Statistical Analysis Plan

Study information

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0.1	*NAME*	20190626	Draft version sent to sponsor and for internal senior review
1.0	*NAME*	20190705	Final version

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1 Abbreviations

Abbreviation	*Explanation*
ADE	*Adverse device effect*
AE	*Adverse event*
ASADE	*Anticipated serious adverse device effect*
ATC	*Anatomical Therapeutic Chemical [classification system]*
BV	*Bacterial vaginosis*
CI	*Confidence interval*
CIP	*Clinical Investigation Plan QRS-CL2-003, Version 2.0*
CRF	*Case report form*
DDP	*Data display plan*
FAS	*Full analysis set*
GDL	*Glucono-delta-lactone*
ICH	*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
ISO	*International Organization for Standardization*
MedDRA	*Medical Dictionary for Regulatory Activities*
NaG	*Sodium gluconate*
PP	*Per-protocol analysis set*
SADE	*Serious adverse device effect*
SAE	*Serious adverse event*
SAP	*Statistical analysis plan*
USADE	*Unanticipated serious adverse device effect*
WHO	*World Health Organisation*

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Investigation Plan and includes a more technical and detailed elaboration of the principal features of the proposed statistical analysis and presentations, and the way in which anticipated analysis problems will be handled.

The Investigational product, Gedea Pessary (commercial name *pHyph*), a slow-release formulation administering 300 mg GDL and 367.5 mg NaG over 45 hours, is generally denoted "treatment" in the SAP.

3 Study objectives

3.1 Primary objective

To investigate the clinical performance, tolerability, and safety of the investigational product.

3.1.1 Primary endpoints

- Clinical cure rate on Day 7
    - Defined as absence of all of the following Amsel criteria:
        - Thin, white, yellow, homogenous discharge
        - Clue cells on microscopy (more than 20% of epithelial cells)
        - Release of fishy odor "i.e. a positive whiff test" when alkali (10% potassium hydroxide [KOH] solution) is added
- Safety and tolerability, based on reported treatment-emergent AEs

3.2 Secondary objectives

To further investigate the clinical performance of the investigational product.

3.2.1 Secondary endpoints

Secondary endpoints:

<u>All patients</u>

- Proportion of patients being negative for each of the 3 Amsel criterion on Day 7 compared to Day 0
- Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) on Day 4 and Day 7, compared to Day 0

- Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 4 and Day 7
- Proportion of patients receiving prolonged treatment
- Usability, measured by patient questionnaire

For patients not receiving prolonged treatment

- Recurrence rate on Day 14 and Day 35, defined as the proportion of patients clinically cured on Day 7 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred

For patients receiving prolonged treatment

- Clinical cure rate on Day 14, defined as the absence of all of the 3 Amsel criteria as defined above
- Proportion of patients being negative for each of the 3 Amsel criterion on Day 14 compared to Day 0
- Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0
- Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42
- Recurrence rate on Day 21 and Day 42, defined as the proportion of patients clinically cured on Day 14 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred
- Proportion of patients receiving rescue treatment on Day 14

Exploratory endpoint variables:

