CLINICAL INVESTIGATION PLAN

AN OPEN-LABELLED STUDY TO EVALUATE CLINICAL PERFORMANCE OF THE GEDEA PESSARY IN ADULT WOMEN WITH VULVOVAGINAL CANDIDIASIS

Study Product:	Gedea Pessary, *p*Hyph gen II
Study Number:	CL4
Sponsor:	Gedea Biotech AB Medicon Village SE-223 81 Lund, Sweden
Clinical Investigation Plan (CIP) document ID:	QRS-CL4-003
CIV ID:	CIV-22-01-038786
CIP Version number:	4.0
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INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Gedea Biotech AB, Sweden, is the Sponsor of the clinical investigation and is funding the investigation. All financial details are provided in the separate contract(s) between the Institution, the Investigator, and the Sponsor or designee. The Sponsor will compensate the Institution for their work in the study. However, the compensation will not be affected by the outcome of the study.

The Sponsor or designee maintains appropriate insurance coverage for clinical investigations and will follow applicable local compensation regulations. All patients in the study can retrieve financial compensation in the case of harm as a consequence of study participation.

The Investigators and key study administrative personnel are presented in the list below. A full contact list will be provided to all sites in the Investigator site file (ISF).

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APPROVAL PAGE

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Clinical Trial Consultants CTC AB

SYNOPSIS

Name of Sponsor:

Gedea Biotech AB

Name of product:

Gedea Pessary (*p*Hyph gen II)

Name of active ingredient:

Glucono-delta-lactone (GDL) and sodium gluconate (NaG).

Title of study:

An open-labelled study to evaluate clinical performance of the Gedea Pessary in adult women with vulvovaginal candidiasis

Clinical investigation plan number:

QRS-CL4-003

Coordinating Investigator:

NAME

Classification of study:

Clinical investigation

Objectives:

Primary objective:

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

Primary endpoint:

Clinical cure rate on Day 7-14, defined as the percentage of patients clinically cured at Day 7-14.

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.

Secondary endpoints:

1. Safety and tolerability, based on reported treatment-emergent adverse events (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 composite vulvovaginal signs and symptoms (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 6.

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, and clinical cure.

Methodology:

This is an open-labelled study to evaluate the clinical performance and safety of treatment with Gedea Pessary in adult women with confirmed VVC.

Number of patients planned:

26 patients

Diagnosis and main criteria for inclusion:

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 form the study.

Investigational products, dose and mode of administration:

Test product: Gedea Pessary, a pessary containing 150 mg GDL and 184 mg NaG, administered vaginally with a CE-marked pessary applicator. The Gedea Pessary (commercial name *p*Hyph) is a Class IIb medical device according to Medical device regulation (MDR) 2017/745.

Study duration:

Planned study time: First patient in: Q1 2023. Last patient out: Q3 2023.

Duration: Patients will be treated for 6 days (Day 0 to Day 5) and have 4 follow-ups (on Day 4, Day 7, Day 14 and Day 25). The total study duration will be 26 days (±3 days), including Screening.

Statistical methods:

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.

The primary performance objective of the trial is to show that the clinical cure rate is above 30 %, i.e. to show that the one-sided 95 % CI for the observed cure rate is above 30 %. The primary

endpoint, clinical cure rate on Day 7-14, will be presented together with a one-sided 95% CI based on the Wilson score.

The secondary endpoint safety and tolerability, based on reported treatment-emergent adverse events (AEs) will be presented descriptively.

All secondary clinical performance endpoints will be presented with descriptive statistics. Binary secondary clinical performance endpoints will show the endpoint estimate together with a two-sided 95% CI based on the Wilson score. Presentation of continuous secondary clinical performance endpoints will include the two-sided 95% CIs for the arithmetic mean.

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ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
ATC	Anatomical therapeutic chemical classification system
BV	Bacterial vaginosis
CA	Competent authority
CI	Confidence interval
CIP	Clinical investigation plan
CIR	Clinical investigation report
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRO	Contract research organisation
CVVS	Composite vulvovaginal signs and symptoms
DPO	Data Protection Officer
eCRF	Electronic case report form
ePRO	Electronic patient reported outcomes (system)
FAS	Full analysis set
FDA	The U.S. Food & Drug Administration
GCP	Good clinical practice
GDL	Glucono-delta-lactone
GDPR	General Data Protection Regulation
GLP	Good laboratory practice
GMP	Good manufacturing practice
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International conference on harmonisation
ICPS	International Programme on Chemical Safety
IEC	Independent ethics committee
ISF	Investigator site file
ISO	International Organization for Standardization
KOH	Potassium hydroxide
MDR	Medical device regulation
MedDRA	Medical dictionary for regulatory activities
NaCl	Sodium Chloride
NaG	Sodium gluconate
OTC	Over the counter

PPAS	Per protocol analysis set
PT	Preferred term
RA	Regulatory authorities
SaaS	Software as a Service
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SOC	System organ class
SOP	Standard operating procedure
VVC	Vulvovaginal candidiasis
U-HCG	Urinary human chorionic gonadotropin
USADE	Unanticipated serious adverse device effect
WHO	World Health Organization

1 STATEMENT OF COMPLIANCE

This clinical investigation will be conducted in accordance with this CIP which has been prepared in accordance with:

- The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) (ICH Harmonised Tripartite Guideline)/Note for Guidance on Good Clinical Practice: CPMP/ICH/135/95, January 1997 (where applicable to medical devices).
- The principles of the European Standard EN International Organization for Standardization (ISO) 14155:2020 Clinical Investigation of Medical Devices for Human Patients – Good Clinical Practice.
- The Medical device regulation (MDR) 2017/745.
- MDCG 2020-10/1 Guidance on safety reporting in clinical investigations (May 2020)
- The latest revision of the Ethical Principles for Medical Research Involving Human Subjects (World Medical Association Declaration of Helsinki).
- The ICH E9 (R1) addendum: Statistical Principles for Clinical Trials.
- Local laws and regulations/applicable regulatory requirements.

2 ETHICAL AND REGULATORY CONSIDERATIONS

The Sponsor or designee will, prior to site initiation, obtain favourable opinion/approval to conduct the study from all regulatory agencies (RAs)/competent authorities (CAs) in accordance with any applicable country specific regulatory requirements.

It is the responsibility of the Sponsor to submit the CIP, any protocol amendments, the patient information sheet and informed consent form (ICF), patient recruitment procedures, the Investigator's Brochure (IB), information on payments and compensation available to patients, Investigator remuneration and other study-specific documentation (as required) to the applicable independent ethics committee (IEC).

Any additional requirements imposed by the IEC, RA or CA after their review shall be followed, as applicable.

The IEC which reviewed and approved the study, as well as the name of the committee chairmen will be included in the Clinical investigation report (CIR). All applicable ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening for eligibility.

The Coordinating Investigator is obliged to submit substantial amendments and other relevant updates to safety information to the IEC. The Sponsor is obliged to submit substantial amendments and other relevant documents to the RA.

No substantial amendments to the CIP may be implemented prior to receipt of written approval from the IEC and/or RA, as applicable, unless the amendments are necessary to avoid immediate hazard for the patient. The Coordinating Investigator will maintain an accurate and complete record of all submissions made to the IEC.

The Sponsor will compensate the study site for their work in the study. However, the compensation will not be affected by the outcome of the study.

Patients will receive a small token of appreciation as compensation for study participation and they will be reimbursed for any reasonable travel cost as a result of participating in this study.

All patients participating in the study can retrieve financial compensation in the case of harm (see Section 13.10).

Each patient will be given full information about the study and will be asked to sign the ICF prior to initiation of any study-related activities (see Section 6.1). Patients will be free to withdraw from the study at any time (see Section 6.6.1).

Each patient should be informed in writing that the study results will be stored and analysed in a computer, maintaining confidentiality in accordance with local data protection laws (see Sections 6.1 and 13.9).

3 INTRODUCTION

3.1 Indication

Vaginal infection is a huge and largely underestimated problem, affecting 70% to 75% of women at some point in their life, and 5% to 8% of adult women have recurrent vulvovaginal candidiasis (VVC) with ≥ 4 episodes yearly.[1,2]

The vaginal microbiome is a dynamic system, composed of a complex mixture of microorganisms in different ratios and quantities, which depend on lactic acid producing bacteria to maintain a weakly acidic environment.[3] Changes to vaginal microflora increase the pH, thereby forming a favourable environment for vaginal pathogens. Vaginal or systemic antibiotics treatment is frequently followed by VVC, likely due to the elimination of the protective bacterial flora, thereby allowing *Candida* overgrowth.[4-8] Infections are also facilitated due to the mucosal effect of increased oestrogen levels and a weakened immune system during pregnancy.[9] Recurrences are more common in pregnant women, and their therapeutic response is reduced compared to non-pregnant women.[10, 11] Further, contraceptive pills, menstruation, and diabetes mellitus have been identified as predisposing factors for VVC.[12, 13] *Candida albicans* is the most prevalent pathogen, which, according to epidemiological studies, is present in between 73% and 92% of vaginal isolations.[14] *Candida glabrata* is the second most prevalent pathogen.[14]

Many women diagnose themselves with VVC and purchase over the counter (OTC) anti-mycotic treatments. However, many misdiagnose themselves and therefore receive unnecessary or inappropriate treatment.[15] In a study of 95 symptomatic women who purchased OTC anti-mycotics for treatment of presumed VVC, only 34% of them were actually diagnosed with VVC.[16] The most common other diagnosises were bacterial vaginosis (BV; 18.9%), mix of BV and VVC (18.9%), and normal (13.7%).

Current treatment strategies for uncomplicated or acute VVC include anti-mycotic vaginal creams or pessaries/vaginal tablets, such as econazole, clotrimazole, or miconazole for 1 to 7 days, or single-dose oral fluconazole. Reported clinical cure rates are variable, which may reflect different clinical cure definitions between studies. Clinical cure rates after 27 to 38 days of intravaginal imidazole treatment (clotrimazole, terconazole, butoconazole, or

miconazole) have been reported in a range of 64% to 87%, across different studies. None of these clinical cure rates were statistically significant.[17, 18] Short-term clinical cure rates have been reported to be 85% 1 to 2 weeks after treatment,[20] but also as low as 35% 7 days after treatment.[19] Mycological cure rates have been reported to be higher compared to clinical cure rates in some studies and lower in others.[19-22]

Severe VVC is characterised by extensive vulvar oedema, excoriations, and fissure formation. Short courses of treatment, which are normally effective in uncomplicated VVC, are often not sufficient.[15] Recommendations for treating severe and complicated VVC include 2 to 3 oral doses of fluconazole, oral itraconazole for 3 days, boric acid vaginal insert for 2 weeks, or topical therapy for 7 to 14 days.[18, 22, 23]

Recurrent VVC is characterised by ≥ 4 yearly episodes, and treatment usually entails intensive initial therapy to induce clinical and mycological remission, followed by a 6-month systemic fluconazole maintenance therapy.[15, 24, 25] While treatment guidelines for recurrent VVC are consistent, recommended treatments are not particularly effective in the long term [17, 24], as 30% to 50% of patients experience recurrence after treatment discontinuation.[15]

Oral anti-fungal therapies are not recommended during pregnancy due to the potential risk of foetal harm and spontaneous abortions.[26-28] Therefore, treatment guidelines recommend that topical, rather than oral, anti-fungal therapy is used in pregnant women.[17]

There are limited data regarding the anti-fungal susceptibility of the *Candida* causing VVC, as VVC cultures are rarely performed. The prevalence of fluconazole-resistance among *C. albicans* isolates has been reported to be between 2.1% and 21% in different studies.[31-34] Fluconazole or itraconazole resistance is found in a larger proportion of non-albicans *Candida* species; resistance to fluconazole was found in 15% of *C. glabrata* isolates and 42% of *Candida krusei* isolates, and resistance to itraconazole was found in 74% and 58% of *C. glabrata* and *C. krusei* isolates, respectively.[33]

In summary, current treatment and prevention strategies for infections in the genital area are limited, and there is a need for novel OTC treatment alternatives which are safe during pregnancy and have low risk for resistance development.

