

## The Safety and Effectiveness of Surgery With or Without Raloxifene for the Treatment of Pelvic Pain Caused by Endometriosis

General Information	
Protocol Identification Number	99-CH-0012
Sponsor	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Phase	II
Indication	endometriosis
Multicenter	Yes
Planned Country	United States
Trial Objective and Purpose	
Trial Purpose Summary	<p>Many women with lower abdominal pain have endometriosis. Endometriosis is a condition in which the lining of the uterus (endometrium) is found outside of the uterus. The diagnosis of endometriosis is usually made at surgery. The treatment of endometriosis includes medical and surgical approaches alone or in combination. The hormone estrogen stimulates the growth of the endometrium and may also stimulate the growth of endometriosis. Medical therapies that act to decrease the level of estrogen can reduce the amount of endometriosis and pain. When therapies are discontinued, symptoms often return. In addition, medical treatment for endometriosis is expensive and is often associated with weak bones (osteoporosis) and hot flashes as a result of low levels of estrogen.</p> <p>Surgical treatment is removal or destruction of the endometriosis tissue. Studies show the pain from endometriosis is relieved longer with tissue removal than with destruction.</p> <p>This study was developed to see if surgery followed by daily doses of Raloxifene (Evista) is effective in reducing pain, for a longer time than surgery in combination with a placebo (inactive "sugar pill") treatment. Raloxifene acts like estrogens in some tissues and not like estrogens in others.</p> <p>Postmenopausal women receiving Raloxifene for the prevention of osteoporosis had an increase in bone density and an improvement of their blood lipids (fat content in the blood). However, unlike estrogen, Raloxifene does not promote the growth of breast tissue or the uterus. If Raloxifene blocks estrogen action in the lining of the uterus (endometrium) of reproductive age women, as it does in post-menopausal women, it may also limit the growth of endometriosis and prevent the return of pain.</p>

Primary Objective	To evaluate the safety and effectiveness of surgical excision of endometriosis in combination with six months of raloxifene (Evista (TM)) compared with surgical excision of endometriosis in combination with placebo, to treat endometriosis-related pelvic pain. Effectiveness will be evaluated as the time interval to the recurrence of pain and the severity of pain.
Other Objective	1. To compare the diagnostic utility of fat-suppressed MRI with laparoscopy for the detection of deeply infiltrating endometriotic lesions.
	2. To assess whether the extent, morphologic appearance or depth of endometriosis as recorded using the ASRM classification system for endometriosis associated with pain at both the beginning and end of the study, is correlated with endometriosis-related pain as measured by questionnaire.
	3. To assess whether tissue, blood and urine markers of angiogenesis and other growth factors are predictive of disease in women with endometriosis-related pain. Specifically, do the levels correlate with the presence or absence of disease at laparoscopy and pain scores during treatment?
	4. To assess any effects of raloxifene (Evista(TM)) treatment on the menstrual cycle, quality of life and sexual function, bone density, adrenal function, and serum lipids.
<b>Trial Design</b>	
Description of Study Design	This is a randomized, double-blind, placebo-controlled study of women of reproductive age who have endometriosis-related pelvic pain. All women will have had laparoscopically diagnosed and surgically excised endometriosis. Women will then be randomized to receive raloxifene (Evista(TM)) or placebo for six months and will be followed for another 18 months to assess recurrence of persistent pain. All women will have a second laparoscopy to look for signs of endometriosis either when they have a return of pain or, after two years of follow-up, for those who remain pain-free. All women will be protected from pregnancy by barrier contraception, abstinence or surgical sterilization for the duration of the study.