All patients

- Effect on vaginal microbiome on Day 0 and Day 7
- Vaginal pH on Day 7

For patients not receiving prolonged treatment

- Effect on vaginal microbiome on Day 35

For patients receiving prolonged treatment

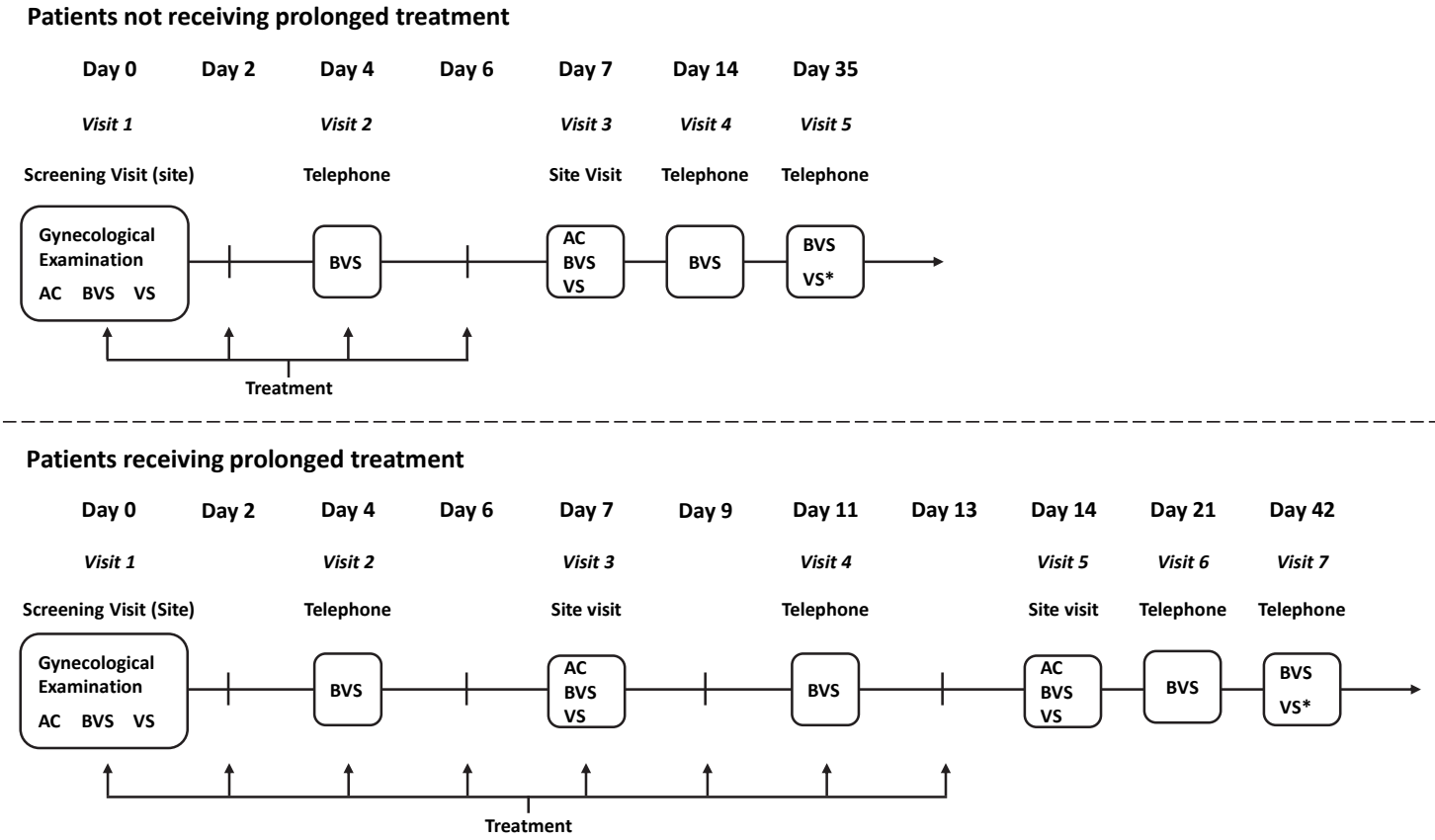
- Effect on vaginal microbiome on Day 14 and Day 42

4 Study design

This is an open-label, single-armed, multi-center study to evaluate clinical performance, tolerability, and safety of Gedea Pessary in 24 adult women with BV. Patients seeking treatment can be screened for study participation. Included patients will have gynecological examination, including collection of vaginal samples, and will receive the investigational product to be self-administered at Day(s) 0, 2, 4, and 6. Patients will again be examined after 7 days. Prolonged treatment at Day(s) 7, 9, 11, and 13 will

be given to patients not cured at Day 7; including re-examination at Day 14. Patients will be followed up by telephone up to 29 days after last treatment administration. Gynecological examinations include collection of Amsel criteria. Vaginal samples will be used for confirming diagnosis and microbiome analyzes. Patient questionnaires will be used for assessing BV symptoms, usability, and AEs.

Figure 1 Study Flow Chart



AC = Amsel's Criteria, BVS = Bacterial Vaginosis Symptoms, VS = Vaginal Swab (*Self-swab at home)
Patients not receiving prolonged treatment applies to patients cured at Day 7. If not cured, the flow chart *patients receiving prolonged treatment* applies. Patients will here receive an antibiotic if not cured at Day 14. Adverse events will be assessed throughout the study.