Given the high frequency of women misdiagnosing themselves with VVC, and self-treating with OTC treatments for VVC even though they in fact have a BV infection or mixed VVC and BV infection[16], there is a need for products that are able to treat both VVC and BV.

3.2 Glucono-delta-lactone, mode of action

3.2.1 Biofilm

It is estimated that approximately 80% of pathogen infections in humans are related to the formation of biofilm, i.e. a complex 3-dimensional structure of pathogens attached to cell walls and to other pathogens. It has been shown that biofilm formation is required for VVC, and that biofilm is coupled to treatment failure, recurrent infections, and enhanced spread of antimicrobial resistance.[35, 36] Biofilm formation is dependent both on pH and the availability of alternative carbohydrate sources. The vulvovaginal tract is generally acidic and rich in lactic acid and acetic acid. Interestingly, it has been shown that the addition of gluconic acid strongly diminished the biofilm formation in *Vibrio cholera*.[37] Prokaryotes, such as *V. cholera*, uses gluconic acid as a carbon source using the Entner-Doudoroff pathway. Similarly, gluconic acid, as well as glucono-delta-lactone (GDL) can be utilised by yeasts and other eukaryotes in the pentose phosphate pathway.

Biofilms are characterised by a transformation of planktonic cells to form hyphae, which can invade the mucous membrane and induce inflammation.[39] The hyphal form, i.e. filamentous cells, can invade tissues and induce inflammation, mediated by Candidalysin, a cytotoxic peptide toxin that destroys the epithelial cells of the vagina.[40] Thus, it is reasonable to assume that GDL functions as an indicator of a favourable environment for several pathogens, such as *Candida*, which favours planktonic cells over hyphae and results in reduced biofilm formation.

We have shown *in vitro* that GDL can significantly reduce the biofilm formation in *C.albicans* and other *Candida* species.[38] The effect on biofilm formation is not only due to a lowering of the pH, as treatment with GDL inhibits the formation of biofilm even at pH 6. For comparison, biofilm formation was measured at different pH levels in phosphate buffer, with significantly less effect. The reduced biofilm formation caused by GDL was accompanied by a significant reduction of hyphal cells, the pathogenic form of *C. albicans*, as shown by time-lapse microscopy. Furthermore, GDL treatment was found to also remove mature biofilm (biofilm grown for 2 days before treatment).

Though it has been reported that *Candida* containing biofilm cannot be found in human vaginal tissue biopsies [41], Harriot *et al* [42] have shown in *in vivo* and *ex vivo* murine models that *C. albicans* forms biofilms, and the general view is that the *Candida* biofilm formation on human vaginal mucosa is an important part of the pathogenic mechanism of VVC.

3.2.2 Lactobacilli

There are different reports and theories on how *Lactobacilli* interacts with *Candida* in the vagina. There is a hypothesis that *Lactobacilli* does not prevent the colonisation of *Candida* but may prevent their proliferation. This is supported by the finding that lactic acid producing bacteria may inhibit the yeast-to hyphae switch.[43] As mentioned in Section 3.1, there is also a correlation between the use of antibiotics and the susceptibility to *Candida* infection, since antibiotics lead to the depletion of favourable vaginal bacteria.

Different research groups have shown that *L. crispatus* and *L. fermentum* can affect the growth and yeast-to-hyphae transition of *C. albicans*, in addition to hydrogen peroxide and organic acids. In these studies, the anti-Candida effects have been excerted by compounds released from these strains of *Lactobacilli.*[44, 45]

Preliminary unpublished data from the Gedea Biotech AB clinical investigation CL1, suggests that women who were treated with *p*Hyph gen I and cured had an increase in the relative abundance of *L. crispatus*, contrary to women who were treated but not cured, where an increase in *L. crispatus* was not seen. Thus, a yeast-to hyphae switch induced by an increase in *Lactobacilli* is likely to be an important part of the mechanism of *p*Hyph treating VVC.

3.3 Product description and previous experience

3.3.1 Non-clinical data

Glucono-delta-lactone is a normal intermediate in glucose metabolism through the pentose phosphate cycle in mammals. Studies in rats have shown that GDL gives similar weight increase as glucose on low-calorie diets.[46] Furthermore, several studies on humans have been performed using oral doses of 3 g to 50 g of GDL and showed no signs of toxicity.[47] There was no evidence of carcinogenicity, teratogenicity, or genotoxicity of GDL, nor of D-gluconic acid or the magnesium, potassium, calcium, or sodium salts thereof. In addition, both the US

Food & Drug Administration (FDA) and the World Health Organization (WHO) International Programme on Chemical Safety (ICPS) accepts GDL as a safe food additive.[48, 49]

In this study, GDL and sodium gluconate (NaG) have been formulated as a more easily soluble and slow-release pessary, the *Gedea Pessary* (*p*Hyph gen II) for increased dosing accuracy and patient compliance. Sodium gluconate is the sodium salt of the anion of gluconic acid and in a water solute, both GDL and NaG are in equilibrium with gluconic acid. Biological evaluation of the pessary has been performed in accordance with ISO 10993 (Biological Evaluation of Medical Devices). The biological evaluation included: cytotoxicity testing (direct cell contact test, ISO 10993-5); *in vivo* irritation (vaginal acute irritation, ISO 10993-10); and sensitisation (local lymph node assay, ISO 10993-10). The tests were performed on Gedea Pessary gen I, by Eurofins Medical Device Testing (Munich, Germany) in compliance with the principles of good laboratory practice (GLP). The cytotoxicity test, which was performed *in vitro* as a direct cell contact test, classified the test item as slight to moderate cytotoxic (scale 1-2 on a 3-grade scale). The *in vitro* cytotoxicity test was a prerequisite to continue with the *in vivo* irritation and sensitisation studies. In the *in vivo* irritation test, no signs of irritation or necrosis were observed in the macroscopic assessment after treatment with Gedea Pessary. Also, there were no indicators for irritation of the vaginal mucosa in the histopathology assessment. The sensitisation test showed no signs of sensitisation after treatment with Gedea Pessary. The biological evaluation test results for Gedea Pessary gen I are also applicable for the Gedea Pessary gen II (QRS-BC-008)[55]. Thus, it can be concluded that the product fulfilled the current biocompatibility requirements for medical devices. For further pre-clinical data, refer to the IB.

3.3.2 Clinical data

The Gedea Pessary (*p*Hyph gen II) used in this clinical investigation has been tested in a randomised, double-blind, placebo-controlled investigation in adult women with BV, the CL3 study. The objective of the investigation was to evaluate clinical performance, and safety of initial and preventive treatment with the Gedea Pessary, as compared to placebo, in women with BV. In the part 1 of the study, treatment for 6 consecutive days was given and the clinical cure rate on Day 7, defined as absence of all of the 3 Amsel criteria was evaluated (pH excluded). 115 patients treated with *p*Hyph and 30 patients treated with placebo were included in the Full Analysis Set (FAS). There were no significant between-group differences in the percentage of women who were clinically cured; 50.4% in the *p*Hyph group and 46.7% in the placebo group. *In vitro* studies performed, showed that the placebo was not inactive, it strongly promoted the growth of *Lactobacillus Iners* and this may explain the high placebo cure rate in the CL3 study[58].

During Part 1 of the CL3 study, 26 AEs were reported by 22 patients (19.1%) in the Gedea Pessary group and 5 AEs were reported by 4 patients (13.3%) in the placebo group. The most commonly reported AEs were Vulvovaginal candidiasis (Gedea Pessary: 5 AEs in 5 patients, 4.3%; Placebo: 1 AE in 1 patient, 3.3%), Vulvovaginal burning sensation (Gedea Pessary: 3 AEs in 3 patients, 2.6%) and Vulvovaginal pruritus (Gedea Pessary: 2 AEs in 2 patients, 1.7%; Placebo: 1 AE in 1 patient, 3.3%).

A total of 8 AEs (Vulvovaginal discomfort [2 events in 2 patients], Dysmenorrhoea, Vulvovaginal pruritus, and Vaginal discharge/Vulvovaginal burning sensation/Vulvovaginal erythema/Vulvovaginal swelling [reported at the same time in 1 patient]) in 4 patients (2.8%, N=145) (Gedea Pessary: 6 AEs in 3 patients, 2.6%; Placebo: 2 AEs in 1 patient, 3.3%) were judged as possibly related. One AE (Vulvovaginal pruritus) in 1 patient (0.9%) in the Gedea

Pessary group was judged as probably related to the study procedure. Most AEs (22 AEs) were of mild intensity, except for 9 AEs (Vulvovaginal candidiasis [2 events], Back pain, COVID-19, Urinary tract infection, and Vaginal discharge/Vulvovaginal burning sensation/ Vulvovaginal erythema/Vulvovaginal swelling [reported at the same time in 1 patient]) in 6 patients (4.1%) that were assessed as moderate. No severe events were reported.

A total of 10 device deficiencies were reported by 9 patients (6.2%; 8 patients in the Gedea Pessary group and 1 patient in the placebo group) during Part 1 of the study. The reported device deficiencies were considering malfunction (tablet falling out and/or that the tablet did not melt completely) of the device (9 device deficiencies) or use error (1 device deficiency).

The part II of the CL3 study has not yet been reported. 72 patients were randomised to once weekly treatment with either Gedea Pessary or placebo during four months or until a BV recurrence was confirmed. There were no SAEs and no local vaginal AEs in the Gedea Pessary arm.

The GDL-and-NaG-containing investigational device, Gedea Pessary *p*Hyph gen I (300 mg GDL, 367.5 mg NaG, administered every second day on Days 0, 2, 4 and 6), has been tested in two open-label clinical investigations in adult women with VVC (CL1 study [50]) or BV (CL2 study [50]).

In both studies, the primary objective was to investigate the clinical performance, tolerability and safety of the Gedea Pessary *p*Hyph gen I. In the first study, CL1, 22 patients with confirmed VVC were evaluated for clinical cure rate on Day 7. Clinical cure rate, defined as the absence of signs and symptoms of VVC in terms of having a composite vulvovaginal signs and symptoms (CVVS) score equal to or below 3, was 41% after 4 administrations with the Gedea Pessary. No serious adverse events (SAEs) occurred and few adverse events (AEs) were reported.[50] The most common AEs were headache, dysmenorrhoea and nasopharyngitis and most were of mild intensity and not assessed as related to the product or procedure. One patient experienced non-application site rash the day after the first administration. The Investigator assessed the reaction as severe, however not related to the product or the procedure, nevertheless the patient´s study participation was ended.

In the CL2 study, 24 patients with confirmed BV were evaluated.[50] The clinical cure rate on Day 7, defined as absence of all of the 3 Amsel criteria, was 82% after 4 administrations with the Gedea Pessary. Also, in this study, no SAEs occurred, and few AEs were reported, which were mainly mild in intensity and not assessed as related to the product or procedure. The most commonly reported AEs were headache and dysmenorrhoea. Single events of headache, dysmenorrhoea (2 events reported by 2 patients), urinary tract infection, vaginal disorder (reported term: "*pain and itching in the vagina*") and vaginal haemorrhage (reported term: "*really bad smelly blood fluid from vagina*") were judged as possibly related to the product and/or the procedure.

In both studies, the usability of the *p*Hyph gen I was assessed as good, however, about a third of patients reported malfunctions of the Gedea Pessary considering the tablet falling out and/or that the tablet did not melt completely. This malfunction was more commonly reported in the CL1 study and may have been caused by the limited amount of vaginal discharge in VVC patients.

