tested vaccines against genital herpes infection, but there is currently no commercially available vaccine that is protective against genital herpes infection.

Condom use also reduces the transmission risk significantly; Condom users are reported to have a 30% lower risk of HSV-2 acquisition compared to those who never used condoms. That being far less when compared to the HIV acquisition rate, is explained by the fact that HSV-2 is primarily transmitted through direct skin-to-skin or skin-to-mucosa contact, and HSV-2 transmission can occur when viral shedding is present in areas not covered by the condom [12, 19]. A recent study in discordant couples where condom efficacy was measured on a per act basis indicates there is a sex differential protective effect: risk of transmission from men to women can be reduced as high as 96% with condom use, but only to 65% from women to men [20].

The above clinical data indicate that the VIBLOK cream can be a valuable addition to the current treatment and preventative strategies.

2. Study Device

VIBLOK is an over-the-counter, non-sterile, single use medical device which is designed to impede the passage of viruses across the skin, such as HSV (herpes simplex virus), by creating a mechanical barrier on the skin. This barrier is achieved as a result of a compound cream which covers the desired area that is to be protected.

2.1. Device Description

VIBLOK is a medical device, applied on the external genital, pubic, and perianal areas of men and women prior to sexual activity in order to cover minor cuts, scrapes and irritations of the skin including the ones associated with grooming of these areas, and to help protect against STIs caused by viruses such as Herpes Simplex. The main ingredients of the cream are a water repelling, high weight, silicone and a water repelling surface treated zinc oxide, similar to the zinc oxide used in diaper rash creams.

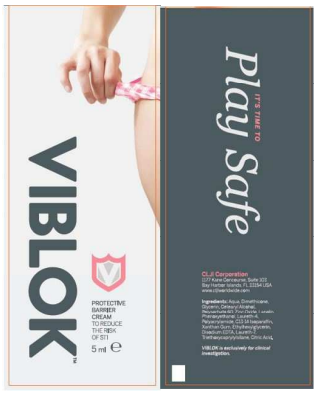

Figure 1 – VIBLOK cream package

The VIBLOK cream is supplied for single-use only, and is packaged in a sachet (Figure 1).

The VIBLOK cream is intended to be applied before sexual activity to all external genital, pubic, and perianal areas – with or without hair -, hereinafter referred to as “skin”, that will come in contact with the partner.

The CLJI VIBLOK cream shall be used per the Instructions for Use (IFU) and after training has been achieved as determined by the study sponsor. Further description of the VIBLOK cream is provided in the IFU and the Investigator’s Brochure (IB).

2.2. Prior Non-Clinical Testing

Results of the *in vitro* and *in vivo* animal testing support the safety and performance of the VIBLOK cream. Further details are provided in the IB.

2.3. Clinical History

The VIBLOK cream has been evaluated for its irritation/ sensitization potential in human subjects with 53 enrollments. The study provides data on 10 consecutive 24 hours product exposures in 3 consecutive weeks, followed by another 48 hours exposure on a previously unexposed test site in 50 subjects. No adverse reactions of any kind were noted during the course of the study.

3. Study Objectives

The objective of the study is to assess the safety and performance of the VIBLOK cream in HSV-2 infected adults. It is expected that data from this study will support an application for the CE Mark.

3.1. Primary Endpoint

The primary safety endpoint will be number of Serious Adverse Device Effects during minimally 26 days of VIBLOK use.

3.2. Secondary Endpoints

Device performance:

- Comparison of HSV-2 DNA detection rate on days with asymptomatic shedding prior and after applying VIBLOK
- Comparison of HSV-2 DNA copy number on days with asymptomatic shedding prior and after applying VIBLOK

Safety endpoints:

- Total number, type, and duration of AEs after 24 days of VIBLOK use.

3.3. Exploratory Parameters

- Sub-analyses to explore relation of device performance to
    - Gender
    - Time between VIBLOK application and sampling
    - Shaving and waxing habits
    - HSV symptoms
- Participant satisfaction using VIBLOK as assessed on the participant questionnaire (appendix 5).

4. Study Population

Participants will be screened and selected from men and women with a (suspected) HSV-2 infection.

For the sake of the sub-analysis on a possible relation of device performance to gender, an effort will be made to enroll an equal amount of men and women. Therefore enrolment will be tracked to ensure enrolment of a minimum of 16 participants of the less represented sex.

4.1. Inclusion Criteria

Candidates for this study must meet ***all*** of the following inclusion criteria:

1. Participant is male or female and at least 18 years of age
2. HSV-2 seropositive by the UW Western blot or Alegria assay
3. History of recurrent genital herpes with at least 3 recurrences in the last year or, if currently on suppressive/ prophylactic therapy, prior to starting the therapy (antiviral therapy has to be stopped at least 7 days prior to initiation of the trial product).

4. General good health at the discretion of the investigator.
5. Willing to not use any topical genital therapy aside from the study device for the duration of the trial.
6. Willing to not use any systemic anti HSV therapy during the entire study starting 7 days prior to baseline.
7. Willing to obtain 2 swabs from external-genital areas once daily for the duration of the trial.
8. Willing to keep a daily trial diary during the treatment period.
9. Negative pregnancy test for women at screening.
10. Willing to use contraceptives for the duration of the study.
11. Subject must be willing and able (in the opinion of the investigator) to understand the patient information and informed consent form and to comply with the clinical trial protocol and procedures.
12. Subject must be willing to give written informed consent.

4.2. Exclusion Criteria

Candidates for the study will be excluded if ***any*** of the following conditions are present:

1. Serious medical conditions, such as diabetes, significant autoimmune disease, cancer or immunosuppression, etc. that at the discretion of the investigator will likely affect study outcomes
2. Treatment with systemic steroids or other immune-modulating agents
3. Participation in any investigational drug or device trial within 30 days prior to screening
4. Pregnancy or breastfeeding, in case of women
5. Any other conditions that in the judgment of the investigator would preclude successful completion of the clinical trial.

5. Investigational Plan

5.1. Study Design

This is a prospective, non-randomized, comparative multi-center safety and performance trial. Up to 84 participants are planned to be enrolled at up to 6 participating investigational centers in Europe. The enrollment period is expected to be approximately 11 months and participant follow-up for subjects with a confirmed HSV-2 infection will last for 26 to 31 days. Participants will be assessed at the following intervals: at screening, during the first application, and approximately 14 and 28 days after first application.

Fourty six adults with recurrent genital herpes due to HSV-2 will be instructed to apply daily VIBLOK. Participants will obtain external genital skin swabs once daily, before and 5-60 minutes after applying the cream in the external genital area, and maintain a diary of genital signs and symptoms (Figure 3 and 4, Appendices 2, 3, and 4).