5 Study population

This study will include patients with BV. Twenty-four (24) patients are planned to be treated under this CIP

Post-menarchal, pre-menopausal females aged 18 years or older seeking treatment for symptoms of BV at study sites' gynecological clinics may be informed about the study and asked about their willingness to participate.

5.1 Sample size

Assuming the true cure rate is equal to 70 %, 22 patients are needed to obtain 90 % chance (90 % power) to show that the one-sided 95 % CI for the observed cure rate is above 40 %. To compensate for a small number of non-evaluable patients, 24 patients will be included.

6 Assessments

6.1 Clinical Performance Assessments

Assessments described below in Section 6.1.1, gynecological examination, will be used to diagnose BV according to the following Amsel criteria:

1. Thin, white, yellow, homogenous discharge
2. Clue cells on microscopy (more than 20% of epithelial cells)
3. pH of vaginal fluid above 4.5
4. Release of fishy odor “i.e. a positive whiff test” when alkali (10% potassium hydroxide [KOH] solution) is added

Presence of 3 out of the 4 Amsel criteria above will serve as diagnosis of BV

Clinical cure is defined as absence of the following 3 Amsel criteria and is a primary study endpoint together with safety and tolerability evaluations:

1. Thin, white, yellow, homogenous discharge
2. Clue cells on microscopy (20% of epithelial cells)
3. Release of fishy odor “i.e. a positive whiff test” when alkali (10% potassium hydroxide [KOH] solution) is added

The Amsel score will also be used for the following secondary endpoints:

- Proportion of patients being negative for each of the 3 Amsel criteria on Day 7 compared to Day 0
- Recurrence rate on Day 14 and Day 35, defined as the proportion of patients clinically cured on Day 7 and thereafter responding “yes” to a yes/no question from the patient questionnaire on whether the symptoms have recurred
- Proportion of patients receiving prolonged treatment
- Clinical cure rate on Day 14, defined as the absence of all of the 3 Amsel criteria as defined above
- Proportion of patients being negative for each of the 3 Amsel criteria on Day 14 compared to Day 0
- Recurrence rate on Day 21 and Day 42, defined as the proportion of patients clinically cured on Day 14 and thereafter responding “yes” to a yes/no question from the patient questionnaire on whether the symptoms have recurred

- Proportion of patients receiving rescue treatment on Day 14

Assessments described in Section 6.1.2, patient questionnaire, will be used to assess the following secondary endpoints:

- Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, irritation) on Day 4 and Day 7, compared to Day 0
- Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0
- Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 4 and Day 7
- Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42
- Usability, measured by patient questionnaire

6.1.1 Gynecological Examination

Patients will have gynecological examinations by the Investigator or an authorized designee on Day(s) 0 and 7; or Day(s) 0, 7, and 14 if receiving prolonged treatment, in order to assess presence of BV according to Amsel's criteria. At Day 0, a vaginal sample for bacterial culture will be taken to confirm diagnosis. Symptoms of BV (fishy smell, burning, and irritation) will also be assessed according to a scoring scale (0-3), where 0 = none (absent), 1 = mild (slight), 2 = moderate (definitely present), and 3 = severe (marked, intense). For handling of missing item data in the calculation of the sum of the 3 BV symptoms scores, see Section 7.1.5, and Section 8.7 below.

NOTE:	Symptoms of BV (fishy smell, burning, and irritation) will always be assessed by patients themselves, asked by the Investigator at site visits and by the Clinical Trial Unit at telephone visits.

6.1.2 Patient Questionnaire

The questionnaire can be found in **Error! Reference source not found.** in the CIP.

The Clinical Trial Unit will call the patients on Day(s) 4, 14 and 35; or Day(s) 4, 11, 21, and 42 if receiving prolonged treatment; and ask questions from the patient questionnaire relating to BV symptoms, usability, concomitant medications, and AEs, if any.

Questions from *Section 1* in the patient questionnaire relating to BV symptoms will be asked to patients over telephone on Day(s) 4, 14, and 35; or Day(s) 4, 11, 21, and 42 if receiving prolonged treatment. A recurrence question will be asked to patients at Days(s) 14 and 35 if not receiving prolonged treatment and at Days(s) 21 and 42 if receiving prolonged treatment.

Questions from *Section 2* in the patient questionnaire relating to usability will be asked to patients on Day 7, and Day 14 if receiving prolonged treatment.

