STATISTICAL ANALYSIS PLAN

Study Title: VIBLOK SAfety and perFormancE Trial

Protocol number: 2015-01

Protocol version Version 5.0, dated May 1, 2017 and date:

Phase of development:

Sponsor: CLJI WORLDWIDE

Plan prepared by: Joop Pfeil, Manager Biostatistics
Estimate Medical Statistics B.V.

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1. Introduction

1.1 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.

Primary Endpoint

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

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.

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 of the study protocol).

1.2 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 participants 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.
Forty 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 of the study protocol).

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

1.3 Statistical hypotheses

Primary endpoint
SADE incidence after minimally 26 days of VIBLOK treatment, will be assessed by calculating the upper limit of the two-sided exact 95% Clopper-Pearson confidence interval which needs to be below 10%.

Secondary endpoints with respect to device performance

Within-participant HSV-2 DNA detection rate on days with asymptomatic shedding. 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 postintervention will be subtracted. The following hypothesis will be tested:

H_0: The number of swabs on which shedding occurs only pre-intervention is the same when compared to the number of swabs on which shedding occurs only post-intervention
H_1: The number of swabs on which shedding occurs only pre-intervention is not the same when compared to the number of swabs on which shedding occurs only post-intervention

HSV-2 copy number on HSV DNA positive samples detected by quantitative real-time PCR on days with asymptomatic shedding will be tested using the following hypothesis:

H_0: The HSV-2 copy number on which shedding occurs only pre-intervention is the same when compared to the HSV-2 copy number on which shedding occurs only post-intervention
H_1: The HSV-2 copy number on which shedding occurs only pre-intervention is not the same when compared to the HSV-2 copy number on which shedding occurs only post-intervention

Secondary endpoint with respect to safety:

The total number and type of AEs after minimally 26 days of VIBLOK use will be analyzed descriptively only. No hypothesis will be tested.

Exploratory endpoints

The sub-analyses

- 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

will be analyzed descriptively only. No hypothesis will be tested.

1.4 Sample size justification

The primary endpoint is the SADE incidence at 28 days of VIBLOK usage.
With a sample size of 36, an exact two-sided 95% 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, it will be compared 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 participants to be enrolled
Taking into account an overall screening failure rate of 45% for absence of a confirmed HSV-2 infection, up to 84 participants will be enrolled to get to the required minimum of 46 adults applying VIBLOK.

1.5 Randomization and blinding

This study is a single-arm open-label study. A randomization procedure is not used and there are no procedures necessary of maintaining the blind.

2. General issues for statistical analyses

2.1 Visit windows

An overview of the visit windows is given below:

Visit Number	Label on Output	Target time point (Day)	Interval (Day)
0	Screening	> -21	≤ 0
1	Day 1	1	1
N/A	Day 3	3	2-5
2	Day 14	14	12-16
3	Day 28	28	26-31

2.2 Protocol violations

2.2.1 Definition of protocol violations

Protocol deviations are defined in accordance with ICH E3 as important protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, participant management or participant assessment.

All important protocol deviations will be assessed prior to closing the clinical database as to exclusion of one or more analysis sets.

All important protocol deviations will be classified into the following categories:
- Informed consent not signed and/or dated
- Wrong version of the informed consent used
- Inclusion / exclusion criteria
- Missed visits
- Visit not within window
- Protocol required data collection / testing
- Other deviation

An important protocol deviation will lead to exclusion of the participant or part of the participant's data from at least one analysis set. Minor protocol deviations, like only few days out of the time window, may not lead to exclusion of any data. Refer to section 2.2.2 as to the procedure whether or not to exclude any data from the statistical analysis.

Premature discontinuation from the study for reasons such as withdrawal of consent or occurrence of adverse events will not be considered to be a protocol deviation. Planned assessments after premature discontinuation will also not be considered to be a protocol deviation.

2.2.2 Determination of protocol violations

The clinical study team will evaluate the list of important protocol deviations as to exclusion of data from analysis sets. The evaluation might be on an ongoing basis during the conduct of the study or once prior to closing the clinical database. The outcome of the evaluation of the important protocol deviations will be

- documented in an Exclusion Memo to be signed off by at least the Biostatistician, Study manager and Sponsor

- stored in a data table (for example a SAS-dataset or Excel spreadsheet) which will be attached to the clinical database

After the sign off of the Exclusion Memo and the generation of the data table, the clinical database will be locked.

