Research Proposal

1. Proposal Title

Acceptability and satisfaction of Dienogest in the treatment of patients with symptomatic endometriosis

Endogest

2. Investigators

Principal Investigator

Asst.Prof. Ammarin Suwan, M.D. Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University

Co-Investigators

Assoc.Prof. Krasean Panyakhamlerd, M.D. Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University

Asst.Prof. Tassawan Rungruxsirivorn, M.D. Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University

Chayanis Apirakviriya, M.D. Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University

3. Rationale

Endometriosis is a chronic, estrogen-dependent disease that affects 10–15% of women during their reproductive years. It is defined by the presence of endometrial-like tissue outside the uterine cavity that induces chronic inflammation, ovarian cyst formation, and fibrosis [1,2]. Although endometriosis is a disease first described in 1861 by Rokitansky, it remains a complex and unsolved issue in medical research. The phenomenon of ectopic endometrial tissue has led to many questions concerning the pathophysiology, etiology, hormonal regulation properties, and, finally, appropriate therapy. The complexity of the different types of endometriotic lesions makes it challenging to compare different studies dealing with the therapeutic approaches to this disease. Therefore, the applied therapies are in part contractionary [3].

The symptoms of endometriosis can include pain, bleeding disorders, and impaired fertility and represent a significant burden on women's health and healthcare systems worldwide [1]. Furthermore, endometriosis is known to compromise women's social relationships, sex quality, and psychologic and mental health [4, 5]. The number of licensed pharmaceutical agents for the treatment of endometriosis is currently limited.

Endovelle (Dienogest 2mg) is approved in Thailand with the indication of endometriosis treatment (Reg.No. 1C 54/63 (NG). The medication demonstrated efficacy in patients with endometriosis by improving dysmenorrhea, premenstrual pain, dyspareunia, and diffuse endometriosis-associated pelvic pain. It also decreases the duration of menstrual bleeding and the size of endometriomas. [6,7,8,9,10].

There are several studies regarding patient satisfaction and outcomes of treatment in endometriosis. These include patient and disease characteristics in clinical practice, treatment adherence, the impact of simultaneous treatments, and trends in incidence and disease management [11,12,13,14]. In Thailand, the investigation of endometriosis needs further investigation, especially in real-world practice. This leads to the aim of our study that to define the reduction of endometriosis-associated pain symptoms using a patient questionnaire with a starting

evaluation and control after 3 and 6 months of use. The study would increase credibility and serves as an essential adjunct to randomized controlled clinical trials by addressing clinically relevant questions that cannot be answered within a controlled setting. [11].

4. Review Literature

Pathogenesis of Endometriosis

Presently, several pathogenetic theories have been proposed to explain the development and establishment of endometriosis including Retrograde menstruation, Coelomic metaplasia, Hematogenous/lymphatic spread, Stem cell recruitment or Embryogenetic [15]. The most widely accepted is Retrograde menstruation theory in combination with a defect in the immune system [15,16]. Though endometriosis is probably a hormone-dependent, proliferative but benign disease, only a few investigations have been carried out to study its progressive character [15,17]. Also, the mechanisms involved in developing endometriosis-associated pain symptoms are still investigated. Postulated that a local prostaglandin may result from macrophages activities have been proposed this process [16,17].

Despite the presence of many controversies regarding the mechanisms responsible for its pathogenesis and progression, it is widely accepted that endometriosis is an estrogen-dependent chronic inflammatory disease [18].

Management of Endometriosis

The management of women with endometriosis is complex since this disorder is not well defined and lacks appropriate cell biological markers. In normal endometrial tissue, several markers, including integrins [19] and gap junctions [20] have been described for an appropriate differentiation related to the menstrual cycle.

Other new developments consider endometriosis a chronic inflammatory and proliferative disease whose onset and development are speculated to be associated with immunological and/or inflammation factors [21, 22, 23]. Omega-6 lipid intake is believed to be one of the causes of inflammation. New treatment strategies are based on the investigation of the pathogenesis of endometriosis because of inflammatory reactions and the association with lipid metabolisms, including arachidonic acid. Arachidonic acid (AA) is a polyunsaturated fatty acid n-6 (PUFA) that is biosynthesized from linoleic acid, an essential component of plant oil, and a substrate to produce chemical mediators such as prostaglandin (PGE2) and leukotriene (LTB4), which appear to be related to the onset of endometriosis and pain. On the other hand, eicosapentaenoic acid (EPA) is an n-3 PUFA and an essential component of fish oil, a substrate for synthesizing similar chemical mediators (PGE3 and LTB5) catalyzed by the same enzyme involved in AA metabolism. These mediators have markedly low levels of inflammatory activity with those produced from AA. Eicosapentaenoic acid may act as a competitive inhibitor of the conversion of AA to PGE2 and LTB4 [24]. As a result, n-3 PUFA, such as EPA and docosahexaenoic acid (DHA), could effectively inhibit inflammation [25,26]. The anti-inflammatory effect of n-3 PUFA has been demonstrated by the fact that the intake of foods with a high content of these lipids has beneficial effects on atherosclerosis, asthma, and rheumatoid arthritis [27,28,29,30,31,32].