Questions from *Section 3* and *Section 4* in the patient questionnaire relating to concomitant medications and AEs, respectively, will be asked to patients at each visit/telephone contact.

6.2 Safety and tolerability assessments

The below will constitute the local tolerability and safety assessments:

- Adverse events and Serious adverse events (SAEs), and
- Rate of withdrawals from the study and/or the study treatment.

7 Method of analysis

7.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline for Statistical Principles for Clinical Trials (1), using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

7.1.1 Presentation of results

If applicable, results will be presented together with the unit.

Continuous data will be summarised using descriptive statistics, and the following parameters will be reported:

- number of patients with evaluable observations and missing observations
- arithmetic mean and standard deviation
- median
- first and third quartiles
- minimum and maximum.

Categorical data will be presented using absolute frequency and percentage. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be the total number of patients in the applicable analysis set, including patients with missing data. For variables with missing values, the number and percentage of patients with missing values will be presented.

Statistical testing will be performed using an overall significance level of 5%. The primary endpoint analysis will be based on one-sided testing, whereas the secondary endpoints analyses will be based on two-sided testing. Corresponding confidence intervals will be presented. See Section 7.9 below for further information.

Data will be presented using an appropriate number of decimal places, to ensure that undue precision is not implied (*e.g.* the number of decimals should not exceed the accuracy of the measuring instrument). Raw data will be presented with the same number of decimals as collected, and derived data with an appropriate number of decimals based on general practice, mathematical rationale or scientific rationale.

Minimum and maximum values will be presented with the same number of decimals as the analysed variable and the other descriptive statistics will be presented with one decimal more. Percentages and proportions will be presented with one decimal. Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as '<.0001'.

Mock tables and graphs are presented in the Data Display Plan (DDP), which is a supplementary document to this analysis plan. Individual patient data listings will be presented according to the ICH E3 guideline for Structure and Content of Clinical Study Reports (2), unless stated otherwise.

7.1.2 Baseline

Unless stated otherwise, the baseline value for a parameter is defined as the last non-missing value before the first self-administration of the study treatment by the patient. The first self-administration is to be performed on the same day as the first study visit (Day 0), after the study visit.

7.1.3 Analysis relative day

The analysis relative day for an assessment/value is defined as the time in days from the date of first administration of treatment to the date of the assessment. The date of first administration of treatment is considered as day 0.

7.1.4 Analysis visit

An analysis visit is defined as a categorical variable used to classify values within an analysis variable into temporal or conceptual groups used for analyses.

The visits as defined in the case report form, CRF, will be used as analysis visits.

In general, data from unscheduled visits will be presented in data listings only and not included in analysis or summary tables. An exception to this is data used to confirm eligibility in association with screening or randomisation where the last assessment will be considered in summaries of screening data.

7.1.5 Handling of missing data

The statistical analysis will be based on the observed data, i.e. no imputation is planned. In case of one or more missing symptom value(s) in the 3 BV symptoms, the sum of the 3 BV symptoms scores will be set to missing, see also Section 8.7 below.

7.1.6 Interim analyses

Not applicable.

7.1.7 Multiplicity

Although there are two co-primary endpoints, no adjustment of e.g. p-values or confidence intervals will be applied. This is for two reasons, the first being that the evaluation of the second co-primary endpoint (safety and tolerability) will only be based on descriptive statistics and data listings, and the second is that both co-primary endpoints have to show favorable results.

For all other statistical analyses of the secondary endpoints, no adjustment due to multiple testing will be performed. It should be noted that the probability of making a type I error increases with the number of statistical tests performed.

7.1.8 Subgroups

Descriptive results of the primary clinical performance endpoint will be presented by study center, and by whether the patients at Day 0 reported 3 or more Bacterial Vaginosis infections during the last 12 months or not.

7.2 Analysis sets

The decision on the classification of patients to each analysis set will be taken at the clean file meeting and documented in the clean file report together with the reasons for excluding patients from analysis sets.

7.2.1 Full analysis set

Full Analysis Set (FAS): This is the primary population and comprises all patients entering the study and having received at least 1 dose of study treatment. Analyses of clinical performance will be performed against this population.

In addition to this, two sub-populations based on this FAS will be formed: “FAS (For patients not receiving prolonged treatment)”, and “FAS (For patients receiving prolonged treatment)”.