2.3 Missing values and outliers/ implausible measurements

Missing values will not be replaced in the statistical analysis.
An investigation may be done concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial.

Assessments directly measured by the participant will not be subject to a reconciliation process.
Therefore, implausible measurements as described in the table below might be removed from the statistical analysis. However, the implausible measurements will be presented in individual data listings. Final decision whether or not to remove implausible measurements from the statistical analysis will be documented in the Exclusion Memo.

Parameter	Implausible measurements
Swab data	Before/after assessment
Swab data	Obvious mistake in date on the swab log

2.4 Pooling algorithm for study centers

All study centers will be pooled in the statistical analyses. However, by center summary statistics will be presented for the primary efficacy parameter.

2.5 Analysis sets

2.5.1 All enrolled set

The All Enrolled Set will consist out of screened participants who provided informed consent. Study specific data will not be collected for participants who fail any of the eligibility criteria and do not apply the study product; these participants will be recorded on a Screening Log where the reason for screening failure will be documented.

2.5.2 As Treated Population

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

2.5.3 Per Protocol Population

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.

2.5.4 Safety Analysis Set

The Safety Analysis Set will include all participants from the As Treated Population who provided safety data.

It is assumed that all participants applying VIBLOK at least once are included in the safety analysis; if that is not so, an explanation will be provided.

2.6 Multiplicity

The primary endpoint for this clinical study is SADE incidence during minimally 26 days of VIBLOK use in the As Treated Population. This analysis will be repeated for the Per Protocol Population. Since the primary endpoint is a safety endpoint and all other statistical analyses are secondary endpoints no correction for multiplicity will be performed to prevent alpha inflation.

2.7 Interim Analysis

A Data Safety Monitoring Committee is established for this study. The aim of the DMC is to protect and serve the VIBLOK SAFE Trial participants, specifically regarding safety, and to assist and advise the Study Sponsor and the Study Steering Committee so as to protect the validity and credibility of the trial. Full details can be found in the DMC Charter.

No adjustments for the Type I error will be made.

2.8 General Issues For Statistical Analyses

Descriptive statistics (N, Mean, Median, STD, min, Max) will be presented for continuous data, frequencies and percentages will be presented for categorical variables. Continuous, non- normally distributed variables will be analyzed using the nonparametric Wilcoxon signed-rank (within group comparisons) test or Wilcoxon rank-sum test (between group comparisons). The latter will be accompanied by Hodges-Lehmann estimates (point estimate and 95% exact confidence interval) to assess the location of the shift between groups. Twosided exact 95% Clopper-Pearson confidence intervals will be calculated for categorical variables. Hypotheses will be tested two-sided using an alpha-level of 5%.

2.9 Data Handling Rules/Derived and Computed Variables

The handling of drop-outs and incomplete data (like diaries etc.) will be described in the Data Handling and Presentation Plan.

3. Study Participants Information

3.1 Participant Disposition

The number of participants who entered and completed each phase of the study will be provided, as well as the reasons for all discontinuations, grouped by major reason:

- Lost to follow-up
- Participant requested withdrawal from the study
- Participant withdrew consent
- Relocated to another geographic location
- Other
- Investigator withdrew participant from the study
- Investigator deems medically necessary
- Failure to maintain adequate study compliance
- Inclusion/exclusion criteria not met
- Other
- Other reason.

A flow chart will be included (see Annex I).
There will also be a listing of all participants discontinued from the study after enrollment, broken down by center, giving a participant identifier, the specific reason for discontinuation, and the duration of applying VIBLOK before discontinuation. Refer to Annex II.

Three attempts will be made to contact the participant in case of lost to follow-up. The method of the attempt (phone, written, e-mail, other) will be presented.

3.2 Protocol Deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the study, participant management or participant assessment will be presented.

Protocol deviations will be summarized by center and grouped into different categories:

- Informed consent not signed and/or dated
- Wrong version of the informed consent used
- Inclusion / exclusion criteria
- Missed visits
- Visit not within window
- Protocol required data collection / testing
- Other deviation

The reason for the deviation, including the root cause, will be summarized by center using the following categories:

- Medical justification
- Participant non-compliance
- Study center error / non-compliance
- Other reason

Whether or not corrective action was needed will be summarized by center.

Individual participants with protocol deviations will be listed, including the description of the deviation, broken down by center.