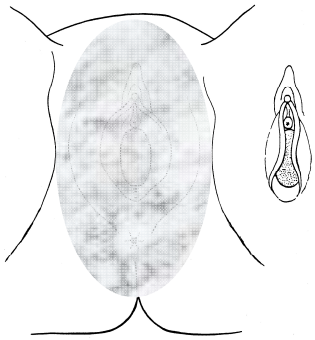

Figure 3: Female genitals with the VIBLOK application area (grey)

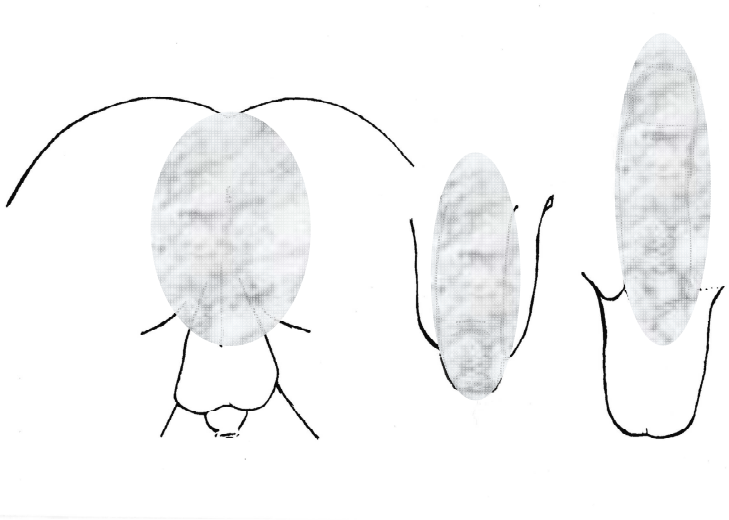

Figure 4: Male genitals with the VIBLOK application area (grey)

5.2. Study Procedures

5.2.1. Informed Consent

The study investigator(s) and support staff will approach adults with (suspected) HSV-2 infection to assess their interest in participating in the study. If the potential participant is interested, they will be provided with the informed consent and the study background,

benefits, risks and study procedures will be explained. If the potential participant is comfortable with proceeding, then they will be asked to sign the approved informed consent, and subject screening will commence. Informed consent must be obtained prior to any screening procedures or tests that are specific to this study.

If new information becomes available that can significantly affect a participant's future health and medical care, then that information will be provided to the participants in written form.

5.2.2. Participant Screening - Visit 0-1

The screening of potential participants will be conducted by one or more study team members. The site research team will be responsible for ensuring and reporting screening of men and women for study eligibility. Cumulative screening and enrollment logs will be maintained by research sites. Reasons for screen failures will be documented in study logs.

All anti-viral therapies shall be stopped minimally 7 days prior to Visit 1.

Women that are more than 1 year post-menopausal will be considered as having no child bearing potential, and the pregnancy test and use of contraceptives is not applicable for them.

Table 2 lists the schedule of events for participants from the initial screening and baseline measures through their bi-weekly follow-up visits. These measures are more fully described in the subsequent sections.

Table 2. Schedule of Events

	Treatment Period				
Activity	**Screening**	**Visit 1**	**FUP call**	**Visit 2**	**Visit 3**
Informed Consent	X				
Review Inclusion/Exclusion Criteria	X				
Medical History (including HSV history)	X				
Interim History (including HSV history)		X		X	X
Targeted Physical Exam (including external genital exam)	X	X*		X*	X*
HSV serology	X				
Urine pregnancy test	X				
Provide Study Device and/or training		X	X	X	
Review device use adherence				X	X
AE assessment		→			
User Questionnaire					X
Daily Swab Collection & Diary		→			

* for women possibly including internal genital exam if symptomatic

The following screening data will be collected for all study subjects prior to enrollment to assess possible eligibility:

- Medical history, standard of care physical examination, including external genital exam

A subject will be considered as "enrolled", once (s)he has signed the Informed Consent. Study

specific data will not be collected for subjects who fail any of the eligibility criteria and do not apply the study product; these subjects will be recorded on a Screening Log where the reason for screening failure will be documented.

5.2.3. Treatment start - Visit 1

Once participant's eligibility is confirmed, i.e. HSV-2 serology is positive, select assessments and laboratory tests will be done prior to document baseline status. These include:

- Physical examination, including a genital examination that for women may include an internal genital examination if symptomatic;
- (Interim) medical history;
- Urine pregnancy test;
- Adverse Events assessment

After the examination, the participant will receive instructions by the site research staff as to how to take swabs and to apply VIBLOK, watch the instruction video, and subsequently takes the first swab, applies VIBLOK, and takes a second swab 5-60 minutes after applying VIBLOK while at the research site. These procedures will be monitored by one person from the site research staff to ascertain that the cream was applied correctly and that the swabs were obtained in the right way. Participants will also be instructed in how to label the swabs and vials. Once the swabbing procedures are correctly done, the participant will be provided the following:

- The study device along with instructions for use;
- The swabbing kits along with instructions for use;
- Diary.

Participants with a negative HSV-2 serolgy will be considered screen failures and exit the study.

5.2.4. Treatment - Follow-up call

Two-five days after visit 1, participants will receive a follow-up call by some-one from the site research staff to verify that participants have a full understanding and no remaining questions concerning the study procedures, specifically with respect to:

- Swabbing procedures
- Application of the VIBLOK cream
- Completion of the diary

In addition, any AEs will be recorded.

5.2.5. Treatment – Visits 2 and 3

During the treatment periods, participants should:

- Complete their diary daily;

- Take swabs daily, before and 5-60 minutes after applying the cream on the external genitals according to the instructions;
- Visit the clinical trial site every other week

Clinical trial site visits will occur approximately 14 and 28 days after Visit 1.

During the clinic visits the following examinations/ evaluations and procedures will be done by site research staff:

- Adverse Events review;
- Targeted physical examination, including a genital examination that for women may include an internal genital examination if symptomatic;
- (Interim) medical history;
- Review and collection of subject's diary;
- Collection of subject swabs;
- Device accountability;

New trial devices and diary will be provided during Visit 2.

During Visit 3, subjects will be asked to complete a questionnaire regarding the usability of the cream (refer to Appendix 5).

5.2.6. Genital herpes recurrence – Unscheduled visits

If a lesion develops that is consistent with genital herpes, swabs should be obtained from the lesion. Participants who have such a recurrence (i.e., papules, vesicles or pustules, ulcers,or crusts) during the treatment period are requested to contact and return to the clinic for an examination as soon as possible. That examination includes a genital examination, and for women may include an internal genital examination.

In case of a recurrence, participants will be instructed to apply their usual treatment or refer to their treating physician whichever is applicable, in order to receive treatment per standard practice. If the subject is successfully treated within 21 days, and meets the inclusion criteria and none of the exclusion criteria, subject may re-enter the study. The concerning follow-up period is prolonged with the number of days the treatment required. These visits shall be recorded as an unscheduled visit.

In case of a second recurrence, the subject shall exit the study.

5.3. Follow-Up Visits

Visit	Exams	Visit window
0	Screening	Subject information and consent
1	Day 1	<21 days after ICF sign off
N/A	Day 3	2-5 days following visit 1

2	Day 14	12-16 days following Visit 1
3	Day 28	26-31 days following Visit 1

Upon Visit 1 and at each follow-up assessment, study staff will confirm the participant's availability for future follow-up and an appointment for the follow-up call will be made.

Planned absences from the area should be recorded to facilitate continued ability to contact a study participant. If a participant cannot be reached for a follow-up visit, the investigator will document on the follow-up data form, the efforts undertaken to contact the participant, referring physicians, family members, or other alternate contacts noted in the study participant's records. These efforts should include 3 attempts of telephone contacts at separate dates and times, and a registered letter.

If the participant cannot be reached in any way for their follow-up visits and misses the scheduled visit, new efforts will be undertaken to locate them at subsequent follow-up visits for safety purposes.

5.3.1. Missed Visits

Participants who miss a follow-up visit will not be considered to be withdrawn from the trial and contact with the participant should continue to be established for the follow-up examinations if applicable. Every participant that started applying VIBLOK, should be encouraged to remain in the study until they have completed the protocol-required follow-up period. If the participant discontinues prematurely from the study, the reason for discontinuation must be documented on the appropriate case report form (CRF). Possible reasons for premature discontinuation may include, but are not limited to the following:

- Withdrawal of consent: Participant decides to withdraw from the study. If a participant withdraws from the clinical investigation, the reason(s) should be recorded. If such withdrawal is due to problems related to the investigational device safety, the investigator shall ask for the participant's permission to follow his/her status/condition outside the investigation.
- Lost to follow-up – All participants should be encouraged to return to the clinic for evaluation during follow-up. If a participant is unable to return to the clinic, 3 separate telephone calls (or emails) should be made to attempt to bring the participant back into the clinic or obtain safety information. All attempts should be documented in the source documents. If the participant does not respond to the 3 telephone calls then the Investigator should send a certified letter to the participant. If applicable, a new round of attempts to contact the participant for return to the clinic for evaluation should be made when the subsequent visit is due.