In contrast, it has been described that a low proportion of n-3 PU-FA and a high proportion of n-6 correlates with painful menstruation and a high rate of autoimmune and endocrine disorders in women with endometriosis [33,34]. These data suggest that n-3 PUFA potentially effectively against inflammation in women with endometriosis. Netsu et al. discovered in mice fed an EPA diet the following: the n-3: n-6 ratio in each endometróticotic tissue increased significantly, and the thickness of the endometriosis interstitium, which is the active site of inflammation, was significantly reduced. The mRNA of the metalloproteinases examined, interleukins, prostaglandins, and NF-kb were also drastically reduced, showing the first vision of a positive influence of omega-3 fatty acids in managing endometriosis and its associated pain symptoms.

Medications for the treatment of Endometriosis

Medical treatment of endometriosis-associated pain is based on suppressing estrogen production and induction of amenorrhea, and treatments are often accompanied by clinically relevant side effects. Endometriosis Guideline of European Society of Human Reproduction and Embryology 2022 recommend hormone treatment for treatment of endometriosis-associated pain included progestogens, combined oral contraceptives, gonadotropin releasing hormone (GnRH) agonists, GnRH antagonists, the levonorgestrel intrauterine system (LNG-IUS), danazol and aromatase inhibitors (e.g., letrozole). Progestogens and continuous COCs containing low estrogen are the first line medications for treatment of endometriosis-associated pain, while the second line medications are GnRHa with add-back therapy and LNG-IUS.

The data on the efficacy combined hormonal contraceptives have been concluded in systemic reviews that they are statistically significant reduction in endometriosis-related pain leads to improvement in quality of life. For progestogens, the most recent Cochrane review reports on the effectiveness in treatment of endometriosis-associated pain. Thus, the clinician should consider progestogens by the side-effect profiles to tailor the medical treatment. Gonadotropin-releasing hormone (GnRH) agonists are generally only prescribed for 3–6 months at a time because of symptoms of estrogen deprivation, including vaginal dryness and hot flushes, and their negative impact on bone mineral density. Likewise, the testosterone analog danazol is no longer broadly prescribed for endometriosis, in particular, because of its androgenizing side effects.

Endovelle (Dienogest 2 mg) was approved in Thailand in with the indication of endometriosis treatment (Reg.No. 1C 54/63 (NG)). Dienogest is a 19-nortestosterone derivative, a fourth generation orally active progestogen with highly selective for progesterone receptors while demonstrating only negligible binding for estrogen, androgen, glucocorticoid, and mineralocorticoid receptors [36,38]. Furthermore, dienogest does not cause metabolic imbalance, and treatment with dienogest can be prescribed as a continuous regimen. The long-term investigation proving that dienogest 2 mg once-daily has a good tolerability and a positive influence on pain-related disease also improved quality of life and sexual function even after 6 months and 12 months of therapy, the improvements are stable until 24 months. Evidence has supported the comparable efficacy of dienogest with GnRH agonists in controlling endometriosis- associated pain symptoms for 6 months. Combined hormonal contraceptives containing estrogen and progestin components may have additional contraindications and side

effects compared with progestin-only including dienogest. Therefore, some experts have suggested progestogens over COCs for the treatment of endometriosis.

Dienogest 2 mg daily for 12 weeks was significantly more effective than placebo for reducing EAPP. The most frequently reported undesirable effects under treatment with Dienogest 2 mg are headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%) and acne (5.1%).

5. Objectives

Primary

To describe the reduction of the endometriosis-associated pain symptoms after 3 months and 6 months of Dienogest treatment by using a questionnaire.

Secondary

1) To evaluate the patient satisfaction with Dienogest after 6 months of treatment

2) To describe the tolerability and safety aspects after the use of Dienogest for 6 months

6. Hypothesis

Primary: Can Dienogest 2 mg reduce symptoms of Endometriosis associated pain?