3.3 Data Sets Analyzed

The frequencies and percentages of participants in each analysis set will be presented. A tabular listing of all participants, visits and observations excluded from the analysis sets will be provided (see Annex III for an example).

3.4 Demographics and Other Baseline Characteristics

The critical demographic and baseline characteristics of the participants, as well as other factors arising during the study that could affect response, will be displayed by use of tables. The data for the All Enrolled Set will be given first followed by data on the As Treated Population, Per Protocol Population and Safety Analysis Set.

The variables, assessed at the screening visit and at Visit 1, displayed will include:

- demographic variables
  - Age (years)
  - Gender (Male / Female)
  - Race/Ethnic Origin (Participant chose not to share this data / African, American or Black / Asian / Caucasian / Hispanic or Latina / Other race/ethnic origin)
- HSV Serology
  - Units HSV-2 IgG antibody (aU/ml)
  - Units HSV-2 IgG antibody (Negative / Positive / Borderline)
  - Units HSV-1 IgG antibody (aU/ml)
  - Units HSV-1 IgG antibody (Negative / Positive / Borderline)
  - Units HSV- IgM antibody (Negative / Positive / Borderline)
  - Overall result of the Western blot or Allegria Essay test (HSV2 positive and HSV1 negative / HSV2 positive and HSV1 positive / HSV2 negative and HSV1 positive / HSV2 negative and HSV1 negative / HSV positive but origin HSV1 or HSV2 unclear)
- Anti-Viral therapy
  - Current use of any anti-viral therapy at screening (Yes / No)
  - Did the participant stop with any anti-viral therapy recently at screening? (Yes / No)
  - Has anti-Viral therapy been stopped at least 7 days ago at Visit 1? (Yes / No (delay visit 1 or withdraw participant))
- Medical History (general)
  - Does the participant have hypertension? (No/Controlled / Uncontrolled)
  - Does the participant diabetes? (No/ Type 1 / Type 2)
  - Does the participant have cardiac disease? (Yes / No)
  - Is the participant HIV positive? (Yes / No / Unknown)
  - Does the participant have any known allergies? (No / Hay Fever, Dust Mites or Animal Dander / Contact Allergy / (Household) Chemicals / Perfume or Body care products / Latex / Other)
  - Does the participant have a significant autoimmune disease? (No/ Multiple Scleroses / Myasthenia Gravis / Crohn Disease / Colitis Ulcerosa / Psoriasis / Vitiligo / Lupus Erythematosus / Rheumatoid arthritis /Other)

- Does the participant have any other for the study relevant medical condition? (Yes / No / Unknown)
- Have there been any changes in medical history since previous visit? (Yes / No)

At visit 1 the actual medical history status will be presented, i.e. the data from the screening visit including the changes reported at Visit 1.

- History of genital herpes
  - Years since first date of diagnosis of genital herpes
  - How was the diagnosis "genital herpes" made (Clinical / Culture or PCR / Blood test)
  - Type of blood test performed (Alegria assay / UW Western blot / Other)
  - The number of recurrences of genital herpes the participant had in the past year (today –1y)
  - Years since last recurrence the participant had
  - Did the participant experience HSV recurrence at Visit 1 since the screening visit? (No / Yes)
- Targeted Physical Exam - General
  - Height (cm)
  - Weight (kg)
  - Heart rate (bpm)
  - Systolic and diastolic Blood pressure (mmHg)
  - Genital
  - Any (new) abnormalities in the inguinal and/or pubis area related to genital herpes? (Yes / No)
  - Any (new) abnormalities in the peri-anal area related to genital herpes? (Yes / No)
  - Any (new) abnormalities in the genital area related to genital herpes? (Yes / No)
  - Any (new) obvious discharge present in the genital, peri-anal, inguinal or pubis area? (Yes / No)
  - Any (new) other abnormalities in the genital, peri-anal, inguinal or pubis area, NOT related to genital herpes but relevant for the study (at the judgement of the investigator)? (Yes / No)

  At visit 1 the actual targeted Genital Exam will be presented, i.e. the data from the screening visit including the new abnormalities reported at Visit 1.
- Grooming Habits
  - Genital grooming habits (None / Shaving / Waxing / Other)
  - Frequency of performing these extra genital grooming habits (Daily / Weekly / Monthly / Other)
  - Did participant change any genital grooming since the screening visit? (Yes / No)

