Statistical Analysis Plan

Study Information:

Sponsor Study Code:	CL4
Study Title:	An open-labelled study to evaluate clinical performance of the Gedea Pessary in adult women with vulvovaginal candidiasis
Protocol Version and Date:	Version 4.0_ 2023-07-04
LINK Medical Study ID:	GED004

Document Control:

Document Version:	2.0
Status:	FINAL
Author:	*NAME* (Clinical Trial Consultants (CTC) AB, based on Final version 1.0 written by *NAME*, LINK Medical AB)

Document History

Version	Modified by (name and role)	Date	Description of Changes
FINAL v1.0	*NAME*	20JUN2022	First final version
FINAL v2.0	*NAME*	25MAR2024	Second updated final version

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1 Acronyms and Abbreviations used in the Document

Acronyms & Abbreviations	
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical [classification system]
CI	Confidence Interval
CIP	Clinical Investigational Plan
CRF	Case report form
CTC	Clinical trial consultants
CVVS	Composite vulvovaginal signs and symptoms
DDD	Defined daily dose
DDP	Data display plan
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
EU	European Union
FAS	Full analysis set
ICH	International Council on Harmonization
KOH	Potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
NC	North Carolina
pH	potential of Hydrogen
PPAS	Per protocol analysis set
PPAS25	Day 25 per protocol analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
USA	United States of America
VVC	Vulvovaginal candidiasis
WHO	World Health Organisation

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Investigation Plan (CIP) 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.

If the SAP suggests changes to the principal features stated in the CIP, these should also be documented in a CIP amendment. Otherwise, it will suffice to record the changes in the SAP.

3 Study Objectives

3.1 Primary Objective

To investigate clinical performance of acute treatment with Gedea Pessary in patients with vulvovaginal candidiasis (VVC).

3.1.1 Primary endpoint

The primary endpoint is the clinical cure rate on Day 7-14, which is defined as the percentage of patients clinically cured at Day 7 to Day 14.

Clinical cure is defined as the absence of signs and symptoms of VVC in terms of having a composite vulvovaginal signs and symptoms (CVVS) score ≤ 3.

Each of the following 6 vulvovaginal signs and symptoms will be individually scored using the scoring scale below.

- Vulvovaginal signs: erythema, oedema and excoriation
- Vulvovaginal symptoms: itching, burning and irritation

Scoring scale: each score should be objectively defined:

0 = none (absent)

1 = mild (slight)

2 = moderate (definitely present)

3 = severe (marked, intense)

The CVVS score is the sum of the 6 individual scores. If any of the 6 individual signs and symptoms are missing, then the CVVS score will be considered missing.

3.2 Secondary Objectives

To investigate the safety of acute treatment with Gedea Pessary and to further investigate the clinical performance of acute treatment with Gedea Pessary in patients with VVC.

3.2.1 Secondary Endpoints/Variables

1. Safety and tolerability, based on reported treatment-emergent AEs (safety endpoint).
2. Proportion of patients having a continued clinical response to treatment at Day 25, defined as the proportion of patients clinically cured on Day 7-14 and thereafter responding “no” to the yes/no question, “Have the symptoms recurred?”
3. Proportion of patients having a cure defined as clinical cure Day 7-14 according to primary endpoint and mycological cure (culture negative for growth of Candida species).
4. Proportion of patients having a reduction in CVVS score on Day 7-14 compared to Day 0.
5. Change in the CVVS score from Day 0 to Day 7-14.
6. Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Days 1-7, Day 11, Day 14 and Day 25, compared to Day 0.
7. Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Days 1-7, Day 11, Day 14 and Day 25, compared to Day 0.

8. Proportion of patients having a mycological cure as assessed by vaginal culture on Day 7-14 and Day 25.
9. Proportion of patients having an absence of Candida hyphae in the wet smear on Day 7-14.
10. Usability, measured by patient questionnaire, on Day 7.

3.3 Exploratory objective

The protocol did not state the objective for the exploratory endpoints, this has been added here.

To investigate if there is a difference in changes in the vaginal microbiome from baseline to day 7, 14, and 25 between patients that are clinical cured and patients that are not clinical cured and if presence of fungus DNA correlates with fungus assessed by culture and clinical cure.

To investigate *in vivo* duration as assessed by change in vaginal pH overall and separately in patients clinically cured and patients not clinically cured. A decrease in vaginal pH would indicate appropriate release duration.

