CLINICAL INVESTIGATION PLAN

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

Study Product:	Gedea Pessary
Study Number:	CL1
Sponsor:	Gedea Biotech AB Medicon Village Scheelevägen 2 SE-223 81 Lund, Sweden
Clinical Investigation Plan (CIP) Number:	QRS-CL1-003
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APPROVAL PAGE

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SYNOPSIS

Name of Sponsor: Gedea Biotech AB
Name of Products: Gedea Pessary (commercial name *p*Hyph)
Name of Active Ingredient: Glucono-delta-lactone (GDL) and sodium gluconate (NaG)
Title of Study: An open-label study to evaluate clinical performance of Gedea Pessary in adult women with vulvovaginal candidiasis (VVC).
Clinical Investigation Plan Number: QRS-CL1-003
Investigators and Study Center(s): *NAME,* VO Kvinnosjukvård, Skånes universitetssjukvård, Lund, Sweden *NAME*, Annerokliniken, Löddeköpinge, Sweden *NAME*, Hoftekliniken, Helsingborg, Sweden Kliniska prövningsenheten, Kliniska Studier Sverige - Forum Söder, Skånes universitetssjukhus, Lund, Sweden
Classification of Trial: Feasibility Clinical Investigation
Objectives: To investigate the clinical performance, tolerability, and safety of the investigational product.
Methodology: This is an open-label, single-armed, multi-center study to evaluate clinical performance, tolerability, and safety of Gedea Pessary in 24 adult women with VVC. On Day 0, patients will have gynecological examination, vaginal samples taken, and will receive the investigational product to be self-administered 2 days apart (Day[s] 0, 2, 4, and 6). Patients will be examined after 7 days with respect to VVC signs and symptoms and if not cured, will receive prolonged treatment on Day(s) 7, 9, 11, and 13. Patients will be followed-up by telephone up to 29 days after last treatment. Vaginal samples will be used for confirming diagnosis and microbiome analyzes. Patient questionnaires will be used for assessing VVC symptoms, usability, and adverse events (AEs).
Number of Subjects Planned: Twenty-four (24) patients
Diagnosis and Main Criteria for Inclusion: Inclusion Criteria: • Adult, post-menarchal, pre-menopausal women aged 18 years or older

- Diagnosis of VVC, defined as having a white or creamy vaginal discharge plus the following findings:
    1. *At least* 2 of the following signs and symptoms of VVC that are characterized as *at least* moderate: itching, burning, irritation, edema, redness, or excoriation.
    2. Potassium hydroxide (KOH) or saline preparation from the inflamed vaginal mucosa or secretions revealing yeast forms (hyphae or pseudohyphae) or budding yeasts.
- Having decisional capacity and providing written informed consent
- Negative urine pregnancy test at screening
- Refrain from using any intravaginal products (i.e., contraceptive creams, gels, foams, sponges, lubricants, or tampons, etc.) during the study period
- Refrain from sexual intercourse or use a condom until Day 7
- Signed informed consent and willing and able to comply with all study requirements

Exclusion Criteria:

- Patients with known or apparent signs of other infectious causes of VVC (BV, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Herpes simplex, or human papillomavirus) at screening
- Patients who are pregnant or breastfeeding
- Patients who were treated for VVC within the past 14 days
- Patients who are currently receiving antifungal therapy unrelated to VVC or has taken antifungal therapy within the past 14 days
- Patients who have used pH-modifying vaginal products within the last 14 days
- Patients who have received an investigational drug in a clinical investigation within 30 days prior to screening
- Known/previous allergy or hypersensitivity to any product constituent or fluconazole
- Any medical condition that in the Investigator's judgments would make the patient unsuitable for inclusion

Investigational Product, Dose, and Mode of Administration:

Gedea Pessary, administered vaginally, containing 300 mg GDL and 367.5 mg NaG.

Study Duration:

Up to 5 weeks for each patient, planned first patient in November 2018.

Criteria for Evaluation:

Primary endpoints:

- Clinical cure rate on Day 7.
    - 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.
        - Each of the following 6 vulvovaginal signs and symptoms will be individually scored using the scoring scale below and then added together to determine the CVVS score.
            - Vulvovaginal signs: erythema, edema, or excoriation
            - Vulvovaginal symptoms: itching, burning, or irritation

- Scoring Scale: each score should be objectively defined.
  - 0 = none (absent)
  - 1 = mild (slight)
  - 2 = moderate (definitely present)
  - 3 = severe (marked, intense)
- Safety and tolerability, based on reported treatment-emergent AEs

Secondary endpoints:

<u>All patients</u>

- Proportion of patients having a reduction in CVVS score on Day 7 compared to Day 0
- Change in the CVVS score from Day 0 to Day 7
- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 4 and Day 7, compared to Day 0
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 4 and Day 7
- Usability, measured by patient questionnaire

<u>For patients not receiving prolonged treatment</u>

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

<u>For patients receiving prolonged treatment</u>

- Proportion of patients receiving prolonged treatment
- Clinical cure rate on Day 14, defined as the absence of signs and symptoms of VVC in terms of having a CVVS score equal to or below 3
- Proportion of patients having a reduction in CVVS score on Day 14 compared to Day 0
- Change in the CVVS score from Day 0 to Day 14
- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42
- Recurrence rate on Day 21, and Day 42, defined as the proportion of patients clinically cured on Day 14 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred
- Proportion of patients receiving prescription for fluconazole on Day 14

Exploratory endpoint variables:

<u>All patients</u>

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

<u>For patients not receiving prolonged treatment</u>

- Effect on vaginal microbiome on Day 35

<u>For patients receiving prolonged treatment</u>

- Effect on vaginal microbiome on Day 14 and Day 42

Safety and Tolerability Endpoints:

See above, safety and tolerability, based on reported treatment-emergent AEs.

Statistical Methods:

Sample size (n=24) is based on having 90 % power to show that the one-sided 95 % confidence interval for the observed cure rate is above 40 %, assuming the true clinical cure rate, as defined in this study, to be equal to 70 % in this patient population.

Clinical performance and safety analyses will be performed against the full analysis set (FAS) population, i.e. all patients who have received at least 1 dose of study treatment. The first co-primary endpoint, the clinical cure rate, will be calculated and presented together with a one-sided 95 % confidence interval based on the exact binomial distribution, whereas the evaluation of the second co-primary endpoint (safety and tolerability) will be based on descriptive statistics and data listings. The secondary endpoints will be presented with the appropriate point estimate together with the 95% confidence interval. Further, all clinical performance and safety endpoints will be presented descriptively.

Clinical Investigation Plan Approval Date:

24OCT2018

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LIST OF ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
ATC	Anatomical therapeutic chemical classification system
BV	Bacterial vaginosis
CI	Confidence interval
CIP	Clinical investigation plan
CRF	Case report form
CRO	Contract research organization
CIR	Clinical investigation report
CTA	Clinical trial agreement
CV	Curriculum vitae
CVVS	Composite vulvovaginal signs and symptoms
eCRF	Electronic case report form
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
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IPCS	International programme on chemical safety
ISF	Investigator site file
ISO	International Organization for Standardization
MedDRA	Medical dictionary for regulatory activities
NaG	Sodium gluconate
OTC	Over-the-counter
PP	Per protocol
RA	Regulatory authorities
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation
SDV	Source data verification
SOP	Standard operating procedure
USADE	Unanticipated serious adverse device effect
VVC	Vulvovaginal candidiasis
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Indication

Vaginal infection is a huge and today largely underestimated problem, affecting between 70% to 75% of women at some point in life, and between 5% to 8% of adult women have recurrent vulvovaginal candidiasis (VVC) with ≥ 4 episodes yearly.[1] As previously described, current antifungal agents for VVC treatment and prevention are prone to resistance development and many patients relapse after treatment.[2] Also, oral antifungal therapies are not recommended during pregnancy due to the potential risk of fetal harm and spontaneous abortions.[3,4] Therefore, treatment guidelines recommend that topical, rather than oral, antifungal therapy is used in pregnant women.[5]

The vaginal microbiome is a dynamic system with a complex mixture of microorganisms in different ratios and quantities, which depend on lactic-acid producing bacteria to maintain a weakly acidic environment, see overview.[6] Changes to vaginal microflora will increase the pH, thereby forming a favorable 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.[7-11] Infections are also facilitated due to the mucosal effect of increased estrogen levels and a weakened immune system during pregnancy.[12] Recurrences are more common in pregnant women, and their therapeutic response is reduced compared to non-pregnant women.[13,14] Further, contraceptive pills, menstruation, and diabetes mellitus have been identified as predisposing factors for VVC.[15,16] *Candida albicans* is the most prevalent pathogen, which has been reported in epidemiological studies as represented in between 85% and 95% of vaginal isolations.[17-19] *Candida glabrata* is the second most prevalent pathogen.[20]