Secondary: Do patients satisfy with Dienogest 2 mg after 6 months of treatment?

7. Keywords

Endometriosis, Pain, Endometriosis associated pain, Dienogest, Acceptability, Satisfactory

8. Research Design

An observation prospective study

9. Research Methodology

Population

Adult female patients aged 18-45 years who visit the Gynecology Outpatient Clinic, King Chulalongkorn Memorial Hospital

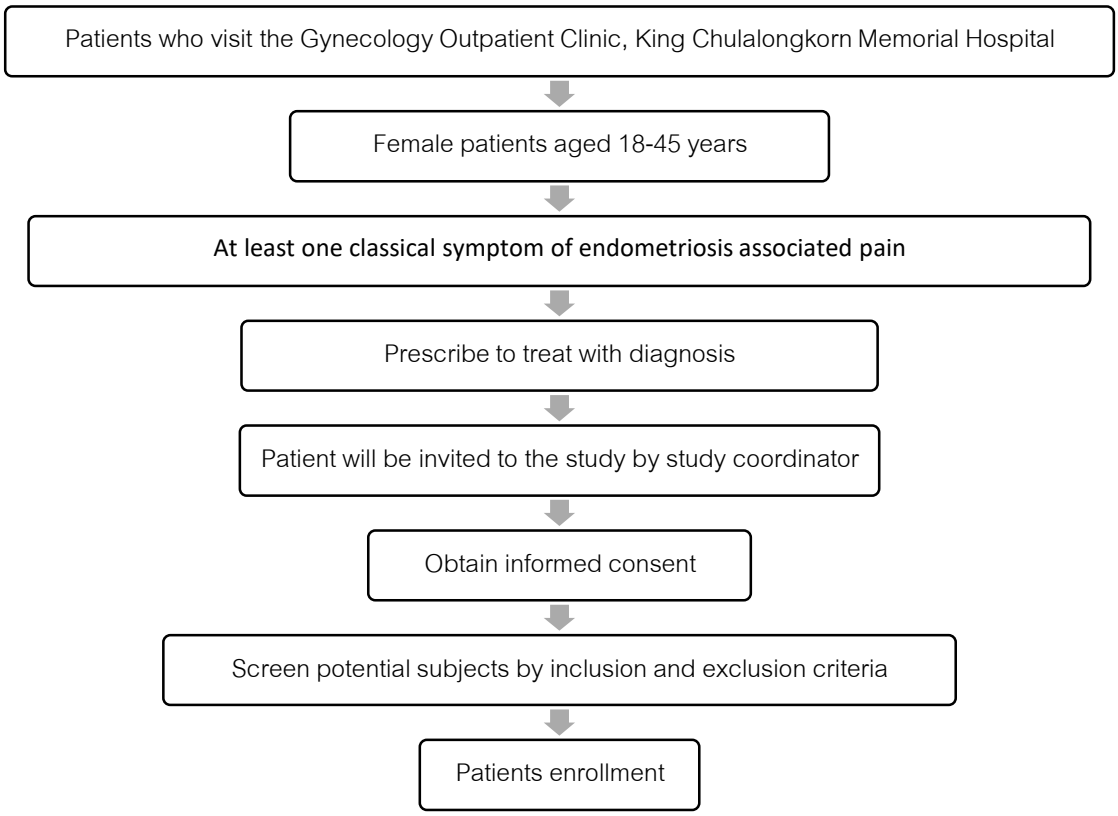
Target Population

Adult female patients aged 18-45 years, with classical symptoms of endometriosis with or without histological confirmation using Dienogest 2 mg for at least 6 months prospectively, will be enrolled.

Control Population

No

Approach to participant



Flow Chart showing how to approach the subjects

Inclusion criteria

- Female patients, age ≥ 18 and ≤ 45 years.
- Present at least one classical symptom of endometriosis associated pain including dysmenorrhea, dyspareunia, chronic pelvic pain, dysdefecation without any other pathology by taking a history or physical examination plus Visual Analogue Scale (VAS) ≥ 4
- Decision taken by the physician to prescribe Dienogest 2 mg