3.3.1 Exploratory endpoints

1. Correlation between vaginal microbiome as assessed by vaginal swab DNA-analysis on Days 0, 7, 14, and 25 and clinical cure.
2. Correlation of presence of fungus as analysed by vaginal swab DNA-analysis on Days 0, 7, 14 and 25 and presence of fungus as assessed by culture
3. Correlation of presence of fungus as analysed by vaginal swab DNA-analysis on Days 0, 7, 14 and 25 and clinical cure.
4. Correlation of presence of fungus as assessed by culture on Days 0, 7, 14 and 25 and clinical cure.
5. Change in vaginal pH will be presented with descriptive statistics overall and separately for clinically cured and not clinically cured patients. A decrease from baseline in vaginal pH will indicate appropriate release duration.

4 Study Design

This is a multi-centre study to evaluate the clinical performance and safety of treatment with Gedea Pessary in adult women with confirmed VVC.

The study population will consist of post-menarchal, pre-menopausal females, 18 years or older, seeking care for VVC symptoms.

A total of 26 patients are planned to be included in the study.

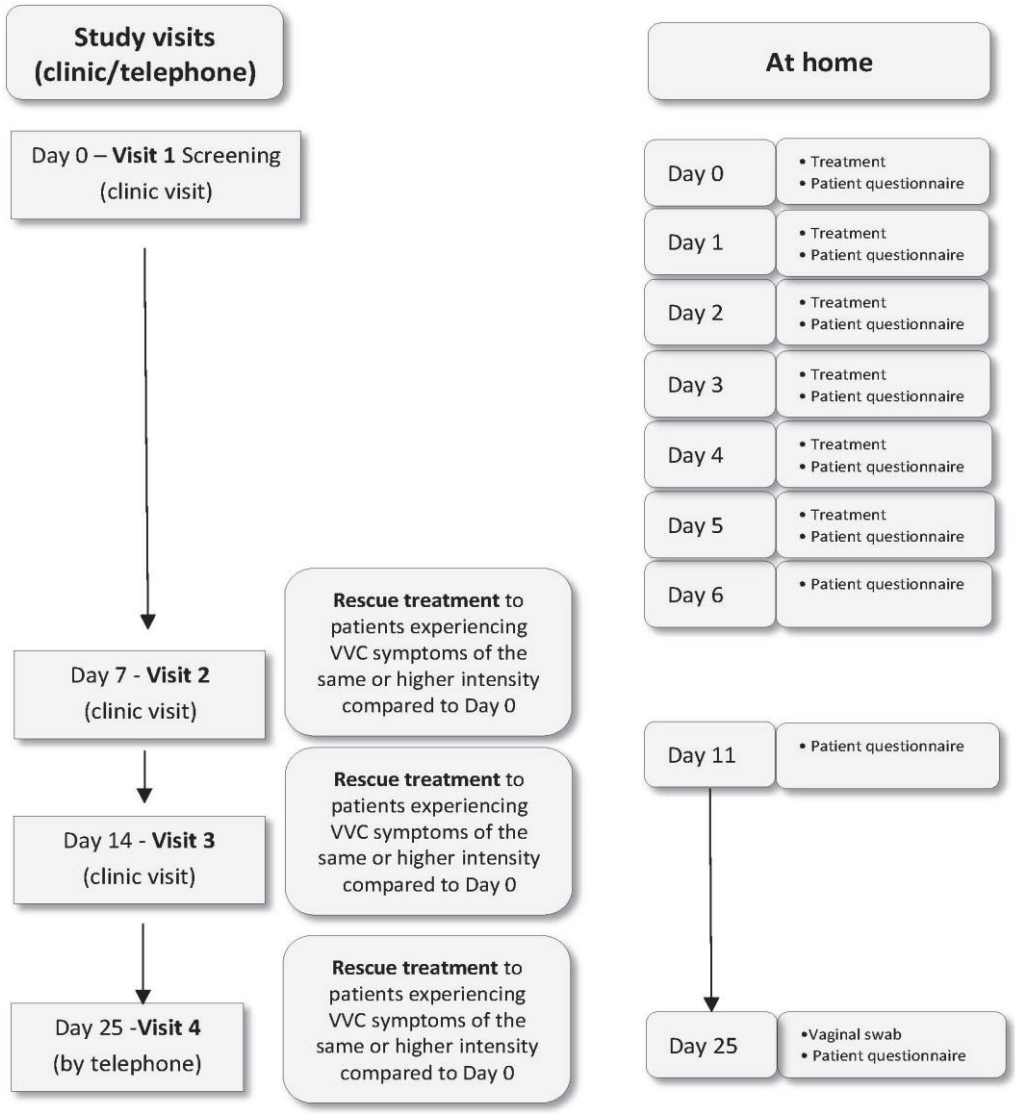
On Day 0 (Screening, Visit 1), eligible patients will undergo a gynaecological examination, including collection of CVVS data, and vaginal samples. Patients will be provided with 6 doses of Gedea Pessary that will be self-administered as a daily treatment (Days 0 to 5).