Many women diagnose themselves with VVC and purchase over-the-counter (OTC) antimycotics for treatment. However, many misdiagnose themselves, leading to unnecessary or inappropriate treatment;[21] Ferris and colleagues found that only 34% of women who purchased OTC antimycotics for VVC did, in fact, have VVC.[22]

Current treatment strategies for uncomplicated or acute VVC include antimycotic 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 over 27 to 38 days for intravaginal imidazoles (clotrimazole, terconazole, butoconazole, or miconazole) are 64% to 87%.[2,23] Short-term clinical cure rates have been reported to be 85%,[2] but also as low as 35% seven days after treatment.[24] Mycological cure rates for oral fluconazole in uncomplicated VVC are 96% after 7 days, 90% after 14 days, and 86% after 28 days.[24]

Severe VVC is characterized by extensive vulvar edema, excoriations, and fissure formation. Short courses of treatment, which are normally effective in uncomplicated VVC, are often not sufficient.[21] 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.[21,25,26] See Table 1 for severe VVC treatment cure rates.

Recurrent VVC is characterized by ≥ 4 yearly episodes, and treatment usually entails intensive initial therapy to induce clinical and mycological remission, followed by 6-month systemic fluconazole maintenance therapy.[21,27,28] While treatment guidelines for recurrent

VVC are consistent, recommended treatments are not particularly effective in the long term[2,27] as 30% to 50% of patients experience recurrence after treatment discontinuation.[21]

There are limited data regarding the antifungal 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.[29-32] 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.[31]

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

Table 1 Severe Vulvovaginal Candidiasis, Treatment Cure Rates

	Terconazole	Clotrimazole	Fluconazole
Clinical Cure Rate			
7-14 days after treatment	81%	89%	76%-89%
30-35 days after treatment	60%	72%	56%-78%
Mycological Cure rate			
7-14 days after treatment	79%	78%	71%-74%
30-35 days after treatment	62%	54%	53%-56%

Relapse rates after 30 to 35 days were between 13%-26%, see[33,34] for details.

1.2 Biofilm and Glucono-Delta-Lactone

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 enhancing 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 utilized by yeasts and other eukaryotes in the pentose phosphate pathway.

Biofilms are characterized by a transformation of planktonic cells to form hyphae, which can invade the mucous membrane and induce inflammation.[38] The hyphal form, i.e., filamentous cells, can invade tissue and induce inflammation, mediated by Candidalysin, a cytotoxic peptide toxin that destroys the epithelial cells of the vagina.[39] Thus, it is reasonable to assume that GDL functions as an indicator of a favorable environment for several pathogens, such as Candida, which favors planktonic cells over hyphae, resulting in reduced biofilm formation.

We have shown that GDL can significantly reduce the biofilm formation in *C. albicans* and other Candida species. 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 remove also mature biofilm (biofilm grown for 2 days before treatment, data not shown).

1.3 Product Description and Previous Experience

1.3.1 Non-Clinical Data

Glucono-delta-lactone is a normal intermediate in glucose metabolism through the pentose phosphate cycle in mammals. Animal studies show that GDL gives similar weight increase as glucose in rats on low-calorie diets.[40] Furthermore, several studies on humans have been performed using oral doses between 3 g and 50 g of GDL with no signs of toxicity.[41] The investigated studies showed no evidence for carcinogenicity, teratogenicity, or genotoxicity of GDL, nor D-gluconic acid or the magnesium, potassium, calcium, or sodium salts thereof. In addition, both the U.S. Food & Drug Administration (FDA) and the World Health Organization International Programme on Chemical Safety (ICPS) accepts GDL as a safe food additive.[42,43]

In this study, GDL and sodium gluconate (NaG) have been formulated as a slow-release vaginal tablet/ pessary. 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 International Organization for Standardization (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 sensitization (local lymph node assay, ISO 10993-10). The tests have been performed by Eurofins Medical Device Testing (Munich, Germany) in compliance with the principles of good laboratory practice (GLP). The cytotoxicity test, which is 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 is a prerequisite to continue with the *in vivo* irritation and sensitization 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 sensitization test showed no signs of sensitization after treatment with Gedea Pessary. Thus, it can be concluded that the product fulfilled the current biocompatibility requirements for medical devices. For further pre-clinical data, refer to the Investigator's brochure (IB).

1.3.2 Clinical Data

The GDL-and-NaG containing investigational device, *Gedea Pessary* (commercial name *p*Hyph), has not been tested in previous clinical trials. Products containing polymerized lactic acid have comparable properties to Gedea Pessary, as lactic acid and GDL have the same ability to inhibit bacterial biofilm formation and lower the pH to a similar extent, see IB. One such product, *Laccure Pessary* (Laccure AB, Helsingborg, Sweden), is buffered to pH 3.5, whereas Gedea Pessary is buffered to pH 3.6. Laccure Pessary has been tested in a clinical trial of 126 patients with confirmed bacterial vaginosis (BV), where 93 patients were treated with 1 or 2 doses of Laccure Pessary and 33 patients formed the control group.[44] The study showed an 80% cure rate for the single-dose treatment. No serious adverse events (SAEs) occurred. The majority of adverse events (AEs) reported were of mild intensity and brief. The

most common events were vaginal itching or vaginal burning, experienced by 10 patients. No differences were seen between groups. The treatment had no visually detectable negative impact on the vaginal mucosa.

Based on published studies on current treatments for VVC, all vaginal and local antimycotics are generally well tolerated.[2] Local irritation is the most frequent adverse event reported in conjunction with topical azole therapy, and headache is the most frequently reported adverse event of oral imidazoles.[23,34] Nausea and diarrhea has been reported as treatment-emergent AEs in a study with oral fluconazole, both at a rate of 1.9%.[24]

Collectively, pre-clinical data indicate that GDL and NaG are safe and may be an effective topical treatment for VVC and a GDL-and-NaG containing slow-release pessary is to be investigated in this clinical trial.

2 STUDY OBJECTIVES

2.1 Primary Objectives

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

Primary endpoints:

- Clinical cure rate on Day 7.
    - 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.[1]
        - Each of the following 6 vulvovaginal signs and symptoms will be individually scored using the scoring scale below and then added together to determine the CVVS score.
            - Vulvovaginal signs: erythema, edema, or excoriation
            - Vulvovaginal symptoms: itching, burning, or irritation
        - Scoring Scale: each score should be objectively defined.
            0 = none (absent)
            1 = mild (slight)
            2 = moderate (definitely present)
            3 = severe (marked, intense)
- Safety and tolerability, based on reported treatment-emergent AEs.

2.2 Secondary Objectives

To further investigate the clinical performance of the investigational product.

Secondary endpoints:

<u>All patients</u>

- Proportion of patients having a reduction in CVVS score on Day 7 compared to Day 0.
- Change in the CVVS score from Day 0 to Day 7.
- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 4 and Day 7, compared to Day 0.

- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 4 and Day 7.
- Usability, measured by patient questionnaire.

For patients not receiving prolonged treatment

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

For patients receiving prolonged treatment

- Proportion of patients receiving prolonged treatment.
- Clinical cure rate on Day 14, defined as the absence of signs and symptoms of VVC in terms of having a CVVS score equal to or below 3.
- Proportion of patients having a reduction in CVVS score on Day 14 compared to Day 0.
- Change in the CVVS score from Day 0 to Day 14.
- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0.
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42.
- Recurrence rate on Day 21, and Day 42, defined as the proportion of patients clinically cured on Day 14 and thereafter responding "yes" to a yes/no question from the patient questionnaire on whether the symptoms have recurred.
- Proportion of patients receiving prescription for fluconazole on Day 14.

Exploratory endpoint variables:

All patients

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

For patients not receiving prolonged treatment

- Effect on vaginal microbiome on Day 35.

For patients receiving prolonged treatment

- Effect on vaginal microbiome on Day 14 and Day 42.

