CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S18

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
SUPPLEMENTAL NEW DRUG APPLICATION

NDA #: 19-726 S-018

Applicant: Zeneca Pharmaceuticals
Wilmington, Delaware 19897

Date of Submission: June 28, 1996

Date Draft MO Review Completed: June 21, 1997

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1. General Information

A. Name of Drug

(1) **Generic:** Goserelin Acetate implant

(2) **Trade:** Zoladex

(3) **Chemical:** L-Glu-L-His-L-Trp-L-Ser-L-Tyr-D-Ser(Bu^t)-L-Leu-L-Arg-L-Pro-AzGly-NH_2 acetate

B. Pharmacologic Category: Long-acting gonadotropin releasing hormone agonist

C. Proposed Indication: Endometrial thinning agent prior to endometrial ablation

D. Dosage form and route of administration: 3.6 mg given as subcutaneous injection

E. Related Drugs:

NDA 19-726 Zoladex (Goserelin Acetate) approved for advanced prostatic cancer, advanced breast cancer and endometriosis

NDA 20-011 Lupron (Leuprolide acetate) depot 3.75 mg intramuscularly monthly (approved for advanced prostate cancer, endometriosis management, and preoperative uterine fibroid management)

NDA 19-886 Synarel (Nafarelin acetate) nasal solution 200 ug intranasally twice a day (approved for endometriosis management)

F. Materials Reviewed

NDA volumes 18.8 through 18.20 as well as 18.24, 18.28 and 18.30 through 18.37

Safety update dated February 27, 1997

Labeling as initially submitted and revised labeling and comments submitted June 19, 1997.

2. Manufacturing Controls

No chemistry review is required as no changes to the approved product are submitted.

3. Pharmacology

A. Pharmacodynamics (in female patients)

(1) Mechanism of Action

When Zoladex is given at high dosage it occupies the majority of LHRH receptors present on the pituitary gonadotrophs which then become internalized, disappearing from the cell surface. Initially there is a supraphysiologic secretion of LH and a stimulation of gonadal function. However, the marked loss of LHRH receptors and the failure of sufficient replenishment, due to the continuing presence of Zoladex, leads to a pituitary cell which has few receptors and which is, therefore, unable to respond to Zoladex. Consequently, LH secretion is markedly suppressed. In men, this suppression leads to testes atrophy, suppression of testosterone secretion and, hence, prostate involution.

In females, a similar down-regulation of the pituitary by Zoladex would be expected to lead to suppression of gonadotropin secretion, ovarian atrophy, a decrease in estradiol to castrate or post-menopausal values and involution of the uterus and mammary gland, as well as regression of sex hormone-responsive tumors, if present.

(2) Results of pharmacodynamic studies

Zoladex 3.6 mg depot, given every 28 days, produces suppression of serum estradiol equivalent to 1000 ug given by daily injection. The 3.6 mg depot dose is therefore considered the optimum dose by the sponsor for treating

premenopausal women when suppression of serum estradiol is required.

Serum estradiol is suppressed to levels consistent with the postmenopausal state within 3 weeks following the first depot injection; this suppression is sustained upon continued administration for 6 months.

Serum estradiol is reversed to pretreatment concentrations within 12 weeks following the last depot administration.

Serum LH and FSH are suppressed within 4 weeks and maintained at follicular phase concentrations during six months of Zoladex therapy.

Zoladex has no effect on serum concentrations of SHBG, testosterone, 5-alpha-DHT or androstenedione.

Zoladex has no effect on glucose tolerance, nor does it affect response to ACTH stimulation.

Serum LH and FSH concentrations are not affected by single injections of aqueous Zoladex or exogenous LHRH 14 days after administration of the depot formulation, indicating hypothalamic suppression.

B. Pharmacokinetics (in female patients)

(1) Blood level data

In female patients, administration of the 3.6 mg depot of Zoladex results in measurable concentrations of the drug in serum throughout the 28-day dosing period.

Serum concentrations of Zoladex and AUC increase proportionally to the dose when comparing the 3.6 and 7.2 mg Zoladex doses.

Pharmacokinetic studies in patients with renal or hepatic impairment using aqueous formulation of Zoladex do not indicate a need for dose adjustment with use of the depot formulation.

(2) Clearance, Metabolism

Clearance of Zoladex following subcutaneous administration of the aqueous formulation in humans is very rapid and occurs via a combination of metabolism and urinary excretion. The metabolism of Zoladex in humans

yields a similar, but narrow, profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology studies.

4. Clinical Background

GnRH (Gonadotropin Releasing Hormone), a hypothalamic releasing hormone, is released in a pulsatile fashion and stimulates LH release, which is also secreted in a pulsatile fashion. When given continuously, the hormone down regulates receptors in the pituitary which results in suppression of LH and FSH, after an initial stimulatory phase, resulting in hypoestrogenic, anovulatory, hypogonadism. Long-acting GnRH analogs are synthetic analogues of GnRH, with various substitutions of the native decapeptide, rendering them more stable.

GnRH agonists have been explored for use in women and are approved for the management of endometriosis and for pre-operative management of uterine fibroids.

Dysfunctional uterine bleeding (DUB) is a term which applies to bleeding from the uterine endometrium that is unrelated to anatomic lesions of the uterus. According to a 1989 American College of Obstetricians and Gynecologists (ACOG) Technical Bulletin, most DUB can be related to failure of ovulation.[1] The bulletin further asserts that in the presence of continual high circulating levels of estrone, uterine bleeding will occur when endometrial growth surpasses the estrogen support on which it is dependent. When estrogen levels become insufficient to support further endometrial growth or to maintain endometrial integrity, desquamation and bleeding will occur. The resultant cycles are usually longer than ovulatory cycles, and bleeding is frequently heavy. In the presence of continual low circulating levels of estrogen, endometrial growth extends over a longer period, with a greater interval between successive flows. In the presence of fluctuating levels of estrogen, there is an increased frequency of bleeding. With each decline in circulating estrogen levels, endometrial integrity is compromised, and bleeding ensues.