7.2.2 Per-protocol analysis set

Per Protocol (PP) Population - This will include all FAS patients without any major protocol deviation, i.e. patients who have completed the study and sufficiently complied with the study protocol, have available primary endpoint data and have received the study treatment according to protocol. The final definition of a major protocol deviation will be decided and defined at the clean file meeting and

documented in the clean file report. If a relevant number of patients are excluded from the PP population, then the analysis of the clinical performance endpoint will be provided for the PP population.

7.2.3 Safety analysis set

The safety analysis set will be based on the same definition as used for FAS. All safety analyses will therefore be performed against the FAS. All patients included in the FAS will be accounted for, including those who did not complete the study along with the reasons for withdrawal.

7.3 Disposition of patients

The following will be presented:

- Number of screened patients, in total.
- Number of screening failures, in total.
- Number of enrolled patients.

Based on the number of enrolled patients, the following will also be presented:

- Number and percentage of patients who did not receive any dose of study treatment.
- Number and percentage of patients who received at least one dose of study treatment.
- Number and percentage of patients who completed the study.
- Number and percentage of patients who withdrew prematurely from the study.
- Number and percentage of patients in each of the analysis sets.

In addition, a frequency table on the primary reason for premature withdrawal from the study will be presented. Percentages for this table will be based on the number of prematurely withdrawn patients.

The number of patients attending each study visit will also be summarised.

7.4 Protocol deviations

Protocol deviations will be presented in a data listing.

The number and percentage of enrolled patients with at least one major protocol deviation leading to exclusion from an analysis set will be presented.

7.5 Demographics and baseline characteristics

Summary statistics and frequencies on demographic data (age) and baseline characteristics (pregnancy test, and diagnosis information) will be presented for all analysis sets.

7.6 Medical history and concurrent diseases

Medical history and concurrent diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1).

For each system organ class and preferred term, the number and percentage of patients with at least one condition in that system organ class or preferred term will be presented. Medical history and concurrent diseases will be presented in separate tables, based on the full analysis set.

Medical history is defined as events stopped prior to baseline. Concurrent diseases are defined as ongoing events and events stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the events:

	Imputed start date	***Imputed end date***
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify the condition based on the reported and/or imputed start and end dates, it will be considered as concurrent. In data listings, the dates will be presented as reported.

7.7 Prior and concomitant medication

Medications will be coded according to the World Health Organisation (WHO) Drug Dictionary and summarised by therapeutic subgroup (ATC level 2) and preferred name.

For each therapeutic subgroup and preferred name, the number and percentage of patients who used at least one medication of that therapeutic subgroup or preferred name will be presented. Prior and concomitant medications will be summarised in separate tables, based on the full analysis set.

If a reported medication cannot be coded with a preferred name, the lowest available higher-level dictionary term will be used instead in the summary tables. If a medication cannot be coded on a lower level than the therapeutic subgroup or the anatomical main group (ATC level 1), that medication will be presented as 'Not codable' under that therapeutic subgroup/anatomical main group.

Prior medication is defined as medication stopped prior to baseline. Concomitant medication is defined as ongoing medication or medication stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the medication:

	Imputed start date	***Imputed end date***
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify a medication based on the reported and/or imputed start and end dates, it will be considered as concomitant. In data listings, the dates will be presented as reported.

Any use of rescue mediation will be identified as any concomitant medication used with “Indication (reason for medication)” equal to “Rescue medication” as recorded in the CRF.

7.8 Compliance

Patients will be asked about investigational product administration by telephone on Day 4 and at the site on Day 7, and also on Day(s) 11 (telephone) and 14 (site) if receiving prolonged treatment. No other measurements of treatment compliance will be made. These compliance data will be summarised for the full analysis set. The rate of compliance is defined as the actual amount of study treatment taken divided by the expected amount of study treatment to be taken. The expected amount is based on the planned duration of treatment (*i.e.* for prematurely withdrawn patients, the expected amount is computed as if the patient had not withdrawn). The expected amount is 4 doses for patients without prolonged treatment and 8 doses for patients with prolonged treatment.

7.9 Primary and secondary endpoints analyses

All analyses of clinical performance endpoints will be performed on the full analysis set, and these analyses will be considered as the main analyses. If a relevant number of patients are excluded from the PP population, the per-protocol analysis set will be used for supportive clinical performance sensitivity analysis of the primary clinical performance endpoint.