The new formulation to be used in the present study (*p*Hyph gen II; 150 mg GDL, 184 mg NaG) is considered to counteract these malfunctions and thereby increase the device efficacy. In addition, the instructions for use have been updated with information that the patients should moist the tablets (by shortly holding the tablet over tap water) before use, to promote

the dissolution. Also, the Gedea Pessary *p*Hyph gen II has been reformulated to be more easily soluble for daily dosing. In the CL3 study, there were, as mentioned above, only 9 reports of tablet falling out and/or that the tablet did not melt completely out of 152 patients included.

Based on published studies on current treatments for VVC, all vaginal and local anti-mycotics are generally well tolerated.[17] Local irritation is the most frequent AE reported in conjunction with topical azole therapy, and headache is the most frequently reported AE of oral imidazoles.[52, 18] Nausea and diarrhoea has been reported as treatment-emergent AEs in a study with oral fluconazole, both at a rate of 1.9%.[19]

Collectively, pre-clinical data indicate that GDL and NaG are safe and may be effective topical treatments for VVC, and a modified formulation of the GDL-and-NaG-containing slow-release pessary (*p*Hyph gen II) for daily dosing is to be further investigated in this clinical investigation.

4 STUDY OBJECTIVES

The objectives and clinical endpoints are stated in this section. Note, however, that as the ICH E9 (R1) addendum has been consulted in the design and analysis of this study, i.e. an estimand approach has been applied, the final definition of the endpoints to be used in the statistical analysis are stated in Section 12.4.

4.1 Primary objective

To investigate the clinical performance of acute treatment with Gedea Pessary in patients with VVC.

4.1.1 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 CVVS score ≤ 3 [53]

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.

4.2 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.

4.2.1 Secondary endpoints

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 6.

4.3 Exploratory objectives

4.3.1 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, and clinical cure.

5 STUDY DESIGN

5.1 General outline

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 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 for reporting of AEs, concomitant medications and potential menstruation onset.

Vaginal sampling for culture and sequencing, as well as vaginal pH measurements will be performed at the clinic on Day 0, Day 7, and Day 14. On Day 25, patients will self-perform vaginal swabs at home for sequencing and vaginal culture.

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. The patient questionnaire will be based on an electronic patient reported outcomes (ePRO) system, i.e. a mobile application (ViedocMe™). The questionnaire is provided in Appendix 1.

An overview of the study design is provided in

Figure 1. For details on the specific assessments to be performed at each study visit and contact see Table 1 and Section 5.4.

Figure 1 Study flow chart

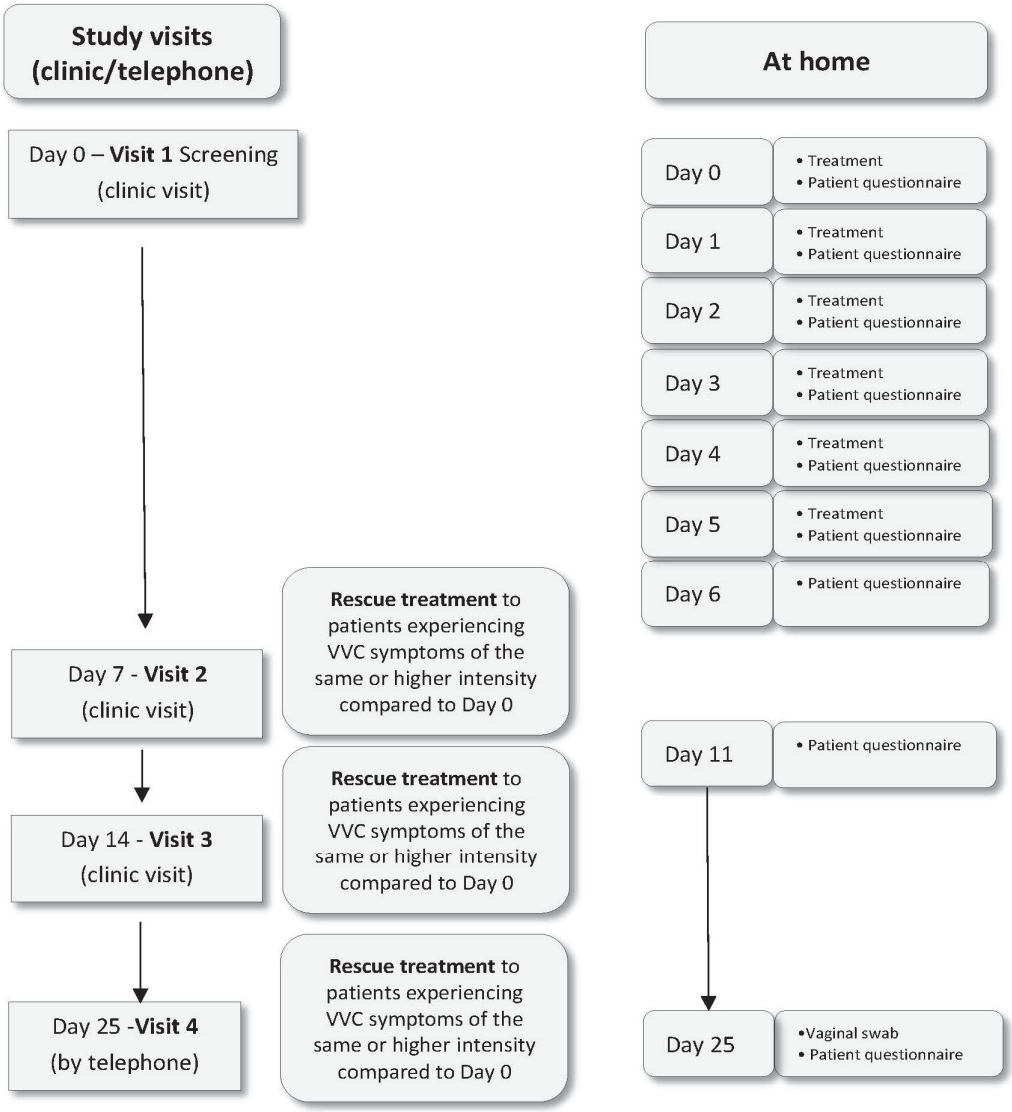


Table 1 Schedule of assessments and procedures

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
Device deficiencies				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). Taken in duplicates Day 0 and 7.

[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.

5.2 Rationale for the study design

As described in Section 3.1, VVC is a major clinical concern, and new effective interventions not associated with antibiotic resistance and major drug interactions would be valuable additions to the current treatment arsenal. This study aims to further investigate the clinical performance and safety of the Gedea Pessary containing GDL and NaG, now formulated for daily dosing (*p*Hyph gen II), in treating VVC.

Previous *in vitro* data show that GDL inhibits both bacterial and fungal biofilm formation, and transforms *Candida* to a non-adhesive form (Section 3.2). Data also indicate that GDL is tolerable and does not pose any special risk to humans (Section 3.3.1).

Due to the widespread clinical problem of VVC and the issues involving current therapies (see Section 3.1) trials involving patients are justified. The clinical performance of Gedea Pessary, *p*Hyph gen I, has been evaluated in 2 open-label clinical investigations (see Section 3.3.2). These studies provided evidence of a good safety/tolerability profile of the Gedea Pessary. The clinical cure rate for VVC was 41%. The rather low clinical cure rate may be due to that the pessaries did not dissolve properly and in some cases fell out from the vagina too early. This theory is based on observations that no or lower pH decrease was reported in patients that were not cured, suggesting that the device did not perform as intended. Also, the number of incidences of pessaries falling out were 3 times higher in patients that were not cured compared to patients that were cured.

In this study, the Gedea Pessary (*p*Hyph gen II) formulated for increased dosing accuracy and patient compliance, will be further investigated in this open-labelled study, similar to the previous CL1 study. This is done to evaluate the performance of the new formulation in VVC patients and to evaluate the potential clinical cure. The reduction of vulvovaginal symptoms day by day during Day 0 to Day 7 will also be investigated. How soon a relief of the symptoms may be achieved is an essential feature of a VVC-treatment and also important to know concerning the timing of offering rescue treatment in a possible future controlled study.

The diagnosis of VVC in the study is based on the FDA Guidance for Industry. The FDA recommendation is that the patients should have 1) 2 or more of the following signs and symptoms: itching, burning, irritation, edema, erythyma, or excoriation; 2) Potassium hydroxide (KOH) or saline preparation from the inflamed vaginal mucosa or secretions demonstrating yeast forms (hyphae or pseudohyphae) or budding yeasts, and 3) vaginal pH ≤ 4.5. However, in this study, pH ≤ 4.5 will not be an inclusion criterion. The low risk profile of the Gedea Pessary allows this less stringent inclusion criteria and the VVC diagnosis will be confirmed post inclusion, by both vaginal culture and microbiome analysis.

The VVC diagnosis will be validated by culture and microbiome analysis. The vaginal microbiome will be analysed to better understand the relation between vaginal dysbiosis and VVC.

To fulfil the primary endpoint (clinical cure), signs and symptoms of VVC must be absent and this is defined in terms of having a CVVS score ≤ 3. This is consistent with the current FDA guidelines and the CVVS score is an established method to define VVC signs and symptoms and clinical cure. [53]

The safety endpoints were selected to assure a sufficient method to assess the safety of the Gedea Pessary. The usability endpoint was selected to ensure the Gedea Pessary is easy to use for the patients.

The dose of 150 mg GDL and 184 mg NaG administered daily for 6 days was chosen based on clinical data from previous studies (see Section 3.3.2). Also, pre-clinical measurements of pH in an *in vitro* dissolution test have shown a pH decrease duration of approximately 24 hours for the *p*Hyph gen II (see the IB).

5.3 Risks and benefits

The investigational device, Gedea Pessary *p*Hyph gen I has been evaluated in accordance with ISO 10993 (Biological Evaluation of Medical Devices). The evaluation included: cytotoxicity testing (Direct cell contact test, ISO 10993-5); *in vivo* irritation (Vaginal acute irritation; ISO 10993-10); and sensitisation (local lymph node assay, ISO 10993-10). The *in vitro* cytotoxicity test classified the test item as slight to moderate cytotoxic (scale 1 to 2 on a 3-grade scale); the *in vivo* irritation test as well as the *in vivo* sensitisation test showed no signs of irritation, necrosis, or sensitisation after treatment with Gedea Pessary.

The vaginal pessary may, in similarity with other vaginally administered products, cause temporary minor discomfort at insertion. The vaginal sampling procedures are similar to sampling procedures used in clinical practice and are unlikely to cause any major inconvenience to patients.

In a previous study with the Gedea Pessary *p*Hyph gen II, there were no SAEs reported.Only single reported events of vulvovaginal discomfort, dysmenorrhoea, vulvovaginal pruritus, and vaginal discharge/vulvovaginal burning sensation/vulvovaginal erythema/vulvovaginal swelling [reported at the same time in 1 patient], could not be ruled out as caused by the Gedea Pessary or the study procedure (see Section 3.3.2). A few patients experienced that the pessary fell out or did not melt completely. This type of device deficiency was more common with the previous formulation Gedea Pessary *p*Hyph gen I, especially in the CL1 VVC study. In the present study, this type of device deficiency will be closely monitored to confirm that the reformulation has reduced the risk also in VVC.

It is anticipated that patients participating in this study may be cured from their VVC, however, there is a risk that they will have no clinical benefit from treatment with the investigational device. This may cause patients to experience symptoms of VVC including vaginal itching, burning or soreness, pain during sexual intercourse, pain or discomfort when urinating, or abnormal vaginal discharge longer than necessary. However, rescue treatment according to standard clinical practice, will be offered to the patient at Visit 2 and Visit 3 (i.e. Day 7 and 14) to patients experiencing VVC symptoms of the same or higher intensity compared to Day 0. Rescue treatment will also be offered to patients with recurrence, or persisting symptoms, on Day 25. Thus, any risk associated with long-term untreated VVC will be avoided. For details on rescue treatment see in Section 7.5.2.