No consistent or predictable correlation between DUB and endometrial morphology has been established. In one report, histologic examination of 1,000 specimens from patients with a clinical diagnosis of DUB demonstrated 547 with normal endometrium.[2] Of the remaining endometrial specimens, 265 were described as hyperplastic. Similarly, it has been reported that 86 of 100 patients with a clinical diagnosis of DUB

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[1] ACOG Technical Bulletin Number 134--OCTOBER 1989

[2] Sutherland AM. Histology of the endometrium in "organic uterine haemorrhage." Lancet 1950; 2(6641):742-745

had a normal endometrium and 14 had an inactive or a hyperplastic endometrium.[3] As can be concluded, in most instances the endometrium in patients with DUB appears morphologically normal.

The primary goal of management of DUB is to normalize or to halt the irregular bleeding. Depending on the desires of the individual woman, hormonal methods (progestin therapy, combined oral contraceptive therapy, combined postmenopausal hormone replacement therapy) or various prostaglandin synthesis inhibitors have been used for the management of DUB.

Hysterectomy, or, alternatively, endometrial ablation therapies, are employed when various schemes of hormonal and iron therapy have failed to control bleeding and subsequent anemia--provided that fertility is no longer desired.

Two main methods of endometrial ablation currently in use are: diathermy resection (via a resectoscope such as used in transurethral resection of the prostate in men)[4], and contact diathermy (using various surgical tools, e.g. roller ball)[5]. These procedures are performed via hysteroscope and usually are accomplished in a "same-day surgery" setting and offer a more rapid post-operative recovery period as compared to total hysterectomy.[6]

It is thought that, since the basal layer of the endometrium extends into the myometrium, it is necessary to extend the ablation procedure to include 2.5-3mm of myometrium in order to avoid regeneration of the endometrium.[7]

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3 Czernobilsky B. Utero-ovarian pathology in dysfunctional uterine bleeding. Clin Obstet Gynecol 1970;13(2):416-433

4 Magos AL. Experience with the first 250 endometrial resections for menorrhagia. Lancet 1991;337:1074-78

5 McLucas B. Endometrial ablation with the roller ball electrode. Journal of Reproductive Medicine 1990;35:1055-1058

6 Gannon MJ, Holt EM, Fairbank J et al. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. British J Med 1991;303:1362-1364

7 Reid PC and Sharp F. Hysteroscopic Nd:YAG endometrial ablation: an in vitro and in vivo laser-tissue interactive study. Presented at the IIIrd European Congress on Hysteroscopy and Endoscopic Surgery, September, Amsterdam 1988. Quoted by Magos AL. Endometrial Ablation Techniques. In: Dysfunctional uterine bleeding Ed: Shaw RW. Chap 8;

The thickness of the endometrium varies depending on the phase of the menstrual cycle from a few millimeters just after menstruation to 12 mm at the end of the secretory phase. The ablation procedure is thus usually recommended to be performed in the immediate post-menstruation period.

Several investigators have employed GnRH agonists for the purpose of pre-thinning of the endometrium prior to ablation. Nisolle and colleagues used two depots of Goserelin and reported 94% "good" result.[8] Abramovich and co-workers reported 86% of subjects had "good" preparation after one depot.[9]

5. Clinical Studies

The sponsor presents information on what they consider two pivotal, one supportive and seven other trial to demonstrate the efficacy and safety of Zoladex for use as an endometrial thinning agent prior to endometrial ablation.

CONTROLLED ("PIVOTAL") STUDIES

I. Protocol 9393IL/0022

"A Randomised, Double-Blind Trial to Compare the Effects of Zoladex™ Depot and Sham Depot on the Preparation of the Endometrium prior to Endometrial Ablation by Loop Resection and the Overall Efficacy of the Procedure"

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Parthenon Publishing, Carnforth, Park Ridge 1990 pp 97-116

8 Nisolle M, Grandjean P, Gillerot S, and Donnez J. Endometrial ablation with the Nd-YAG laser in dysfunctional bleeding. Minimally Invasive Therapy 1991;1:35-39

9 Sheena P, Parkin D et al. Use of an LHRH analogue to prepare the uterus for hysteroscopic surgery. 26th British Congress of Obstetrics and Gynaecology

45 investigators/sites were established and 37 contributed patients (numbers ranging from 1 to 40) to this study. Of the 37, 29 were European, one South African and seven Canadian.

A. Objective

The stated objective of this trial was to show that in patients who receive Zoladex 3.6 mg depot to thin the endometrium prior to resection:

1 Post-operative menstrual blood loss is considerably reduced or abolished compared to patients who have received sham injections

2 The endometrium is thinned to such an extent as to render surgery easier, shorter in duration and with fewer complications compared to patients who have received sham injections.

3 Patients' perception of the success of their surgery exceeds that of patients receiving a sham injection.

B. Rationale

See "Clinical Background Section" above

C. Experimental Design and Conduct

Double-blind, multicenter, prospective, randomised, parallel group comparison of eight weeks therapy Zoladex versus sham depot with six months follow-up.

1. Patient population

a. Demography

358 premenopausal women presenting with dysfunctional uterine bleeding with no organic pathology in whom an endometrial ablation procedure is appropriate were recruited into the trial; 180 were randomised to Zoladex and 178 to Sham.

The subjects were balanced between the two groups with respect to race, age, uterine cavity length and duration of menstrual cycle at baseline. The treatment groups were significantly different for weight at baseline (Zoladex mean 71.8kg, Sham mean 66.3kg, p=.0004).

Of the 358 patients, 1 withdrew prior to receiving treatment (Sham), 5 during treatment (3 Zoladex, 2 Sham) and 6 withdrew at or after surgery

(3 Zoladex, 3 Sham).

b. Inclusion/Exclusion criteria

The criteria are listed in NDA volume 18.24, pages 89-91 and are appropriate. Basically women aged 30 or greater who were candidates for endometrial ablation with regular menstrual cycles, negative cytology and histology, appropriate sized uterus with no anatomic pathologies, non-pregnant, desiring infertility, currently not using hormonal therapies or IUDs, with no known or suspected endocrine disorder and not receiving concomitant non-steroidal anti-inflammatory drugs were candidates.

c. Withdrawal criteria

Patients were withdrawn from the trial when they either deteriorated, were lost to follow-up, experienced a serious adverse event, were non-compliant, withdrew informed consent or became pregnant.