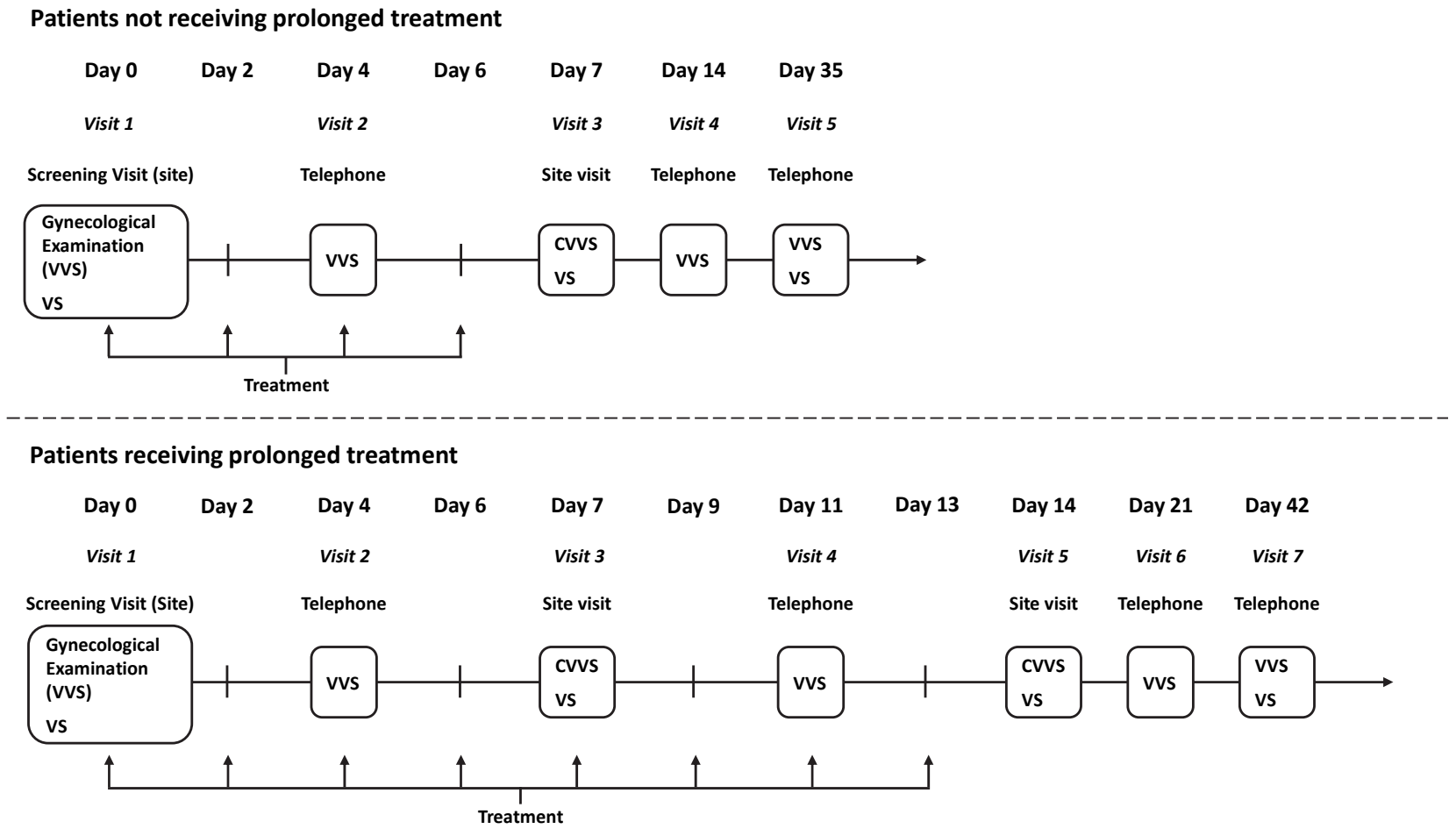
3 STUDY DESIGN

3.1 General outline

This is an open-label, single-armed, multi-center study to evaluate clinical performance, tolerability, and safety of Gedea Pessary in 24 adult women with VVC. Patients seeking treatment can be screened for study participation. Included patients will have gynecological examination, including collection of CVVS data, vaginal samples taken, and will receive the

investigational product to be self-administered at Day(s) 0, 2, 4, and 6. Patients will again be examined after 7 days and CVVS data will be collected. Prolonged treatment at Day(s) 7, 9, 11, and 13 will be given to patients not cured at Day 7; including re-examination at Day 14. Patients will be followed up by telephone up to 29 days after last treatment administration. Vaginal samples will be used for confirming diagnosis and microbiome analyzes. Patient questionnaires will be used for assessing VVC symptoms, usability, and AEs.

Figure 1 Study Flow Chart



VVS = Vulvovaginal Symptoms, VS = Vaginal Swab, CVVS = Composite Vulvovaginal Signs and Symptoms
Patients not receiving prolonged treatment applies to patients cured at Day 7. If not cured, the flow chart *patients receiving prolonged treatment* applies. Patients will here receive fluconazole if not cured at Day 14. Adverse events will be assessed throughout the study

3.2 Rationale for Study Design

As described in Section 1.1, 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 investigate the clinical performance and safety of the Gedea Pessary containing GDL and NaG 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 (see Section 1.2). In addition, a device comparable to Gedea Pessary with regards to its pH-lowering and biofilm-inhibiting properties, used for treating BV, have shown high cure rates.[44] Data also indicate that GDL is tolerable and does not pose any special risk to humans (Section 1.3.1).

Based on this, it may be argued that a trial involving patients is justified due to the widespread clinical problem of VVC and the issues involving current therapies (see Section 1.1). Further, due to that the pessary has not been evaluated clinically prior to this study and the lack of proper comparators, a single-arm design has been chosen, allowing evaluation of clinical performance on a smaller number of patients. Due to the open-label design, risks for introducing assessor bias have been minimized by the use of well-defined and documented scales, as well as objective laboratory assessments.

The dose of 300 mg GDL and 376.5 mg NaG administered 2 days apart on Day(s) 0, 2, 4, and 6[a] was chosen based on pre-clinical data, specifically an *in vitro* dissolution test of the Gedea Pessary using a vaginal fluidic model (see IB). Measurements of pH in the *in vitro* dissolution test showed a pH-decrease duration of approximately 45 hours.

3.2.1 Risks and Benefits

The investigational device, Gedea Pessary 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 sensitization (local lymph node assay, ISO 10993-10). The *in vitro* cytotoxicity test, classified the test item as slight to moderate cytotoxic (scale 1–2 on a 3-grade scale); the *in vivo* irritation test as well as the *in vivo* sensitization test showed no signs of irritation, necrosis or sensitization 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 are unlikely to cause any major inconvenience to patients. In the Laccure pessary study,[44] there were no SAEs and vaginal itching was the most common AE.

There is a risk that patients will have no clinical benefit from the investigational device. This may cause patients to experience symptoms including vaginal itching, burning or soreness, pain during sexual intercourse, pain or discomfort when urinating, or abnormal vaginal discharge longer than necessary.[1,45] However, fluconazole will be offered on Day 14 if any symptoms should still be present, thus avoiding any risk associated with long-term untreated VVC.

[a] And on Day(s) 7, 9, 11, and 13 if receiving prolonged treatment

Subjects included in the study must refrain from using other intravaginal products, thus mitigating the risk of interactions with concomitant vaginally-administered products. The investigational device acts locally on the vaginal mucosa and most likely will most likely not affect any concomitant systemic treatment.

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

3.3 Recruitment

Patients will be recruited at study sites' gynecological clinics. Post-menarchal, pre-menopausal females 18 years or older seeking for VVC symptoms may be informed verbally and in writing about the study and screened following signed informed consent. 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. The recruitment of patients will start only after the approval of the clinical investigation plan (CIP) by the regulatory authorities (RA) and the independent ethics committee (IEC). No study procedures will be performed unless the patient has provided written informed consent to study participation. See also Section 4.1.

3.4 Schedule of Assessments and Procedures

Table 2 Schedule of Assessments and Procedures, No Prolonged Treatment

Evaluations	**Day 0** **Screening** ***Visit 1*** **Visit**	**Day 2**	**Day 4 (+2 days)** **Follow-up** ***Visit 2*** **Telephone**	**Day 6**	**Day 7 (+2 days)** **Follow-up** ***Visit 3*** **Visit**	**Day 14 (±2 days)** **Follow-up** ***Visit 4*** **Telephone**	**Day 35 (±2 days)** **Follow-up** ***Visit 5*** **Telephone**
Informed Consent	X						
Eligibility Criteria	X						
Pregnancy Test (Urinary)	X						
Medical History	X						
Concomitant Medications	X		X		X	X	X
Gynecological Examination including vulvovaginal signs	X				X		
Vulvovaginal Symptoms	X		X		X	X	X
Recurrence						X	X
Fungal Microscope Assessment	X				X		
Vaginal Swab for Culture	X						
Vaginal Swab for Sequencing*	X				X		X
Treatment	X	X	X	X			
Vaginal pH	X				X		
Usability					X		
Adverse Events	X		X		X	X	X
Product Accountability					X		

* Self-swab at Day 35.