Exclusion criteria

- Current Body mass Index (BMI) > 30 kg/m^2
- Patients with severe acute or chronic diseases (e.g. pancreatitis, hypertriglyceridemia, liver disease, benign or malignant liver tumor, malignant sex-hormone dependent diseases of genitals or breasts)
- Intake of herbal medicines or medicines which induce microsomal enzymes, especially cytochrome-P450-enzyme, e.g. Phenytoin, Phenobarbital, Primidon Bosentan, Carbamazepine, Rifampicin, Topiramate, Felbamat, Griseofulvin, a few HIV protease inhibitors (e.g. Ritonavir), and non-nucleosidic Reverse-Transcriptase-Inhibitors (e.g. Efavirenz) as well as preparations of Aaron´s beard.
- History of cardiovascular events

- Advanced hypertension or diabetes
- Known hypersensitivity to components of Dienogest
- Undiagnosed abnormal vaginal bleeding
- Use of drugs containing Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir during and two weeks before start of the study
- Patients using intrauterine devices (IUD) or intrauterine systems (IUS)
- Pregnancy
- Breast feeding
- Patients who are postmenopausal
- Patients switching from a GnRH agonist, hormonal contraception, or progestin treatment within 3 months
- Participation in any other trial 30 days before starting to use Dienogest

Withdrawal criteria

- Hypersensitivity to dienogest
- Patients who request to withdraw
- When the surgery is indicated for endometriosis
- Any health condition that physician recommend to stop hormone treatment
- Pregnancy after enrollment
- Serious adverse events to dienogest that physician recommend to stop using dienogest
- Patient does not have any response to dienogest treatment and willing to switch to other treatment
- Patient request to stop dienogest with any reason

Informed consent process

After patients have prescribed the dienogest for endometriosis on their first visit, study co-investigator or the person who is not a patient's physician will invite patients to private room/area and explain all information related to the study.

Written and verbal versions of the participant information and informed consent will be presented to the participants or legally authorized representative detailing no less than the exact nature of the study, the implications and constraints of the protocol, the known side effects, and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care and with no obligation to give the reason for withdrawal.

The participant and/or legally authorized representative will be allowed as much time as wished to consider the information and the opportunity to question the investigator, their family physician, or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained through the participant's dated signature and the dated signature of the person who presented and obtained the informed

consent. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the principal investigator. The two original signed informed consent will be obtained and one set of documents will be given to the participants, another one will be retained at the study site. Informed consent will be obtained before any study-related procedures are undertaken.

The participant or legally authorized representative must personally sign and date the latest approved version of the informed consent form before any study-specific procedures are performed.

Methodology

An observational prospective study will be conducted at King Chulalongkorn Memorial Hospital. The expected duration of subject participation is approximately 6 months.

Subjects visiting gynecology complaining about pelvic pain that the investigator suspect related to endometriosis will be identified. Thereafter, the investigator or assignee will provide information about the trial. If the patient agrees to participate, informed consent will be written. Screening procedures and baseline assessment will then take place.

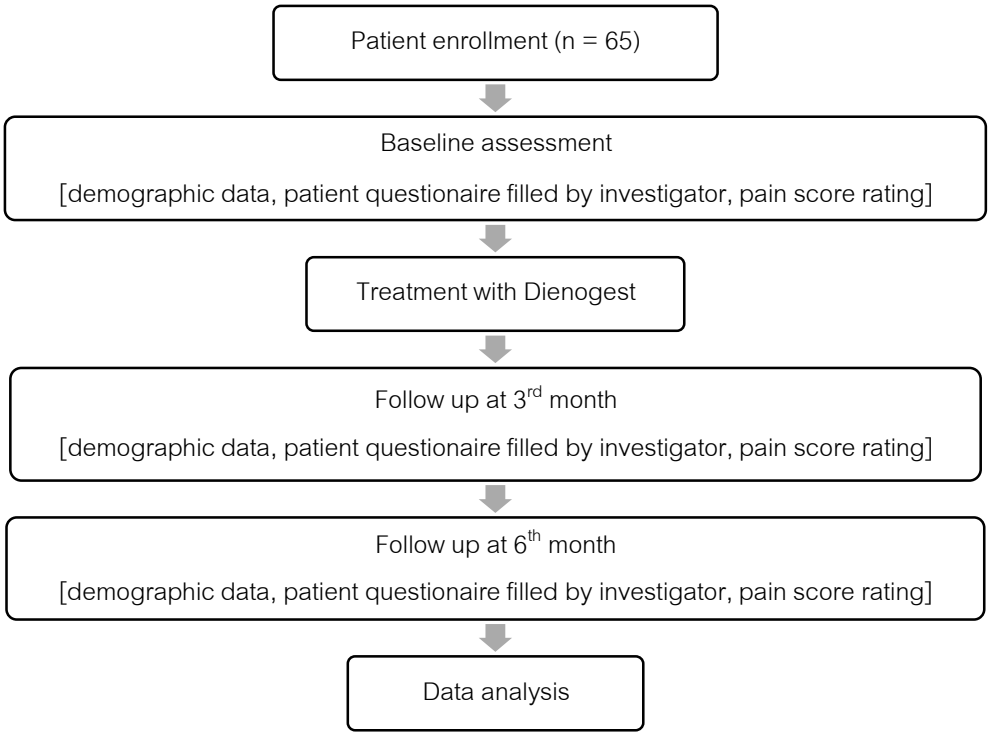
Subjects will be followed up at 3rd and 6th month after taking dienogest for endometriosis treatment at Gynecology Outpatient Clinic, King Chulalongkorn Memorial Hospital.