2. Procedure

a. Specific formulations used in the study

Zoladex was supplied as a biodegradable, white cylindrical rod in which drug was dispersed in a matrix of D,L-lactide-glycolide copolymer. Each depot contained goserelin acetate equivalent to 3.6 mg goserelin in a disposable syringe mounted on a 16-gauge hypodermic needle designed for subcutaneous use.

Batch number 47026/92 of Zoladex (formulation number F5589) was used during the study.

Sham depot (formulation number F6328) was supplied as the empty sterilized, purpose-designed applicator.

b. Dosage schedule

Zoladex depots (3.6 mg goserelin) or sham depots were injected subcutaneously into the anterior abdominal wall every 28 days for 8 weeks (2 injections) with endometrial ablation performed 6 weeks +/- 3 days after the first injection.

The timing of the first injection was based on the length of the patient's

menstrual cycle, with the goal that the endometrium would be at its thinnest stage (day 7 of the cycle) at the time of surgery for all subjects.

c. Patient visits

A pre-randomization visit including informed consent and vaginal ultrasound or hysteroscopy occurred at least one menstrual cycle before randomization. Follow-up visits were made at 12 and 24 weeks after surgery.

The schedule of visits and assessments is shown here as Table 1:

TABLE 1 Trial plan to show timing of events and schedules

Procedure	Week Visit	screen	0 1	4 2	6 3	18 4	30 5
Informed consent		✓					
Medical assessment			✓	✓	✓	✓	✓
Concomitant medication			✓	✓	✓	✓	✓
Depot administration			✓	✓			
Objective assessments							
Height			✓				
Weight			✓		✓		✓
Vaginal hysteroscopy or vaginal ultrasound*		✓			✓		✓
Endometrial thickness by ultrasound					✓		
Uterine length		✓	✓				
Operative measures					✓		
Histology					✓		
Endometrial biopsy		✓#					
Post-operative assessments						✓	✓
Cervical smear test		✓+					
Subjective assessments							
Menstrual details			✓				✓
Pain score			✓				✓
Patient acceptability							✓
Adverse events			✓	✓	✓	✓	✓
Laboratory**							
Haematology			✓		✓		✓
Biochemistry			✓		✓		✓
Pregnancy test			✓	✓	✓		✓

*Whichever is investigator's normal practice
#If not done in past 2 months
+If not done in past 12 months
**Where blood samples were taken on the same day as depot administration, sampling was performed first

d. Primary endpoints(s)

Menstruation pattern 6 months post-operation; in particular the presence of amenorrhea.

Endometrial thickness (ultrasound)

e. Secondary endpoints

Histologic appearance of the endometrium
Operative fluid absorption
Duration of surgery
Dysmenorrhea score
Presence of hematometra post-operatively
Patient acceptability

f. Concomitant medications

During the trial subjects were not to receive treatment with any hormonal agents or non-steroidal anti-inflammatory drugs (including aspirin).

Prophylactic antibiotics could be administered according to the usual practice of the investigator.

3. Safety considerations

Appropriate laboratory and physical assessments were made as per Table 1 (above)

All adverse events were recorded. Serious adverse events were to be recorded and relayed appropriately.

4. Efficacy considerations

a. Primary outcomes

1. Menstrual blood loss

Menstrual blood loss charts were given at the pre-randomization visit. At visit 1 this chart was used to record menstrual history and was used post operation to record the frequency and severity of vaginal bleeding and dysmenorrhea. Charts were given at the 12 week post procedure

visit to complete for 12 weeks before returning for the six month follow-up visit.

The information recorded on the menstrual blood loss chart was used to derive the menstrual blood loss "score" for each cycle as outlined in Table 2:

Derivation of blood loss score from blood loss chart

Type of protection used	Degree of soiling	Blood loss score
Tampon	light	1
	moderate	5
	complete	10
Towel	light	1
	moderate	5
	complete	20
	small clot	1
	large clot	5

2. Endometrial thickness

Endometrial thickness was assessed by transvaginal ultrasound at visits 3 (pre-op) and 5 (follow-up). The double thickness of the endometrium was measured where it was found to be thickest.

Surgery was scheduled on Day 7 of the cycle when the endometrium was expected to be at its thinnest in the Sham group.

b. Secondary endpoints

Menstrual pain was assessed by the patient according to the visual analog scale and recorded on the menstrual chart.

Endometrial histology was assessed for thickness, gland activity, stroma and stromal vessels

Intra-operative assessments included measurement of the cavity, the ablation procedure was performed whether or not the endometrium appeared thinned and the endometrial ablation was performed using a

continuous flow hysteroscope and resection carried out using a 4 mm loop. Rollerball techniques were allowed in the corneal and fundal region. Irrigation fluid could be either Glycine or Sorbitol. Irrigation bags were weighed. The amount of fluid absorbed was calculated and recorded.

The quality of the endometrium was recorded using a scoring system based on the operator's subjective impression based on thickness and appearance. After the procedure, the ease of the operation was recorded. The duration of the operation was be recorded as well as complications or unexpected further interventions.

5. Statistical considerations - see also statistical review

a. Trial size

Sample size was estimated on the basis of prediction of rates of amenorrhea. In a previous publication, Serden and Brooks reported amenorrhea rates for patients with no pretreatment (48%), thinning with Danazol (46%) or leuprolide acetate (65%), another of the GnRH analogs.[10]

The sponsor asserts that the literature suggests that amenorrhea rates for the Goserelin group would be anywhere between 40 and 65%. Although there is a lack of data for the rates for patients with no pre-thinning, the numbers estimated for this trial (136 patients per group) would be sufficient to allow detection of a 20% difference (90% power, 5% significance level).

The sponsor also predicted that a difference in endometrial thickness of 1.2 mm could be detected with 60 patients per group, assuming a standard deviation of 2mm, an alpha of .05 and 90% power.

b. Analysis plans--a "modified" intent-to-treat analysis was performed--see statistical review for more detailed review.