Patients who discontinue prematurely will be included in the analysis of results, and will not be replaced.

5.3.2. Study Termination

The Data Monitoring Board and Sponsor have the right to discontinue a site or terminate the trial for the following reasons:

- The DMB and Sponsor may terminate the study for safety reasons
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for any reason
- The Sponsor may decide to close a study site when the Investigator fails to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Insufficient adherence to protocol requirements
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority

If the study is terminated early, all specified follow-up data on participants enrolled prior to termination will be collected and reported.

6. Study Material & Methods

6.1. Study Device

Investigational devices will be supplied to the research site by DelaRange on behalf of CLJI. The trial devices will be labeled as Investigational Use Only (specific language will vary based on geography). Each device will have a unique product identifier, and this information will be included both in the participant's medical file as well as given to them after the procedure. The Instructions for Use for the VIBLOK cream are provided.

6.2. Storage & Labeling

The VIBLOK cream is to be stored as specified on the unit labels, and in a secure location where only study personnel can access the device for use. The VIBLOK cream will be appropriately labeled to identify their investigational nature.

6.3. Device Accountability

The Investigator shall maintain records of the receipt and disposition of the investigational device. A device disposition log supplied by CLJI to the research site will be used to record devices received from DelaRange, participant hand-out, use, and discards, and devices returned to DelaRange. The participants should return all devices, including emptied packages to research site, and the Investigator shall return to CLJI used and unused devices/ packages, along with the completed device disposition log at completion of the investigation. Use of the VIBLOK cream is prohibited outside of this protocol.

Device disposition will be verified by the clinical monitor periodically throughout the study.

7. Evaluation of Safety

7.1. Definitions

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

A Serious Adverse Event (SAE) is any adverse event that:

a) leads to death

b) leads to a serious deterioration in the health of the subject that

1. results in a life-threatening illness or injury
2. results in a permanent impairment of a body structure or a body function
3. requires in-patient hospitalization or prolongation of existing hospitalization
4. results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function

c) leads to fetal distress, fetal death, congenital abnormality or birth defect

Adverse Device Effects and Serious Adverse Device Effects are those AEs and SAEs that occur as an untoward or unintended response to a medical device. These events include those which result from insufficiencies or inadequacies in the Instructions for Use or deployment of the device as well as user error.

Unanticipated Serious Adverse Device Effect (USADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, Investigator's Brochure, informed consent form or other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of subjects.

Adverse events may be volunteered by participants, elicited from questioning by Investigator or designee, or collected via observation by the Investigator. In addition, participants will be instructed to contact the investigator, and/or study coordinator if any significant adverse events occur between study evaluation visits.

7.2. Adverse Event Assessments

The Investigator will determine whether or not the event is related to the device and/or procedure, and whether or not the event meets serious criteria. Pre-existing medical conditions or symptoms reported prior to the participant's enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition or symptoms then an AE must be recorded.

If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the study AE Form The causal relation of the event to either the investigational device or to the procedure will be categorized by the Investigator as follows:

None – AE is not associated with the investigational device or procedure.

Remote – AE had minimal or no temporal relationship to the use of the investigational device and/or a more likely alternative etiology exists.

Possible – AE had a strong temporal relationship to the use of the investigational device or procedure and there is no contradicting evidence that can reasonably explain the subject's condition.

Probable or Definite – AE had a strong temporal relationship to the use of the investigational device or procedure and another etiology is highly unlikely.

All AEs will be reviewed by the Study Safety Officer. The AE will be assessed as to its seriousness and relationship to the device, the procedure, and whether it was anticipated or not anticipated.

7.3. Device Deficiency

Device deficiency is an inadequacy of a medical device with respect to its integrity, quality, durability, reliability, safety or performance. It includes malfunctions, user errors and inadequate labeling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

a) If either suitable action had not been taken,
b) If intervention had not been made, or
c) If circumstances had been less fortunate.

Reporting conventions for device deficiencies that could result in an SAE are the same as those for an actual SAE.

7.4. Adverse Event Reporting

AEs are reported beginning from enrollment until participant participation has ended (i.e. completion of study or withdrawal of consent). Adverse events must be followed until resolution, AE has stabilized, or the study has been completed.

All Serious Adverse Events (SAE) must be reported to CLJI Worldwide within 24 hours of the Investigator becoming *aware* of the event or according to local regulations (whatever is more stringent). Information may be entered into the electronic adverse event form or reported directly to the Safety Officer of CEpartner4U:

Ton Pennings

Phone: +31 (0) 343 444 875
Cell: +31 (0) 6 516 536 26

Fax: +31 (0) 343 442 162
e-mail: t.pennings@cepartner4u.com

At the time of initial notification, the following minimal information must be provided:

- Identifiable participant: participant number
- Identifiable reporter: study site
- Adverse event description
- Causal relationship to device and procedure
- Awareness date

The site will provide to CLJI Worldwide (or designee) a copy of anonymized supporting documentation (such as hospital record, laboratory results, autopsy results) of all SAEs.

SAEs will be reported to the ethics committee (EC) and regulatory authorities as required by national regulations or by the EC itself.

All SADEs must be reported to CLJI Worldwide within 24 hours of the Investigator becoming aware of the event or according to local regulations (whatever is more stringent). The AE Forms of the CRF must be completed with 5 working days for all SADEs. The Investigator is also responsible for notifying his/her EC of all SADEs occurring at his/her site (and any additional information as required by EC or local regulations). All SADEs must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the SADE must be recorded.

CLJI will notify all participating clinical Investigators, ECs, and competent authorities as necessary of all SADEs that occur during this study within with the specified reporting time after he/she first receives notice of the effect. Investigators are responsible for reviewing information received about SADEs.

Device deficiencies which could have led to a serious adverse device effect should undergo the same reporting as serious adverse events, i.e., they should be reported to CLJI Worldwide within 24 hours of awareness; and to the ethics committee and regulatory authorities as required by national regulations or by the ethics committee.

8. Risk Evaluation

8.1. Potential Risks to Study Participants

For purposes of this study, adverse events that may be anticipated are associated with the use of VIBLOK cream as well as the procedures used to deploy the cream.

Anticipated risks have been minimized to the furthest extent possible (full details of the risk management procedures can be found in the CIB), but the nature of the patient's disease state has inherent risks [22].

8.1.1. Risks/ Adverse Events associated with the disease state

Complications associated with an HSV-2 infected population may include, but are not limited the following:

- Recurrences of genital herpes
- Systemic symptoms, including fever headache, malaise and myalgia's
- Local pain and itching
- Dysuria
- Tender lymphadenopathy

8.1.2. Risks/ Adverse Events associated with VIBLOK cream

In addition to the events listed in the previous section, the additional adverse events listed below are specifically associated with the VIBLOK cream and its application. The lack of data associated with long term VIBLOK usage prevents predicting the incidence of these risks. Additional complications include, but may not be limited to:

- Toxic, hypersensitive or allergic reaction

- Epithelial sensitization

8.1.3. Risks associated with study procedures

Study procedures may impose additional risks to study participants. In case of the SAFE Trial this theoretically could concern an increased risk for HSV infection of

- housemates, or
- other places than the extra-genital region

due to the frequent sampling and/ or touching of the extra-genital area.