Baseline assessment (first visit)

1. Record the demographic data on case record forms (CRFs) including age, gender, body weight, height and BMI
2. Ensure that subject enrollment have followed inclusion and exclusion criteria including drug allergy history.
3. Collect data of the medical condition and concomitant medication.
4. Record vital sign, heart rate and blood pressure, justification need to be included if this measurement is skipped.
5. Interview the subject by asking some questions per 'patient questionnaire' to check the endometriosis history, the current endometriosis symptoms, to rate the pain score, to record the other medicines for endometriosis treatment if any.

Follow up at 3rd and 6th month

1. Record the demographic data (age, gender, body weight, height and BMI), vital sign, heart rate and blood pressure. Justification needs to be included if vital sign measurement is skipped.
2. Interview the subject by asking some questions per 'patient questionnaire' to check the current endometriosis symptoms, to rate the pain score, to record the other medicines for endometriosis treatment if any, to monitor the side effect of study medicine (dienogest), to check the satisfaction of dienogest treatment.



Flow Chart showing the study activities after patient enrollment

Biological material management

No

The Number of Participants

For testing two dependent means (two-tailed test) (48)

Based on data from previous dienogest study (49)

SD.(σ) = 20, Delta (Δ) = 7

Alpha (α) = 0.05, Z(0.975) = 1.959964

Beta (β) = 0.20, Z(0.800) = 0.841621

Sample size (n) = 65

10. Data Collection

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the CRF), clinical charts, laboratory and pharmacy records, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic data record).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

11. Data Analysis and Statistics

- Descriptive statistic to analyze Baseline characteristic by mean+/- SD for normal distribution data, median (IQR non-normal distribution data, number and percentage for categorical data

- Paired-t test for normal distribution data or Wilcoxon signed rank test for non-normal distribution data

- SPSS version 22

12. Ethical Consideration

The researcher will follow the 3 principles of ethics in research involving humans:

- Respect for person: by providing complete information until subjects understand it well and make an independent decision to give their consent to participate in the research. The principle of providing benefit does not cause harm.

- Beneficence/Non-maleficence: Subjects will get benefit from the use of dienogest without drug-related costs during the study to treat the symptoms related to Endometriosis These symptoms usually do not improve on their own without treatment. This medicine may cause some adverse reactions, including breast engorgement, spotting, headache, nausea, and vomiting. However, while the volunteers are in the research project, their health will be closely monitored. If there are any unusual symptoms while in the research project, subjects can contact the research doctor (Dr. Ammarin Suwan) so that doctors can evaluate side effects and provide appropriate treatment. If the above symptoms are a result of participation in this research project, volunteers will be treated without cost.

- Confidentiality of the volunteers is maintained: The data record does not have any identifier to identify the volunteers. And the principle of justice, inclusion and exclusion criteria is declared. Risks and benefits are distributed equally.

13. Expected or Anticipated Benefit Gain

13.1 For subject

Subject will receive the free dienogest medicine for their treatment.

13.2 For profession

Data will be benefit for endometriosis treatment in TH patients.

13.3 For social

There will be an option of generic medicine to treat patient with reasonable cost.

14. Challenges

- Compliance of participants

- Side effects from medication

15. Risk and Investigator's Responsibility

There may be the risk of adverse drug reaction caused by Dienogest.