D. Efficacy and Safety Results

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[10] Serden Sp and Brooks PG. Preoperative therapy in preparation for endometrial ablation. J Reprod Med 1992;37:679-681

1. Efficacy

The efficacy analyses reported by the applicant were conducted on a modified intent-to-treat basis. All randomized subjects who had data for an endpoint were included in the analysis of that endpoint.

Amenorrhea was experienced by 40% of the Zoladex patients and 26% of the Sham group. These results are reported by the sponsor as the odds ratio (2.11) with a 95% confidence interval (1.27, 3.50). The estimated odds of experiencing amenorrhea 24 weeks post-surgery in the Zoladex group were twice those in the Sham group and this is a significant difference (p=.0039).

The mean endometrial thickness (by ultrasound) immediately pre-surgery was 1.57 mm for the Zoladex group and 3.41mm for the patients receiving Sham. This difference was statistically significant (p=.0001).

The sponsor also presents information regarding the incidence of amenorrhea or severe hypomenorrhea (combined) and provides analyses of changes in total menstrual blood loss scores. These were not planned analyses and offer no findings requiring discussion here.

The duration of surgery was significantly shorter (p=.0001) in the Zoladex group (mean 17.5 minutes) than in the Sham group (mean 21.9 minutes). Operators recorded "easier" surgery in patients in the Zoladex group significantly more often than for the Sham group (p=.0001). There was evidence of a difference between the groups in favor of Zoladex for fluid absorption during surgery (p=.0325). There were no significant differences for the change in pain score or patient satisfaction with the procedure.

Endometrial activity was recorded as either active, inactive or atrophic. The number of patients with atrophic glands at surgery was significantly greater (p=.0001) for the Zoladex group (119 or 68%) versus Sham (18 or 10%).

By visual inspection at surgery, the operators rated the endometrium as atrophic in 79% of patients in the Zoladex group and 10% in the Sham group.

2. Safety

167 (93%) of patients receiving Zoladex and 134 (76%) of patients in the Sham group had at least one adverse event. The proportion of patients with serious adverse events (13% Zoladex, 11% Sham) was similar. Three (2%) patients in the Zoladex group and three (2%) patients in the Sham group withdrew from the trial as a result of an adverse event.

Protocol violations and deviations were few and treatment comparisons were likely not affected.

Reasons for withdrawal are given here as Table 3:

Reasons for withdrawal from the trial

Centre/Patient number	Treatment group	Reason for Withdrawal
0006	ZOLADEX	Adverse event
0009	ZOLADEX	Patient did not attend for visit, unwilling to continue
0014	ZOLADEX	Adverse event
0028	ZOLADEX	Adverse event
0030	ZOLADEX	Surgical complications (cervical tear)
0032	ZOLADEX	Ablation not performed due to technical problems. (Cervical problem on day of surgery 28/3/95)
0002	Sham	Adverse event
0002	Sham	Protocol non-compliance
0013	Sham	Adverse event
0014	Sham	Adverse event
0016	Sham	Patient was given a non-trial ZOLADEX depot
0017	Sham	Protocol non-compliance

*Withdrawn before completing therapy

Withdrawals for adverse events were evenly distributed between the groups and included reports of pre-surgical adverse events in three subjects which included unintended pregnancy, headache and nervousness, one adverse event reported at the time of surgery in the Sham group--"ruptured uterus" and reports for two subjects post-surgery, one with back pain and one with menorrhagia.

The ruptured uterus case involved a 45 year old patient who suffered perforation of the uterus during the endometrial resection procedure. She was withdrawn from the trial. A hysterectomy was performed seven days later.

Twenty-four patients (13%) in the Zoladex group and 20 patients (11%) in the Sham group experienced serious adverse events. The most common serious events were headache (2.8%) in the Zoladex group and abdominal pain and uterine hemorrhage (combined 2.3%) in the Sham group. One patient in each group experienced hematometra.

Adverse events occurring with an incidence of at least 5% are presented here are Table 4:

Adverse events occurring with an incidence of at least 5%

COSTART preferred term by body system	Number of patients			
	ZOLADEX 3.6 mg		Sham	
	n	%	n	%
Whole body				
Headache	57	32	38	22
Abdominal Pain	19	11	18	10
Pelvic Pain	16	9	11	6
Back Pain	8	4	13	7
Cardiovascular				
Vasodilatation	103	57	31	18
Migraine	12	7	7	4
Hypertension	11	6	3	2
Digestive				
Nausea	9	5	11	6
Nervous				
Nervousness	9	5	5	3
Depression	5	3	12	7
Respiratory				
Pharyngitis	11	6	16	9
Sinusitis	5	3	10	6
Skin and appendages				
Sweating	28	16	8	5
Urogenital				
Dysmenorrhoea	13	7	15	9
Metrorrhagia	12	7	3	2
Uterine Haemorrhage	11	6	7	4
Vulvovaginitis	9	5	1	1
Menorrhagia	8	4	9	5
Vaginitis	2	1	10	6

Those that appear to occur more often in the Zoladex group include headache, vasodilatation, sweating and vulvovaginitis. These findings might be expected due to the pharmacologic effect of hypoestrogenemia created by GnRH analog therapy.

The incidence of post-operative complications was similar for both groups. The most common complication was hemorrhage which occurred in 13% of patients in the Zoladex group and 15% of patients in the Sham group. The ultrasound examination performed 24 weeks after surgery showed that 6.4% of patients in the Zoladex group and 3.0% of patients in the Sham group had hematometra.

In terms of clinical laboratory data there were no important differences between the treatment groups in the mean values of hematology and biochemistry variables assessed throughout the study.

E. Conclusion

1. Sponsor's conclusion

"Post-operative menstrual blood loss was considerably reduced in both treatment groups. The incidence of amenorrhea in the Zoladex group was significantly greater than that in the Sham group. The endometrium was significantly thinner in the Zoladex group immediately pre-surgery, and patients in the Zoladex group were associated with significantly easier and shorter surgery. Patient satisfaction with the success of their surgical procedure was high in both groups as a result of the high level of competence of the surgeons."

2. Reviewer's conclusion

This trial was designed to detect a 20% difference in amenorrhea rates at six months post procedure with the assumption that the rates in the Zoladex and Sham groups would be 65% and 45% respectively. The actual rates observed in the trial were 40% and 26% and, although the magnitude of the observed difference was less than expected, this result was statistically significant.