Patients will visit the clinic on Day 7 (+2 days, Visit 2) for gynaecological examinations, including collection of composite vulvovaginal signs and symptoms (CVVS) data for the assessment of clinical cure and reporting of AEs and concomitant medications. On Day 14 (±2 days, Visit 3), patients that did not have a clinical and mycological cure Day 7 will re-visit the clinic for additional gynaecological examinations, including collection of CVVS data for the assessment of clinical cure. Rescue treatment will be offered during visits 2 and 3, if necessary. Patients will have a final telephone follow-up on Day 25 (±3 days, Visit 4), for reporting of AEs, concomitant medications and potential menstruation onset.

Patient questionnaires for assessing VVC symptoms, will be used during the treatment period (Days 0 to 5), 1 day after the treatment (Day 6) and on Days 11 and 25. Usability will be assessed on Day 7, also via the patient questionnaire.

An overview of the study design is provided in Figure 1.

Figure 1 Study flow chart



5 Study Population

The study population will consist of post-menarchal, pre-menopausal females, 18 years or older, seeking care for VVC symptoms. To be included in the study, patients should have a VVC diagnosis. Patients with known or apparent signs of other infectious causes of VVC and patients who were treated for VVC within the past 14 days, or are currently receiving anti-fungal therapy unrelated to VVC will be excluded from the study.

5.1 Sample Size

Assuming a true proportion of 54% clinically cured in the treated group a sample size of 24 patients is needed to obtain 80% power to show that the one-sided 95% confidence interval (CI) for the clinical cure rate is above 30%. To compensate for patients with missing data a total of 26 patients will be included.

6 Assessments

An overview of the assessments performed during the study are presented in Table 1.

Table 1. Schedule of assessments and procedures

Evaluations	**Day 0**	**Day 0-5**	**Day 6**	**Day 7 (+2 days)**	**Day 11 (±1 day)**	**Day 14 [a] (±2 days)**	**Day 25 (±3 days)**
	Screening	**Treatment**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**
	Visit 1		***At home***	***Visit 2***	***At home***	***Visit 3***	***Visit 4 (Telephone)***
Informed consent	X						
Demography	X						
Eligibility criteria	X						
Pregnancy test (urinary)	X						
Medical and surgical history	X						
Prior and concomitant medications	X			X		X	X
Menstruation (date of end/onset)	X			X		X	X
Gynaecological examination incl. CVVS	X			X		X	
Vulvovaginal symptoms (via patient questionnaire or telephone)		X	X		X		X
Fungal microscopy assessment	X			X		X	
Vaginal swab for culture[b]	X			X		X	X
Vaginal swab for sequencing[b]	X			X		X	X
Treatment dispensing	X						
Treatment with Gedea Pessary[c]		X (Daily)					
Vaginal pH (pH strip test)	X			X			
Patient questionnaire/Usability			X				
AEs				X		X	X
Product accountability[d]				X			
Rescue treatment				X[e]		X[e]	X[f]

[a] Only for patients with no clinical and mycological cure Day 7.

[b] Self-swab on Day 25(presence of Candida + sequencing analysis of the vaginal microbiome).

[c] Treatment to be self-administered by the patient at home, at night before going to bed.

[d] Patients should be asked to return all used and not used treatment packages.

[e] Offered if the VVC symptom score on that day is equal to or higher than the score at the inclusion visit (Day 0).

[f] If symptoms recur on Day 25, or symptoms persist, rescue medication could be offered according to standard clinical practice.

6.1 Demography and baseline characteristics

Demographic information will be collected at Screening (Day 0) and will include initials, sex, birth date and ethnic origin (Caucasian, Asian or Pacific Islander, African descent, Mixed/multi-racial, or other).