Description of Interventions	A Screening A1 Medical evaluation (medical history, physical examination, laboratory testing, questionnaire, symptoms calendar) A2 Preoperative evaluation (MRI, blood and urine sample and laboratory testing, home recording of symptoms and pain, menstrual calendar) A3 Operative evaluation and surgical excision of implants (pregnancy test, laparoscopic surgery, biopsy and inspection of excised lesions) B Medical Treatment C Monitoring D Recurrence of pain E Adverse events evaluation F Study completion evaluation
Randomized Study?	Yes
Blinding	
Control	
Study Configuration	Interventional
Subject Participation Duration	24 Months
Primary Endpoint	
Other Endpoints	
<b>Selection of Subjects</b>	
Minimum Age	18 Years
Maximum Age	45 Years
Study uses Healthy Subjects?	No
Subject Gender	Female
Inclusion Criteria	Women between the ages of 18 and 45 years, who have their reproductive organs.
	Excellent health other than a three month history of pelvic pain and documented endometriosis at laparoscopy. Chronic medications may be acceptable at the discretion of the internist associate investigator (LN). Use of antidepressants, medications for migraines and headaches, allergy medications, and treatment of bowel symptoms such as irritable bowel disease will be allowed.
	<ul style="list-style-type: none"> <li>• Do not desire pregnancy for the duration of the study.</li> <li>• Are using abstinence, mechanical (condoms, diaphragms) or sterilization methods of contraception and are willing to continue using them throughout the study.</li> <li>• Willing and able to give informed consent.</li> <li>• Willing and able to comply with study requirements.</li> <li>• Less than grade III overweight or BMI less than 40 kg/m(2).</li> </ul>

Exclusion Criteria	Women with other causes of chronic pelvic pain including infectious, gastrointestinal, musculoskeletal, neurologic or psychiatric.
	Significant abnormalities in the physical or laboratory examination including renal and liver function more than twice the normal range.
	<ul style="list-style-type: none"> <li>• Hysterectomy or bilateral salpingo-oophorectomy.</li> <li>• Pregnancy.</li> <li>• Lactation.</li> <li>• Use of hormonal contraception, selective estrogen receptor modulators, progestins, estrogens, steroids, or ovulation induction in the last 3 months.</li> <li>• Other medical or surgical treatment for endometriosis in the last 6 months.</li> <li>• Untreated abnormal pap smear or other gynecologic condition.</li> <li>• History of venous thrombosis events including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.</li> <li>• Allergy to study drug.</li> <li>• History of stroke, complicated migraine, or documented transient ischemic attack.</li> <li>• Manic depressive illness or untreated major depression.</li> </ul>
<b>Statistics</b>	
Number of Subjects	140

Statistical Method Descriptions	<p>Of the women who complete screening questionnaires for this protocol, we expect that only 50% will have endometriosis. Thus, we anticipate that 350 women will be screened to accrue 162 who are candidates for laparoscopy. We estimate that it will take one year to recruit the entire cohort. It is estimated that 90% of those presenting for laparoscopy will have endometriosis. Based on the clinical experience of the investigators, about 100% of women who begin the clinical study after surgical treatment of endometriosis may drop out. About 10% of those with excision will have a return of symptoms by 12 months and 50% within two years. A fifty percent reduction in the recurrence of pain is anticipated with the use of raloxifene. A sample size of 63 women per group will be required to evaluate this effect with 80% power using 2-tail test of significance at <math>p : 0.05</math>. Therefore of 156 women who have laparoscopy, 140 will be expected to have endometriosis at laparoscopy and will be enrolled in the study. Of those, 126 women will complete the study.</p> <p>Interval analyses will be done at 6, 12, 18 and 24 months, and will be conducted by Dr. Lee and Dr. Nieman. Assuming it will take one year to accrue the entire study cohort, the interval analyses at 6 months will review study progress, patient recruitment, and side effects but not the study endpoint. Interval analyses at T2, 18 and 24 months will assess the time to recurrence of pain and pain severity in addition to patient recruitment and side effects. Lan and DeMets boundaries methods will be used for the interval data analysis. P value spending function will be used to accommodate the uncertainty of the progression of the study. If any serious adverse events are noted, study subject(s) will be unblinded and assessment of drug safety will be made. If adverse events such as death or deep venous thrombosis, attributable to study treatment occur, the study be stopped (class 4 common toxicity criteria occurring with investigational agents using NCI classification system).</p> <p>To evaluate the efficacy of treatment, the time to recurrence of pain will be analyzed using the logrank test which also accounts for those patients who do not experience the recurrent pain (36). The severity of pain will be graded by an ordinal score and analyzed. For example, the score zero will be assigned to the pain-free patients and the more severe the pain the higher score will be assigned. Statistical methods for ordinal score data will be applied to the analysis of the severity of pain data. If an interim analysis shows a statistically significant difference between the treatment groups, then the study may be terminated early.</p>
Statement of the Proposed Statistical Model(s)	
Description of Interim Analyses	