At the time of surgery the endometrium was thinner and showed more atrophy in patients in the Zoladex group than in patients in the Sham group.

There were no new or unexpected adverse events for Zoladex seen in this trial. Operative complications did not appear to be impacted by use of drug therapy.

In summary, it appears that this trial supports the use of Zoladex to produce a thinned endometrium in preparation for endometrial ablation procedures.

CONTROLLED (PIVOTAL) STUDIES (CONTINUED)

II. Protocol 9393IP/0003

"A Prospective Randomised Study comparing Goserelin and Danazol in Preparing the Endometrium for Laser Ablation in Patients with Dysfunctional Uterine Bleeding"

Principal Investigator: **Mr R Garry MBBS D Obst RCOG MRCOG MD FRCOG**
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This study involved a single investigator at a single site in the United Kingdom.

A. Objectives

1. To compare Zoladex and Danazol as treatments for endometrial preparation prior to endometrial laser ablation in women with dysfunctional uterine bleeding.

2. To compare the two treatment regimens in terms of tolerability, fluid absorption during the procedure and endometrial thinning.

3. To determine whether four or eight weeks treatment prior to surgery is preferable.

4. To compare the clinical outcome six months following surgery in the four treatment groups.

B. Rationale

See "Clinical Background" above.

C. Experimental Design and Conduct

This study was an open, randomised, parallel, comparative (Zoladex versus Danazol) study of 160 premenopausal women with DUB recruited from a single center.

1. Patient population

   a. Demography

      160 premenopausal women (age 20 years or more) with DUB were randomised to one of four groups: Zoladex for 4 weeks, Zoladex for 8 weeks, Danazol for 4 weeks, Danazol for 8 weeks.

The subjects were balanced between the groups in terms of their age and weight.

Six patients withdrew before taking any trial medication. Of the 154 who received trial medication, 15 did not complete the study--3 Zoladex 4 weeks, 1 Zoladex 8 weeks, 5 Danazol 4 weeks and 6 Danazol 8 week patients.

Initially the protocol called for forty patients (10 in each group) to collect all menstrual sanitary protection (tampons/pads) used over a 4 week period before entry to the study for menstrual blood loss assessment. This was changed by protocol amendment to remove this measurement from the study.

b. Inclusion/Exclusion criteria

DUB to such a degree as to warrant a hysterectomy. Patients must be at least 20 years of age, and not pregnant or breast feeding, who desire infertility, have uterine size less than 16 weeks gestational size (and at surgery less than 12 weeks size with cavity smaller than 12 cm), and are without serious concomitant illnesses or concomitant or recent use of hormonal, Danazol or GnRH therapies.

c. Withdrawal criteria

Patients could be withdrawn from the study for protocol violations, serious adverse events, pregnancy, inability to continue therapy (drop-outs), investigator decision or "any suspicion that litigation may occur".

2. Procedure

a. Specific formulations used in the study

(1) Zoladex

Zoladex was supplied as a white cylindrical rod in which drug was dispersed in a matrix of D, L-lactide-glycolide copolymer. Each depot, formulation number F5589, contained goserelin acetate equivalent to 3.6 mg goserelin. The batch numbers used during the study were 21273C91 and EU328B.

(2) Danazol

Danazol was supplied as commercially available capsules of 200 mg strength to be taken orally (Batch number 49327\91).

b. Type of experimental controls

In this study an active control group (Danazol) was used. The study was not blinded. Danazol is not approved for this indication in the US. It has been licensed within the UK for use as a pre-thinning agent prior to endometrial ablation since December 1992 and is currently the only agent licensed in the UK for this indication. The recommended dose in the UK is 400-800 mg daily for 3-6 weeks.

c. Dosage schedule

(1) Zoladex

Patients who received Zoladex had either one or two 3.6 mg subcutaneous injections (given at 28 day intervals for those receiving two) into the anterior abdominal wall using a pre-loaded syringe with a 16 gauge needle for a drug therapy duration of 4 or 8 weeks.

(2) Danazol

Patients who received Danazol had a 200 mg capsule four times daily for 4 or eight weeks.

d. Patient visits/schedule of assessments

Patients had scheduled visits. At visit 1, inclusion and exclusion criteria were confirmed and patients were randomised to one of four groups. Patients started their study medication during menstruation.

Group 1--Zoladex for 4 weeks
Group 2--Zoladex for 8 weeks
Group 3--Danazol for 4 weeks
Group 4--Danazol for 8 weeks

At entry into the study vaginal ultrasound assessment of endometrial thickness and uterine size was performed and endometrial biopsy was obtained.

At Visit 2 (28 days after start) Groups 1 and 3 proceeded to the laser ablation procedure. Groups 2 and 4 continued medications.

Four weeks later Groups 2 and 4 underwent laser ablation procedures.

The endometrial laser ablation was carried out using a 30 degree operating hysteroscope and Nd-YAG laser energy. The endometrium was ablated using the bare-fibre dragging technique.[11] The duration of the procedure was recorded as was the amount of fluid absorbed and any operative complications.

The final visit was at 24 weeks post surgery

e. Concomitant medications

Except for Zoladex and Danazol, no other drugs which are known to affect sex hormone status were allowed during the treatment period. There was no restriction on the concurrent administration of other drugs.

3. Safety considerations

Hematology and biochemistry measurements were obtained at weeks 0, 4, and 8 (if appropriate) prior to surgery and also 24 weeks following surgery.

Adverse events were recorded at visits prior to and after surgery. Serious adverse events were recorded and appropriately conveyed.

Incidences of post-operative complications were recorded.

4. Efficacy considerations

The original protocol called for assessments of: endometrial thickness by ultrasound and histological measures, visual inspection of the endometrium, duration of the operation, degree of difficulty of the operation, fluid absorption during ablation and endometrial atrophy status. Acceptability issues were also addressed by asking patients concerning satisfaction with the results of the procedure, improvement in menorrhagia and whether the patient planned to undergo further ablation therapy or hysterectomy.