All study patients will perform a pregnancy test (urine dipstick) at Screening (Day 0). Pregnancy is an exclusion criterion. If pregnancy is confirmed in a patient during the study, the patient will be withdrawn, and the pregnancy will be followed.

The Investigator or delegee will ask about onset and end of last menstruation on the Day 0 visit, and ask for possible menstruation onset on Day 7, Day 14 the Day 25. Intermittent bleeding should also be possible to register in the eCRF as AE.

6.2 Prior and concomitant medications

Information about any concomitant medication, including OTC medications and vitamins used by patients within 14 days prior to inclusion and during the study, will be collected at all site visits for all patients and also at the telephone contacts. The generic name or trade name, dosage and reason for use shall be recorded in the eCRF for all medications.

6.2.1 Rescue medication

On Days 7 and 14, patients having VVC symptoms of the same or higher intensity compared to the inclusion visit (Day 0), will be offered rescue treatment, if considered necessary. Rescue treatment will be according to standard clinical routines, as described below. Any rescue treatment will be administered after all assessments have been completed during the visit.

Patients will receive a prescription of fluconazole (50 mg as a single dose, orally) or clotrimazole pessary (500 mg as a single dose, intra-vaginally) and if necessary, topical treatment with 1% clotrimazole or 1% clotrimazole/1% hydrocortisone.

In addition, patients with recurrence or persistent symptoms on Day 25 (i.e., symptoms recurred on Day 25) may also be offered rescue treatment, according to the standard clinical routines mentioned above. The site will decide whether a visit to the clinic is needed and if rescue medication should be prescribed.

Patients taking rescue medications prior to the visit where clinical cure is assessed (Day 7 or Day 14), will be considered in the statistical analysis as described in Section 7.9.1.

The use of any rescue medication will be recorded in the eCRF.

6.2.2 Restrictions

During the study, the following medications are not allowed and should be avoided:

1. Anti-fungal medication related to VVC – explicitly anatomical therapeutic chemical (ATC) codes J02A and D01AC.
2. Other treatments for VVC (e.g. probiotics like Candicur and Multigyn).

Since use of concomitant anti-fungal therapy or other treatments related to VVC due to lack of efficacy prior to CVVS evaluation used for the primary endpoint definition is considered an intercurrent event, a review of all concomitant medication will be performed prior to data base lock to classify the concomitant medication as an intercurrent event or not.

6.3 Medical and surgical history

6.4 Gynaecological examination

Patients will undergo a gynaecological examination by the Investigator or an authorised designee at the site visits (on Day 0, Day 7 and Day 14), in order to assess:

- Vulvovaginal symptoms (itching, burning, and irritation) will be assessed by patients themselves according to a scoring scale (0-3) as per the patient questionnaire, on Days 0 to 6, Day 11 and Day 25 (see Section 6.5.1). On Day 0, 7 and 14 the investigator will ask the patient regarding the vulvovaginal symptoms and record this in the eCRF.

- Vulvovaginal signs (erythema, oedema and excoriation) will be assessed by the Investigator or authorised designee on Day 0, Day 7 and Day 14
- VVC diagnosis (assessed by the Investigator or designee): The diagnosis is based on CVVS score and microscopic analysis of a KOH or saline preparation, during the site visits (Day 0, Day 7 and Day 14). The assessments will be recorded in the eCRF. The diagnosis criteria are the following.
    - Having a white or creamy vaginal discharge
    - At least 2 of the following signs and symptoms of VVC that are characterised as at least moderate1: itching, burning, irritation, oedema, erythema, or excoriation.
    - KOH or saline preparation from the inflamed vaginal mucosa or secretions revealing yeast forms (hyphae or pseudohyphae) or budding yeasts.

For definition of clinical cure see Section 3.1.1.

6.5 Patient questionnaire

Questions will be asked directly in the electronic patient reported outcomes (ePRO) system via mobile phone or computer (ViedocMe™). Patient initiated ViedocMe forms will be tied to the same study day as it was initiated. However, forms that are initiated during the period 00:00 to 04:00 will be tied to the previous study day. In case of multiple assessments during the same study day (while also taking the mandatory forms into account), the first non-missing assessment will be used in analyses and summaries. If there are proofs like e-mail communication, or other proofs that a patient initiated form, initiated later, belongs to a previous day, this may be accepted.