If the stated assumptions that the statistical evaluation is built upon can be questioned, suitable alternative methods may be applied. For example, a 95% confidence interval based on a non-parametric method may be applied if assumption of data belonging to the normal distribution seems not to hold.

All study endpoints (primary, secondary, and exploratory), as well as the related variables specified in the list below in Section 7.9.2, will be presented descriptively.

7.9.1 Primary endpoints

- Clinical performance endpoint: Clinical cure rate on Day 7 will be calculated and presented together with a one-sided 95 % confidence interval based on the exact binomial distribution (Clopper-Pearson).
- Clinical safety endpoint: Safety and tolerability will be assessed according to Section 7.10.2.

The primary clinical performance endpoint is the Clinical cure rate on Day 7, where clinical cure is defined as the absence of all of the Amsel criteria stated in Section 3.1.1 above. The primary performance objective of the trial is to show that the Clinical cure rate is above 40 %, i.e. to show that the lower limit of the one-sided 95 % CI for the observed cure rate is above 40 %.

Hypotheses for the primary clinical performance endpoint
Null hypothesis: Clinical cure rate is less than or equal to 40 %.
Alternative hypothesis (one-sided): Clinical cure rate is above 40 %.

The primary clinical safety endpoint, i.e. safety and tolerability based on reported treatment-emergent AEs, will be analysed descriptively only, see Section 7.10.2 below, and will thus not be connected to any formal hypothesis testing.

7.9.2 Secondary clinical performance endpoints

The secondary clinical performance endpoints are either binary or continuous.

The usability data, as measured by the patient questionnaire and which contain both binary and continuous endpoints, will only be presented descriptively.

The other binary secondary clinical performance endpoints will be calculated and presented together with a two-sided 95 % confidence interval based on the exact binomial distribution (Clopper-Pearson). No hypothesis testing will made on the binary endpoints.

The only remaining clinical performance endpoint that is considered as a continuous endpoint is the change in the sum of the 3 BV symptoms scores. Here, applying Student's t distribution, a two-sided 95% confidence intervals for the arithmetic mean will be presented.

Hypothesis for the continuous secondary clinical performance endpoint "Change in the sum of the 3 BV symptoms scores"
Null hypothesis: Change from baseline is = 0.
Alternative hypothesis (two-sided): Change from baseline ≠ 0.

Below follows a list of all secondary endpoints followed by information on which are binary and which are continuous. Note that, as described in Section 3.2.1 above, the analyses of the secondary endpoints will be performed on 3 different patient categories. These are denoted as A, B, and C below.

A. All patients

i] Proportion of patients being negative for each of the 3 Amsel criterion on Day 7 compared to Day 0
ii] Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) on Day 4 and Day 7, compared to Day 0
iii] Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 4 and Day 7
iv] Proportion of patients receiving prolonged treatment
v] Usability, measured by patient questionnaire

The endpoints i], ii], iv], and the first 4 questions in endpoint v] are binary variables.
The endpoints iii], and the 5th question in v] are considered as continuous variables.

B. For patients not receiving prolonged treatment

vi] Recurrence rate on Day 14 and Day 35, defined as the proportion of patients clinically cured on Day 7 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred

The endpoint vi] constitute binary variables.

C. For patients receiving prolonged treatment

vii] Clinical cure rate on Day 14, defined as the absence of all of the 3 Amsel criteria as defined above
viii] Proportion of patients being negative for each of the 3 Amsel criterion on Day 14 compared to Day 0
ix] Proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0
x] Change in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42
xi] Recurrence rate on Day 21, and Day 42, defined as the proportion of patients clinically cured on Day 14 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred
xii] Proportion of patients receiving rescue treatment on Day 14

The endpoints vii], viii], ix], xi], and xii] are binary variables.
The endpoints x] are considered as continuous variables.

In connection to the endpoints described above, the underlying variables listed below not constituting endpoints (denoted as "other related variables" in the CIP), will be presented descriptively, see DDP.

- BV symptoms: fishy smell (can take integer values in the interval 0-3)
- BV symptoms: burning (can take integer values in the interval 0-3)
- BV symptoms: irritation (can take integer values in the interval 0-3)
- Sum of all BV symptoms score (can take integer values in the interval 0-9)

7.9.3 Exploratory endpoints

The exploratory endpoints, see also Section 7.2 in the CIP, are listed below.