5. Statistical considerations - see also statistical review

The original protocol gave a sample size determination based on fluid

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[11] Goldrath, MH et al. Laser photovaporization of endometrium for the management of menorrhagia Am J Obste Gynecol, 140:14;1981

absorption during laser ablation. It was proposed that a difference in 400 mL between treatment groups would be considered to be of clinical importance. To have an 80% power at a significance of 5%, it was estimated that 140 patients would be required to complete the study.

Although the patient estimates were based on the level of fluid absorption during the procedure, irrigation methods have since changed, invalidating this measurement.

A protocol amendment was submitted which provided a new calculation with sample size estimates based on a difference in endometrial thickness of 1.2 mm between treatments. The sponsor states that it was calculated that 60 patients per group would give a 90% power to detect a difference in endometrial thickness of 1.2 mm between the compared groups. Thus, the sponsor indicated that combining the results for the one and two month data for each drug would allow this comparison. The sponsor asserts in the study report that the major endpoint for statistical analysis was the endometrial thickness measured by ultrasound. "The other primary endpoints were fluid absorption during the operation, tolerance of treatments and outcome at 6 months".

Secondary endpoints were the laboratory (hematology and biochemistry) parameters.

The analysis plan involved comparison of all Zoladex patients with all Danazol patients as well as planned analyses of the one and two month Zoladex groups with pre-treatment assessments.

D. Results of Study--Efficacy and Safety

1. Efficacy

On ultrasound assessment the mean preoperative endometrial thickness for the Zoladex group was 0.8 mm and was 0.94 mm for the Danazol group. The median value was the same for the two groups. No difference was found.

The sponsor presents results of the various parameters with the following results: No difference between the Zoladex and Danazol groups in the assessment of visual inspection of the endometrium, histological thickness of the endometrium, or degree of difficulty/complications of the procedure. The sponsor presents favorable findings for the Zoladex group over Danazol for the uterine cavity length on vaginal ultrasound, endometrial atrophy satisfaction, histological assessment of the endometrial glands/stroma, fluid absorption, duration of operation and improvement in menorrhagia at follow-up.

In comparing the two Zoladex groups to baseline it was found that the thickness of the endometrium was significantly less for the Zoladex 8 weeks treatment group than for the Zoladex 4 weeks group (p=.0001). The difference between the two Zoladex treatments in median endometrial thickness was not significant (.5mm) .

There was trend favoring the Zoladex 8 week group in the findings of histological thickness of the endometrium and histological assessment of glands/stroma.

There were no differences between the Zoladex 4 and 8 week group (when compared to baseline) in the areas of uterine cavity length, visual inspection, endometrial atrophy satisfaction, fluid absorption, duration of operation, degree of difficulty/complications or improvement at six months follow-up.

In terms of bleeding patterns at six months follow-up, the following table presents findings:

Table 5

	ZOLADEX		Danazol	
Improvement in Menorrhagia	**n**	**%**	**n**	**%**
Amenorrhoea	18	(24)	4	(6)
p value (amenorrhoea only)		p = 0.0045		
Hypomenorrhoea	39	(53)	32	(49)
Normal Flow	15	(20)	26	(40)
Not improved	2	(3)	3	(5)
Total	74	(100)	65	(100)

Odds ratio (for improvement in menorrhagia ZOLADEX\danazol) = 3.090.
95% CI = (1.592, 6.077)
p value p = 0.0008

As can be seen, there was a statistically significant difference between the treatment groups for amenorrhea rates. Zoladex patients were more likely to experience amenorrhea than Danazol patients.

In terms of comparison of the 4 and 8 week Zoladex groups, the eight week group showed a significant difference in endometrial thickness (mean difference 0.5mm) on ultrasound. This was confirmed in the analysis of histological thickness which showed a significantly thinner endometrium in the 8 week group than the 4 week group (p=.040). There was no difference between the 4 and 8 week groups in all other relevant parameters.

At the six-month follow-up assessment there was no difference between the 4 and 8 week Zoladex group in rates of amenorrhea (24% for each group) or other improvements in bleeding patterns. As described above (Table 5), there was a significant difference in comparison to the Danazol group.

2. Safety

Of the 154 patients who received medication, seven patients withdrew while on trial medication and 8 patients withdrew after completing medication. None of the Zoladex subjects were withdrawn because of adverse events, Six of the Danazol patients were withdrawn because of an adverse event.

The six adverse events which led to withdrawal in the Danazol group included 3 subjects with skin rashes, one with lethargy and weight gain, one with malaise, fatigue and nausea, and one with depression, breast tenderness and weight gain.

Of the eight subjects who withdrew after completing trial medication, five (2 Zoladex and 3 Danazol) did not attend the post-operative follow-up visit. One Zoladex patient had a uterine perforation as the instruments were introduced prior to the laser ablation procedure and two Danazol patients were found to have large fibroids at surgery (protocol violations).

Protocol violations and deviations are described and are not thought to impact results.

Thirty-five percent of the Zoladex 4 week group, 79% of the Zoladex 8 week group, 53% of the Danazol 4 week group and 80% of the Danazol 8 week group experienced at least one adverse event.

For patients who received Zoladex the most frequently reported adverse events were headache, hot flushes and leucopenia. Patients who received Danazol most frequently reported weight gain, nausea, hot flushes, headache and back pain.

Adverse events reported by at least 5% of patients are shown here as Table 6:

Adverse events reported by at least 5% of patients in one or both treatment groups

COSTART Body System	COSTART Preferred Term (abbreviated)	Number of Patients Reporting Event	
		ZOLADEX	danazol
BODY AS A WHOLE	BACK PAIN	1	5
	HEADACHE	8	8
CARDIOVASCULAR	VASODILATATION	35	5
DIGESTIVE	NAUSEA	3	7
HEMIC AND LYMPHATIC	LEUKOPENIA	5	3
METABOLIC AND NUTRITIONAL	WEIGHT GAIN	1	30
SKIN AND APPENDAGES	RASH	0	4
UROGENITAL	BREAST PAIN	0	4

Fourteen events were serious adverse events and are listed here:

Zoladex 4 week	1 leucopenia 1 post-op hemorrhage
Zoladex 8 week	1 leucopenia 1 leucocytosis 1 post-op hemorrhage
Danazol 4 week	1 post-op hemorrhage 1 post-op infection 1 leucopenia 1 "itchy" rash* 1 depression, weight gain, breast tenderness*
Danazol 8 week	2 "itchy" rash* 1 weight gain and lethargy* 1 malaise, fatigue and nausea*

* led to withdrawal from trial

While the reports of leucopenia and leucocytosis fit the criteria for serious adverse events, none gave rise to clinical concern (the lowest measurement was a single report at $3.4x10^9$/L which resolved at next measure, the single leucocytosis was reported as $13x10^9$/L at post-op follow-up).