All residual risks have been classified as low after risk control measures. Risks that were classified as “High risk level” before risk control are listed in Appendix 1 of the IB.

Patients included in the study must refrain from using other intravaginal products to mitigate any risk of interactions with concomitant vaginally administered products. The investigational device acts locally on the vaginal mucosa and will most likely not affect any concomitant systemic treatment. No possible interactions with concomitant medical treatments are expected.

Taken together, as the anticipated levels of discomfort are transient and mild, and that risks associated with long-term untreated VVC are avoidable, the use of the investigational product Gedea Pessary appears to offer clinical benefits at a reasonable risk level.

The Sponsor Gedea Biotech AB realises that extraordinary measures may need to be implemented and the management of the investigation may need to be adjusted due to unexpected risks, including the outbreak and pandemic spread of the coronavirus disease of 2019 (COVID-19). For example, participants safety, participants being in self-isolation/quarantine, limited access to public places (including clinics and hospitals) due to the risk of spreading infections, and healthcare professionals being committed to critical tasks, may affect the conduct of the study.

The study has been designed in a way so that many assessments are performed at home by the patients and follow-up visits are conducted over the phone. There are only a few extra visits to the clinic planned for the patients outside of their routine clinical care.

Patients with VVC are not considered a risk group for infection with serious COVID-19 illness. The increased risk, for patients participating in this investigation, of contracting COVID-19 is considered low.

All patients' visits to the clinics/hospital will occur in facilities which are not used for patients with COVID-19. Recommended procedures to prevent COVID-19 infection, as recommended by the local public health agencies in the countries where the study will be executed, will be followed.

Taken all the above into consideration, Gedea Biotech AB considers that the benefits of initiating the study outweighs the risks related to COVID-19.

During the investigation, the site initiation visits may be performed remotely and the possibility to use remote monitoring will be implemented. Deviations to the CIP that are due to the COVID-19 will be tracked separately and described in the CIR.

5.4 Study visits and procedures

All study visits and procedures are described in the following subsections and summarised in Table 1.

5.4.1 Day 0; Screening and enrolment

Patients seeking treatment for symptoms relating to VVC may be informed about the study and, if agree to participate, sign the ICF. After the ICF is signed, patients will undergo a gynaecological examinations, where the Investigator or an authorised designee will assess the presence of vulvovaginal signs (erythema, oedema, or excoriation) and symptoms (itching, burning, or irritation) and score each sign and symptom, as described in Section 9.1.

Vaginal samples will be examined under a microscope for yeast forms (hyphae or pseudohyphae) or budding yeast. Two vaginal secretion samples will also be collected by a vaginal swab. One sample will be cultured to verify the presence of *Candida* and the other (taken in duplicates) will be used for sequencing analysis of the vaginal microbiome prior to treatment (Section 10.1.1). If the Investigator assesses that the patient has VVC, based on the gynaecological examination and the fungal microscopy, the patient will receive the investigational product to be self-inserted vaginally at home during 6 consecutive days (Days 0 to 5). In addition, the Investigator will measure the vaginal pH, as described in Section 10.1.2.

The Investigator or delegee will ask the patient about onset and end of last menstruation. The patient should not be enrolled, or the enrolment should be postponed, if menstruation is foreseen to occur at the time of the Day 7 visit.

Procedures to be performed:

- Informed consent
- Demography
- Eligibility criteria
- Pregnancy test (urinary)
- Recording of
    - Medical and surgical history
    - Prior and concomitant medications
    - Onset and end of last menstruation
- Gynaecological examination by Investigator or authorised designee, evaluating vulvovaginal signs (erythema, oedema, and excoriation) and symptoms (itching, burning, and irritation) according to a scoring scale (0-3).
- Fungal microscopy assessment (KOH or saline preparation)
- Vaginal swab for:
    - Culture
    - Sequencing
- Vaginal pH
- Treatment dispensing for self-administration by patients at home.

5.4.2 Day 0 to Day 5; Treatment administration

During Days 0 to 5, patients will self-administer the investigational product, at night before going to bed.

Patients will be reminded about the administration and will also receive questions about VVC symptoms (itching, burning, or irritation) via the mobile application (ViedocMe™) (see Section 9.1.2).

Procedures to be performed:

- Daily self-administration of treatment (Gedea Pessary) by patients.
- Patient questionnaire (via mobile application)
    - Vulvovaginal symptoms (itching, burning, and irritation), evaluated by patients according to a scoring scale (0-3).

Note that VVC symptoms will also be assessed on Day 6, although no treatment is administered. Additionally, the patient will complete the questionnaire regarding Usability (via mobile application) at Day 6.

5.4.3 Day 7 (+2 days); Follow-up visit

Patients will visit the clinic on Day 7 to have gynaecological examination performed. The Investigator or an authorised designee will assess the presence of vulvovaginal signs (erythema, oedema, and excoriation) and symptoms (itching, burning, and irritation) and score each sign and symptom on a scale of 0 to 3 (see Section 9.1.2).

Vaginal samples will be examined under a microscope for yeast forms (hyphae or pseudohyphae) or budding yeast. Vaginal secretion samples collected by swabs will be used for culture and for sequencing analysis of the vaginal microbiome (this sample will be taken in duplicates). If the patient is menstruating at this timepoint, the visit should be postponed until the menstruation is over, even though the visit will happen outside the visit window.

Procedures to be performed:

- Gynaecological examination by Investigator or authorised designee, evaluating vulvovaginal signs (erythema, oedema, and excoriation) and symptoms (itching, burning, and irritation) according to the scoring scale (0 to 3).
- Fungal saline microscopy assessment
- Vaginal swab for
    - Culture
    - Sequencing
- Vaginal self-swab for:
    - Sequencing
- Vaginal pH
- Recording of
    - Concomitant medications
    - AEs
    - Potential menstruation onset
- Product accountability – patients should be asked to return all used and not used treatment packages

Rescue treatment, according to standard clinical practice, will be offered if the intensity of the VVC symptoms is the same or higher compared to the inclusion visit (Visit 1, Day 0). See details in Section 7.5.2.

An assessment of mycological cure will be done as soon as the results from the laboratory are received. A mycological cure is defined as no presence of *Candida* species. If the patient has both a clinical and mycological cure at Day 7, the Day 14 visit should be cancelled.

5.4.4 Day 11 (±1 day); Follow-up at home

On Day 11, patients will be reminded to complete the patient questionnaire (via mobile application) for self-assessment of VVC symptoms (itching, burning, or irritation) according to a scoring scale (0-3) (see Section 9.1.2).

5.4.5 Day 14 (±2 days); Follow-up visit

Patients with clinically and mycologically cured VVC at Day 7, or patients initiating rescue treatment Day 7 (even if they are clinically cured according to the CIP), will not perform the Day 14-visit. For these patients, this visit will be omitted.

Patients without clinically and mycologically cured VVC at Day 7 will visit the clinic on Day 14 to have gynaecological examination performed. The Investigator or an authorised designee will assess the presence of vulvovaginal signs (erythema, oedema, and excoriation) and symptoms (itching, burning, and irritation) and score each sign and symptom on a scale of 0 to 3 (see Section 9.1.2).

Vaginal samples will be examined under a microscope for yeast forms (hyphae or pseudohyphae) or budding yeast. Vaginal secretion samples collected by swabs will be used for culture and for sequencing analysis of the vaginal microbiome. If the patient is menstruating at this timepoint, the visit should be postponed until menstruation is over.

The Investigator or delegee will ask the patient about potential menstruation onset.

Procedures to be performed:

- Gynaecological examination by Investigator or authorised designee, evaluating vulvovaginal signs (erythema, oedema, and excoriation) and symptoms (itching, burning, and irritation) according to the scoring scale (0 to 3).
- Fungal microscopy assessment (KOH or saline preparation)
- Vaginal swab for
    - Culture
    - Sequencing
- Recording of:
    - Concomitant medications
    - AEs
    - Potential menstruation onset

Rescue treatment, according to standard clinical practice, will be offered if the intensity of VVC symptom is the same or higher compared to the inclusion visit (Visit 1, Day 0). See details in Section 7.5.2.

5.4.6 Day 25 (±2 days); Follow-up visit

All patients will be contacted by the investigational site staff by telephone and asked about concomitant medications, AEs and potential menstruation onset. In addition, patients will be asked about symptom recurrence; “Have the symptoms recurred – yes/no?”. If the answer is “yes”, then the patient will be managed according to standard clinical practice. The site will decide if the patient should return to the site and if rescue medication should be prescribed (see Section 7.5.2).

Patients will also be reminded to complete the patient questionnaire for self-assessment of vulvovaginal symptoms, and to collect vaginal samples by self-swab. If the patient is menstruating at this time point, the patient should take the sample on the first day after menstruation. The self-swab samples will be sent by post to the laboratory for culture and sequencing of vaginal microbiome.

Procedures to be performed:

- Patient questionnaire (via mobile application)
    - Vulvovaginal symptoms of VVC (itching, burning, or irritation), evaluated by patients according to a scoring scale (0-3).
- Vaginal self-swab for
    - Culture
    - Sequencing
- Recording of
    - Concomitant medications
    - AEs

- Potential menstruation onset

5.4.7 Early withdrawal visit

If a patient is prematurely withdrawn from the study for any reason, the patient must be followed-up for at least safety purposes and if the patient is withdrawn prior to the Day 14 visit (if this visit is applicable), the patient should be asked to visit the site for follow-up assessments (see Section 6.6.3 for withdrawal procedures).

If a withdrawal occurs during a study visit, the electronic case report form (eCRF) for that specific visit shall be completed as far as possible.

The following assessments should be performed to the extent possible on the day for early withdrawal:

- Reason for withdrawal.
- Vaginal swab (self-swab as applicable) for
  - Culture
  - Sequencing
- Recording of
  - Concomitant medications
  - Vulvovaginal signs (if a visit is performed)
  - AEs
  - Potential menstruation onset
- Product accountability – if not already performed on previous visit, patients should be asked to return all used and not used treatment packages.
- Patient questionnaire (via mobile application)
  - Vulvovaginal symptoms (itching, burning, and irritation), evaluated by patients according to a scoring scale (0-3).
  - Usability (if not already obtained).

6 SELECTION OF STUDY POPULATION

6.1 Patient information and informed consent

The recruitment of patients will start only after the approval of the CIP including the patient information sheet and ICF by the RA/CA and the IEC, as applicable (see Section 2).

The Investigator must always use IEC-approved patient information sheet that must not be changed without prior Sponsor and IEC approvals. No study procedures will be performed unless the patient has provided written informed consent to study participation.

It is the responsibility of the Investigator, or any authorised designee, to give each patient adequate verbal and written information about the nature of the investigation, its purpose, expected duration, the benefits and risks involved in the study participation. This information will emphasise that the participation in the investigation is voluntary and that the patient may withdraw from the investigation at any time and for any reason. All patients will be given the opportunity to ask questions about the investigation and will be given sufficient time to decide whether to participate in the investigation.

Each patient should be informed in writing that the data from the study will be stored and analysed, maintaining confidentiality in accordance with local data protection laws.

Before any clinical investigation-related procedures are undertaken, the ICF must be signed and dated by the patient (or their legally acceptable representative and/or witness, as applicable) and by the Investigator, or the qualified designee who gave the patient the verbal and written information.

The ICF will incorporate (or be accompanied by a separate document incorporating) information on the processing of the patient data within the scope of this study which complies with relevant data protection and privacy legislation. If any data are transferred to European Economic Area countries outside the countries where the study is executed, the data will not identify any persons taking part in the clinical investigation in accordance with the EU General Data Protection Regulation (GDPR).