  At visit 1 the actual grooming habits will be presented, i.e. the data from the screening visit including the changes reported at Visit 1.
- Medication vs Treatment
  - Any use of medication, topical cream or other product on a continuous basis, for the treatment or maintenance of genital herpes or any other medical condition as mentioned in the medical history? (Yes / No)
  - Treatment in case of an outbreak of genital herpes to alleviate/ treat the genital herpes on top of any treatment/maintenance of genital herpes on a continuous basis (No additional treatment / Prescription medication /

Nonprescription medication / (Topical) cream / Any other treatment). More than one answer allowed.
- Are there any changes in medication, topical cream or any other product to alleviate genital herpes since screening visit? (Yes / No)

- Pregnancy test (female only)
  - Did the participant perform a urine pregnancy test at screening visit? (Yes, pregnant / Yes, not pregnant / No, pregnancy test to be performed at visit 1 at the latest / No, participant is not of child bearing potential)
  - Has a urine pregnancy test been performed at visit 1? (Not applicable, pregnancy test performed during screening visit / Yes, pregnant withdraw participant from study / Yes, not pregnant / No, complete a protocol deviation and withdraw participant from study)
- Instructions of use
  - Has the participant been instructed to take the swab(s)?
  - Has participant been instructed to store the swabs correctly?
  - Has participant been instructed to apply the VIBLOK correctly?
  - Has the participant been instructed to complete the diary correctly?
  - Has the participant been instructed to complete the swab log(s) correctly?
  - Has the participant been instructed what to do in case of genital herpes outbreak?

  Possible answers to the questions are:
  - No
  - Yes, speed of the participant to perform task correctly is fast
  - Yes, speed of the participant to perform task correctly is medium -
    Yes, speed of the participant to perform task correctly is slow

In addition to tables giving group data for these baseline variables, relevant individual participant demographic and baseline data, and all concomitant medication for all individual participants enrolled (broken down by center) will be presented in by-participant tabular listings.

3.5 Measurements of Treatment Compliance

Frequencies and percentages will be presented of whether or not the participant did return all used and unused Viblok packages at Visit 2 and 3.

3.6 Post Visit 1 data

The critical characteristics of the participants, as well as other factors arising during the study and collected after Visit 1 that could affect response, will be displayed by use of tables. The data for the As Treated Population will be given first followed by data on the Per Protocol Population.

The variables displayed will include:
- Administrative information
  - FU call performed (Yes / No)
- Verification study procedures
  - Did the participant have full understanding and no remaining questions with respect to the swabbing procedures? (Yes / No)

- Did the participant have full understanding and no remaining questions with respect to the application of the VIBLOK Cream? (Yes / No)
- Did the participant have full understanding and no remaining questions with respect to the completion of the diary? (Yes / No)
- Did the participant have full understanding and no remaining questions regarding any other study procedure(s)? (Yes / No) • Medical History (general)
- Does the participant have hypertension? (No/Controlled / Uncontrolled)
- Does the participant diabetes? (No/ Type 1 / Type 2)
- Does the participant have cardiac disease? (Yes / No)
- Is the participant HIV positive? (Yes / No / Unknown)
- Does the participant have any known allergies? (No / Hay Fever, Dust Mites or Animal Dander / Contact Allergy / (Household) Chemicals / Perfume or Body care products / Latex / Other)
- Does the participant have a significant autoimmune disease? (No/ Multiple Scleroses / Myasthenia Gravis / Crohn Disease / Colitis Ulcerosa / Psoriasis / Vitiligo / Lupus Erythematosus / Rheumatoid arthritis /Other)
- Does the participant have any other for the study relevant medical condition? (Yes / No / Unknown)
- Have there been any changes in medical history since previous visit? (Yes / No)

The actual medical history status will be presented, i.e. the data from the previous visit including the changes reported at the respective visit.