6.5.1 Vaginal candidiasis symptoms and pessary administration

The following information will be collected in the ePRO system.

Pessary administration:

At Days 0 to 5, the patient should confirm that they have administered the pessary:

Question on treatment days:

Have you applied the pessary?

- Yes
- No

If no, please provide reason: (free text).

Scoring of vulvovaginal candidiasis symptoms:

The vulvovaginal candidiasis (VVC) symptoms will be rated by all patients on Days 0 to 6, Day 11 and Day 25.

The VVC symptoms will be rated according to 0-3 scale, as shown below.

	0 = none (absent)	**1** = mild (slight)	**2** = moderate (definitely present)	**3** = severe (marked, intense)
Itching				
Burning				
Irritation				

6.5.2 Usability

The below questions about usability will be filled in by all patients on Day 6.

1. Is the vaginal pessary easy to use?

- Yes
- No

If no, provide reason: (free text).

2. Did all pessaries remain in the vagina during treatment?

- Yes
- No

(if No) 2a. During how many dose administrations did you experience that the pessary did not remain in the vagina?

- Once
- 2-3
- 4-5
- All

2b. When the pessary does not remain, how would you describe what most frequently is happening?

- Just small pieces are falling out
- Large pieces are falling out

  Please specify after how long time they generally falls out.

  - Within 12 hours
  - Between 12-24 hours after administration
  - More than 24 hours after administration
- The whole pessary is falling out

  Please specify after how long time it falls out.

  - Within 12 hours
  - Between 12-24 hours after administration
  - More than 24 hours after administration

3. How do you generally regard the treatment?

1	2	3	4	5	6	7	8	9	10
Not satisfied									Very satisfied

6.6 Microbiology assessment

Vaginal samples will be collected via a vaginal swab by the Investigator or delegee on site visits (Day 0, Day 7 and Day 14) or by patients themselves at home, on Day 25.

The collected samples will be used for the following analyses.

- **Microscopic analysis; presence of hyphae:** KOH or saline test for fungus, using samples collected on Day 0, Day 7 and Day 14. Briefly, vaginal samples will be covered with 10% to 20% KOH, or 0.9% isotonic NaCl solution, and inspected under a microscope. Presence of hyphae

indicates Candida and will serve as an immediate, preliminary VVC diagnosis (present, absent, traced).

- **Candida culture:** Samples collected on Days 0, 7, 14 and 25, will be sent to laboratory for culture and confirmation of the VVC diagnosis/mycological cure. Vaginal swab culture result (positive, negative) and spieces present (C.albicans, C. tropicalis, C. glabrata, C. krusei, Other) will be recorded in the eCRF.
- **Sequencing of the vaginal microbiome:** Vaginal swabs for sequencing of the vaginal microbiome will be collected on Days 0, 7, 14, and 25.
  The effects of the investigational product on the vaginal microbiome will be assessed. Collected samples will be sent to a central laboratory for assessment of bacterial and fungus species, through DNA sequencing.

6.7 Vaginal pH

Patients' vaginal pH will be assessed on Day 0 and on Day 7 by the Investigator or delegee using a pH-test strip. Vaginal pH will be used for assessments of investigational product *in vivo* duration. If the vaginal pH on Day 7 is lower than the pH on Day 0, that would indicate appropriate release duration.

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

All results will be presented by treatment group and in total, unless stated otherwise. It should be clearly stated which unit applies to each presented variable.

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

- number of subjects 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.

Significance tests will be two-sided and performed at the 5% significance level, unless stated otherwise. When reporting the results of significance tests, p-values will be presented.

All confidence intervals presented will be two-sided with a nominal confidence level of 95%, unless stated otherwise.

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 two significant digits. 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 will be presented in a Data Display Plan (DDP), which will be a supplementary document to this analysis plan. The DDP will be finalised prior to database lock. Individual subject 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 administration of the investigational product. The start of the treatment period is explicitly defined as 18.00 at the day of screening.

7.1.3 Analysis Relative Day

The analysis relative day for an assessment/value is defined as the time in days from the first administration of the investigational product to the date of the assessment. The date of first administration of the investigational product is considered as Day 0, and earlier dates will correspond to a negative day.

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 randomization where the last assessment will be considered in summaries of screening data.

7.1.5 Handling of Missing Data and outliers

In general, no imputation of missing data will be performed.