Table 3 Schedule of Assessments and Procedures, Prolonged Treatment

Evaluations	Day 0 Screening *Visit 1* Visit	Day 2	Day 4 (+2 days) Follow-up *Visit 2* Telephone	Day 6	Day 7 (+2 days) Follow-up *Visit 3* Visit	Day 9	Day 11 (+2 days) Follow-up *Visit 4* Telephone	Day 13	Day 14 (+2 days) Follow-up *Visit 5* Visit	Day 21 (±2 days) Follow-up *Visit 6* Telephone	Day 42 (±2 days) Follow-up *Visit 7* Telephone
Informed Consent	X										
Eligibility Criteria	X										
Pregnancy Test (Urinary)	X										
Medical History	X										
Concomitant Medications	X		X		X		X		X	X	X
Gynecological Examination including vulvovaginal signs	X				X				X		
Vulvovaginal Symptoms	X		X		X		X		X	X	X
Recurrence										X	X
Fungal Microscope Assessment	X				X				X		
Vaginal Swab for Culture	X										
Vaginal Swab for Sequencing*	X				X				X		X
Treatment	X	X	X	X	X	X	X	X			
Vaginal pH	X				X						
Usability					X				X		
Adverse Events	X		X		X		X		X	X	X
Product Accountability					X				X		

* Self-swab at Day 42.

3.5 Study Visits and Procedures

3.5.1 Day 0; Screening and Enrollment

Patients seeking treatment for symptoms relating to VVC may be informed about the study and, if agreeing to participate, sign the informed consent form (ICF). After enrollment, patients will have gynecological examinations performed, where the Investigator or an authorized designee will assess the presence of vulvovaginal signs (erythema, edema, or excoriation) and ask about symptoms (itching, burning, or irritation) and score each sign and symptom, as described in Section 6.1.

Vaginal samples will be examined by microscope to reveal yeast forms (hyphae or pseudohyphae) or budding yeast. Two (2) vaginal secretion samples will also be collected by swab. One (1) of the samples will be cultured to verify presence of Candida and 1 sample will be used for sequencing analysis of the vaginal microbiome prior to treatment (Section 7.2). If the Investigator assesses that the patient has VVC, based on examination and the KOH test, the patient will receive the investigational product to be self-inserted vaginally at home on Day 0. Additional doses will also be dispensed to be administered by patients on Day(s) 2, 4, and 6. In addition, the Investigator will measure vaginal pH.

Procedures performed:

- Informed consent
- Eligibility criteria
- Pregnancy test (urinary)
- Recording of:
    - medical history,
    - concomitant medication, and
    - adverse events
- Gynecological examination by Investigator or authorized designee evaluating signs (erythema, edema, or excoriation) and symptoms (itching, burning, or irritation) of VVC according to the scoring scale
- Fungal KOH microscope assessment
- Vaginal swab for:
    - culture, and
    - sequencing
- Vaginal pH
- Treatment dispensing and self-administration by patients

3.5.2 Day 2; Treatment Administration

Procedures performed:

- Treatment self-administration by patients

3.5.3 Day 4 (+2 Days); Follow-up Telephone Contact

On Day 4, patients will self-administer the investigational product and will be contacted by telephone by the Clinical Trial Unit. Telephone contact up to Day 6 will be allowed if Day 4 falls on a weekend. The treatment should nevertheless be self-administered on Day 4. Patients

will be asked questions from the patient questionnaire about: VVC symptoms (itching, burning, or irritation); concomitant medications; and AEs, if any.

Procedures performed:

- Treatment self-administration by patients
- Symptoms of VVC (itching, burning, or irritation) evaluated by patients according to the scoring scale
- Recording of:
    - concomitant medications, and
    - adverse events

3.5.4 Day 6; Treatment Administration

Procedures performed:

- Treatment self-administration by patients

3.5.5 Day 7 (+2 Days); Follow-up Visit

Patients will visit the clinic on Day 7 to have gynecological examination performed. The Investigator or an authorized designee will assess the presence of vulvovaginal signs (erythema, edema, or excoriation) and symptoms (itching, burning, or irritation) and score each sign and symptom.

Vaginal samples will be examined by microscope to reveal yeast forms (hyphae or pseudohyphae) or budding yeast and secretion samples collected by swab to be used for sequencing analysis of the vaginal microbiome. Vaginal pH will also be assessed.

If VVC symptoms are still present, patients will have prolonged treatment and receive additional doses of investigational product to be administered at home on Day(s) 7, 9, 11, and 13.

In addition, patients will be asked questions from the patient questionnaire to assess: usability; concomitant medications; and AEs, if any.

Procedures performed:

- Gynecological examination by Investigator or authorized designee evaluating signs (erythema, edema, or excoriation) and symptoms (itching, burning, or irritation of VVC according to the scoring scale
- Fungal KOH microscope assessment
- Vaginal swab for sequencing
- Vaginal pH
- Recording of:
    - concomitant medications,
    - adverse events, and
    - usability
- Treatment dispensing and self-administration by patients if receiving prolonged treatment

3.5.6 Day 9; Treatment Administration

Applicable to patients receiving prolonged treatment

Procedures performed:

- Treatment self-administration by patients

3.5.7 Day 11 (+2 Days); Follow-up Telephone Contact

Applicable to patients receiving prolonged treatment

Patients receiving prolonged treatment on Day 7 will self-administer the investigational product and will be contacted by the Clinical Trial Unit by telephone on Day 11. Telephone contact up to Day 13 will be allowed if Day 11 falls on a weekend. The treatment should nevertheless be self-administered on Day 11. Patients will be asked questions from the patient questionnaire about: VVC symptoms (itching, burning, or irritation), concomitant medications; and AEs, if any.

Procedures performed:

- Treatment self-administration by patients
- Symptoms of VVC (itching, burning, or irritation) evaluated by patients according to the scoring scale
- Recording of:
    - concomitant medications, and
    - adverse events

3.5.8 Day 13; Treatment Administration

Applicable to patients receiving prolonged treatment

Procedures performed:

- Treatment self-administration by patients

3.5.9 Day 14 (± 2 Days); Follow-up Telephone Contact

Applicable to patients NOT receiving prolonged treatment

Patients not receiving additional doses of investigational product on Day 7 will be contacted by the Clinical Trial Unit by telephone on Day 14. Patients will be asked questions from the patient questionnaire about VVC symptoms (itching, burning, or irritation), recurrence, concomitant medications, and AEs, if any.

Procedures performed:

- Vulvovaginal candidiasis recurrence
- Symptoms (itching, burning, or irritation) of VVC evaluated by patients according to the scoring scale
- Recording of:
    - concomitant medications, and
    - adverse events

3.5.10 Day 14 (+2 Days); Follow-up Visit

Applicable to patients receiving prolonged treatment

Patients receiving prolonged treatment at Day 7 due to still-present VVC symptoms will visit the site on Day 14 to have gynecological examination performed and vulvovaginal signs (erythema, edema, or excoriation) and symptoms (itching, burning, or irritation) assessed by the Investigator or an authorized designee. Patients will receive fluconazole should symptoms still be present.

Vaginal samples will be examined by microscope to reveal yeast forms (hyphae or pseudohyphae) or budding yeast and secretion samples collected by swab to be used for sequencing analysis of the vaginal microbiome.

In addition, patients will be asked questions from the patient questionnaire to assess usability and AEs, if any.

Procedures performed:

- Gynecological examination by Investigator or authorized designee evaluating signs (erythema, edema, or excoriation) and symptoms (itching, burning, or irritation) of VVC according to the scoring scale
- Fungal KOH microscope assessment
- Vaginal swab for sequencing
- Recording of:
    - concomitant medications,
    - adverse events, and
    - usability

3.5.11 Day 21 (± 2 Days); Follow-up Telephone Contact

Applicable to patients receiving prolonged treatment

Patients receiving prolonged treatment on Day 7 will be contacted by the Clinical Trial Unit by telephone on Day 21. Patients will be asked questions from the patient questionnaire pertaining to VVC symptoms (itching, burning, or irritation). Questions on concomitant medications, recurrence, and AEs, if any, will also be asked.