A copy of the patient information sheet, including the signed ICF, will be provided to the patient. The date of informed consent must be recorded in the source documentation and in the eCRF. The patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

If any new information becomes available that may influence the patient's decision to participate in the study, the Investigator will contact and inform all currently enrolled patients and obtain additional informed consent, as applicable (see Section 13.5).

6.2 Recruitment

Post-menarchal, pre-menopausal females, 18 years or older, seeking care for VVC symptoms (itching, burning, or irritation) should be considered. Patients with confirmed VVC, may be informed verbally and in writing about the study and asked about their willingness to participate (clinical routine samples and gynaecological examination may be used for confirmation of the VVC diagnosis).

Patients may also be pre-informed about the study by the use of advertisement through social media; these patients will directly book appointments with the clinic.

After signing of the ICF, the screening procedures may start and available clinical routine samples may be used for confirmation of VVC diagnosis).

Patients who have signed the ICF shall be listed on a Screening and enrolment log together with an assigned Screening number. Patients not fulfilling *all* inclusion criteria as described in Section 6.3, or fulfilling *any* of the exclusion criteria listed in Section 6.4, shall be considered Screening failures. Screening failure reasons shall be stated in the Screening enrolment log, and recorded in the eCRF.

The patient should not be enrolled, or the enrolment should be postponed, if menstruation is foreseen to occur at the time of the Day 7 visit.

6.3 Inclusion criteria

1. Having decisional capacity and providing written informed consent.
2. Adult, post-menarchal, pre-menopausal women, aged 18 years or older
3. Diagnosis of VVC, defined as:
    - Having a white or creamy vaginal discharge

- *At least* 2 of the following signs and symptoms of VVC that are characterised as *at least* moderate[a]: 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.

4. Negative urine pregnancy test at Screening.
5. Refrain from using any intravaginal products (i.e. contraceptive creams, gels, foams, sponges, lubricants, or tampons, etc.) until Day 14.
6. Refrain from sexual intercourse or use a condom until Day 7.
7. Signed informed consent and willing and able to comply with all study requirements.

6.4 Exclusion criteria

1. Patients with known or apparent signs of other infectious causes of vaginal infection (BV, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Herpes simplex, or human papillomavirus) at Screening.
2. Patients who are pregnant or breastfeeding.
3. Patients who were treated for VVC within 14 days prior to Screening.
4. Patients who are currently receiving anti-fungal therapy unrelated to VVC or has taken anti-fungal therapy within 14 days prior to Screening.
5. Patients who have received an investigational drug in a clinical investigation within 30 days prior to Screening.
6. Known/previous allergy or hypersensitivity to any product constituent or fluconazole.
7. Any medical condition that in the Investigator's judgements would make the patient unsuitable for inclusion.
8. More than 3 previous VVC infections during the last 12 months.

6.5 Restrictions

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

1. Anti-fungal medication related to VVC.
2. Other treatments for VVC (e.g. probiotics like Candicur and Multigyn).

Also see further information on rescue medication in Section 7.5.2 and prior and concomitant medications in Section 8.4.

6.6 Withdrawal of patients and termination of the investigation

6.6.1 Withdrawal from study and termination criteria

Patients shall be informed by the Investigator and through the ICF about their rights to withdraw their participation in the study at any time and for whatever reason without affecting

[a] scoring scale:
0 = none (absent)
1 = mild (slight)
2 = moderate (definitely present)
3 = severe (marked, intense)

their right to an appropriate follow-up investigation. If possible, the reason for withdrawal should be documented.

The Investigator may, at his or her discretion, withdraw a patient from the study and/or discontinue study treatment and assessments at any time. The specific reasons for discontinuing a patient from the treatment or the study shall be documented in the eCRF.

6.6.2 Reasons for treatment discontinuation or withdrawal from the study

Reasons for a patient to discontinue treatment or withdraw from study include, but are not limited to:

- Informed consent withdrawal
  The patient may withdraw from the study or be withdrawn by a legal representative, if applicable, at any time without stating a reason and without prejudice to further treatment or medical care.
- Safety reasons
  The Investigator or Sponsor may withdraw patients from treatment if judged that an AE poses an unacceptable risk or consequence to the patient.
- Medical reasons
  The Investigator may withdraw patients from the study if judged that a medical condition poses an unacceptable risk or consequence for the patient to continue in the study. The rationale and the medical condition responsible for the Investigator-initiated withdrawal shall be documented.
- Lost to follow-up
  Reasonable efforts shall be made to reach patients not returning for scheduled visits or not being reachable by telephone. Such efforts may include, e.g. calling the patient at least 3 times at different hours and leaving voice messages.
- Other reasons for study withdrawal
  Other reasons include but are not limited to failure of the patient to comply with study procedures or requirements.

6.6.3 Procedure for withdrawal of a patient

If a patient does not return for a scheduled follow-up visit, every effort should be made to contact the patient, to collect answers on the patient questionnaire and information on concomitant medications, vulvovaginal signs and AEs, if any (see Section 5.4.7 for more details). If possible, the reason for withdrawal should be sought and recorded in the eCRF.

If the withdrawal from treatment is due to lack of clinical performance or for safety reasons of the investigational product, the patient will if possible continue to be followed-up in the study.

If a withdrawal from the study occurs during a study visit, the eCRF for that specific visit shall be completed as far as possible.

Any AE should be followed-up until the AE is resolved or the Investigator decides that the AE is stable and needs no further follow-up.

If a patient is not prematurely withdrawn from the study, the last day for follow-up will be Day 25 (Visit 4).

AEs ongoing at the last day for follow-up shall be assessed as chronic or stable. Wherever possible, other assessments should be carried out according to the CIP at the time of withdrawal.

6.6.4 Procedure for discontinuation of treatment

If a patient permanently discontinues treatment, the date and reason for discontinuation (if known) will be documented in the eCRF.

After discontinuation of treatment in a patient, the patient will continue in the study and should be followed-up as described above (Section 6.6.3).

6.6.5 Replacements

Re-screening is allowed.

Patients that are withdrawn or discontinued during the study will not be replaced or re-entered into the study.

6.6.6 Sponsor termination of study

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons. In such a case, the Investigator will be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interest. Breaking of the treatment code (unblinding) will be performed and the Investigator will be informed.

If the study is prematurely terminated or suspended for any reason, the Investigator has to inform the patients and to assure appropriate patient follow-up, including give information regarding treatment received. The Sponsor should promptly inform the study site, and the RA/CA on the termination or suspension and the reason(s) for the termination or suspension. The IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator, as specified by the applicable regulatory requirements.

7 TREATMENTS

7.1 Treatment groups

Patients in this study will receive the test product Gedea Pessary

In the study, 26 patients will be treated with Gedea Pessary to be self-administered daily for 6 days (Day 0 to Day 5).

7.2 Identity of the investigational product

7.2.1 Test product/Gedea Pessary

The test product, Gedea Pessary (commercial name *p*Hyph), is a Class IIb medical device according to MDR 2017/745, containing 150 mg GDL and 184 mg NaG.

Gedea Pessary is a white, convex, bullet-shaped pessary, approximately 17 mm in length, to be administered vaginally with a CE-marked pessary applicator (Schägner GmbH, Steinmauern, Germany) (Figure 2 and Figure 3).

Figure 2 Gedea Pessary and the Gedea Pessary blister package

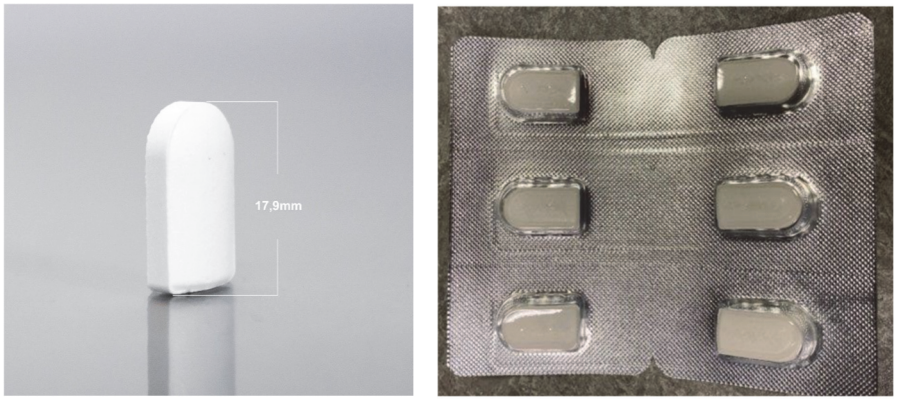
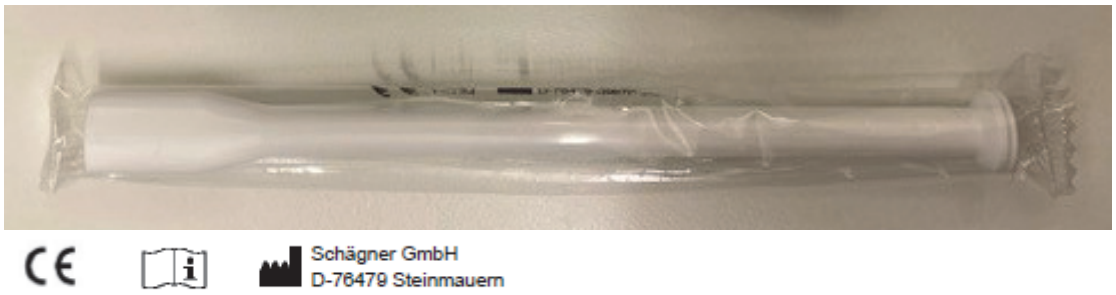


Figure 3 Vaginal tablet applicator



7.2.2 Manufacturing, packaging and labelling of investigational product

Gedea Biotech AB is the responsible manufacturer of the investigational products (Gedea Pessary). Gedea Biotech AB has subcontracted production, packing, labelling and release testing of the clinical investigation material for use in the clinical investigation to Galenica AB (Malmö, Sweden). Batch release is performed by Gedea Biotech AB Quality Assurance Director.

The investigational products will be packed in blister packs containing 6 pessaries packed together with 6 pessary applicators in a cardboard box (Figure 2 and Figure 3). The cardboard box will be labelled with "Gedea Pessary *p*Hyph", batch number, study number, package number, manufacturing date and expiry date. The label used in the study will be written in the local language.

Labels will be prepared in accordance with good manufacturing practice (GMP), the Medical Devices Directive 93/42/EEC and local regulatory guidelines.

7.2.3 Stability program

The stability of Gedea Pessary *p*Hyph pessaries has been evaluated and confirmed in a technical stability study at the conditions 25°C (up to 9 months, as of May 2021) and 40°C (up to 6 months) and in a clinical stability study, confirming stability up to 6 months at the conditions 25°C and 40°C. The stability program is planned up to 36 months, and extension

of shelf life will be done accordingly. For further information, refer to the Investigator's Brochure (IB).

7.2.4 Storage and handling of investigational products

The investigational products Gedea Pessary will be stored at room temperature (15°C--25°C) and protected from direct sunlight or freezing. The investigational products *must not* be used outside of the study. For further information, refer to the IB.

It is the responsibility of the Investigator to ensure that the investigational product is stored in its original packaging in a secure location with access only by authorised personnel, separate from other medications. The temperature should be noted daily (working days only unless automatic temperature readings are available).

7.2.5 Doses and treatment regimens

Each patient will self-administer a total of 6 doses of Gedea Pessary in the study. The pessary is slow-release formulated, administering 150 mg GDL and 184 mg NaG, over 24 hours.

The pessary will be self-administered vaginally by the patient at night, before going to bed. Instructions for use will be distributed at the first visit, advising patients on how to use the product together with the applicator. The patients will also be trained by site personnel in how to use the product, no previous experience of use is needed.

