SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZOLADEX™ long-acting depot injection

ACTIVE INGREDIENT: goserelin acetate (equivalent to 10.8-mg goserelin)

Trial title (number): A Multicenter Controlled Trial of Goserelin Acetate (ZOLADEX™) 3-Month 10.8-mg Depot Plus Iron Versus Sham Plus Iron for the Preoperative Management of Premenopausal Women with Iron Deficiency Anemia due to Uterine Fibroids (9393IL/0025)

Clinical phase: Phase III

First subject recruited: 10 February 1997
Last subject completed: 30 August 1999
AstraZeneca approval date: 21 December 2001

Publications: none at the time of report preparation

OBJECTIVES

The primary objective of this trial was to compare goserelin acetate 3-month 10.8-mg depot (referred to as ZOLADEX 10.8 mg hereafter) plus iron versus sham plus iron in premenopausal women with iron-deficiency anemia due to fibroids in terms of the mean increase in hemoglobin from randomization to before surgery, 12 weeks after randomization, or the time of autologous blood donation or receipt of transfusion, whichever occurred first.

Secondary objectives of the trial were to compare the 2 treatments for the following end points:

(1) the percentage of patients who achieved an increase in hemoglobin concentration greater than or equal to 2 g/dl by the time of surgery, 12 weeks after randomization, or the time of autologous blood donation or receipt of transfusion, whichever occurred first

(2) the percentage of patients who achieved hematologic recovery, defined as hemoglobin greater than or equal to 12 g/dl, by the time of surgery, 12 weeks after randomization, or the time of autologous blood donation or receipt of transfusion, whichever occurred first

(3) relief of the following symptoms associated with uterine fibroids: excessive menstrual bleeding, fatigue, pelvic pain, and pelvic pressure
(4) the number of patients who required blood transfusion(s) at pre-, peri-, and postoperative visits
(5) the number of patients who were eligible to provide blood for autologous blood transfusion
(6) changes in fibroid and total uterine volumes from the time of trial entry to before surgery
(7) the safety and tolerability of ZOLADEX 10.8 mg or sham, each combined with iron therapy

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METHODS

Design: Phase III, randomized, multicenter, double-blind trial to be conducted at 35 investigational sites in North America. The trial consisted of a 12-week treatment period, followed by a 24-week follow-up period. Patients were randomized to receive a single depot injection of ZOLADEX 10.8 mg or a sham injection in a double-blind manner, and oral ferrous sulfate 325 mg 3 times daily in an unblinded manner during the 12-week treatment period. Surgery (hysterectomy or abdominal myomectomy) was planned for Week 12 (± 3 days).

Population: A total of 108 premenopausal women with iron-deficiency anemia due to uterine fibroid(s) who were candidates for surgical management were to be recruited.

Key inclusion criteria: at least 18 years or older with 3 consecutive menstrual cycles before randomization and a history of excessive menstrual bleeding causing iron-deficiency anemia; uterine size of at least 8 weeks gestation on pelvic examination and with documentation (by pelvic or vaginal ultrasound) of 1 or more fibroids at least 3 cm in diameter; diagnosis of iron-deficiency anemia (confirmed by the central laboratory), defined as a hemoglobin concentration of 10.0 g/dl or less; willingness to undergo surgery and candidacy for hysterectomy or conventional abdominal myomectomy; written informed consent

Key exclusion criteria: pregnancy or breast feeding; treatment with a luteinizing hormone releasing hormone (LHRH) analogue within the past 6 months; sex-hormone therapy (including contraceptives) within the past month; treatment with any systemic drug at doses that would suppress the hypothalamic-pituitary adrenal axis (ie, glucocorticosteroids); treatment within the past 2 weeks with any drug that could affect menstrual blood loss (ie, antifibrinolytics and antiprostaglandins); blood transfusion within the past 8 weeks or blood donation within the past 2 weeks; history or presence of adrenal, pancreatic, ovarian, or pituitary tumors; osteoporosis, Cushing's disease, or other metabolic bone disease; gynecologic malignancy or premalignancy; history or presence of coagulopathies or blood dyscrasias other than iron-deficiency anemia; thalassemia, sickle cell anemia, or folic acid deficiency; presence of calcified fibroid(s) only (presence of both calcified and non-calcified fibroids in a single patient was acceptable); known hypersensitivity to LHRH, LHRH agonists or analogues, or any of the components found in ZOLADEX 10.8 mg

Dosage: All patients were given either a single subcutaneous ZOLADEX 10.8-mg depot injection plus oral ferrous sulfate (325 mg 3 times daily) for 12 weeks or a single sham injection plus oral ferrous sulfate (325 mg 3 times daily) for 12 weeks. The ZOLADEX 10.8-mg depot

was formulation F6054, lot numbers N63116 and N73132; the sham injection was formulation F12083, lot number N63117. Iron therapy was provided in a commercially available tablet form and was packaged by the sponsor (formulation number F10169; lot number F00939).
Key assessments: Hemoglobin concentration was the primary measure of efficacy. Secondary efficacy assessments included symptoms associated with uterine fibroids, requirement of blood transfusion, ability to donate blood for autologous transfusion, and measurement of fibroid and total uterine volume. Safety assessments included recording of adverse events, clinical laboratory evaluations, bone mineral density (BMD) measurements, surgical parameters, and menstrual diary cards.
Statistical considerations: Efficacy analyses were not conducted because the use of ZOLADEX for this indication is not being pursued.

RESULTS
Demography: A total of 110 women from 19 centers received a single ZOLADEX 10.8-mg depot injection (N=54) or a sham injection (N=56). The majority of patients in each treatment group (69% of all subjects) were black, and the mean age in each group was 40 years.
Safety: Overall, 89% of subjects in each treatment group reported 1 or more adverse events. The most common adverse events across all subjects were pelvic pain, vasodilation (hot flashes), and headache. The incidence of vasodilation (hot flashes), pain, nausea, sweating, and insomnia was higher (by at least 10%) in subjects who received ZOLADEX 10.8 mg, and the incidence of uterine hemorrhage was higher among those who received the sham injection.
No deaths were reported during the trial.
A total of 5 subjects (2 in the ZOLADEX 10.8-mg group and 3 in the sham injection group) withdrew from the trial because of adverse events. In 3 of the 5 subjects (1 in the ZOLADEX 10.8-mg group and 2 in the sham injection group), the adverse events that led to withdrawal were serious but were not considered drug related. A total of 15 subjects (5 in the ZOLADEX 10.8-mg group and 10 in the sham injection group) had 1 or more serious adverse events during the trial. None of the serious adverse events was considered drug related.