HSV is transmitted via direct contact with infected secretions, such as during sexual intercourse. Casual contact, sharing of bathroom, toilet seats, etc. have not been implicated in HSV transmission. Furthermore, sampling and cream application is only done when participants are asymptomatic, which in principle is not different from normal hygienic or sexual behavior. Therefore, swabbing of the genital area by a study participant does not pose a risk to housemates.
The likelihood of spreading the virus to another part of the body is nil, since autoinoculation does not occur in persons who are infected outside of the primary episode as then immunity has been established. Of note, in that respect is that the University of Washington the HSV research group has been using self-collected swabs for study of HSV for >25 years, and neither autoinoculation, nor exposure of housemates has ever been suspected as a result of these procedures.

In summary, the likelihood for imposing additional risks to study participants and their housemates due study procedures is considered negligible.

8.2. Methods to Minimize Risk

Product handling and procedure guidance are provided in the Training Materials, and will be used for device training to minimize risks associated with device use.

Additionally, efforts will be made to minimize and/ or early capture of these possible risks through site/investigator selection and management. Site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures as well as support the associated requirements for research. Also trial management structure is designed to provide disciplined oversight of the trial activities including monitoring of site and personnel performance.

Site and investigator criteria include the following:

- Investigational site personnel must be experienced and skilled in treating participants with viral STI's.
- Good collaboration with general practitioners to ensure proper participant follow-up.
- The study site must have an adequately staffed research department with a minimum of one dedicated study coordinator.
- Able to enroll a minimum of 5 participants

Although the risk associated with the study procedures is considered negligible as compared to normal practice, the study participants will be instructed to wash their hands thoroughly after their (daily) sampling.

8.3. Benefits

There are no proven benefits from participation in this study and usage of the investigational device.

The study may indirectly be of benefit to study participants if they are determined to be a frequent asymptomatic shedder of HSV-2 and, therefore, a potential transmitter of infection while not having symptoms

Possible benefits for future people using the VIBLOK cream will be based upon results of this and other studies of VIBLOK.

Information gained from the conduct of this study may be of benefit to patients with the same medical condition in the future. The long-term results of using the VIBLOK cream are not known at the present time. There are no alternative treatments. The Clinical Investigator's Brochure has a full assessment of the clinical risk associated with the VIBLOK cream.

8.4. Risk-Benefit Analysis

Use of VIBLOK according to the instructions is expected to reduce the risk for HSV-2 transfer from one person to the other via skin-to-skin contact during sexual intercourse. However, as indicated in section 8.3 there is no proven benefit for the study participants.

Participants enrolled in this clinical study will be at risk of those events listed in section 8.1.2. These risks are considered at an acceptable level with no known residual risk as all VIBLOK ingredients have been used for many years, and the ingredient zinc oxide is listed in the European Pharmacopeia (also refer to the VIBLOK Investigator's Brochure). All adverse events will be carefully monitored throughout the study.

Hence it is believed that the participants participating in this study are not at greater risk than any other people with an HSV-2 infection.

8.5. Definitions

The definitions used in this protocol are consistent with those referenced in ISO 14155:2011.

Term	Definition	Reference/ Justification
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device.	ISO 14155: 2011

Term	Definition	Reference/ Justification
Serious Adverse Event (SAE)	*Adverse Event* that: a) led to a death, b) led to a serious deterioration in the health of a study subject that • resulted in a life-threatening illness or injury, • resulted in permanent impairment of a body structure or body function, • required in-patient hospitalization or prolongation of existing hospitalization, • resulted in a medical or surgical intervention to prevent permanent impairment to body structure or a body function. c) leads to fetal distress, fetal death or a congenital abnormality or birth defect The following is not considered an SAE: Hospitalization for diagnostic or elective surgical procedures, planned at or before the enrollment for a pre-existing condition.	ISO 14155: 2011
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. This definition also includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. And events resulting from use error or from intentional misuse.	ISO 14155: 2011
Serious Adverse Device Effect (SADE)	Adverse Device Effect that resulted in any of the consequences characteristics of a Serious Adverse Event.	ISO 14155: 2011
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problems associated with a device that relates to the rights, safety, or welfare of patients.	ISO 14155: 2011
Device Malfunction or deterioration	Failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.	GHTF/SG2/N 54R8:2006
Endpoints, Clinical Safety (after 26 days)	• SADE incidence • Nature, frequency, duration, severity, seriousness and causality of adverse events	
Endpoints, Performance (after 26 Days)	• Comparison of HSV detection rate on days with asymptomatic shedding prior and after applying VIBLOK • Comparison of HSV copy number on days with asymptomatic shedding prior and after applying VIBLOK	
Pre-Existing Condition	A pre-existing condition is one that is present at the start of study treatment. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.	
Recurrent Hospitalization **Re-Hospitalization**	Re-hospitalization for HSV-2 recurrences and/or complications related to the cream.	

9. Statistical Considerations

This clinical study is a prospective, non-randomized, comparative multi-center safety and performance trial.

9.1. Sample Size Determination

The primary endpoint is the SADE incidence at 28 days of VIBLOK usage.

With a sample size of 36, an exact two-sided 95.0% confidence interval for a single proportion will show that the SADE incidence is below 10% at an expected incidence of 0.1%. Taking into account a drop-out rate of 15%, the estimated sample size needed is 42 study participants applying the VIBLOK cream.

The secondary endpoint is VIBLOK performance.

Statistical analysis will evaluate whether the disagreement rate in positivity between the pre- and post-treatment swabs is indicative of a decrease in detection frequency. For each person, the number of swabs on which shedding occurs only pre-intervention will be assessed, and then the number of swabs on which shedding occurs only post-intervention will be subtracted. If this number averages above zero, it indicates that the detection rate is decreased following intervention, and therefore a protective effect of the intervention with regard to shedding. Since this number is not distributed according to a known distribution, we will compare it to zero using a non-parametric test, the Wilcoxon signed-rank test. With an 8% anticipated asymptomatic shedding rate, 80% power and type I error of 5%, 40 participants taking samples for 28 days are needed to show a 50% reduction post-intervention, i.e. after applying VIBLOK.

Taking into account a drop-out rate of 15%, up to 46 adults applying VIBLOK cream are needed.

Total number of subjects to be enrolled.

Taking into account an overall screenfailure rate of 45% for absence of a confirmed HSV-2 infection, up to 84 subjects will be enrolled to get to the required minimum of 46 adults applying VIBLOK.

9.2. Timing

Participants will undergo screening and, once the HSV-2 infection is confirmed, baseline visits, and then follow-up visits at 14, and 28 after baseline, in addition there will be a follow-up call after 2-5 days after the baseline visit.

9.3. Analysis Sets

The *As Treated* (AT) *Population* will consist of all participants that were enrolled in the trial and that applied VIBLOK at least once.

The *Per Protocol* (PP) *Population* will consist of all participants who fulfil the protocol in the terms of the eligibility and that applied VIBLOK for at least 26 days.

The primary and secondary endpoints will be reported based on the AT population.

Descriptive and summary statistical analysis will also be performed on all primary and secondary endpoints on the PP population.

Prior to final statistical analysis, designated staff will develop a memo that describes the exclusions from analysis populations.

9.4. Missing Data

All possible steps will be taken to minimize missing data in the study, including monitoring of data forms for completeness and efforts to track and maintain contact with study participants during the follow-up period. Missing data will not be imputed and the data will be analyzed as is. An investigation may be made concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial.

9.5. Endpoints

9.5.1. Primary Endpoint

The primary endpoint for this clinical study is SADE incidence after minimally 26 days of VIBLOK treatment in the AT population. This analysis will be repeated for the PP population.