<u>All patients</u>
xiii] Effect on vaginal microbiome on Day 0 and Day 7
xiv] Vaginal pH on Day 7

<u>For patients not receiving prolonged treatment</u>
xv] Effect on vaginal microbiome on Day 35

<u>For patients receiving prolonged treatment</u>
xvi] Effect on vaginal microbiome on Day 14 and Day 42

The endpoints related to vaginal microbiome (endpoints xiii], xv], and xvi]) will be presented after study completion.

Vaginal pH, i.e. endpoint xiv] is considered as a continuous variable and will be presented descriptively.

7.10 Safety evaluation

All evaluations of safety data will be performed on the full analysis set.

7.10.1 Extent of exposure

See Section 7.8 above. Furthermore, as a measure of investigational product *in vivo* duration, patients' vaginal pH will be assessed on Day(s) 0 and 7. Vaginal pH lower at follow-up visits compared to Day 0 indicate appropriate release duration. Summary statistics on the vaginal pH will be presented.

7.10.2 Adverse Events

Adverse events will be coded according to MedDRA.

Only treatment-emergent adverse events, i.e. adverse events starting after administration of first dose of study treatment, will be presented as described below. Any adverse events reported to start before administration of first dose of study treatment will be listed separately. In the reminder of this section, the term "adverse event" should be interpreted as "treatment-emergent adverse event".

An overview of all adverse events will be presented, including the number and percentage of patients with at least one, and the total number, of the following:

- Adverse events.
- Serious adverse events.
- Adverse events leading to withdrawal of the investigational product.
- Fatal adverse events.
- Adverse events, broken down by severity (intensity).
- Adverse events, broken down by causality assessment (relationship).

The International Organization for Standardization (ISO) terms ADE, SADE, ASADE, USADE introduced in the CIP constitute adverse events where relationship to investigational device or study procedure is indicated. The classification of an untoward medical event as USADE or ASADE will be done retrospectively. The event will initially be captured as a serious adverse event.

The incidence of adverse events will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of adverse events as well as the number and percentage of patients with at least one adverse event in that system organ class or preferred term will be presented. The incidence of serious adverse events will be presented in the same way.

Separate tables for the incidence of adverse events broken down by severity and the incidence of adverse events broken down by causality assessment will also be presented by system organ class and preferred term.

There will also be tables on the most frequently reported adverse events, on system organ class level and on preferred term level. The decision on the frequency cut-off for these tables will be taken during the analysis of the adverse events data in consultation with the author of the clinical study report and could be influenced by factors such as the overall number of adverse events, study design, and the nature of the indication. The frequency cut-off should be mentioned in a table note.

Device deficiencies, as captured by the Device Event CRF module, will be presented in data listings only. If any device event is considered as also constituting an adverse event, it should be reported also as an adverse event.

7.10.3 Laboratory

The following laboratory variables are included in this study:

Microbiology assessments

- Assessment of BV according to Amsel's criteria performed? (Yes/No)
- Presence of at least 3 of the 4 Amsel's criteria stated in section 6.1 in CIP and SAP? (Present/Absent)
- Vaginal swab taken for culture? (Yes/No)
- Vaginal swab culture result (Positive/Negative)
    - If positive, species found should be indicated (5 categories + other)
- Vaginal swab taken for sequencing? (Yes/No) If No, specify reason (text)

Gynecological examination:

- Gynecological examination performed? (Yes/No)
- Vaginal pH (see Section 7.10.1 above)

The categorical microbiology laboratory parameters, as specified above, will be summarized in frequency tables by visit.

7.10.4 Physical examination

Not applicable.

7.10.5 Vital signs

Not applicable.

7.10.6 Electrocardiogram

Not applicable.

7.11 Changes to planned analysis

A clarification regarding the secondary endpoint

- Proportion of patients receiving prolonged treatment

is made. This endpoint is obviously intended to be based on “All patients”. However, in the CIP, this endpoint was unintentionally listed under the heading “For patients receiving prolonged treatment”. In this document it has therefore been listed in the correct heading “All patients”.

A subgroup analysis, based on whether the patients at Day 0 reported 3 or more Bacterial Vaginosis infections during the last 12 months or not, has been added for the primary clinical performance endpoint, see Section 7.1.8 above.