- History of genital herpes
  - Did the participant experience HSV recurrence at Visit 1 since the screening visit? (No / Yes)
- Targeted Physical Exam
  - General
  - Heart rate (bpm)
  - Systolic and diastolic Blood pressure (mmHg)
  - Genital
  - Any new abnormalities in the inguinal and/or pubis area related to genital herpes? (Yes / No)
  - Any new abnormalities in the peri-anal area related to genital herpes? (Yes / No)
  - Any new abnormalities in the genital area related to genital herpes? (Yes / No)
  - Any new obvious discharge present in the genital, peri-anal, inguinal or pubis area? (Yes / No)
  - Any new other abnormalities in the genital, peri-anal, inguinal or pubis area, NOT related to genital herpes but relevant for the study (at the judgement of the investigator)? (Yes / No)

  The actual targeted Genital Exam will be presented, i.e. the data from the previous visit including the new abnormalities reported at the respective visit.
- Grooming Habits
  - Genital grooming habits (None / Shaving / Waxing / Other)
  - Frequency of performing these extra genital grooming habits (Daily / Weekly / Monthly / Other)

- Did participant change any genital grooming since the screening visit? (Yes / No) The actual grooming habits will be presented, i.e. the data from the previous visit including the changes reported at the respective visit.

- Medication vs Treatment
  - Are there any changes in medication, topical cream or any other product to alleviate genital herpes since previous visit? (Yes / No)
  - Anti HSV medication recorded on the participant's diary
  - Any anti HSV medication taken (Yes / No)
  - The percentage of days anti HSV medication taken in relation to the total number of days of participation.
- Review and collection of particpant's diary
  - Did the participant complete the participant diary according procedure? (Yes / No, complete protocol deviation)
- Collection of participant swabs
  - Did the participant collect all required swabs according protocol? (Yes / No, complete protocol deviation)
  - Did the participant complete the swab log according protocol? (Yes / No, complete protocol deviation)
  - Did the participant complete the swab lesion log according protocol? (Yes / No, complete protocol deviation / Not applicable)
- Collection of participant questionnaire
  - Did the participant complete the participant questionnaire? (Yes / No, complete protocol deviation)
- Unscheduled FU information
  - Type of unscheduled follow-up (Phone call / In-Clinic visit)
  - Reason unscheduled follow-up (Genital Herpes outbreak / Other)
  - What type of treatment did the participant start to alleviate the outbreak of genital herpes? (No treatment / Prescription medication / Non Prescription medication / (Topical) cream / Any other treatment). More than one answer allowed.
  -

In addition to tables giving group data for these variables, relevant individual participant data, and all concomitant medication for all individual participants enrolled (broken down by center) will be presented in by-participant tabular listings.

4. Efficacy Evaluation

4.1 Primary Efficacy Endpoint

4.1.1 Definition

The primary endpoint concerns a safety endpoint. There is no primary efficacy endpoint.

4.1.2 Analysis Methods

Not applicable.

4.2 Secondary Efficacy Endpoints

4.2.1 Definition

Within-participant HSV-2 DNA detection rate on days with asymptomatic shedding 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 postintervention will be subtracted. It will be tested whether the number of swabs on which shedding occurs only pre-intervention is the same when compared to the number of swabs on which shedding occurs only post-intervention.

HSV-2 copy number on HSV DNA positive samples detected by quantitative real-time PCR For each person, the mean PCR HSV-2 copy number on days with asymptomatic shedding occurring only pre-intervention will be calculated, and then the mean PCR HSV-2 copy number on days with asymptomatic shedding occurring only post-intervention will be subtracted. It will be tested whether the HSV-2 copy number on which shedding occurs only pre-intervention is the same when compared to the HSV-2 copy number on which shedding occurs only post-intervention.

4.2.2 Analysis Methods

Within-participant HSV-2 DNA detection rate on days with asymptomatic shedding

If the difference between the number the number of swabs on which shedding occurs only pre-intervention and the number of swabs on which shedding occurs only post-intervention 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, it will be compared to zero using the non-parametric Wilcoxon signed-rank test.

HSV-2 copy number on HSV DNA positive samples detected by quantitative real-time

The difference of the mean PCR HSV-2 copy number on days with asymptomatic shedding occurring only pre-intervention and occurring only post-intervention will be compared to zero using the non-parametric Wilcoxon signed-rank test.

Both analyses will be based on the As Treated Population and repeated for the Per Protocol Population.

Exploratory Poisson regression analyses may also be performed exploring the effect of other covariates like center, age and gender.

4.3 Exploratory Endpoints

4.3.1 Definition

Sub-analyses will be performed as follows:

- To explore VIBLOK's blocking ability in relation to

  Gender

Between gender differences will be assessed for she secondary efficacy endpoints.