9.5.2. Secondary Endpoints

Secondary endpoints with respect to device performance are:

- Within-participant HSV-2 DNA detection rate on days with asymptomatic shedding
- HSV-2 copy number on HSV DNA positive samples detected by quantitative real-time PCR on days with asymptomatic shedding

The secondary endpoint with respect to safety is:

- Total number and type of AEs after minimally 26 days of VIBLOK use.

Secondary analyses will be performed in the AT population. The analyses will be repeated for the PP population.

9.5.3. Exploratory Endpoints

Subanalyses will be performed as follows:

- To explore VIBLOK's blocking ability in relation to
    - Gender
    - Time between VIBLOK application and sampling
    - Shaving and waxing habits
- Participant satisfaction using VIBLOK as assessed on the participant questionnaire

Exploratory analyses will be performed in the AT population. These analyses will not be repeated for the PP population.

9.6. Endpoint Analysis

All statistical analyses will be performed by CLJI or a designee. Participant data listings and tabular and graphical presentations of results will be provided. All clinically relevant baseline and follow-up variables will be tabulated. Descriptive statistics will be used for continuous variables (e.g., mean, standard deviation, sample size, minimum, and maximum) and frequency tables or proportions for discrete variables.

Swab samples will be analyzed by a core laboratory for HSV DNA and the mean HSV-2 copy number on HSV-2 DNA positive samples.

Further details of the statistical methods will be provided in the Statistical Analysis Plan.

10. Study Administration

10.1. General Study Organization

CLJI Worldwide is the Study Sponsor, and has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies. The Sponsor will have certain direct responsibilities and will coordinate other responsibilities to the specified committees, core labs and other support services as necessary.

CLJI Worldwide will be responsible for submitting the Investigational Plan and all changes to it to the national competent authority and local EC to obtain ongoing approvals as needed.

CLJI Worldwide and Core Laboratories will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial as appropriate.

CLJI Worldwide will submit all reports required by the appropriate regulatory authorities as identified in this section of the regulation. This may include unanticipated and serious adverse device effects, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and protocol violations.

10.2. Steering Committee

The Steering Committee will be responsible for general oversight of the trial. This committee will meet periodically to monitor clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. The committee will be comprised but not limited of Prof. C. Boucher, Prof. A. Wald, Dr A. Wensing, and Dr A. Muetstege with at least one of the medical doctors (MD) being a study investigator.

10.3. Data Monitoring Committee

The Data Monitoring Committee (DMC, also known as the Data Safety Monitoring Board, DSMB) will consist of at least 3 members, with minimally one member independent from the Sponsor, the investigators, or anyone involved in the clinical care of the study participants. (S)he will not have scientific, financial, or other conflict of interest related to the Sponsor or the investigators.

The DMC committee will review all safety data and will monitor the rates of SAEs, device and procedure failures, and any device-related adverse events from this clinical study and make recommendations based upon the safety analyses. It will also be responsible for the developing a charter and deciding on early termination of the trial as necessary. The frequency of the DMC meetings will be determined prior to study commencement; however, the DMC may call a meeting at any time if there is reason to suspect safety is an issue. DMC oversight for this trial is expected to be rigorous with frequent review of all essential safety data.

10.4. Core Laboratories

A Core laboratory will be established for the analyses of the swabs, and serology. Standardized protocols for acquiring and transmitting electronic records will be developed and documented prior to study initiation.

10.5. Clinical Sites

CLJI Worldwide will select qualified investigators, ship devices only to participating investigators, obtain a signed Clinical Study Agreement and provide the investigators with the information and training necessary to conduct the study. CLJI Worldwide will retain copies of all study-related correspondence with study sites.

10.6. Site Training

Clinical sites will be chosen that have had experience with patients with viral STIs. Additional training of appropriate clinical site personnel will be the responsibility of the Sponsor. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor will present a formal training session to study site personnel which will review the instructions for use of the device, the Investigational Plan, techniques for the identification of eligible patients, instructions on in-hospital data collection, standardized data collection for core laboratory analysis, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor, and through regular site monitoring. The sponsor reserves the right to enforce retraining for sites who have demonstrated study or procedure compliance issues.

10.7. Study Monitoring

CLJI Worldwide, or its designee, will conduct investigational site monitoring to ensure that all investigators are in compliance with the protocol and the Investigator's Agreement, and that all study participants have been properly consented with the current version of the informed consent document. CLJI Worldwide will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove either the investigator or the investigational site from the study.

Routine on-site monitoring visits shall include verification of the following:

- Compliance with the protocol, any subsequent amendment(s), ISO14155 and maintenance of regulatory requirements; deviations shall be discussed with the principal investigator(s) or authorized designee, documented and reported;
- Only authorized individuals are participating in the clinical investigation;
- The investigational device is being used according to the protocol and instructions for use;

- Investigational site resources, equipment and the investigational site team, remain adequate throughout the duration of the clinical investigation;
- Signed and dated informed consent forms have been obtained from each participant at the point of enrollment or before any clinical-investigation-related procedures are undertaken, using an informed consent form approved by the ethics committee;
- Source documents and other clinical investigational records are accurate, complete, up to date, stored and maintained appropriately;
- CRFs and queries are complete, recorded in a timely manner, and consistent with source documents; (hence the monitor will perform 100% source verification of the inclusion/exclusion criteria, all adverse events and all endpoints. Further, a random sample of at least 10% of the participants (at least 2 participants per site) will be fully source verified);
- All adverse events and device deficiencies are reported to CLJI without unjustified delay;
- All serious adverse events and deviations are reported to the EC, if required;
- The storage and investigational device accountability are correct and the device accountability process is being followed;
- All other required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation;
- Current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file;
- Participant withdrawal has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee;
- Participant non-compliance with the requirements stated in the informed consent has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee;
- Suitability of the attempts to contact lost to follow-up participants and any intermediaries;
- The principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation, and
- Any corrective and preventive actions, as needed, have been implemented and are effective.

Monitors shall be appropriately qualified per the following requirements:

- Qualified in the field of the applicable regulations and ISO14155:2011 through training and experience as well as scientific or clinical knowledge;
- Knowledgeable on the use of the investigational device(s) and relevant requirements, protocol and informed consent process;
- Trained on the CLJI' clinical quality assurance and quality control system

All monitoring activities shall be documented in a written report. The frequency of monitoring visits will depend on enrollment and center compliance, but each center will at least be visited once per year. Further details are laid out in the monitoring plan.

CLJI Worldwide will review significant new information, including unanticipated adverse events and ensure that such information is provided to the DMC, study investigators and to all reviewing ECs and regulatory agencies as necessary.

Efforts will be made to ensure that data collection compliance is monitored and communicated to the Investigators in a timely manner throughout the trial.

10.8. Data Management

CLJI Worldwide will provide data management through an electronic data capture (EDC) system.

CLJI Worldwide will prepare written progress reports and a final report based on data in the database and will also coordinate with the DMC to ensure data reports are available in a timely manner for all reviews. The core laboratory will be also coordinated by the Sponsor and/or respective vendor so that core lab data for each participant is recorded in the e-CRF.

10.9. Publication Policy

The Study Steering Committee members will plan and review the study publication strategy and review proposed papers and presentations. The committee co-chairmen will develop the format for submission and review of proposed publications. The committee will ensure accuracy of data reporting and will provide editorial assistance and review as needed. Investigators will be required to submit requests for presentation or publication for committee review and approval.

Publication or presentation of the overall clinical study results and/or site specific results of study devices which have not been released, and which still may be undergoing development, requires the prior written approval of CLJI Worldwide. After CLJI Worldwide has had the opportunity to review and comment upon the publication or presentation of the overall clinical and/or site-specific results then Institutions and Investigators will comply with the publication/presentation protocol set forth in the Clinical Study Agreement.