Weight changes and laboratory value assessments did not show any significant differences between the groups nor did they raise any clinical concerns.

E. Conclusion

1. Sponsor's conclusion

"For the clinician and his patient, Zoladex appears to be better tolerated, and produces a greater degree of endometrial suppression with a least as good endometrial thinning as Danazol. It also produces a greater reduction in the uterine cavity size, shortens the treatment time and reduces the risk of the potentially fatal complication of excess fluid absorption. Zoladex is associated with higher amenorrhea and oligomenorrhea rates and lower treatment failures rates than Danazol.

One depot of Zoladex produced satisfactory endometrial suppression and control of menstrual loss in 95% of cases. Two depots produced a thinner

endometrium, more endometrial suppression and a greater reduction in uterine cavity size with associated slight reduction in treatment time. These marginally improved operating conditions were associated with a slightly better clinical outcome as after 8 weeks treatment there were no clinical failures."

2. Reviewer's conclusion

This study supports the claim that Zoladex creates a thin endometrium in preparation for endometrial ablation procedures. Although no placebo group is included for comparison, the Zoladex group did show a significantly thinner endometrium as compared to baseline (off therapy) measurements.

At six months follow-up, the rates of amenorrhea for the Zoladex group (24% for both) appear lower than expected from endometrial ablation procedures. The Danazol control group showed a 4% rate of amenorrhea at the six month post-procedure visit. This difference of 20% between groups is significant. The risk of making comparisons to an unapproved control is usually most important when one is making claims of equivalence. This finding of superiority provides strong support for Zoladex therapy. If one considers the Danazol group as a placebo control group, the conclusion could be that Zoladex and the "placebo" show no difference in endometrial thickness after 4-8 weeks of therapy, but results do confirm a significant advantage of Zoladex over this "placebo" group for post-operative amenorrhea at six months.

As endometrial thinning is truly a surrogate for the clinically relevant outcome of amenorrhea post-procedure, this finding of improved amenorrhea over the Danazol group is strongly supportive of the claim for this drug.

No unexpected adverse events were discovered in this trial. No new safety concerns for Zoladex use were raised.

CONTROLLED STUDIES (CONTINUED)

III. <u>"Supportive Study" Protocol ZX1600/9001</u>

"A Single Center Open Randomised Parallel Group Study to Compare the Effects of Zoladex and Danazol on Endometrial Atrophy Prior to Endometrial Resection"

Principal Investigator: **Mr CJG Sutton MA MB Bchir MRCOG FRCOG**
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This study was a single center, open, randomised, parallel group study to compare the effects of Zoladex and Danazol on endometrial atrophy prior to endometrial resection in women with DUB.

Appropriate inclusion/exclusion criteria were employed. Zoladex was given as two injections for 8 weeks of therapy. Danazol was given as 4x200 mg tablets each day for 8 weeks. The endometrium was assessed by ultrasound measurement at 8 weeks just prior to endometrial resection. Patients were assessed at 12 weeks post-procedure.

A total of 120 patients were enrolled, 60 in each group. It was calculated that this number would give a 90% chance of detecting a difference in endometrial thickness of greater than 20% between the compared groups (at 5% significance level).

Ten patients withdrew before taking trial medication. A total of 110 patients received trial medication: 55 Zoladex and 55 Danazol. Of these 110, 13 did not complete the study (4 Zoladex and 9 Danazol). Seven of the Danazol patients withdrew prior to surgery, two had post-op procedures or failed to attend the 12 week post-op visit. All four of the Zoladex patients withdrew post-procedure as either having further procedures performed or failed to attend the 12 week post-op visit.

Withdrawals, protocol violations and demographic variables were similar between the groups and similar to findings for the two pivotal trials already described.

Zoladex was found to produce a significantly thinner endometrium ($p=.0015$) than Danazol. The difference between the treatments in median endometrial thickness was 0.9mm. This Zoladex advantage was supported by the histologic assessment of the endometrium.

There was no significant difference found between the groups for improvement in menorrhagia or patient satisfaction at 12 weeks.

Adverse events as elicited in a "tolerance" questionnaire at 12 weeks is shown here as Table 7:

Analysis of the symptoms elicited in the tolerance questionnaire

Symptom	Table Number	Odds ratio for treatment effect ZOLADEX . danazol)	95% Confidence interval	p-value
Oily hair or skin	38	2.79	1.06 to 7.38	0.038
Hot flushes	39	0.17	0.06 to 0.46	<0.001
Sweating episodes	40	0.35	0.15 to 0.82	0.016
Vaginal dryness	41	0.40	0.17 to 0.95	0.038
Headaches	42	0.34	0.14 to 0.79	0.012
Libido	43	0.34	0.13 to 0.92	0.034
Mood swings	44	1.33	0.60 to 2.94	0.48
Ankle oedema	45	1.22	0.41 to 3.61	0.72
Voice changes	46	1.09	0.30 to 4.04	0.89
Hirsutism	47	2.14	0.51 to 9.03	0.30
Depression	48	0.71	0.31 to 1.64	0.42
Acne	49	0.92	0.41 to 2.07	0.84
Breast size	50	1.39	0.61 to 3.16	0.44

As can be seen, the pharmacologic effects of Zoladex and Danazol are well represented with Zoladex showing a significantly higher rate of hot flushes, sweating episodes, vaginal dryness, headache and change in libido than the Danazol group.

There was a mean weight loss in the Zoladex group and a mean weight gain in the Danazol group. The difference between the groups was 2.13 kg which was significant ($p = .006$).