The majority of patients treated with dienogest experience changes in their menstrual bleeding pattern. Menstrual bleeding patterns were assessed systematically using patient diaries and were analyzed using the WHO 90 days reference period method. During the first 90 days of treatment with Dienogest 2mg the following bleeding patterns were observed (n=290; 100%): Amenorrhea (1.7%), infrequent bleeding (27.2%), frequent bleeding (13.4%), irregular bleeding (35.2%), prolonged bleeding (38.3%), normal bleeding, i.e. none of the previous categories (19.7%). During the fourth reference period the following bleeding patterns were observed (n=149; 100%): Amenorrhea (28.2%), infrequent bleeding (24.2%), frequent bleeding (2.7%), irregular bleeding (21.5%), prolonged bleeding (4.0%), normal bleeding, i.e. none of the previous categories (22.8%). Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (See adverse event table).

The frequencies of adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs) reported with Dienogest 2 mg are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are defined as common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100).

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders		anemia
Metabolism and nutrition disorders	weight increase	increased appetite
Psychiatric disorders	depressed mood sleep disorder nervousness loss of libido altered mood	anxiety depression mood swings
Nervous system disorders	headache migraine	autonomic nervous system imbalance disturbance in attention
Eye disorders		dry eye
Ear and labyrinth disorders		tinnitus
Cardiac disorders		unspecific circulatory system disorder palpitations
Vascular disorders		hypotension
Respiratory, thoracic and mediastinal disorders		dyspnoea
Gastrointestinal disorders	nausea abdominal pain flatulence abdominal distension vomiting	diarrhoea constipation abdominal discomfort gastrointestinal inflammation gingivitis

System Organ Class	Common	Uncommon
Skin and subcutaneous tissue disorders	acne alopecia	dry skin hyperhidrosis pruritus hirsutism onychoclasis dandruff dermatitis abdominal hair growth photosensitivity reaction pigmentation disorder
Musculoskeletal and connective tissue disorders	back pain	bone pain muscle spasms pain in extremity heaviness in extremities
Renal and urinary disorders		urinary tract infection
Reproductive system and breast disorders	breast discomfort ovarian cyst hot flushes uterine / vaginal bleeding including spotting	vaginal candidiasis vulvovaginal dryness genital discharge pelvic pain atrophic vulvovaginitis breast mass fibrocystic breast disease breast induration
General disorders and administration site conditions	asthenic conditions irritability	Oedema

[Ref: Endovelle SmPC]

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

- An occurred pregnancy during the clinical trial or observation phase will be considered as a serious adverse event.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

  The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Investigator will follow up the subject who has ADR during the study until recover

ADR report will be according to IRB Chulalongkorn University

16. Timeline

12 months

17. Venue of the Study

Gynecology Outpatient Clinic, King Chulalongkorn Memorial Hospital

18. Tabulation of Research Activities and Timeline

Activity	*Timeline/Plan*
Research question and Literature review	July-October 2022
Research proposal presentation	October 2022
IRB*	December 2022
Patients' recruitment	After IRB approve
Data collection and Data analysis	First month after IRB approve, duration 6 months
Manuscript writing	First month after study completion

*IRB = Chulalongkorn IRB

19. Post trials access to study drug

ผู้ป่วยจะไม่ได้รับยาฟรีจากโครงการวิจัยนี้ แต่สามารถรับการตรวจและจ่ายยาได้ต่อตามสิทธิการรักษาของผู้ป่วย

Patient will not get the free medication from this study. The medication can be prescribed at gynecology outpatient clinic according to medical welfare of patient.

20. Sponsor

บริษัท เอ็กเซลทิส (ประเทศไทย) จำกัด สนับสนุนผลิตภัณฑ์ยาเอนโดเวล 2 มิลลิกรัม
ตามจำนวนที่สั่งใช้กับอาสาสมัครในโครงการวิจัยนี้ เป็นเวลา 6 เดือน และงบประมาณ ดังนี้

1)	ค่าตอบแทนคณะผู้วิจัยและทีมงาน	650,000 บาท
2)	หมวดค่าใช้สอย	390,000 บาท
	ค่าตอบแทนอาสาสมัครและค่าใช้จ่ายอื่นที่เกี่ยวข้องกับอาสาสมัคร	195,000 บาท
	ค่าใช้เครื่องมือ และอุปกรณ์	130,000 บาท
	ค่าบริการ (เช่น ค่าบริการการทดสอบ การวิเคราะห์ผล)	65,000 บาท
3)	เงินอุดหนุนดำเนินงานของส่วนงาน (20%)	208,000 บาท
รวมทั้งสิ้น		1,248,000 บาท

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42. Summary of product characteristics (SmPC) of Endovelle Reg.No.1C 54/63 (NG)