Sensitivity analyses to evaluate the effect of missing data for the primary endpoint is described in Section 7.9.2.

Data listings will include the observed values. Outliers will generally be included in all analyses. However, individual values might be excluded based on scientific decisions taken at clean file.

7.1.6 Interim Analyses

Not applicable, no interim analyses will be performed.

7.1.7 Multiplicity

There is only one primary variable and therefore no adjustment for multiple comparisons were made.

For the secondary variables, no adjustments for multiple comparisons were made; 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

Two subgroup analyses will be performed descriptively. Clinical cure as defined in the primary endpoint will be summarized stratified by site and the number of previous infections. The latter will be grouped as 0-1 infections, 2 infections or 3 infections. A Wilson score CI will be presented for the proportion of clinical cure stratified by number of infections.

7.2 Analysis Sets

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

7.2.1 Full Analysis Set

The full analysis set (FAS) is defined as all subjects who received at least one administration of the investigational product.

7.2.2 Per Protocol Analysis Set

The per protocol analysis set (PPAS) is defined as the subset of subjects in the full analysis set for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified.

The decision as to which protocol deviations should be considered as reason for exclusion from the per protocol analysis set should be made at the clean file meeting and documented in the clean file report.

7.2.3 Day 25 Per Protocol Analysis Set

The day 25 per protocol analysis set (PPAS25) is defined as the subset of subjects in the FAS for whom no protocol deviation judged as having an impact on the day 25 analyses was reported or identified.

The decision as to which protocol deviations should be considered as reason for exclusion from the PPAS25 should be made at the clean file meeting and documented in the clean file report.

7.3 Disposition of Subjects

The following will be presented:

- Number of screened subjects
- Number of screening failures
- Number of enrolled subjects
- Number of subjects who received at least one administration of the investigational product.
- Number of subjects who completed the study.
- Number of subjects who withdrew prematurely from the study.
- Number of subjects in each of the analysis sets.

In addition, the primary reason for premature withdrawal from the study will be presented.

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

7.4 Protocol Deviations

Protocol deviations will be presented in a data listing.

7.5 Demographics and Baseline Characteristics

Summary statistics and frequencies on demographic data (age, sex and ethnic origin) and consent details (childbearing potential, number of VVC infections during last 12 months) will be presented for the FAS.

7.6 Medical History and Concurrent Diseases

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

For each system organ class and preferred term, the number and percentage of subjects with at least one condition in that system organ class or preferred term will be presented. Medical history and concurrent diseases will be presented 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 ATC classification system' (ATC/DDD Index 2022) and summarized by therapeutic subgroup (ATC level 2) and chemical substance (ATC level 5).

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

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.

7.8 Compliance

Compliance will be calculated as specified in Section 8.3. Compliance will be summarised for the full analysis set.

7.9 Efficacy Evaluation

All endpoints, clinical performance and safety, will be performed on the FAS and will be considered as the main analyses. Supportive analyses for clinical performance will be performed on the PPAS for all efficacy endpoints, except Day 25 assessments, which will be performed on PPAS25.

7.9.1 Estimand consideration

The study estimands will be defined based on the 5 attributes listed in the ICH E9 (R1) guideline:

***The treatment.** See Sections 7.1 and 7.2 of the CIP.

***The population.** See study inclusion and exclusion criteria in Sections 6.3 and 6.4 of the CIP, and the description of the main analysis set populations that will be used in Section 7.2.

***The endpoint.** The final endpoints are defined in Sections 7.9.2 and 7.9.3. When the composite strategy has been used to account for the identified intercurrent events, the intercurrent events have been incorporated into the final endpoint definition, see further information below in Sections 7.9.2 and 7.9.3.

***Other intercurrent events.** In this study, the strategy for addressing intercurrent events has been chosen to be built into one of the other attributes, namely the endpoint attribute, i.e. the composite strategy has been applied to the identified intercurrent events.

***Population-level summary of the endpoint.** This is described in Section 7.9.2 and 7.9.3.

7.9.2 Primary Variable

The primary endpoint is the clinical cure rate on Day 7-14, which is defined as the percentage of patients clinically cured at Day 7 to Day 14.

Clinical cure is defined as the absence of signs and symptoms of VVC in terms of having a CVVS score ≤ 3.

Each of the following 6 vulvovaginal signs and symptoms will be individually scored using the scoring scale below.