Briefly, patients will be instructed to wash their hands and vaginal area prior to use; place a tablet into the applicator and insert as far into the vagina as is comfortable (without forcing), or until half of the applicator is inside; discard the applicator after use; not use tampons or other vaginal products while using this product.

7.3 Investigational product accountability

The Investigator is responsible for full traceability of the investigational product from the manufacturer to patients until return or disposal. This shall be ensured by use of product accountability records, documenting quantity at storage and deliveries to and from storage.

Shipping records of investigational product deliveries from the manufacturer shall be kept at study sites, including *at least* the following information

- Investigational product name and quantity received
- Delivery date
- Batch number
- Expiry date

Dispensing logs shall be kept at study sites, documenting *at least* the following information:

- Investigational product name
- Batch number
- Expiry date
- Dispense date
- Number of units dispensed
- Patient (patient number) receiving the investigational product
- Number of units remaining in stock

Patients will be asked to return all used and not used treatment packages.

Any non-functioning investigational products or applicators shall be documented. All returned, unused or expired investigational products must be returned to the Sponsor for destruction unless otherwise stated in writing by the Sponsor. Any used or opened unused materials *must not* be reused.

7.4 Method of assigning patients to treatment groups

Not applicable.

7.5 Additional products and material

7.5.1 Additional material

The Sponsor will provide the study sites with study specific kits containing vaginal swabs for culture and sequencing of the vaginal microbiome. The kits will be developed specifically for the study and include all material needed as well as instructions and pre-paid envelopes where applicable.

Study sites will provide pH-test strips and urine dipstick pregnancy tests (urinary human chorionic gonadotropin [U-HCG]). pH-test strips and urine dipsticks used as per clinical routine at the site may be used.

The Investigator is responsible for full traceability of the vaginal swabs from the manufacturer to patients until return or disposal. This shall be ensured by use of accountability records documenting quantity at storage and deliveries to and from storage.

Shipping records of vaginal swab kit deliveries from the manufacturer shall be kept at study sides, including at least the following information.

- Swab kit batch number and quantity received
- Delivery date
- Expiry date

Dispensing logs shall be kept at study sites, documenting *at least* the following information.

- Swab kit batch number
- Expiry date
- Dispense date
- Number of units used
- Patient receiving the swab kit
- Number of units remaining in stock

All unused or expired swab kits must be returned to the Sponsor for destruction unless otherwise stated in writing by the Sponsor. Any used, or opened unused materials *must not* be reused.

7.5.2 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. For

details on VVC symptom score see Section 9.1.2 Rescue treatment will be according to standard clinical routines, as described below.

Patients will receive a prescription of fluconazole (50-150 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. Rescue medication will not be provided by the Sponsor, however the Sponsor will reimburse the cost.

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 12. In general, these patients should stay in the study and continue to be followed-up.

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

7.6 Treatment compliance

Patients will be asked about investigational product administration via the mobile application on each treatment day (Day 0 to Day 5).

Vaginal pH assessments on Days 0 and 7 will be used as a measure 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. It will be measured by site personnel on Day 0 and Day 7.

No other measurements of treatment compliance will be made.

8 ASSESSMENTS

The assessments performed during the study are described in the subsections below.

For details on clinical performance assessments (gynaecological examination and patient questionnaire), see Section 9. For details on safety assessments (clinical laboratory assessments, AEs and device deficiencies), see Section 10.

8.1 Informed consent

The procedures used for screening and obtaining informed consent at Day 0 are described in Section 6.1.

8.2 Demography

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).

Full information about the patients' Social Security Number or similar and name is to remain confidential in the records of the respective Investigator.

8.3 Eligibility criteria

Eligibility criteria should be checked during Screening (Day 0) and verified before enrollment. The criteria are specified in Sections 6.3 and 6.4.

8.4 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, shall be collected at all site visits (Day 0 and Day 14) for all patients and also at the telephone contacts (Day 7 and Day 25). The generic name or trade name, dosage and reason for use shall be recorded in the eCRF for all medications.

NOTE:

VVC-treatment or any anti-fungal therapy unrelated to VVC within 14 days prior to inclusion, is not allowed (see Section 6.4).

During the study, anti-fungal therapy and other treatments related to VVC should be avoided (unless rescue treatment at Day 14) (see Section 6.5).

See further information on rescue medication in Section 7.5.2.

8.5 Medical and surgical history

Medical and surgical history will be collected during the Screening visit (Day 0). It should be obtained by interview and include descriptions of all relevant medical conditions and procedures within 14 days prior to Screening, as judged by the Investigator.

The number of previous VVC infections during the last 12 months prior to inclusion, should be noted, according to exclusion criterion #8 (see Section 6.4).

Relevant pre-treatment events (pre-treatment AEs) occurring between the signing of ICF and first administration of the investigational product will be registered in the medical history log of the eCRF.

8.6 Pregnancy test

All study patients will perform a pregnancy test (urine dipstick) at Screening (Day 0).

Pregnancy is an exclusion criterion (see Section 6.4). If pregnancy is confirmed in a patient during the study, the patient will be withdrawn, and the pregnancy will be followed (see Section 10.4).

8.7 Menstruation

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.

8.8 Administration of investigational product

For details on the administration procedures, see Section 7.2.5.

For restrictions during the treatment period, see Section 6.5.

9 CLINICAL PERFORMANCE

9.1 Clinical performance assessments

Assessments described in Section 9.1.1 will be used to diagnose VVC.

A CVVS score will be used for assessment of the primary endpoint, clinical cure on Day 7-14 (see Section 4.1.1).

Further, the CVVS score will also be used for assessment of the secondary endpoints 2, 3 and 6 (see Section 4.2.1).

Assessments described in Section 9.1.2, patient questionnaire, will be used to assess the secondary endpoints 4 and 10 (see Section 4.2.1).

9.1.1 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 (assessed by the patient):** 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 9.1.2).
- **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* moderate[a]: 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 Section 4.1.1.

9.1.2 Patient questionnaire

The patient questionnaire can be found in Appendix 1.

The patient questionnaire is relating to VVC symptoms (itching, burning, and irritation) and pessary administration. Questionnaire should be filled in via the mobile application ViedocMe™ (see Section 11.1.2) on Days 0 to 6, Day 11 and Day 25.

Questions about usability should be filled in by all patients on Day 6.

[a] scoring scale:
0 = none (absent)
1 = mild (slight)
2 = moderate (definitely present)
3 = severe (marked, intense)

10 SAFETY AND TOLERABILITY ASSESSMENTS

Assessments described in Section 10.1, will be used to assess the secondary endpoints 7, 8, and 9 (see Section 4.2.1) and the two exploratory endpoint (see Section 4.3.1).

Assessments described in Section 10.2, AEs will be used to assess the secondary endpoint 1 (see Section 4.2.1).

10.1 Clinical laboratory evaluation

10.1.1 Vaginal swab samples

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. For the testing made at home, labelled swabs will be given to the women who then will do the testing as per provided instructions. The swabs for vaginal culture will need to be sent for analysis to ensure receipt by the lab within 48 hours. Swabs for sequencing of the vaginal microbiome can be stored in ambient temperature for a month. These samples will be gathered and stored in < -70°C until analysis at the end of the study.

The collected samples will be used for the following analyses.

- **Microscopic analysis; presence of hyphae:** KOH or saline preparations 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.
- **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.
- **Sequencing of the vaginal microbiome:** Vaginal swabs for sequencing of the vaginal microbiome will be collected on Days 0, 7, 14, and 25. On Days 0 and 7, the swabs will be taken in duplicates.
  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.

Samples sent to the central laboratories will be coded with no possibility to identify the patients, and all samples will be destroyed directly after the analysis has been completed. Samples that are analysed at the investigational site will be destroyed directly after analysis. No samples will be kept for future research.

10.1.2 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.

10.2 Untoward medical events and AEs

10.2.1 Adverse event

An AE is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs including abnormal laboratory findings in patients, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Note:

a. This definition includes events that are anticipated as well as unanticipated events.

b. This definition includes events occurring in the context of a clinical investigation-related to the investigational device, the comparator or the procedures involved.

10.2.2 Adverse device effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

NOTE 1 This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2 This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

The following events are not considered untoward medical events/AEs:

- Medical interventions planned before study initiation given that the status of the participant has not worsened since signing the consent form or the intervention has had to be done at an earlier date.
- Conditions or diseases known when the patient signs the ICF, are not considered untoward medical events AEs. These will be registered in the medical history eCRF page.

10.2.3 Serious Adverse Events

A SAE is an AE that led to any of the following:

a) Death,
b) Serious deterioration in the health of the subject that resulted in any of the following:
   - Life-threatening illness or injury
   - Permanent impairment of a body structure or a body function
   - Hospitalisation or prolongation of patient hospitalisation
   - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
   - Chronic disease
c) Foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

NOTE: Planned hospitalisation for a pre-existing condition, or a procedure required by the current CIP, without serious deterioration in health during the course of the study, is not considered an SAE.

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

An unanticipated serious adverse device effect (USADE) is a SADE, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

An anticipated serious adverse device effect (ASADE) is an effect, which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

SAEs related to procedures imposed by the CIP but not with the use of the device should not be considered Serious Adverse Device Effects.

The classification of an untoward medical event as USADE or ASADE will be done retrospectively. The event will initially be captured as an SAE.

10.2.4 Definitions of adverse event ratings

10.2.4.1 Severity/intensity

Untoward medical events/AEs will be rated according to their severity/intensity. The following rating will be done by the Investigator:

Mild: Transient symptoms, no interference with daily activities of the participant.

Moderate: Clear symptomatology that moderately affects the daily activities of the participant.

Severe: Symptoms that clearly affects or hinders daily activities of the participant.

10.2.4.2 Causality assessment/relatedness

The relationship between the use of the medical device[a] (including the medical - surgical procedure) and the occurrence of each AE shall be assessed and categorised.[b] During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the IB, the CIP or the Risk Analysis Report shall be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The above considerations apply also to the SAEs occurring in the comparison group.

[a] Intended as both medical device investigated in the investigation and comparator.

[b] Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat AEs.

For the purpose of harmonising reports, each SAE will be classified according to 4 different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the SAE to the investigational[a] medical device or procedures:

Not related: Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible -and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

Possible: The relationship with the use of the investigational device or comparator or the relationship with study procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the investigational device or comparator or the relationship with study procedures seems relevant and/or the event cannot reasonably be explained by another cause.

Causal relationship: The SAE is associated with the investigational device or comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that;

[a] Investigational device: any device object of the clinical investigation, including the comparators.

  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the patient is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis[a], when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Investigators will distinguish between the SAEs related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An AE can be related both to the procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the Investigators will make the maximum effort to define and categorise the event and avoid these situations. Where the Sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

Particular attention shall be given to the causality evaluation of USADE. The occurrence of an USADE could suggest that the clinical investigation places patients at increased risk of harm than was to be expected beforehand.

10.2.4.3 Outcome

The outcome or the result of the untoward medical event/AE for a participant will be rated by the Investigator as;

[a] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

Recovered/ resolved:	Fully recovered spontaneously or after medical or surgical intervention, i.e. the status is the same as the pre-study status.
Resolved with sequelae:	As a result of the event the participant has remaining significant symptoms or loss of function as, but not limited to, blindness, deafness, or paralysis. All untoward medical events that the participant has not fully recovered from and has significant remaining symptoms or loss of function should be handled as serious untoward medical events/SAEs.
Ongoing:	The status of the participant has not improved, and the symptoms are unchanged.
Death	
Unknown:	The status of the participant is unknown. This term is to be used only when no other term applies, e.g. when the participant is lost to follow-up.

10.2.5 Capturing and reporting of untoward medical events/AEs

Patients will be asked about AEs or events related to the investigational device and/or procedure at all site visits and telephone contacts.