Procedures performed:

- Vulvovaginal candidiasis recurrence
- Symptoms (itching, burning, or irritation) of VVC evaluated by patients according to the scoring scale
- Recording of:
    - concomitant medications, and
    - adverse events

3.5.12 Day 35 (± 2 Days); Follow-up Telephone Contact

Applicable to patients <u>NOT</u> receiving prolonged treatment

On Day 35, the Clinical Trial Unit will contact patients not receiving prolonged treatment and ask questions from the patient questionnaire relating to VVC symptoms (itching, burning, or irritation). Patients will also be asked questions on concomitant medications, recurrence, and

AEs, if any. In addition, patients will self-collect vaginal samples by swab for sequencing and send samples by post to laboratory.

Procedures performed:

- Vulvovaginal candidiasis recurrence
- Symptoms (itching, burning, or irritation) of VVC evaluated by patients according to the scoring scale
- Vaginal swab for sequencing
- Recording of:
    - concomitant medications, and
    - adverse events

3.5.13 Day 42 (± 2 Days); Follow-up Telephone Contact

Applicable to patients receiving prolonged treatment

Patients receiving prolonged treatment will be contacted over telephone by the Clinical Trial Unit on Day 42 and asked questions from the patient questionnaire relating to VVC symptoms (itching, burning, or irritation). Patients will also be asked questions on recurrence, concomitant medications, and AEs, if any. Patients will collect vaginal samples by self-swab to be sent by post to laboratory for sequencing.

Procedures performed:

- Vulvovaginal candidiasis recurrence
- Symptoms (itching, burning, or irritation) of VVC evaluated by patients according to the scoring scale
- Vaginal swab for sequencing
- Recording of:
    - concomitant medications, and
    - adverse events

3.6 Early Withdrawal Procedures

See Section 4.6 for withdrawal procedures. Patients refusing to visit the site for follow-up visits shall be contacted by telephone, if possible, to collect answers to the patient questionnaire, and AEs, if any. Patients receiving fluconazole on Day 14 will be followed up for safety assessments.

4 SELECTION OF STUDY POPULATION

4.1 Patient Population and Number of Patients

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

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

Patients may also contact the site directly and book appointments after seeing study advertisement on social media.

The Investigator must always use IEC-approved patient information that must not be changed without prior Sponsor and IEC approvals, see Section 11 for further details.

Patients who have signed the ICF shall be listed on a screening-and-inclusion log together with an assigned screening number. Patients not fulfilling *all* inclusion criteria as described in Section 4.2, or fulfilling *any* of the exclusion criteria listed in Section 4.3, shall be considered screening failures. Screening failure reasons shall be stated in both the Screening Visit electronic case report form (eCRF) pages and the screening-and-inclusion log.

4.2 Inclusion Criteria

Inclusion and exclusion criteria in the fungal study should follow the FDA Vulvovaginal signs-and-symptoms score:

- Adult, post-menarchal, pre-menopausal women aged 18 years or older
- Diagnosis of VVC, defined as having a white or creamy vaginal discharge plus the following findings:
    - *At least* 2 of the following signs and symptoms of VVC that are characterized as *at least* moderate: itching, burning, irritation, edema, redness, or excoriation.
    - Potassium hydroxide (KOH) or saline preparation from the inflamed vaginal mucosa or secretions revealing yeast forms (hyphae or pseudohyphae) or budding yeasts.
- Having decisional capacity and providing written informed consent.
- Negative urine pregnancy test at screening.
- Refrain from using any intravaginal products (i.e., contraceptive creams, gels, foams, sponges, lubricants, or tampons, etc.) during the study period.
- Refrain from sexual intercourse or use a condom until Day 7
- Signed informed consent and willing and able to comply with all study requirements.

4.3 Exclusion Criteria

- Patients with known or apparent signs of other infectious causes of VVC (BV, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Herpes simplex, or human papillomavirus) at screening.
- Patients who are pregnant or breastfeeding.
- Patients who were treated for VVC within the past 14 days.
- Patients who are currently receiving antifungal therapy unrelated to VVC or has taken antifungal therapy within the past 14 days.
- Patients who have used pH-modifying vaginal products within the last 14 days.
- Patients who have received an investigational drug in a clinical investigation within 30 days prior to screening.
- Known/previous allergy or hypersensitivity to any product constituent or fluconazole.

- Any medical condition that in the Investigator's judgments would make the patient unsuitable for inclusion.

4.4 Withdrawal and Termination Criteria

Subjects shall be informed through the ICF about their rights to withdraw from the study at any time, without prejudice to further treatment or medical care. The Investigator may, at his or her discretion, withdraw a patient from the study and discontinue study treatment and assessments at any time. The specific reasons for discontinuing a patient from the study shall be documented in the eCRF.

4.5 Reasons for Withdrawal

Reasons for patient withdrawal 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 if judged that an AE poses an unacceptable risk or consequence to the patient.
Medical reasons:	The Investigator may withdraw patients 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:	Includes but are not limited to failure of the patient to comply with study procedures or requirements

4.6 Handling of Withdrawals

If a patient withdraws from the study before study completion, the reason for withdrawal should be sought and recorded on the eCRF. If the withdrawal is due to the performance or safety of the investigational device, the Investigator will ask for permission to follow-up patients outside of the study. If a withdrawal occurs during a study visit, the eCRF for that specific visit shall be completed as far as possible.

Any AEs 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 the study Day 35 if not receiving prolonged treatment or Day 42 if receiving prolonged treatment. AEs ongoing at study Day(s) 35 or 42 shall be assessed as chronic or stable. Wherever possible, end-of-study assessments should be carried out at the time of withdrawal.

4.7 Replacements

Withdrawn or discontinued patients shall not be replaced or re-entered into the study

4.8 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, Investigators will be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of patient's interest.

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. The Sponsor should promptly inform the study sites, and the RA 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.

5 TREATMENTS

5.1 Investigational Product

The investigational product, Gedea Pessary (commercial name *p*Hyph), is a GDL-and-NaG containing pessary to be administered vaginally with a CE-marked vaginal tablet applicator (Schägner GmbH, Steinmauern, Germany). The device is intended to treat vaginal Candida infections, see Figure 2 and Figure 3 for product image and applicator label. Gedea Pessary is a Class IIa medical device according to MDD 93/42/EEC (the Swedish regulation SFS 1993:584 and LVFS 2003:11).

NOTE: The terms investigational product, Gedea Pessary, investigational device, pessary, and vaginal pessary are used interchangeably in the CIP

Gedea Pessary is a white, convex, bullet-shaped tablet, approximately 2 cm in length, contract-manufactured by Galenica AB (Malmö, Sweden). The pessary is slow-release formulated, administering 300 mg GDL and 367.5 mg NaG over 45 hours. Each patient will administer a total of 4 pessaries in the study or 8 if receiving prolonged treatment. The investigational products will be packed in blister packs containing 4 pessaries labeled with *Gedea Pessary* and batch number. Blisters will be packed together with 4 vaginal tablet applicators in a cardboard-box labeled with *Gedea Pessary*, *for investigational use only*, production date, and expiry date (Figure 4).

It is the responsibility of the Investigator to ensure that the investigational products are stored in their original packaging in a secure location with access only by authorized personnel, separate from other medications. The investigational product shall be stored at room temperature (15˚C -25˚C), protected from direct sunlight or freezing. The investigational products *must not* be used outside of the study. For further reference, refer to the IB.

Instructions for use will be distributed at the first visit, advising patients on how to use the product together with the applicator. 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.

Figure 2 Gedea Pessary and Applicator

Figure 3 Vaginal Tablet Applicator Label

Figure 4 Investigational Product Label

Gedea Pessary *p*Hyph
(300 mg Glucono-delta-lakton / 367.5 mg Natriumglukonat)

Sats nr: 20401-1808-47 Förp.: .....(.....)
Studienummer: CL1

Innehåller: 1 st blisterkarta med 4 vaginaltabletter
4 st applikatorer

Används enligt särskild instruktion

Tillverkningsdatum: **2018-08-24**
Utgångsdatum: **2019-02-23**

Förvaring: 15°C-25°C Förvaras utom syn- och räckhåll för barn

Uteslutande för kliniska prövningar
Sponsor/Tillverkare: Gedea AB, Medicon Village, Scheelevägen 2, 223 81 Lund, Sweden
Kontraktstillverkare: Galenica AB, Medeon Science Park, 205 12 Malmö, Sweden

5.1.1 Investigational Product Accountability

The investigational products may be released to the Investigator when the clinical trial agreement (CTA) has been signed by all involved parties and appropriate approvals has been given from the IEC.