- Vulvovaginal signs: erythema, oedema and excoriation
- Vulvovaginal symptoms: itching, burning and irritation

Scoring scale: each score should be objectively defined:

0 = none (absent)

1 = mild (slight)

2 = moderate (definitely present)

3 = severe (marked, intense)

The CVVS score is the sum of the 6 individual scores. If any of the 6 individual signs and symptoms are missing, then the CVVS score will be considered missing. The last non-missing assessment of CVVS in the interval of Day 7-14 will used. However, if the patient received rescue medication between the CVVS assessments at Day 7 and 14, CVVS data from Day 7 will be used. The same derivation will be made for secondary and exploratory endpoints made during the same time interval Day 7-14.

In the estimand setting, the primary endpoint will take the following identified intercurrent events into account:

1. Concomitant anti-fungal therapy or other treatments related to VVC due to lack of clinical performance prior to CVVS evaluation used for the primary endpoint definition.
2. Treatment discontinuation due to lack of clinical performance.
3. Rescue medication prior to the CVVS evaluation used for the primary endpoint definition.

Rescue medication prior to the CVVS evaluation used for the primary endpoint definition. From a practical perspective, bullet points 1 and 3 above will be regarded as the same in this study. Applying the composite strategy to account for these intercurrent events, these have been incorporated in the endpoint definition. Thus, to be defined as clinically cured on Day 7-14, the patient needs to have the last available CVVS score equal to or below 3 at Day 7-14, and that none of the above stated intercurrent events have occurred. If the CVVS score is above 3, or any of the intercurrent events has occurred, the patient is defined as not clinically cured on Day 7-14.

Patients with missing CVVS score at Day 7-14 and no intercurrent events will be considered as missing in the analysis.

The primary endpoint clinical cure rate on Day 7-14, as defined in the section will be calculated and presented together with a one-sided 95 % CI based on the Wilson score.
The primary performance objective of the trial is to show that the clinical cure rate is above 30 %, i.e. to show that the lower limit of the one-sided 95 % CI for the observed cure rate is above 30 %.

Hypotheses for the primary clinical performance endpoint
Null hypothesis: Clinical cure rate is less than or equal to 30 %.
Alternative hypothesis (one-sided): Clinical cure rate is above 30 %.

7.9.3 Secondary Performance Variables

All secondary clinical performance endpoints will be presented with descriptive statistics. The following binary secondary clinical performance endpoints will show the endpoint estimate together with a two-sided 95% CI based on the Wilson score.

- Proportion of patients having a continued clinical response to treatment at Day 25, defined as the proportion of patients clinically cured on Day 7-14 (taking into account the intercurrent events and applying the composite strategy as described in Section 7.9.1) and thereafter responding “no” to the yes/no question, “Have the symptoms recurred?” and no rescue medication has been given up to day 25
- Proportion of patients having a cure defined as clinical cure Day 7-14 according to primary endpoint (taking into account the intercurrent events and applying the composite strategy as described in Section 7.9.1) and mycological cure at Day 7-14 (culture negative for growth of Candida species).
- Proportion of patients having a reduction in CVVS score on Day 7-14 compared to Day 0.
- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Days 1 to 7, Day 11, Day 14 and Day 25, compared to Day 0.
- Proportion of patients having a mycological cure as assessed by vaginal culture on Day 7-14 and Day 25.
- Proportion of patients having an absence of Candida hyphae in the wet smear on Day 7-14.

Presentation of the continuous secondary clinical performance endpoints below will include the two-sided 95% CIs for the arithmetic mean.

- The change in CVVS score from Day 0 to Day 7-14 (last available assessment).
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) to each post baseline assessment.

Usability will be measured on Day 6, by a patient questionnaire (see Appendix 1). The questionnaire contains 2 yes/no (i.e. binary) variables, 2 categorical variables and the question, “How do you generally regard the treatment?”, rated on a 1-10 integer scale. These endpoints will be presented descriptively, treating the question rated on the 1-10 scale as a continuous variable. In case of multiple assessments of usability, the first non-missing value will be used.

7.9.4 Adverse events

Adverse events will be coded according to MedDRA.

An overview of all adverse events will be presented, including the number and percentage of subjects 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.
- Adverse events, broken down by causality assessment.

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 subjects with at least one adverse event in that system organ class or preferred term will be presented.