In the event that the multicenter publication has not been completed within one (1) year from the date of the completion or termination of the Study, then notwithstanding the foregoing, the site may individually publish a Proposed Publication regarding its individual results from the Study, provided that the Proposed Publication is first reviewed by Sponsor.

During agreed upon interval and at the conclusion of the trial, a multicenter abstract reporting the primary results will be prepared and presented at a major conference. A multicenter publication will also be prepared for publication in a reputable scientific journal. No publication of results from any single center experience will be allowed until the primary endpoint and secondary endpoints are analyzed, in order to allow for preparation and publication of the multicenter results. The analysis of other pre-specified and non-pre-specified endpoints will be performed by CLJI Worldwide. Additional proposed investigations will require the approval of CLJI Worldwide.

CLJI Worldwide will provide statistical support for the publication process.

11. Ethical & Regulatory Considerations

The VIBLOK cream is not commercially available in any country. The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as updated in Fortaleza Brazil in 2013) and in compliance with ISO14155:2011 and any regional or national regulations. The clinical investigational plan (including the Investigator's Brochure, protocol, and informed consent document) to study the VIBLOK cream must be reviewed and approved by the appropriate national competent authority and local or regional Ethic Committee (EC) where the clinical investigation is to be

conducted before enrollment of participants may begin. Any additional requirements imposed by the ethics committee or regulatory authority shall be followed.

Changes to the investigational plan that may increase the risk or present new risks to the participant must be approved in writing by CLJI Worldwide, the regulatory authorities and the EC before the change is implemented.

11.1. Ethics Committee Approval

Ethics Committee (EC) approval or acknowledgement of the lead EC approval to participate in this trial is required from each institution joining this investigation. Prior to participant enrollment, a signed copy of the EC approval letter must be submitted to CLJI Worldwide certifying investigational plan approval. Investigators are responsible for submitting and obtaining initial and continuing review if necessary (at intervals not greater than once a year) of the clinical investigation by their reviewing EC.

11.2. Informed Consent

Subject Information/Informed Consent is mandatory and must be obtained from all subjects prior to their participation in this trial.

Any modifications to the Informed Consent must be approved by CLJI Worldwide, and as necessary by the EC. Copies of revised versions and the final Subject Information/Informed Consent must be provided to CLJI.

A copy of the EC approved Informed Consent along with a copy of each patient's signed consent must be maintained by each investigator. A signed copy of the consent form must be given to each participant.

11.3. Confidentiality

The participant's name and personal data will remain confidential and will not be published in any way. Participants will be identified on all e-CRFs by a unique reference number. E-CRFs are confidential documents. The sponsor's monitor or representative and regulatory and Ethics Committee representatives, auditors and inspectors may have access to medical files in order to verify authenticity of data collected. Accordingly, data will only be available to the sponsor, the Investigator, Investigators' staff, the investigation statistician, and if requested to the advisory committee and regulatory authorities.

The Investigator will maintain as part of the investigation file a list identifying all patients entered into the study.

11.4. Records and Reports

11.4.1. Records

Records to be maintained by the investigator include:

- Clinical trial investigational plan and all amendments, all approved versions
- Signed clinical trial agreement
- EC approval letter, including final informed consent
- EC membership list
- Correspondence relating to the trial

- CVs for all investigators and research coordinator
- Site personnel signature list
- Clinical monitor sign-in log
- Patient screening/enrollment log
- Reports (includes annual reports, final reports from investigator and sponsor)

The following records must be maintained for each participant enrolled in the trial:

- Signed Informed Consent (latest approved site version)
- All completed e-CRFs
- Supporting documentation of any complications and/or safety events.

CLJI Worldwide requests that the investigator retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occurs post trial procedure. CLJI Worldwide reserves the right to secure data clarification and additional medical documentation on participants enrolled in this trial.

11.4.2. Reports

Adverse event reporting requirements are discussed in Section 7.4.

CLJI Worldwide will make reports on this investigation available to the DMC and Study Steering Committee when necessary and in accordance with the respective charters.

CLJI Worldwide must be notified within 24 hours of any unanticipated adverse device effects, withdrawal of EC approval or major protocol violations.

Upon completion or termination of the trial, the principal investigator for each site must submit a final written report to CLJI Worldwide and the Ethics Committee as required by the regulations. The report must be submitted within 3 months of completion or termination of the trial.

11.5. Protocol Deviations

The investigator will not deviate from the protocol without the prior written approval of CLJI Worldwide except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the participant's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the CLJI Worldwide clinical research personnel must be notified within 24 hours of the incident.

All protocol deviations need to be recorded in the respective section of the e-CRF and reported according national and ethics committee requirements. Periodic monitoring of protocol compliance will be performed for each site. The sponsor maintains the right to place a moratorium on enrollment in sites deemed to have excessive protocol compliance issues. In cases of major protocol violation, e.g., failure to obtain informed consent or violation of inclusion/exclusion criteria, the principal investigator is required to make a written statement attesting to retraining or other action(s) to be taken at his/her site to avoid such violations in the future.

11.6. Protocol Amendments

Changes to the protocol that may be made during the clinical study will be made by prior written agreement between CLJI Worldwide and the Principal Investigator. An amendment will be effective when: a) signed by the Principal Investigator and CLJI Worldwide and b) the amendment has been approved by the EC, if required by the Institution's policies.

11.7. Record Retention Policy

All clinical sites will maintain study records for a minimum of fifteen years after marketing approval is obtained. Record retention dates will be provided to all parties concerned by CLJI Worldwide.

12. References

[1] Stanberry LR, Cunningham AL, Mindel A, Scott LL, Spruance SL, Aoki FY, et al., et al. Prospects for control of herpes simplex virus disease through immunization. Clin Infect Dis 2000; 30: 549-66

[2] Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, et al., et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997; 337: 509-15

[3] Brown Z. Preventing herpes simplex virus transmission to the neonate. Herpes2004; 11: 175A-86A

[4] Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002; 185: 45-52

[5] Strick LB, Wald A, Celum C. Management of herpes simplex virus type 2 infection in HIV type 1-infected persons. *Clin Infect Dis* 2006; 43: 347-56

[6] Celum C, Levine R, Weaver M, Wald A. Genital herpes and human immunodeficiency virus: double trouble. *Bull World Health Organ* 2004; 82: 447-53

[7] Serwadda D, Gray RH, Sewankambo NK, Wabwire-Mangen F, Chen MZ, Quinn TC, et al., et al. Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. *J Infect Dis* 2003; 188: 1492-7

[8] Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006; 20: 73-83.

[9] Reynolds SJ, Quinn TC. Developments in STD/HIV interactions: the intertwining epidemics of HIV and HSV-2. Infect Dis Clin North Am 2005; 19: 415-25

[10] Reynolds SJ. The role of HSV-2 suppressive therapy for HIV prevention.. Future Microbiol. 2009 ; 4: 1095–1097

[11] Larson T et al. Fomites and Herpes Simplex Virus. J Infect Dis 1985 Apr; 151(4)

[12] Martin E. et al. A Pooled Analysis of the Effect of Condoms in Preventing HSV-2 Acquisition. Arch Intern Med. 2009 July 13; 169(13): 1233–1240

[13] Berger JR, Houff S Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008 May;65(5):596-600.

[14] Bryson YJ. et al. Current status and prospects for oral acyclovir treatment of first episode and recurrent genital herpes simplex virus. J Antimicrob Chemother. 1983 Sep;12 Suppl B:61-65.

[15] Mertz GJ et al., Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. JAMA 1984 Sep 7;252(9):1147-51.