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:

- Product quantity at storage, and
- Deliveries to-and-from storage.

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

- Investigational product name and quantity received,
- Delivery date,
- Batch number, and
- 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 used,
- Patient receiving the investigational product, and
- Number of units remaining in stock.

Any nonfunctioning devices or applicator shall be documented. All 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.

5.2 Additional Products and Material

The Sponsor will provide kits for vaginal swabs for culturing and sequencing. The Sponsor will provide the study sites with pH meters for vaginal pH analysis. Study sites will provide urine pregnancy tests (urinary human chorionic gonadotropin [U-HCG]) and other materials, as applicable.

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, and
- 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, and
- 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.

5.2.1 Rescue Medication

Fluconazole will be used as rescue medication in this investigation, and patients will receive a prescription for fluconazole if considered necessary to relieve their VVC symptoms on Day 14. Patients withdrawing at any point in the investigation may receive fluconazole if considered necessary by the Investigator. The dose of fluconazole will be decided by the Investigator on an individual basis. The use of rescue medication will be recorded in the eCRF.

5.3 Selection of Investigational Device and Doses

Refer to Section 3.2

5.4 Treatments Administered

The pessary will be self-administered vaginally by the patient. The pessary should be inserted high into the vagina. The pessary should be used with the co-supplied vaginal tablet applicator. The patients should insert the applicator gently and deeply into the vagina, and then slowly depress the plunger to release the pessary. Instructions for use will be distributed to patients at the first site visit. See also Section 5.1.

5.5 Method of Assigning Patients to Treatment Groups

Not applicable

5.6 Blinding

Not applicable

5.7 Prior and Concomitant Medication

Information about any concomitant medication, including OTC medications and vitamins taken by patients during the study and within 14 days prior to inclusion shall be documented in the eCRF. The generic name or trade name, dosage, and reason for use shall be recorded for all medications.

NOTE:	Antifungal medication during the study and within 14 days prior to inclusion is strictly prohibited

See Appendix 1, *Section 3* for specific questions.

5.8 Treatment Compliance

Patients will be asked about investigational product administration by telephone on Day 4 and at the site on Day 7, and also on Day(s) 11 (telephone) and 14 (site) if receiving prolonged treatment. No other measurements of treatment compliance will be made.

6 CLINICAL PERFORMANCE

6.1 Clinical Performance Assessments

Assessments described below in Section 6.1.1, gynecological examination, will be used to collect the following 6 vulvovaginal signs and symptoms:

- Vulvovaginal signs of: erythema, edema, and excoriation; and
- Vulvovaginal symptoms of itching, burning, and irritation.

The intensity of each of the signs and symptoms will be scored as:

0 = none (absent),
1 = mild (slight),
2 = moderate (definitely present), or
3 = severe (marked, intense).

The scores will be added together and the sum defined as the CVVS score.

A CVVS score equal to or below 3 on Day 7 will be defined as clinical cure, and is a co-primary study endpoint together with safety and tolerability evaluation.

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

- Proportion of patients having a reduction in CVVS score on Day 7 compared to Day 0.
- Change in the CVVS score from Day 0 to Day 7.
- Recurrence rate at Day 14 and Day 35, defined as the proportion of patients clinically cured at Day 7 and thereafter responding “yes” to a yes/no question from the patient questionnaire on whether the symptoms have recurred.
- Proportion of patients receiving prolonged treatment.
- Clinical cure rate on Day 14, defined as the absence of signs and symptoms of VVC in terms of having a CVVS score equal to or below 3.
- Proportion of patients having a reduction in CVVS score on Day 14 compared to Day 0.
- Change in the CVVS score from Day 0 to Day 14.
- Recurrence rate at Day 21, and Day 42, defined as the proportion of patients clinically cured at Day 14 and thereafter responding “yes” to a yes/no question from the patient questionnaire on whether the symptoms have recurred.
- Proportion of patients receiving prescription for fluconazole at Day 14.

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

- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 4 and Day 7, compared to Day 0.
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 4 and Day 7.
- Usability, measured by patient questionnaire.

- Proportion of patients having a reduction in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) on Day 11, Day 14, Day 21, and Day 42, compared to Day 0.
- Change in the sum of the 3 vulvovaginal symptoms scores (itching, burning, and irritation) from Day 0 to Day 11, Day 14, Day 21, and Day 42.

6.1.1 Gynecological Examination

Patients will have gynecological examinations by the Investigator or authorized designee on Day(s) 0 and 7; or Day(s) 0, 7, and 14 if receiving prolonged treatment, in order to assess vulvovaginal signs of erythema, edema, and excoriation. During the examinations, patients will also be asked about any vulvovaginal symptoms of itching, burning, and irritation.

NOTE: The Investigator will always assess *vulvovaginal signs* of erythema, edema, and excoriation. Vulvovaginal *symptoms* of itching, burning, and irritation will always be assessed by patients themselves and asked about by the Investigator at site visits.

6.1.2 Patient Questionnaire

The questionnaire can be found in Appendix 1.

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

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

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

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

7 SAFETY AND TOLERABILITY ASSESSMENTS

7.1 Medical and Surgical History

Medical and surgical history will be collected during the Screening Visit.

7.2 Clinical Laboratory Evaluation

Vaginal samples will be collected by vaginal swab on Day(s) 0 and 7 by the Investigator and on Day 35 by patients (also on Day 14 by Investigator and Day 42 by patients if receiving prolonged treatment). Collected samples will be used accordingly:

- The potassium hydroxide (KOH) test for fungus from samples from Day(s) 0, 7, and 14 if receiving prolonged treatment. Briefly, vaginal samples are covered with

10% – 20% KOH and inspected by microscope. Presence of hyphae indicate Candida and will serve as an immediate, preliminary VVC diagnosis.

- Samples collected on Day 0 will be sent to laboratory and cultured to confirm the VVC diagnosis. Time for lab results is approximately 1 week; patients will be included based on the KOH test as described above.
- Sequencing of samples collected on Day(s) 0, 7, and 35 (by patients). If receiving prolonged treatment, samples will by collected on Day(s) 0, 7, 14, and 42 (by patients). These samples will be analyzed after study completion to assess effects of the investigational product on the vaginal microbiome.

Patients' vaginal pH will be measured for assessments of investigational product *in vivo* duration on Day(s) 0 and 7. Vaginal pH lower at follow-up visits compared to Day 0 indicate appropriate release duration.

7.3 Untoward Medical Events / Adverse Events

The definitions are the definitions in the current version of the ISO 14155. The categorization will adhere to the following table in ISO 14155;

Table 4 Untoward Medical Events / Adverse Events Categorization

<table>
<tr><th>ADVERSE EVENTS</th><th>Non-device related</th><th colspan="2">Device-or-procedure related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]
(3.2)</td><td colspan="2">Adverse Device Effect
(ADE)
(3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event
(SAE)[b]
(3.37)</td><td colspan="2">Serious Adverse Device Effect
(SADE)
(3.36)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect
(ASADE)
(3.42, Note)</td><td>Unanticipated Serious Adverse Device Effect
(USADE)
(3.42)</td></tr>
</table>

References in parentheses refer to sections in the standard ISO 14155:2011

[a] Includes all categories.

[b] Includes all categories that are serious

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

The AE may be directly related to the use of an investigational medical device and are then called an adverse device effect (ADE). This includes events due to insufficient or incomplete instructions, use, implantation, or dysfunction of the tested product. Misuse and errors while using the product are also included in the ADE definition.

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.
- All conditions or diseases known at the time when the subject signs the informed consent form, are not considered untoward medical events / AEs. These will be registered in the medical history CRF page.

7.4 Serious Untoward Medical Events / Serious Adverse Events

An SAE is an AE that lead to serious deterioration in the health of the subject, that resulted in one or more of the below:

- death, or
- an immediately life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- requires intervention to prevent life-threatening illness, or injury or permanent impairment to a body structure or a body function, or
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the current CIP, without serious deterioration in health, 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

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

7.5 Definitions of Adverse Event Ratings

7.5.1 Severity

Untoward medical events / AEs will be rated concerning their severity. The rating will be done by the Investigator. The rating used will be the following:

Mild:	Transient symptoms, no interference with daily activities of the participant;
Moderate:	Clear symptomatology that moderately affects the daily activities of the participant; or
Severe:	Symptoms that clearly affects or hinders daily activities of the participant.