8 Derived variables

8.1 Disposition of patients

A screening failure is defined as a screened but not enrolled patient. An enrolled patient is defined as having passed the screening procedures and given informed consent. An enrolled patient who has received at least 1 dose of study treatment is qualified to be included in FAS.

8.2 Demographics and baseline characteristics

8.2.1 Age

Age will be computed as the integer part of the time in years between the date of birth and the date the written informed consent was signed, using the SAS function `yrdif()` with the basis parameter set to 'age'. For patients for whom only the year of birth is collected, age will be computed as the difference between the year the informed consent was signed and the year of birth.

8.3 Body mass index

Not applicable.

8.4 Change from baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value. This is applicable for the change in the sum of the 3 BV symptom scores (fishy smell, burning, and irritation) from Day 0 to specified follow-up visits, as well as for vaginal pH from Day 0 to Day 7.

8.5 Clinical cure rate

Clinical cure rate is based on a binary variable, where a clinically cured patient is defined as absence of all of the following Amsel criteria:

- Thin, white, yellow, homogenous discharge
- Clue cells on microscopy (more than 20% of epithelial cells)
- Release of fishy odor "i.e. a positive whiff test" when alkali (10% potassium hydroxide [KOH] solution) is added

8.6 Proportion of patients being negative for each of the Amsel criteria

The proportion of patients being negative for each of the Amsel criteria is based on binary variables.

A patient being negative for Amsel criterion 1 is defined as a patient with absence of the following Amsel criterion:

- Thin, white, yellow, homogenous discharge

A patient being negative for Amsel criterion 2 is defined as a patient with absence of the following Amsel criterion:

- Clue cells on microscopy (more than 20% of epithelial cells)

A patient being negative for Amsel criterion 3 is defined as a patient with absence of the following Amsel criterion:

- Release of fishy odor “i.e. a positive whiff test” when alkali (10% potassium hydroxide [KOH] solution) is added

The endpoints related to this, see Section 3.2.1 above, are phrased ”Proportion of patients being negative for each of the 3 Amsel criterion on Day 7 compared to Day 0”, and ”Proportion of patients being negative for each of the 3 Amsel criterion on Day 14 compared to Day 0”. These endpoints will ba calculated as stated in Section 8.6, i.e. without consideration of Day 0 values, but the number of patients being negative at Day 0 will be stated in a footnote in the result tables for these endpoints.

8.7 Proportion of patients having a reduction in the sum of the 3 BV symptoms scores

The proportion of patients having a reduction in the sum of the 3 BV symptoms scores (fishy smell, burning, and irritation) compared to Day 0 is based on a change from baseline variable, see Section 8.4 above, where a patient with reduction is defined as when the change from baseline in the sum of the 3 BV symptoms scores is < 0. If at least one symptom score is missing, the sum of the 3 BV symptoms scores will be set to missing.

8.8 Recurrence rate

Recurrence rate is based on a binary variable, where a recurred patient is defined as a patient clinically cured on Day 7 and thereafter responding “yes” at specified follow-up visits to a yes/no question from the patient questionnaire on whether the symptoms have recurred.

8.9 Proportion of patients receiving prolonged treatment

The proportion of patients receiving prolonged treatment is based on a binary variable which indicate whether a patient has received prolonged treatment or not, i.e. received study treatment on at least one of the days 7, 9, 11, or 13.

8.10 Proportion of patients receiving rescue treatment on Day 14

The proportion of patients receiving rescue treatment (an antibiotic treatment, as defined in the CIP) on Day 14 is based on a binary variable which indicate whether a patient has used rescue treatment or not, i.e. as shown by collected CRF concomitant meciation data, where start date of the rescue medication should be from or after Day 14. Start and stop date of use of such rescue medication will be presented in data listings.

8.11 Compliance/Exposure

See Section 7.8 above.

9 References

1. **ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials E9. February 1998.**

2. ICH Harmonised Tripartite Guideline for Structure and Content of Clinical Trial Reports E3. November 1995.

10 Signoff

We have read this SAP for the QRS-CL2-003 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Gedea Biotech AB: *NAME*

SIGNATURE AND DATE

Link Medical Research AB *NAME*

SIGNATURE AND DATE

Link Medical Research AB *NAME*

SIGNATURE AND DATE