[16] Koelle D.M. and Corey L. Herpes simplex: insights on pathogenesis and possible vaccines. Ann Rev Med. 2008;59:381-95.

[17] Wald et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. J Clin Invest. 1997 Mar 1;99(5):1092-7

[18] Wald et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med. 1996 Jan 1;124(1 Pt 1):8-15.

[19] Wald, et al, Effect of Condoms on Reducing the Transmission of Herpes Simplex Virus Type 2 From Men to Women. JAMA 2001

[20] Margaret AS. et al. Effect of Condom Use on Per-act HSV-2 Transmission Risk in HIV-1, HSV-2-discordant Couples. Clin Infect Dis 2016; 62 (4):456-461

[21] Wald et al. Helicase–Primase Inhibitor Pritelivir for HSV-2 Infection. N Engl J Med 2014;370:201-10.

Appendix 1: English master Informed Consent

Appendix 2: Daily Home PCR Instructions for Women

Thank you for volunteering for this study. Please read this sheet over carefully to understand how the study is being done.

Study Supplies

You will receive the following supplies:

- Dacron-tipped swabs (similar to Q-Tips®)
- Small plastic vials (with green, yellow, and red labels)
- Color coded labels
- A storage box
- VIBLOK cream
- Mirror
- A bag for transport
- A swab collection log
- A study diary

Sample Labels

The labels are preprinted with your study, clinic, and participant number. For each sample you collect, please fill in the date and time you collected the sample.

Study Diary

It is important that you bring your study diary to **each** clinic visit. Fill out the diary immediately before you obtain your swab samples. Please record this information as accurately as possible.

Storage of Samples

Vials with and without swabs can be stored at room temperature. When you return to the clinic for your next appointment, please bring the storage box with all the swab samples and your diary.

Communicating with the Clinic

If you develop symptoms of a recurrence or have any questions, please contact the <specify the department>. If you have ANY unusual urinary, genital, or rectal symptoms, such as a urinary tract infection, rash, or bleeding, call the clinic as soon as possible for an appointment. Every effort will be made to accommodate your schedule for clinic visits. Please call in at the earliest sign of symptoms so that a visit can be scheduled as soon as possible.

Weekdays: <specify contact information>
After Hours: <specify contact information>

Collecting Daily Swab Samples

Please read the following instructions carefully, it is very important that you collect samples in the same order as given in the instructions.

Please collect two extra-genital swabs per day: one **before** and one 5-60 minutes **after** VIBLOK application.

Please also collect a swab from a herpes **lesion** during an outbreak: do not apply VIBLOK when you develop a lesion and contact the clinic when you first notice symptoms.

Collect samples **once a day** before bathing or showering, or at least one hour after bathing or showering. Thoroughly wash and dry your hands before beginning.

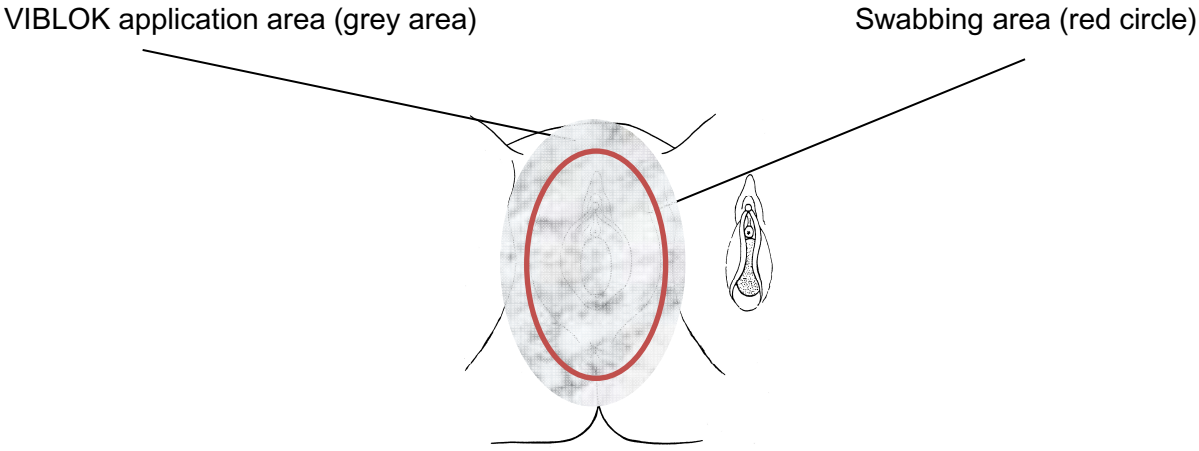

Figure 2.1. Female genitals with VIBLOK application and swabbing area.

1/ To collect the EXTRA GENITAL swab in the green-labeled vial before VIBLOK:

1. Unwrap 1 sterile swab and hold it by the plastic shaft. Try not to touch the Dacron tip with your hands.

2. Gently put the swab on your labia.
3. Rotate the swab in a full circle. Gently remove the swab from your labia.
4. Rub the same swab from the outer (hairy) edges of your labia to the smooth skin below the vaginal opening, covering the entire area.
5. Rub the swab over the skin between your vagina and anal opening (anus).
6. Rub the swab in a circular motion over your rectal area, covering a radius of about 1.0 cm around the anus.

2/ Closing the vials and labeling:

1. Place the collected swab into the vial with the green color coded label.

2. Pull the swab out of the vial 0.5 cm, break (or cut) off the end of the plastic shaft, and discard it in the trash.
3. Securely replace the screw top of the vial.
4. Complete the swab collection log, with the full date (for example: 17-AUG-2015) and time of collection.
5. Place the labeled vial inside the grid box.

3/ Apply VIBLOK

1. Apply one packet of VIBLOK™ evenly and thoroughly to all external genital (including labia and clitoris), pubic, and perianal areas with or without hair.
2. Ensure application from minimally 2 cm outside of the outer (hairy) edges of your labia to the smooth skin below the vaginal opening, covering the entire area, the skin between your vagina and anal opening (anus), and your rectal area, covering a radius of about 2,5 cm around the anus. Apply more than one packet if needed.
3. Wait 5 to 60 minutes.

4/ To collect the EXTRA GENITAL swab in the yellow-labeled vial after VIBLOK:

1. Repeat the procedure as described under 1/ and 2/ using the vial with the yellow color coded label
2. Make sure to rub the swap only in the area where you applied VIBLOK: Keep a distance of at least 1 cm to the outer edges.
3. Use the mirror from your sampling kit if needed.

5/ To collect a LESION swab in the red-labeled vial:

If you develop a herpes lesion, please rub a separate swab over this area and place the swab in one of the red-labeled vials. Do **not** apply VIBLOK when you develop a herpes lesion and call the clinic when you first notice symptoms.

Repeat the procedure as described under 2/.

6/ After collection of the swabs

After you have collected the daily swabs, ensure to

1. thoroughly wash and dry your hands
2. have completed the participant diary

Appendix 3: Daily Home PCR Instructions for Men

Thank you for volunteering for this study. Please read this sheet over carefully to understand how the study is being done.

Study Supplies

You will receive the following supplies:

- Dacron-tipped swabs (similar to Q-Tips®)
- Small plastic vials (with green, yellow, and red labels)
- Color coded labels
- A storage box
- VIBLOK cream
- Mirror
- An bag for transport
- A swab collection log
- A study diary

Sample Labels

The labels are preprinted with your study, clinic, and participant number. For each sample you collect, please fill in the date and time you collected the sample.

Study Diary

It is important that you bring your study diary to **each** clinic visit. Fill out the diary immediately before you obtain your swab samples. Please record this information as accurately as possible.

Storage of Samples

Vials with and without swabs can be stored at room temperature. When you return to the clinic for your next appointment, please bring the storage box with all the swab samples and your diary.