7.5.2 Relatedness

The Investigator's assessment of an AE's relationship to the device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The likely relationship of an AE to the device should be assessed by the Investigator according to the following definitions:

Not Related: Relationship to the device or procedures can be excluded when:

- the event is not a known[a] side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event 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 serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event 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[b], when applicable;
- harms to the subject are not clearly due to use error;
- 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 serious event.

Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: The relationship with the use of the investigational device 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

[a] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

[b] 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.

assessed or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal Relationship: The serious event is associated with the investigational device 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
  - 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 subject 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.

7.5.3 Outcome

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

Resolved: Fully recovered spontaneously or after medical or surgical intervention, i.e., the status is the same as the pre-study status.

[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.

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.

7.6 Capturing and Reporting of Untoward Medical Events / Adverse Events

Patients shall be asked about AEs at all visits (both site visits and telephone contacts). Questions for collecting AEs are specified in Appendix 1, *Section 4*.

Adverse events can also be obtained from:

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

All AEs and ADEs, will be captured in the section for AEs in the eCRF or in case of serious events in the section for SAEs, SADEs, or USADEs.

All events fulfilling the definition of 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. 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.

7.7 Reporting of Serious Untoward Medical Events / Serious Adverse Events

The Investigator will report any SAE to the Sponsor authorized representative **immediately but not later than within 24 hours after awareness** that the event has occurred by completing the SAE eCRF pages.

Further reportable events, according to MEDDEV 2.7.3 rev. 3 have to be reported by the Sponsor/authorized representative to the National Competent Authority (NCA) where the event occurred using an SAE Report Table.

The following events are considered reportable:

- Any SAE
- Any device deficiency (See Section 7.9) that might have led to a SAE if:
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate

- New findings/updates in relation to already reported events.

The following timelines apply in case of:

- Serious public health threat:
  - Immediately, but not later than 2 calendar days after awareness by Sponsor.
- Death or unanticipated serious deterioration in state of health:
  - Immediately, but not later than 2 calendar days after awareness by Sponsor.
- Others:
  - Immediately, but not later than 7 calendar days after awareness by Sponsor.

7.8 Follow-up of Untoward Medical Events / Adverse Events

Any AE that is ongoing when the patient is withdrawn 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 the study Day 35/42. AEs ongoing at study Day 35/42 shall be assessed as chronic or stable.

7.9 Device Deficiencies

A device deficiency will in this study be defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety[a], or performance.

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented in the eCRF. Device deficiencies include malfunctions, use errors, and inadequate labeling.

7.10 Tolerability

Based on AEs

7.11 Pregnancy

Subjects must be instructed to immediately inform the Investigator if any pregnancy should occur from the time of signing the informed consent form and 6 weeks onwards. Any confirmed study-subject pregnancy 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-authorized representative. Subjects becoming pregnant will be withdrawn from the study and followed until delivery, additional information on the infant will be collected until the infant is 1 month old. Adverse events in connection with the pregnancy, in the fetus, 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, fetus, and infant fulfilling any criteria for seriousness. Procedures and timelines for AE/SAE reporting applies to reporting of AEs/SAEs in the pregnant subject, the fetus, and the infant.

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

8 DATA HANDLING AND QUALITY ASSURANCE

8.1 Data Management

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

The data management routines include procedures for handling of CRF, eCRF and database set-up and management, data entry, data verification and validation (quality control of database), and documentation of the performed activities, including information of discrepancies in the process. The eCRF/ data entry screens, and the database/programs will be designed in accordance with the CIP and LINK standard operating procedure (SOP) system.

8.1.1 Data Collection

The clinical investigation data will be collected via eCRF completed by the Investigator or other qualified personnel at the site, and by the Clinical Trial Unit. Together these constitute a remote electronic data system, which complies with the associated requirements of EN ISO 14155:2011.

8.1.2 The Web-Based Case Report Form

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant 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.

Authorized trial site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized 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.

The CRF specification provided in this CIP will be the basis for the set-up of the eCRF in Viedoc4™. However minor deviations might be necessary due to technical issues that cannot be foreseen during the CIP writing process.

8.1.3 The Entering of Data into the Electronic Case Report Form

The eCRFs should always reflect the latest observations on the patients participating in the trial. Therefore, the eCRFs should be completed as soon as possible during or after the patient's visit. 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.

8.1.4 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 authorized 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.

8.1.5 Signing of Data

Electronic CRF 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.

8.1.6 Database Lock

All changes 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; and all queries are solved, medical coding approved, and SAE reconciliation performed; the database will be locked.

8.2 Patient Records and Source Data

The data may be recorded directly in the eCRF, which will then be considered as source data. The origin of source data in the investigation will be further specified in a separate document ("Origin of Source Data").

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 subjects,
- All visits during the investigation period,
- All AEs/ADEs SAEs/SADEs, and
- Treatments and medications.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded in the CRFs.

8.3 Record Retention

The Investigator will retain copies of the records for a period of 15 years from the close-out visit. 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 CRFs (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 of at least 15 years. Archiving of data is performed according to industry standards such as in PDF/A format.

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

8.4 Monitoring, Audits, and Inspections

During the investigation, the Monitor will have regular contacts with the investigational site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigational team are carrying out the procedures stated in the CIP. All data must be accurately recorded in the eCRF and source data verified (comparison of eCRF data with the patient's medical records and other records at the investigational site). The eCRF and other records must be accessible during the visit.

The Monitor or other Sponsor personnel will be available between visits if the Investigator or other staff at the site needs information or advice.

Authorized representatives of the Sponsor or RA may visit the site to perform audits or inspections, including source data verification.

8.5 Training of Staff

A delegation log will be completed for each investigational site team member to indicate which activities the Investigator has authorized 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 and that new information of relevance to the performance of this clinical investigation is forwarded to the staff involved.

9 STATISTICAL METHODS AND PLANNED ANALYSIS

The statistical planning, analysis and reporting work will follow LINK SOP system. All analyses described below will be performed using SAS Version 9.4.[46]

For continuous data, number of missing and non-missing records, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented. All mean, median, confidence interval (CI), and standard deviation (SD) values will be formatted to one more decimal place than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. Categorical data, including both nominal and ordered variables, as well as binary variables, will be presented by frequencies and percentages. Percentage values will be presented with 1 decimal place. In case of any hypothesis testing, p-values will be presented using a maximum of 4 decimal places.

The statistical analysis will be based on the observed data. However, if missing data, due to patient withdrawals or other reasons, or outliers, are considered to be an issue, measures will be taken in order to reduce bias or, in case bias is unavoidable, conservatively direct the bias.

Details on the presentation of descriptive statistics, analytical methods, and handling of statistical issues will be given in the statistical analysis plan (SAP).

9.1 Statistical Analysis

The clinical performance endpoints will be presented with the appropriate point estimate together with the 95% confidence interval. Any possible statistical testing will be performed using an overall significance level of 5%.

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

Statistical analysis will be based on all data, however, results will also be presented by site.

If the stated assumptions that the statistical evaluation is built upon can be questioned, suitable alternative methods may be applied. For example, a 95% confidence interval based on a non-parametric method may be applied if assumption of data belonging to the normal distribution seems not to hold. This, together with further details on the statistical analysis and identification of any possible exploratory or subgroup analysis, will be given in the SAP.

Sensitivity analyses may be performed to evaluate the robustness of the results.

Any deviations or changes to the study protocol specified statistical analyses will be documented and justified in the SAP and the Clinical Investigation Report (CIR).

9.1.1 Analysis Data Sets and Populations

The two different analysis datasets that will be considered for analysis is as below:

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

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

All safety analyses will be performed against the FAS. All patients included in the FAS will be accounted for, including those who did not complete the study along with the reasons for withdrawal.

Subject disposition table presenting the number and percentage of patients reaching each study milestone will be reported. The reasons for withdrawal from the study will be tabulated.

Patients who not qualify for the FAS population will be listed.

9.1.2 Demographic and other Baseline Characteristics

All demographic and other baseline data will be summarized descriptively. Demographic and baseline assessments will be presented descriptively using the principles stated in Section 9 above.

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

Prior or concomitant medications will be coded using WHODD and summarized by ATC class.

Prior medications will be identified as those with a start date before Day 0 and will be presented as part of the baseline data. The concomitant medications will be defined as those with a start date equal to or after Day 0.

9.1.3 Exposure to Treatment

Treatment compliance data, see Section 5.8, will be presented descriptively.