7.9.5 Exploratory endpoints

The endpoint

- Correlation between bacterial vaginal microbiome as assessed by vaginal swab DNA-analysis on Days 0, 7, 14, and 25 and clinical cure.

will not be analysed by CTC. Hence, it is not elaborated on further in this SAP.

The endpoint

- Correlation of presence of fungus as analysed by vaginal swab DNA-analysis on Days 0, 7, 14 and 25 and presence of fungus as assessed by culture

will be addressed descriptively in a frequency table by timepoint. Results will be presented for each fungus species and overall, for any fungus in culture or swab DNA-analysis respectively.

In addition, to assess magnitude of shifts over time the value of fungus as analysed by vaginal swab DNA-analysis will be summarised per timepoint stratified by the magnitude of fungus as assessed in culture, with the latter being expressed as weak, moderate or abundant growth. Results will be presented for each fungus species. The endpoints

- Correlation of presence of fungus as analysed by vaginal swab DNA-analysis on Days 0, 7, 14 and 25 and clinical cure.
- Correlation of presence of fungus as assessed by culture on Days 0, 7, 14 and 25 and clinical cure.

will be addressed descriptively by frequency tables by timepoint. In addition, the magnitude (value) of fungus as analysed by vaginal swab DNA-analysis will be summarized descriptively per timepoint stratified by clinical cure. Furthermore, the relationship between magnitude (value) of each fungus species analysed in culture, and expressed as weak, moderate or abundant, and clinical cure will be summarised descriptively in a frequency table.

Additionally, number of previous infections (0-1, 2 or 3) will be correlated to levels of fungus as analysed by vaginal swab DNA-analysis by summarizing the latter descriptively per timepoint stratified by previous infections.

Change in vaginal pH will be presented with descriptive statistics overall and separately for clinically cured and not clinically cured patients. A decrease from baseline in vaginal pH will indicate appropriate release duration.

All analyses described in this section involving clinical cure will be done for clinical cure as defined in the primary endpoint, i.e. over the period Day 7-14, as well as for clinical cure at Day 7 and 14 respectively.

7.10 Changes to Planned Analysis

7.10.1 Vaginal pH endpoint

Vaginal pH was not defined in the CIP as an endpoint. This was added as an exploratory endpoint that will be analysed as described in Section 7.9.5. In addition, an objective for this endpoint was added.

7.10.2 Clarification on exploratory endpoint regarding correlation of fungus and clinical cure

The CIP stated as exploratory endpoint:

“Correlation of presence of fungus as analysed by vaginal swab DNA-analysis on Days 0, 7, 14 and 25 and presence of fungus as assessed by culture, and clinical cure.”

This endpoint has been separated to three endpoints in Section 7.9.5 to clarify the different correlations to be investigated.

7.10.3 Subgroup analyses have been added

Two subgroup analyses have been added summarising the primary endpoint by site and number of previous infections respectively. The idea being to capture any potential treatment heterogeneity upon stratification on these variables.

7.10.4 Day 25 per protocol analysis set

A new analysis population, PPAS25, has been added to be used for efficacy assessments at Day 25. The idea being to take into account protocol deviations affecting Day 25 efficacy analyses specifically (which is not covered explicitly by PPAS).

7.10.5 The section of exploratory endpoints have been elaborated on

New analyses compared to the CSP have been proposed, for example correlation analyses using the magnitude and not only the presence of fungus (see section 7.9.5 above).

8 Derived Variables

8.1 Disposition of Subjects

A screening failure is defined as a patient with a screening visit (Day 0) but answering ‘No’ to the question ‘Is the patient continuing in the study’ at the screening visit.

8.2 Change from Baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value.

Percentage change from baseline will be computed as 100 times the change from baseline divided by the baseline value.

8.3 Compliance

Two separate calculations will be used to derive compliance (%).

Patient reported compliance will be calculated as 100 × the number of ordinary study days (0 to 5) the patient responded yes to the question ‘Did you apply the pessary’ divided by 6.

Pessary kit derived compliance will be calculated as 100 × 6 x (number of pessary kit returned – number of pessaries lost – number of returned unused pessaries) to the clinic divided by 6. Note that this definition implies non-compliance in case of failure to bring back kits to the clinic.

Total study compliance will subsequently be derived as the maximum of patient reported compliance and pessary kit compliance.

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.

9 Signoff

We have read this SAP for the CL4 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

DocuSigned by:

NAME

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