The sponsor's conclusion is that "both Zoladex and Danazol produce sufficient endometrial thinning for the purposes of transcervical resection of the endometrium, with Zoladex producing a significantly thinner more atrophic endometrium. Equivalent operative and surgical follow up parameters are demonstrated in the two treatment groups. Based on the withdrawals from the two treatment groups, Zoladex appears to be the better tolerated"

Reviewer's Conclusion:

In this trial, 12 week post-procedure amenorrhea rates were similar for the Zoladex and Danazol groups. The study was powered to show differences in the surrogate endpoint of endometrial thickness. Zoladex was found to produce a significantly thinner endometrium than Danazol after 8 weeks of therapy. No new safety concerns were raised.

OTHER STUDIES

The sponsor presents study reports for seven further studies in which Zoladex was used prior to endometrial resection procedures.

Protocol 9393IT/0002

This was an open, randomized, multicenter trial comparing the efficacy and tolerability of Zoladex with no pre-treatment in women requiring endometrial resection for DUB. Subjects received either no pre-treatment or Zoladex, 2 depots for eight weeks of therapy. 72 patients were enrolled in a 1:1 randomization. The investigator concluded that fluid absorption was statistically significantly less in the Zoladex group; that surgery was significantly easier with Zoladex.

Amenorrhea rates at six months post procedure were higher in the Zoladex group (41%) than in the no pre-treatment group (24%) but the difference between groups was not significant ($p=.171$). In this study it appears that surgeons could choose to perform "partial endometrial ablations" which would not be aimed at post-procedure amenorrhea and this could have impacted these results.

Endometrial thickness by histology at surgery was 1.87mm for the Zoladex group and 3.38mm for the Surgery alone group ($p=<.0001$)

Stampe-Sorenson Study (available as published abstract only)

This published abstract reports an open, randomized trial comparing Zoladex for four or 8 weeks to no pre-treatment therapy in patients with menorrhagia undergoing "loop" endometrial resection. 20 subjects each were randomized to Zoladex 4 week, Zoladex 8 week and no pre-treatment groups.

In this study, the rates of amenorrhea/hypomenorrhea at three months post-procedure where significantly in favor of Zoladex therapy (25% for no pre-treatment, 58% for the Zoladex 4 week group--$p=<.05$, and 84% for the Zoladex 8 week group $p=<.001$).

Gannon Trial

This single center trial was an open, randomized, factorial design trial to compare one month Zoladex with Danazol and no pre-treatment in patients with menorrhagia. The ablative technique involved a comparison of loop versus rollerball.

In this trial 84 subjects were randomized to Zoladex, 80 to Danazol and 165 to no pre-treatment. Patients were assessed at 4 and 12 months after surgery.

Withdrawals, adverse events and protocol violations were within expectations.

When assessed by ultrasound, Zoladex produced a thinner endometrium (4.8mm) than Danazol (5.4mm) and a significantly thinner endometrium than no active treatment (7.2mm).

Loss to follow-up was high (67%). For those with follow-up information (the report does not specify at 4 or at 12 months), Zoladex was associated with a better outcome than Danazol for pos-operative amenorrhea, although no difference was found in comparison to the surgery alone group.

Fraser Trial

This was a single center, open, randomized comparative trial of Zoladex with Danazol for eight weeks of treatment prior to ablation with the rollerball technique. 60 patients were randomized in a 1:1 ratio.

Menstrual blood loss was decreased following ablation but not significantly different between groups. Although the sponsor asserts that 74% of Zoladex users and 64% of Danazol users reported amenorrhea at 6 months, from review of the report it appears that about 40% in each group experienced no bleeding at the final visit.

Abramovich Trial (Publication)

This was a single center open randomized comparison of hysterectomy and hysteroscopic endometrial ablation in 204 patients with DUB and also compared loop and laser ablative techniques. The subjects undergoing hysteroscopic resections received Zoladex, one injection, prior to surgery.

For the ablation group loss to follow up was low, 20 percent experienced amenorrhea and 60% hypomenorrhea at six months and 22% and 62% at 12 months respectively.

Skar Trial

This was a single center open, non-randomized pilot trial to assess the effect of 8 weeks of Zoladex on uterine size and endometrial thickness in 13 patients with DUB undergoing loop ablative procedures. Due to the small size the sponsor did not present information other than for descriptive safety assessments. No information on endometrial thickness or menstrual bleeding post-therapy is provided.

Rolland Trial (Publication)

This was a post-ablation follow-up report comparing 4 to 12 weeks Zoladex (32 subjects) and other GnRH analogs (Buserelin--5 subjects, Nafarelin--61 subjects) and progestins (Danazol--36 subjects, lynestrenol--4 subjects) with no pre-treatment (1 subject). No significant differences were described.

6. Need for Postmarketing Surveillance

No specific Phase IV commitments are required at this time.

7. Labeling Review

Initial labeling review and comments were transmitted to the Sponsor on June 16, 1997. The sponsor responded with proposed revisions on June 19, 1997.

My comments are included in my response directly on the June 19th draft proposed labeling.

8. Overall Evaluation and Conclusions

The major trials presented in this submission have shown that Zoladex 3.6 mg, either 4 or eight week therapy, can create a thin endometrium as compared to either Placebo or Danazol (unapproved for this indication in the US).

The Zoladex groups showed an advantage over placebo and Danazol in amenorrhea rates six months after ablative therapies.

Side effects were consistent with the labeled effects of GnRH therapy in pre-menopausal women. No new concerns were raised through this review.

Safety Update

A safety update was submitted on Febraury 26, 1997. This report includes information from a 12 month postcard follow-up in the Zoladex versus sham depot trial (Protocol 9393IL/0022). All the other trials submitted were complete at the time of NDA submission.

Amenorrhea at 12 months improved from 40% to 46% for the Zoladex group and from 26% to 29% in the Sham group.

No new safety concerns are identified in this follow-up report.

9. Recommendations

Approval with appropriate label changes.

6/21/97
Lisa D. Rarick, MD

cc: NDA Arch.
HFN-340
HFD-580 (NDA 19-726)
HFD-580/LRarick/HJolson/ADunson\\WPFiles/19726.18