Communicating with the Clinic

If you develop symptoms of a recurrence or have any questions, please contact the <specify the department>. If you have ANY unusual urinary, genital, or rectal symptoms, such as a urinary tract infection, rash, or bleeding, call the clinic as soon as possible for an appointment. Every effort will be made to accommodate your schedule for clinic visits. Please call in at the earliest sign of symptoms so that a visit can be scheduled as soon as possible.

Weekdays: <specify contact information>
After Hours: <specify contact information>

Collecting Daily Swab Samples

Please read the following instructions carefully, it is very important that you collect samples in the same order as given in the instructions.

Please collect two extra-genital swabs per day: one **before** and one 5-60 minutes **after** VIBLOK application.

Please also collect a swab from a herpes **lesion** during an outbreak: do not apply VIBLOK when you develop a lesion and contact the clinic when you first notice symptoms.

Collect samples **once a day** before bathing or showering, or at least one hour after bathing or showering. Thoroughly wash and dry your hands before beginning.

VIBLOK application area (grey area)

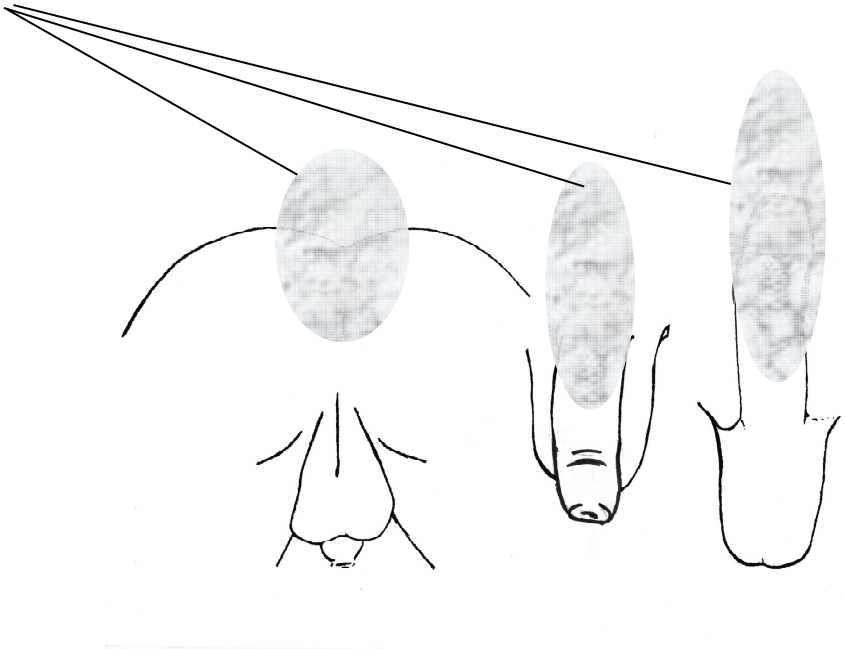

Figure 3.1. Male genitals with VIBLOK application and swabbing area.

1/ To collect the EXTRA GENITAL swab in the green-labeled vial before VIBLOK:

1. Unwrap 1 sterile swab and hold it by the plastic shaft. Try not to touch the Dacron tip with your hands.

2. Rub the swab, starting at the tip of the penis, over the whole length of the penis to the base, covering the entire area.
3. Rub the swab over the skin between your penis and anal opening (anus).
4. Rub the swab in a circular motion over your rectal area, covering a radius of about 1 cm around the anus.

2/ Closing the vials and labeling:

1. Place the collected swab into the vial with the green color coded label.

2. Pull the swab out of the vial 0.5 cm, break (or cut) off the end of the plastic shaft, and discard it in the trash.
3. Securely replace the screw top of the vial.
4. Complete the swab collection log, with the full date (for example: 17-AUG-2015) and time of collection.
5. Place the labeled vial inside the grid box.

3/ Apply VIBLOK

1. Apply one packet of VIBLOK™ evenly and thoroughly to all external genital, penile shaft, pubic and perianal areas – with or without hair, minimally 2 cm outside of the swabbing area.
2. Ensure application starting at the tip of the penis, over the whole length of the penis to the base, covering the entire area, the skin between your penis and anal opening (anus), and your rectal area, covering a radius of minimally 2,5 cm around the anus. Apply more than one packet if needed.
3. Wait 5 to 60 minutes.

4/ To collect the EXTRA GENITAL swab in the yellow-labeled vial after VIBLOK:

1. Repeat the procedure as described under 1/ and 2/ using the vial with the yellow color coded label
2. Make sure to rub the swap only in the area where you applied VIBLOK: Keep a distance of at least 1 cm to the outer edges.
3. Use the mirror from your sampling kit if needed.

5/ To collect a LESION swab in the red-labeled vial:

If you develop a herpes lesion, please rub a separate swab over this area and place the swab in one of the red-labeled vials. Do **not** apply VIBLOK when you develop a herpes lesion and call the clinic when you first notice symptoms.

6/ After collection of the swabs

After you have collected the daily swabs, ensure to

1. thoroughly wash and dry your hands
2. have completed the participant diary

Appendix 4. Participant Diary

Day of the month		1	2	3	4	5	6	7	8	9	10
Time Skin Swab Collected											
Time VIBLOK Swab Collected											
Time in case of genital area shaved											
Time in case of genital area waxed											
Time in case of other hair removal											
Specify other hair removal method if applicable											
Anti-HSV medication taken											
Symptoms											
No Symptoms											
Itching, burning, tingling											
Lesions (sores, blisters, ulcers, crusts)											
Other (describe below)											
Lesion Locations											
Genital (Men: penis, scrotum; Women: vagina, labia, vulva, groin, pubis)											
Rectal (perineum, perianal)											
Buttock											
Other: _____											

Day of the month		11	12	13	14	15	16	17	18	19	20
Time Skin Swab Collected											
Time VIBLOK Swab Collected											
Time in case of genital area shaved											
Time in case of genital area waxed											
Time in case of other hair removal											
Specify other hair removal method if applicable											
Anti-HSV medication taken											
Symptoms											
No Symptoms											
Itching, burning, tingling											
Lesions (sores, blisters, ulcers, crusts)											
Other (describe below)											
Lesion Locations											
Genital (Men: penis, scrotum; Women: vagina, labia, vulva, groin, pubis)											
Rectal (perineum, perianal)											
Buttock											
Other: _____											

Day of the month		21	22	23	24	25	26	27	28	29	30	31
Time Skin Swab Collected												
Time VIBLOK Swab Collected												
Time in case of genital area shaved												
Time in case of genital area waxed												
Time in case of other hair removal												
Specify other hair removal method if applicable												
Anti-HSV medication taken												
Symptoms												
No Symptoms												
Itching, burning, tingling												
Lesions (sores, blisters, ulcers, crusts)												
Other (describe below)												
Lesion Locations												
Genital (Men: penis, scrotum; Women: vagina, labia, vulva, groin, pubis)												
Rectal (perineum, perianal)												
Buttock												
Other: _____												

Appendix 5. Participant questionnaire

Participant questionnaire and debriefing: ***to be filled out by the participant during visit 4.***		
Question	Circle one option	Free text
I found VIBLOK	1. Very easy to use 2. Somewhat easy to use 3. Difficult to use	
The use was	1. Simple and clear 2. Somewhat confusing 3. Very confusing	
The VIBLOK user documentation was	1. Excellent 2. Adequate 3. Inadequate	
If VIBLOK was available for use, I would	1. Use it 2. Use it only in very special cases 3. Never use it	
What I liked best about VIBLOK was		
What I liked least about VIBLOK was		
What suggestions do you have for improving VIBLOK?		