Time between VIBLOK application and sampling

- The timing of the post VIBLOK sample in relation to the difference between the pre and post VIBLOK HSV-2 sample values

Shaving and waxing habits

- The genital grooming habits in relation to in the pre-VIBLOK HSV-2 sample value.
- The genital grooming habits in relation to the difference between the pre and post VIBLOK HSV-2 sample value

- Participant satisfaction using VIBLOK as assessed on the participant questionnaire
  - Ease of use of VIBLOK (Very easy to use / Somewhat easy to use / Difficult to use)
  - The use of VIBLOK (Simple and clear / Somewhat confusing / Very confusing)
  - VIBLOK user documentation (Excellent / Adequate / Inadequate)
  - Use of VIBLOK if VIBLOK was available for use (Participant would use it / Participant would use it only in very special cases / Participant would never use it)
  - The best participant liked about VIBLOK
  - The least participant liked about VIBLOK
  - Suggestions of participant for improving VIBLOK

- Symptoms (Itching, burning, tingling / Lesions (sores, blisters, ulcers, crusts) / Other) as recorded on the participant's diary.
- Location of the lesion (Genitals / Rectal (perineum, perianal) / Buttock / Other) as recorded on the participant's diary.

4.3.2 Analysis Methods

- To explore VIBLOK's blocking ability in relation to

  Gender

  Between gender differences will be assessed for the secondary efficacy endpoints using the Wilcoxon rank-sum test. Hodges-Lehmann estimates (point estimate and 95% exact confidence interval) will be used to assess the location of the shift between males and females.

  Time between VIBLOK application and sampling

  The relation between the timing of the post VIBLOK sample and the difference between the pre and post VIBLOK HSV-2 sample values will be explored by a graph (x-axis will be the timing, y-axis will be the difference in HSV-2 values).

  Shaving and waxing habits

  - The genital grooming habits in relation to in the pre-VIBLOK HSV-2 sample value will be explored by descriptive statistics of the pre-VIBLOK HSV-2 sample value by grooming habit (None / Shaving / Waxing / Other) and by frequency of habit (Daily / Weekly / Monthly / Other / No Shaving habit).

- The genital grooming habits in relation to the difference between the pre and post VIBLOK HSV-2 sample value will be explored by descriptive statistics of the difference between the pre and post VIBLOK HSV-2 sample value by grooming habit (None / Shaving / Waxing / Other) and by frequency of habit (Daily / Weekly / Monthly / Other / No Shaving habit).

- Participant satisfaction using VIBLOK as assessed on the participant questionnaire

  Frequency distributions will be presented for

  - Ease of use of VIBLOK (Very easy to use / Somewhat easy to use / Difficult to use)
  - The use of VIBLOK (Simple and clear / Somewhat confusing / Very confusing)
  - VIBLOK user documentation (Excellent / Adequate / Inadequate)
  - Use of VIBLOK if VIBLOK was available for use (Participant would use it / Participant would use it only in very special cases / Participant would never use it)

  Only listings will be provided for

  - The best participant liked about VIBLOK
  - The least participant liked about VIBLOK
  - Suggestions of participant for improving VIBLOK

- Symptoms (Itching, burning, tingling / Lesions (sores, blisters, ulcers, crusts) / Other) as recorded on the participant's diary.
  - Any symptoms (Yes / No)
  - The percentage of days with any symptoms in relation to total number of days of participation.
  - Any Itching, burning, tingling (Yes / No)
  - The percentage of days with any Itching, burning, tingling in relation to total number of days of participation.
  - Any lesions (sores, blisters, ulcers, crusts) (Yes / No)
  - The percentage of days with any lesions in relation to total number of days of participation.
  - Any other symptom (Yes / No)
  - The percentage of days with any other symptom in relation to total number of days of participation.
- Location of the lesion (Genitals / Rectal (perineum, perianal) / Buttock / Other) as recorded on the participant's diary.
  - Any location (Yes / No)
  - The percentage of days with any location in relation to total number of days of participation.
  - Any rectal (perineum, perianal) location (Yes / No)
  - The percentage of days with any rectal location in relation to total number of days of participation.
  - Any buttock location (Yes / No)
  - The percentage of days with any buttock location in relation to total number of days of participation.
  - Any other location (Yes / No)

- The percentage of days with any other location in relation to total number of days of participation.

All exploratory analyses will be based on the As Treated Population. These analyses will not be repeated for the Per Protocol Population.