9.2 Primary and Secondary Endpoints Analysis

9.2.1 Primary Endpoints Analysis

- Clinical cure rate on Day 7 will be calculated and presented together with a one-sided 95 % confidence interval based on the exact binomial distribution.
- Safety and tolerability will be assessed according to Section 9.2.3.

9.2.2 Secondary Endpoints Analysis

Below is the list of all secondary endpoints (highlighted in italics) and other related variables, together with information on variable types, followed by additional information on the planned statistical analysis and presentation of the endpoints. Note that the analyses of the secondary endpoints will be performed on different patient categories as described in Section 2.2.

a) CVVS score (can take integer values in the interval 0-18)
a1) Vulvovaginal signs: erythema (can take integer values in the interval 0-3)
a2) Vulvovaginal signs: edema (can take integer values in the interval 0-3)
a3) Vulvovaginal signs: excoriation (can take integer values in the interval 0-3)
a4) Sum of all vulvovaginal signs score (can take integer values in the interval 0-9)
a5) Vulvovaginal symptoms: itching (can take integer values in the interval 0-3)
a6) Vulvovaginal symptoms: burning (can take integer values in the interval 0-3)
a7) Vulvovaginal symptoms: irritation (can take integer values in the interval 0-3)
a8) Sum of all vulvovaginal symptoms score (can take integer values in the interval 0-9)
b1) *Cure rate on Day 14* (based on values yes/no on the individual level, i.e. binary variable)
b2) *Proportion endpoints* (based on values yes/no on the individual level, i.e. binary variables)
c) *Change in CVVS score* (can take values from -18 to +14)
d) *Change in sum of all vulvovaginal symptoms score* (can take values from -9 to +8)
e) *Recurrence rates* (based on values recurrence=yes/no on the individual level, i.e. a binary variable)

f) *Usability*, *measured by patient questionnaire* (the questionnaire contains 4 specific yes/no (i.e. binary) variables, and a 5th question, "How do you generally regard the treatment?", rated on a 1-10 integer scale).

In summary, the secondary endpoints:

- b1), b2), e), and the first 4 questions in f) are considered as binary variables
- c),d), and the 5th question in f) are considered as continuous variables

The binary endpoints categorized as b1), b2), and e) above, will be calculated and presented together with a two-sided 95 % confidence interval based on the exact binomial distribution.

Two-sided 95% confidence intervals will be presented for endpoints c), and d) using a parametric method assuming normally distributed data, i.e. arithmetic mean will be presented together with the 95% confidence limits.

Further, all study endpoints (primary, secondary, and exploratory), as well as the related variables specified in the list above, will be presented descriptively.

9.2.3 Tolerability and Safety Analysis

As part of the local tolerability and safety assessments, the following will be evaluated:

- Tolerability,
- Adverse events and SAEs, and
- Rate of withdrawals from the study and/or the study treatment.

9.2.3.1 Local Tolerability

Based on AEs

9.2.3.2 Adverse Events

The AEs will be presented descriptively by means of frequency and percentages to evaluate both the rate of incidence and event occurrence among the different treatment groups. The descriptive tables will be presented with respect to intensity, seriousness, and relationship to the treatment.

9.3 Sample Size Determination

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

10 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN AND CLINICAL INVESTIGATION PLAN VIOLATIONS

The Investigator is not allowed to deviate from the CIP, except in an emergency.

10.1 Deviations

A deviation is a planned departure from the requirements of the CIP in order to deal with unforeseen circumstances.

Non-emergency Deviations:	In the event of a non-emergency deviation, prior approval by the Sponsor is required. If the deviation may affect the rights, safety, or welfare of participants or the scientific integrity of the clinical investigation, IEC approval is also required prior to implementation.
Emergency Deviations:	Emergency deviations required for the safety and welfare of the patient will be implemented by the Investigator and notified to the Sponsor as soon as possible after implementation.

The Sponsor is responsible for analyzing deviations and assessing their significance. Corrective action will be implemented to avoid repeated deviations, which may include suspending the clinical investigation and/or amending the CIP.

10.2 Clinical Investigation Plan Violations

Clinical Investigation Plan violations are deviations made without permission as a result of error or fraud/misconduct. Where the Monitor or Sponsor identifies that the Investigator is out of compliance, this will be notified to the Investigator in writing, with a request to correct the source of the deviation immediately. Corrective action will be implemented to avoid repeated non-compliance, which will usually include re-training and may include terminating the clinical investigation at the site.

10.3 Reporting of Deviations and Clinical Investigation Plan Violations

Depending on the nature of the deviation, they will either be recorded by the Investigator on the eCRF or documented by the Monitor and signed by the Investigator. 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 IEC as soon as possible after the Sponsor has become aware of them.

11 SPECIAL REQUIREMENTS AND PROCEDURES

11.1 Good Clinical Practice

This clinical investigation will be conducted in accordance with Note for Guidance on Good Clinical Practice: CPMP/ICH/135/95, January 1997 (where applicable to medical devices) and the principles of the European Standard EN ISO 14155:2011 Clinical Investigation of Medical Devices for Human Patients – Good Clinical Practice.

11.2 Ethics

11.2.1 Institutional Ethics Review

The final CIP, including the final version of the patient information and consent form, must be approved or given a favorable opinion in writing by an IEC before enrollment of any patient into the investigation. The Investigator is responsible for informing the IEC of any amendment to the CIP as per local requirements.

11.2.2 Ethical Conduct of the Clinical Investigation

The clinical investigation will be conducted in compliance with applicable regulatory requirements and with the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association (Appendix 2).

11.2.3 Patient Information and Consent

All patients will receive written and verbal information regarding the investigation prior to any investigation-related procedures. This information will emphasize 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.

Before any clinical investigation-related procedures are undertaken, the ICF will 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.

If any data is transferred to EEA countries outside Sweden, the data will not identify any persons taking part in the clinical investigation in accordance with the EU General Data Protection Regulation (GDPR).

11.3 Patient Protection Procedures

11.3.1 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.

11.3.2 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 authorized representatives of the investigational site, Sponsor, RA, 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.

11.3.3 Insurance

The Sponsor has arranged the appropriate product liability and clinical trials insurance to cover the requirements of this clinical investigation.

11.4 Report and Publication

A final report of the investigation (a “Clinical Investigation Report” [CIR]) should be completed, even if the investigation is prematurely terminated. The report will be prepared by the Sponsor according to the guideline presented in Annex C of ISO 14155-1:2011(E).

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 author order will be determined out of number of completed subjects. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

11.5 Confidentiality

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 informed consent form 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 subjects to give their consent not only to the participation in the study, but also to the processing of personal data. See also Section 11.3.2.

12 CLINICAL INVESTIGATION TIME TABLE AND TERMINATION

Clinical investigation start (first patient first visit):	10 Nov 2018
Inclusion completed (last patient first visit):	10 Jan 2019
Last patient out (last patient last visit):	February 2019

13 REFERENCES

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Appendix 1 Patient Questionnaire

Section 1. Vulvovaginal Symptoms

Day(s) 0, 4, 7, 14, and 35; or Day(s) 0, 4, 7, 11, 14, 21 and 42 if receiving prolonged treatment. Questions will be asked by the Investigator at Day(s) 0, 7, and 14 (for patients receiving prolonged treatment); and by the Clinical Trial Unit at remaining days.

Scoring of symptoms

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

The question "Have the symptoms returned, so that you need to seek medical care?" (yes/no) will be asked at Day(s) 14 and 35 if not receiving prolonged treatment and at Day(s) 21 and 42 if receiving prolonged treatment.

Section 2. Usability

Day 7 and Day 14 if receiving prolonged treatment:

Is the vaginal tablet easy to use?

- Yes
- No
- If no, provide reason: _____

Do you find the use of the vaginal tablet gentle?

- Yes
- No
- If no, provide reason: _____

Is the treatment odor free?

- Yes
- No

Is the treatment smear-free and dripless?

- Yes
- No

How do you generally regard the treatment?

1	2	3	4	5	6	7	8	9	10

Not satisfied Very satisfied

Section 3. Concomitant Medications

Day(s) 4, 7, 14, and 35; or Days(s) 4, 7, 11, 14, 21, and 42 if receiving prolonged treatment); patients will be asked: “since the last study visit or telephone contact, have you changed dose or taken any new medication?

Section 4. Adverse Events

The following question will be asked at each patient contact: “since the last visit / telephone contact, have you had any health problems?”

Appendix 2 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the

specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 3 Investigator Signature Pages

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: CL1

Site No.:

Principal Investigator:

Signature: _____ Date: _____