Questions to be asked:

- *Have you experienced any health problems since the last visit/telephone contact?*
- *Has there been any event related to the investigational device or procedure?*

AEs can also be obtained from:

- Signs and symptoms from patient examinations.
- Laboratory values.
- Spontaneous reports by patients or their relatives.

All AEs and ADEs, will be captured in the forms for AEs or device events in the eCRF. In case of a serious event, SAE, SADE or USADE will be recorded in the respective form as applicable.

All events fulfilling the definition of an untoward medical event will be captured and reported from the time when the participant signs the ICF and to the last visit in the study or until the participant has left the study.

Relevant pre-treatment events (pre-treatment AEs) occurring between the signing of ICF and first dose will be registered in the medical history log of the e-CRF.

Untoward medical events may need follow-up after the last visit in the study before being rated as recovered or given a final status according to the definitions above.

10.2.6 Reporting of SAEs

The Investigator will report any SAE or device deficiency that might have led to a SAE (see below) to the Sponsor authorised representative **immediately but not later than within 24 hours after awareness** that the event has occurred by completing the SAE eCRF pages.

If the eCRF is unavailable, an initial paper SAE report form may be used and sent to Sponsor authorised representative (device_sae@ctc-ab.se), however the SAE must be registered in the eCRF as soon as the eCRF is functioning.

Applicator device deficiencies that caused a SAE or might have led to a SAE have to be reported by the Sponsor to the manufacturer of the CE-marked applicator. All other further reportable events according to MDR 2017/745 have to be reported by the Sponsor/authorised representative to the National Competent Authority where the event occurred using a summary SAE tabulation (Summary Reporting Form, MDCG 2020-10/1).

The following events are considered reportable:

a) Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) Any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) Any new findings in relation to any event referred in points a) and b).

In case of SADEs and device deficiencies that could have led to an SAE, the Sponsor shall determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

10.2.6.1 Reporting to national competent authorities

The reporting of events to the national competent authorities must follow these reporting timelines:

- All reportable events as described in section 10.2.6 which that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **immediately, but not later than 2 calendar days** after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event.

  This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

- Any other reportable events as described in 10.2.6 or a new finding/update to it must be reported **immediately, but not later than 7 calendar days** following the date of awareness by Gedea Biotech AB of the new reportable event or of new information in relation with an already reported event.

10.2.6.2 Reporting to Investigators

The Sponsor is responsible for informing in writing all Principal Investigators. This reporting is applicable for all the events outlined in section 10.2.6.1 above and will be made on ongoing basis.

10.2.7 Follow-up of untoward medical events/AEs

Any AE that is ongoing when the patient withdraws from the investigation should be followed-up until the AE is resolved or the Investigator decides that the AE is stable and needs no further follow-up.

The last day for follow-up will be Day 25.

AEs ongoing at the last visit shall be assessed as chronic or stable.

10.3 Device deficiencies

The below is applicable both for the Gedea Pessary and the applicator.

Patients will be asked about events related to the investigational device and/or procedure at the Day 7 visit.

A device deficiency will, in this study, be defined as an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Inadequacy of device safety refers to properties of the device that could have or have led to an AE.

All device deficiencies shall be documented in the form for device events in the eCRF. The information recorded will include a description of the device deficiency as well as information about whether there was any injury to the subject or user as a result of the deficiency. If an injury occurred, an AE or SAE should also be recorded in the eCRF.

If no SAE occurred as a result of the device deficiency, the Investigator shall assess whether or not the device deficiency could have led to an SAE if:

a) suitable action had not been taken
b) treatment/intervention had not occurred
c) circumstances had been less fortunate

The Sponsor will also review all device deficiencies during the investigation and determine and document in writing whether they could have led to an SAE.

If the Investigator or the Sponsor judges that the device deficiency could have led to an SAE, the device deficiency will be subject to similar safety reporting procedures as for SAEs, described in applicable sections above.

If necessary, the device deficiencies seen will be categorised at the database lock meeting.

10.4 Pregnancy

Patients must be instructed to immediately inform the Investigator if any pregnancy should occur from the time of signing the ICF and during the study period. Any confirmed pregnancy in a study patient shall be reported by the Investigator on a Pregnancy Report Form immediately but not later than 24 hours of awareness and submitted to the Sponsor authorised representative (device_sae@ctc-ab.se).

Patients becoming pregnant will be withdrawn from the study and followed until delivery and additional information on the infant will be collected until the infant is 1 month old. The outcome of the pregnancy must be reported on a Pregnancy Report Form.

AEs in connection with the pregnancy, in the foetus, and in the infant up to 1 month of age will be reported. Any abortions (including elective abortions) together with abortion rationale should be reported and handled as SAEs, as well as any complications relating to the pregnancy, foetus and infant fulfilling any criteria for seriousness. Procedures and timelines for AE/SAE reporting applies to reporting of AEs/SAEs in the pregnant patient, the foetus and the infant.

11 DATA MANAGEMENT

Data management refers to the activities defined to achieve safe routines to efficiently enter patient information into a database, avoiding errors.

Customised data management system will be developed for this study using Viedoc™ software, owned, developed and maintained by Viedoc Technologies AB. Information entered into the data entry system will be by patient study identification number; names will not be linked with patient data in the database. Study sites will maintain records in secure areas linking the patient name with the identification number assigned for the study. Study sites will have full access to their own data and be able to view these data remotely. Study staff will not be able to view patient data associated with other sites. The software is designed to be compliant with Title 21 Code of Federal Regulations Part 11.

Clinical Trial Consultants will provide the data management services for this study. The data management routines include procedures for handling of eCRF, database set-up and management, data entry, data verification and validation (quality control of the database), and documentation of the performed activities, including information of discrepancies in the process. Further details of the data management services and processes will be described in the Data management plan. The eCRF/data entry screens, and the database/programs will be designed in accordance with the CIP and Clinical Trial Consultants standard operating procedure (SOP) system.

11.1 The web-based case report form

Clinical data (including AEs and concomitant medications) will be entered into the eCRF (Viedoc4™). The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents, unless the eCRF is considered source.

Authorised study site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to get access to live version of the eCRF and any data being entered into the system for any trial patient.

11.1.1 The entering of data into the electronic case report form

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are further described in Section 13.3.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the patient's visit.

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off all collected data.

11.1.2 Electronic patient reported outcomes

The patients themselves will record data using an ePRO system, a mobile application, ViedocMe™, linked to the eCRF system Viedoc™. ViedocMe™ is provided as a Software as a Service (SaaS) application. The ePRO includes password protection and internal quality checks. Text reminders will be sent to the patient through the ePRO. All data registered in the ePRO is stored together with the eCRF data.

The data from the ePRO system are stored exactly the same way as the rest of the patient data in the eCRF Viedoc™, with the same security and control. Only authorised personnel with provided access to the system will be able to review the data.

The data entered in the ePRO system will be sent encrypted into the eCRF. No data are ever stored locally on the patient's device.

Each patient will receive a unique user name and PIN code for their ePRO account. Once generated, the site personnel will not be able to see the PIN code. The patient's telephone number and email address connected to their user account will also always be encrypted. Email address and telephone number are not possible to extract from the ePRO once entered and the site personnel cannot see these. Only the participating patient can change this information within their own user account. The telephone number and email will not be possible to link to the patient data.

The data entered by the patient in the ePRO system cannot be changed without the patient's consent.

11.1.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the Investigator or authorised designee. The Monitor cannot enter data in the eCRFs.

Once clinical data have been submitted to the central server via the eCRF, corrections to the data, made by the site personnel, will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with date and time will be logged.

Roles and rights of the site personnel responsible for entering clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible Monitor or Data Manager will raise a query in the eCRF. The appropriate investigational personnel will answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study personnel, time, and date are logged.

11.1.4 Signing of data

The eCRF records will be automatically appended with the identification of the creator, by means of their unique user ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique user ID and password; date and time stamps will be added automatically at time of electronic signature.

11.1.5 Audit trail and database lock

All changes in the eCRF will be fully recorded in a protected audit trail, and a reason for the change will be required.

Once all data have been entered, verified, and validated, including all queries are solved, medical coding approved and SAE reconciliation performed, the database will be locked to prevent any further changes in the clinical study data.

11.2 Medical coding

Before database lock, medications will be coded according to the WHO anatomical therapeutic chemical (ATC) classification system (ATC-index).

Medical history and AEs will be coded using the medical dictionary for regulatory activities (MedDRA).

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The principal features of the statistical analysis of the data are described in this section. More details of the planned statistical analysis will be provided in a separate statistical analysis plan (SAP) that will be finalised prior to database lock. Any deviations from the planned statistical analysis will be documented in the CIR.

The statistical planning, analysis and reporting work will follow CTC's SOP system. All analyses described below will be performed using SAS (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA)[54].

12.1 Statistical analysis; data presentation

Continuous data will be summarised using descriptive statistics, where the following parameters will be reported: number of evaluable and missing observations, mean and standard deviation, median, quartiles, and extreme values (minimum and maximum).

Categorical data will be presented as absolute and relative frequencies.

All tests will be two-sided and performed at the 5% significance level unless stated otherwise.

Baseline will be the last non-missing value prior to treatment if not stated otherwise.

12.2 Analysis data sets and populations

The full analysis set (FAS) is defined as all patients who received at least 1 treatment dose.

The per protocol analysis Set (PPAS) is a subset of the FAS and consists of patients who sufficiently complied with the CIP. Criteria for inclusion in the PPAS will be specified in the SAP.

All clinical performance analyses will be performed on both the FAS and the PPAS. The analyses performed on the FAS are to be considered as main and the analyses performed on the PPAS as supportive.

The safety analyses will be performed on the FAS.

12.3 Demographic, other baseline characteristics, prior and concomitant medications and compliance

The disposition of patients, demographic data and relevant baseline characteristics (including medical and surgical history and menstruation data), as well as prior and concomitant medication will be presented descriptively.

Medical history will be coded according to MedDRA and will be presented by system organ class (SOC) and preferred term (PT) as part of the baseline data.

Prior and concomitant medications will be coded using WHO ATC-index and summarised by ATC Class.

Treatment compliance data will be presented descriptively. For details on compliance assessment see Section 7.6

12.4 Primary and secondary endpoints analysis

12.4.1 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 above.

***The population.** See study inclusion and exclusion criteria in Sections 6.3 and 6.4, and the description of the main analysis set populations that will be used in Section 12.2.

***The endpoint.** The final endpoints are defined in Sections 12.4.2 and 12.4.3. 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 12.4.2 and 12.4.3.

***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 12.4.2.

12.4.2 Primary endpoint analysis

In the estimand setting, the primary endpoint will, in addition to the definition stated in Section 4.1.1, 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.

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 %.

Sensitivity analyses to evaluate the effect of missing data for any of the 6 individual vulvovaginal signs and symptoms scores included in the CVVS score will be performed. Details on the sensitivity analyses will be described in the SAP.

12.4.3 Secondary endpoints analysis

12.4.3.1 Adverse events

An overview of all AEs, including SAEs, intensity, relationship to the investigational product, and deaths, will be presented by SOC and PT according to MedDRA.

Incidence of AEs and SAEs will be presented by SOC and PT. AEs will also be presented by intensity and relationship to IMP.

For all summaries of AEs, the number and percentage of patients, as well as the number of events will be presented.

12.4.3.2 Performance endpoints

All secondary clinical performance endpoins 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 12.4.2) 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 12.4.2) 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 7, by a patient questionnaire (see Appendix 1). The questionnaire contains 4 specific yes/no (i.e. binary) 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 as a continuous variable.

12.5 Exploratory endpoints analysis

The analysis of the two exploratory endpoints (see Section 4.3.1) will be described in the SAP.

12.6 Sample size determination

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% CI for the clinical cure rate is above 30%. To compensate for patients with missing data a total of 26 patients will be included.