5. Safety Evaluation

5.1 Extent of Exposure

The duration of exposure will be assessed as the number of days between the date of Visit 1 (Day 1) and the date of the last date of diary completion with non-missing time skin or VIBLOK swab collected.
The duration of exposure will be summarized for the As Treated Population and Per Protocol Population.

5.2 Adverse Events

5.2.1 Primary endpoint

The primary endpoint of this study is a safety endpoint:
The number of Serious Adverse Device Effects during minimally 26 days of VIBLOK use. A two-sided exact 95% Clopper-Pearson confidence interval will be calculated. The study will be considered a success in case the upper limit of the 95% confidence interval is below 10%.
The analysis will be based on the As Treated Population and repeated for the Per Protocol Population.

5.2.2 Display of adverse events

All adverse events occurring after initiation of study treatment (including events likely to be related to the underlying disease or likely to represent concomitant illness) will be displayed in summary tables.

The tables will list each adverse event, the number of participants in whom the event occurred, and the rate of occurrence.
Adverse events will be grouped by the following categories:

- Any event
- Bleeding / Anaemia
- Bowel
- Cardiac
- Malignancies
- Miscellaneous
- Neurological
- Pulmonary
- Renal
- Urogenital
- Vascular
- Genital

- Skin
- Infection
- Trauma
- Other

The analysis of adverse events comprises the following categories:

- Any adverse event
- Any adverse event by consideration
- Adverse events considered to be a toxic reaction
- Adverse events considered to be an allergic reaction
- Adverse events considered to be an infection
- Adverse events considered to be other
- Any adverse event by severity
- Possibly, probably or definitely related to investigational device adverse events
- Possibly, probably or definitely related during application of the investigational device adverse events
- Possibly, probably or definitely related after application of the investigational device adverse events
- Possibly, probably or definitely related to study procedure adverse events
- Adverse events related to a pre-existing / other medical condition
- Adverse event related complications associated with an HSV 2 infection
- Any adverse event
- Recurrence of genital herpes
- Systemic symptoms
- Fever
- Headache
- Malaise
- Myalgia(s)
- Local pain and itching
- Dysuria
- Tender lymphadenopathy
- Unanticipated adverse events
- Adverse events by action taken
- No action taken
- Drug Therapy
- Any
- Prescription
- Non-Prescription
- Surgical intervention or other invasive therapy
- Hospitalization
- Other treatment / procedure
- Withdraw from study due to AE
- Adverse events by outcome
- Resolved
- Resolved with sequelae
- Ongoing
- Ongoing at time of exit
- Unknown / Lost to Follow-up

- Death
- Reportable adverse events

Serious adverse events will only be listed as it will be expected that there will only be very few or no serious adverse event.

5.2.3 Listings of adverse events by participant

All adverse events for each participant, including the same event on several occasions will be listed, giving both the adverse event classification and the original description used by the investigator. The listing will be by investigator and will include:

- Participant identifier
- Age, race, sex, weight
- The adverse event (adverse event classification, reported term) • Diagnostic test and test results
- Duration of the adverse event
- Seriousness
- Severity (e.g. mild, moderate, severe, life threatening)
- Causality assessment (relatedness).
- Action taken
- Outcome
- Date of onset
- Date PI or site became aware of (S)AE

Any abbreviations and codes will be clearly explained on each page.

5.3 Deaths, other serious adverse events, and other significant adverse events

5.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

Listings, containing the same information as called for in section 5.2.3 above, will be provided for the following events.

5.3.1.1 Deaths

All deaths during the study will be listed by participant.

5.3.1.2 Other serious adverse events

All serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) will be listed.