In the previous Gedea VVC study, a clinical cure rate of 41% was seen.[50] By using a new formulation, pHyph gen II, in the CL4 study, a higher cure rate is expected. The data from CL1 indicates that for a large number of patients, the pessary did not stay in the vagina and/or did not resolve properly.[50] Taken these problems into account when changing the formulation, it is estimated that a cure rate of 54% can be achieved. Other treatments have shown a clinical cure rate of between 50 and 87% but a somewhat lower cure rate for pHyph gen II is acceptabel due to its dual high clinical cure for BV, high safety profile, and for the OTC market the medical device is intended for.[17,18,56, 57]

13 STUDY MANAGEMENT

The Sponsor Gedea Biotech AB has delegated the following tasks to CTC, whose SOP system will be followed.

- Study management, including examining and assessment of investigational sites, institutions and medicl device storage facilities (including all data and documents related to the investigation) and monitoring (further described in the below sections).
- Setting up and maintaining the Trial master file.
- Medical writing, including preparation of the CIR.
- Device vigilance and handling of safety events in accordance with local requirements (see Section 10.2).
- Data management, including cleaning of the database (eCRF) and data validation (see Section 11).
- Biostatistics, including programming, preparation of listings, tables and figures and quality check of statistical analysis (see Section 12).

13.1 Clinical monitoring

Before the initiation of the investigation, the study Monitor will:

- Determine the adequacy of the facilities.
- Discuss with the Investigator and site personnel (as applicable) their responsibilities with regard to MDR, ISO14155, CIP adherence and local regulations.

At an initiation meeting, the Monitor will review the investigation procedures with the Investigator and the Investigator's staff and document this in compliance with the ISO 14155 Guidelines.

During the investigation, the Monitor will have regular contacts with the investigational site, including site visits to:

- Provide information and support to the Investigator and staff.
- Confirm that facilities remain acceptable.
- Confirm that the study team is adhering to the CIP.
- Confirm that data are being accurately recorded in the eCRF.
- Ensure that accountability checks for the investigational products are being performed.
- Conduct source data verification, which will require direct access to all original records for each patient (e.g. Medical records).

The Monitor will be available (by phone and email) between visits whenever the Investigator or other personnel at the site needs information, advice or help. The frequency of the monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality and overall site performance. Initiation visits and monitoring visits may be performed remotely.

All documentation and correspondence pertaining to the study (raw data, letters etc.) should be kept in accordance with ISO 14155.

13.2 Training of staff

A delegation log will be completed for each investigational site team member to indicate which activities the Investigator has authorised them to perform. This must be updated prior to a new or existing team member undertaking any new responsibility.

The Investigator will ensure that appropriate training relevant to the clinical investigation is given to the medical, nursing and other staff involved before start of any study-related work in the study. The Investigator will also ensure that new information of relevance to the performance of this clinical investigation is forwarded to the staff involved. All training completed in the study will be documented in a training log.

13.3 Patient records and source data

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They include laboratory notes, memoranda, material dispensing records, patient files, etc. The origin of source data in the investigation will be further specified in a separate document (Origin of source data form).

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the Monitor at each monitoring visit. The Investigator must submit a completed eCRF for each patient who signed the ICF. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study ID and Patient Number. Any personal information, including the patient's name, should be removed or rendered illegible to preserve individual confidentiality.

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements, including, but not limited to:

- Study code
- Patient Screening number and/or patient number
- That informed consent for participating in the study was obtained, signed and dated by the patient.
- All visits during the investigation period
- All AEs/ADEs, SAEs/SADEs and device deficiences
- Treatments and medications
- The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRFs.

13.4 Audits and inspections

The purpose of an audit or inspection is to systematically and independently examine all study-related activities to document that they were conducted, recorded, analysed and accurately reported according to the CIP and the background regulatory demands.

Audits or inspections may therefore be performed by authorised representatives of the Sponsor, by CTC or by a RA/CA at the investigational site during or after the investigation.

These visits may include source data verification and confidentiality documents are therefore created. This implies that auditors/inspectors will have the right to inspect the investigational sites at any time during and/or after completion of the investigation and will have direct access to source documents, including patients' medical records. By participating in this study, the Investigator agrees to this requirement.

The Investigator should contact the Monitor immediately if they are contacted by a RA/CA about an inspection at their study site.

13.5 Changes to the plan and ICF

During the study, study procedures will not be changed without the mutual agreement of the Investigators and the Sponsor. Changes to the CIP and/or the ICF must be approved by the Sponsor, IEC and if applicable, the regulatory authority before implementation. In case of acute safety risks, changes may be implemented without prior approval. In this case any implemented change must be properly documented by the Investigator and the Sponsor must be immediately notified.

If an amendment to the CIP substantially alters the study design, or increases the potential risk to the patients, the Investigator will be responsible to contact and inform all currently enrolled patients about this new information and obtain additional written informed consent This information must also be provided to new patients prior to their entry into the study.

13.6 Deviations from the clinical investigation plan

Deviations from the CIP should not occur. Investigators ascertain they will apply due diligence to avoid deviations to CIP. Under no circumstances should the Investigator contact Sponsor or Sponsors delegate to request approval of a protocol deviation, as no authorised deviations are permitted. If the Investigator feels a deviation would improve the conduct of the study this must be considered in an amendment to the CIP and unless such an amendment is agreed upon Sponsor and approved by the RA/CA and/or IEC (as applicable) it cannot be implemented. All significant deviations to the CIP will be recorded and reported in the CIR.

However, the Investigator is expected to take any immediate action required for the safety of any patient included in this investigation, e.g. in case of an emergency, even if this action represents a deviation from the CIP. In such cases, Sponsor or Sponsors delegate should be notified of this action as soon as possible. Any deviation will be logged, including documentation of the reason and date for the deviation. If repeated violations or deviations occur, a corrective and preventive action procedure will be implemented, and the involved Investigator(s) may be disqualified for study participation.

Emergency deviations and violations which may affect the rights, safety or welfare of participants; or the scientific integrity of the clinical investigation; will be notified to the RA and/or IEC as applicable according to local laws and regulations, as soon as possible after the Sponsor has become aware of them.

Deviations from the CIP that are due to the COVID-19 pandemic spread will be tracked separately and described in the CIR.

13.7 Clinical investigation timelines

The recruitment period is planned to proceed until 26 patients have been enrolled, where the intended first patient's first visit is in Q1 2023 and the intended last patient's last visit in Q4 2023.

13.8 Declaration of end of investigation

The end of the clinical investigation is defined as the last patient's last visit.

The RA/CA and the IEC will be informed that the clinical investigation has ended within 90 days of the end of the investigation. If the investigation has to be terminated early, this period will be reduced to 15 days and the reasons will be clearly explained.

13.9 Patient protection procedures

13.9.1 Procedures in case of medical emergency

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the clinical investigation.

13.9.2 Patient data protection

The written patient information explains that the data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation, and that authorised representatives of the investigational site, Sponsor, RA/CA or an IEC require access to those parts of the medical records relevant to the clinical investigation, including medical history, for verification of data and appropriate conduct of the clinical investigation.

Confidentiality of patient data will be maintained at all times. Patient anonymity will be guaranteed and documentation relating to a patient will be kept in a secure location.

In case of any data breach, Gedea Biotech's Data Protection Officer (DPO) should be contacted and informed of the data breach. An investigation (root cause analysis) of the data breach must be performed to establish the extent and impact of the breach and corrective action(s)/corrective action(s) will be initiated. The DPO will report the breach to the authorities.

13.9.3 Patient confidentiality

The patients have the right to request access to their personal data and the right to request rectification of any data that is not correct and/or complete. The Sponsor or designee personnel whose responsibilities require access to personal data agree to keep the identity of each patient confidential.

All processing of personal data will be stored confidential and handled according to legislations concerning the protection of personal data. Patients will be identified only by code. The ICF shall contain information about what personal data to be collected in the study and that this will be kept confidential. The provided information shall be sufficient to enable all patients to give their consent not only to the participation in the study, but also to the processing of personal data.

13.10 Insurance

The Sponsor has arranged the appropriate product liability and clinical study insurance to cover the requirements of this clinical investigation (Chubb European Group SE).

13.11 Reporting and publication

A final CIR should be completed, even if the investigation is prematurely terminated. The report will be prepared by the Sponsor according to the MDR and ISO 14155-guidelines. The CIR will be completed within one year of the end of the clinical investigation or within three months of the early termination or temporary halt and will be submitted to the CAs in the countries where the study has been executed. The submission will be made according to local submission procedures.

All publications and presentations must be based upon the CIR.

All information supplied by the Sponsor in connection with this investigation will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this investigation.

The Investigator may publish results from this investigation; however, as some of the information regarding the investigational medical device and development activities may be of a strictly confidential nature, the Sponsor must first be given the opportunity to review any publication manuscript prior to submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this investigation. If an Investigator is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration, internal presentation and for promotion.

The study and a summary of the study results will be made publicly available at www.ClinicalTrials.gov.

13.12 Record retention

The Investigator will retain copies of the records for at least 10 years after the investigational device has been placed on the market or longer if mandated by local requirements or specified in the clinical trial agreement. The Investigator must take measures to prevent accidental or premature destruction of these documents. In all cases, the Investigator must contact the Sponsor prior to disposing of any records related to the clinical investigation. Included in records to be retained are the patients' medical records, signed CIP, copies of paper forms (if applicable), signed ICFs, IEC approval letters, product accountability records, correspondence concerning the clinical investigation, and any other documents to identify the patients (including the Patient Identification Log).

The electronic data retention period is the same as above-mentioned for records. Archiving of data are performed according to industry standards such as in PDF/A format.

In addition, if the Investigator is no longer able to fulfil the role of Investigator (e.g. if he/she retires), a new Investigator will be appointed in consultation with the Sponsor.

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Appendix 1 Patient Questionnaire

Questions will be asked directly in the electronic patient reported outcomes (ePRO) system mobile application ViedocMe™.

Section 1. Vaginal candidiasis symptoms and pessary administration

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)
Irritation				
Itching				
Burning				

Section 2. Usability

All patient should reply to the following questions on Day 6.

Questions – 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 thatn 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

Section 3. Reminders

Patients will receive the following reminders and questions via the mobile application:

- **Administration**

Reminder about administration of the investigational product on Days 0 to 5 and VVC symptom scoring on Days 0 to 6, Day 11 and Day 25.

The investigational product is to be self-administered at night before going to bed.

Please score your vulvovaginal symptoms.

-

- **Sampling reminder and questions at Day 25**

1. Have both vaginal swab samples been taken?

- Yes
- No

Appendix 2 Principal Investigator Signature Page

I have read the Clinical Investigation Plan including all appendices, and I agree to all of the terms as described. I will conduct the clinical investigation according to the procedures specified herein.

Study Code: **CL4**

Site/Institution:

Principal Investigator:

Signature: _____ Date: _____

Printed name: _____

Appendix 3 List of Participating Sites and Principal Investigators

Name of Institution /Site	**Site address**	**Principal Investigator**	**Contact details, Principal Investigator**
Danderyds sjukhus Kliniska vetenskaper Obstretrik och gynekologi	SE-182 88 Stockholm, Sweden	*NAME*	Phone: *TELEPHONE* E- mail: *NAME*
Karolinska Universitetssjukhuset Huddinge Kvinnoforskingsenheten B79	SE-141 86 Stockholm, Sweden	*NAME*	Phone: *TELEPHONE* E- mail: *NAME*
Carlanderska sjukhuset, Forskningsenheten	Carlandersparken 1, SE-405 45 Gäteborg, Sweden	*NAME*	Phone: *TELEPHONE* E- mail: *NAME*
Clinical Trial Consultants AB	Dag Hammarskjölds väg 10B, SE-752 37 Uppsala, Sweden	*NAME*	Phone: *TELEPHONE* E- mail: *NAME*