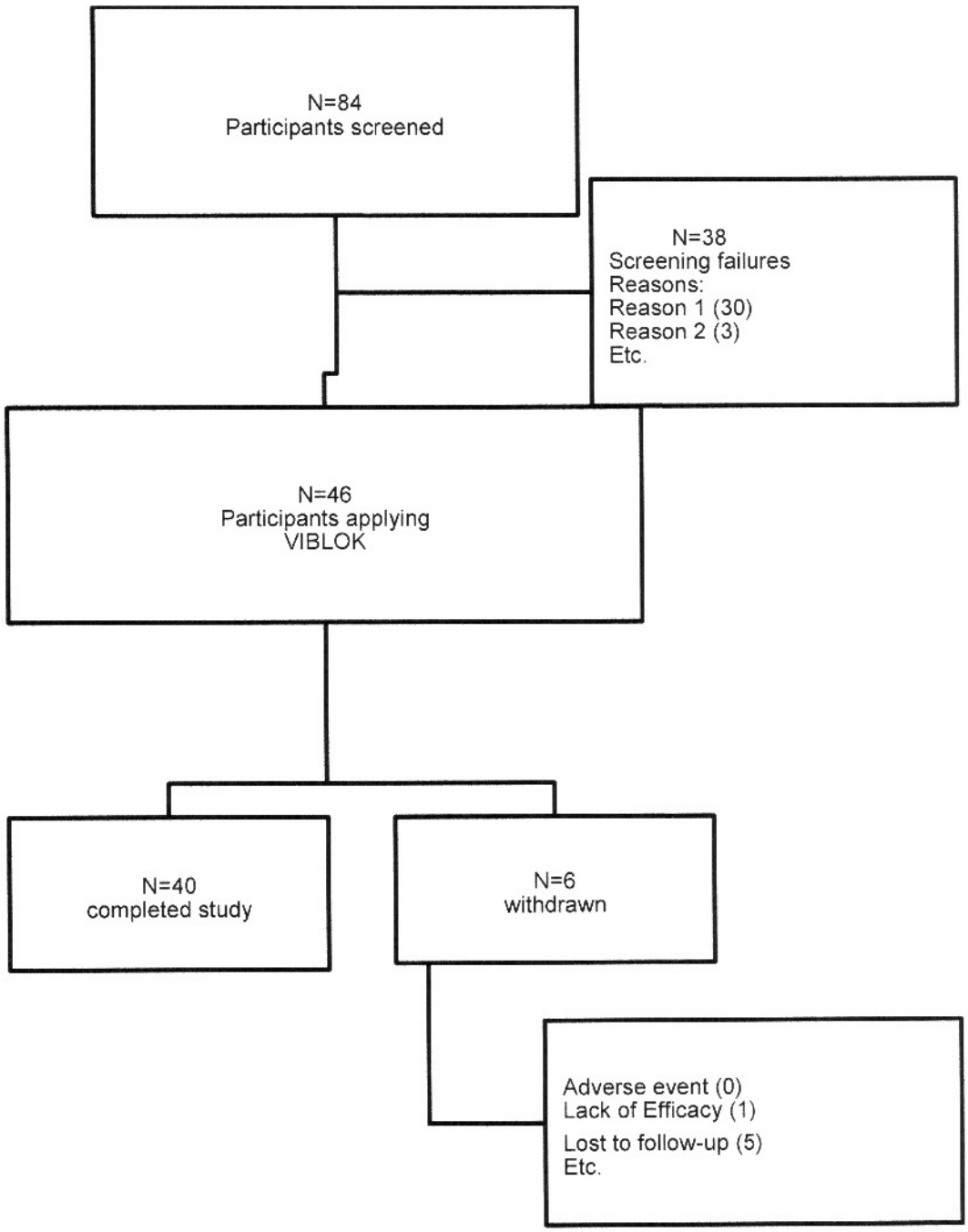
5.3.1.3 Other significant adverse events

Any events that led to an intervention, including withdrawal of VIBLOK or significant additional concomitant therapy, other than those reported as serious adverse events, will be listed.

5.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

There will be brief narratives describing each death, each other serious adverse event, and those of the other significant adverse events that are judged to be of special interest because of clinical importance. Events that were clearly unrelated to VIBLOK will be omitted.

6. ANNEX I DISPOSITION OF PARTCIPANTS



7. ANNEX II LISTING OF PARTICIPANTS WHO DISCONTINUED STUDY PRODUCT

Centre: X1 Participant: yyy

Reason for Discontinuation	Age	Last Visit	Duration	Concomitant Medication

Lost to followup	67	2	15	Medication y

Centre: X1 Patient: zzz

Reason for Discontinuation	Age	Last Visit	Duration	Concomitant Medication
Lack of efficacy	45	2	12	Medication z

Centre: X2 Patient: xxx

Reason for Discontinuation	Age	Last Visit	Duration	Concomitant Medication
Withdrawal of informed consent	22	1	20	Medication x

8. ANNEX III LISTING OF PARTICIPANTS AND OBSERVATIONS EXCLUDED FROM ANALYSES

Centre: X1 Patient: yyy

Age	Parameter	Visit	Analysis Set	Reason (s)
67	all	all	Per Protocol Population	Did not complete 26 days of treatment