SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ZOLADEX™ 3.6 mg and 10.8 mg depot injections

ACTIVE INGREDIENT: Goserelin acetate
(equivalent to 3.6 mg and 10.8 mg goserelin)

Trial title (number): An Open-label, Multicentre, Parallel Group Trial to Investigate the Return of Ovarian Function Following the Administration of Two ZOLADEX 10.8 mg Depots or Six ZOLADEX 3.6 mg Depots in Women With Endometriosis - Follow on Study from Trial 9393IL/0026 (9393IL/0027)

Clinical phase: IIIb

First patient recruited: 12 March 1997
Last patient recruited: 29 April 1998
Data cut off: 14 July 1999[1]
AstraZeneca approval date: 7 July 2000

Publications: None at the time of this report.

OBJECTIVE
The objective of this trial was to investigate return of ovarian function in women with endometriosis who received a second ZOLADEX 10.8 mg depot (administered 12 weeks after the initial ZOLADEX 10.8 mg depot received in Trial 9393IL/0026) or a further three 4-weekly ZOLADEX 3.6 mg depots (the first depot administered 12 weeks after the initial ZOLADEX 3.6 mg depot received in Trial 9393IL/0026).

[1] By this date, all patients had been followed-up for 12 months after completing trial treatment.

METHODS

Design: This is an open-label, multicentre, parallel group comparison of the return of ovarian function following administration of either 2 ZOLADEX 10.8 mg depots or 6 ZOLADEX 3.6 mg depots in patients with endometriosis. The duration of trial treatment for both groups was 24 weeks (12 weeks in Trial 9393IL/0026 followed by 12 weeks in this trial). The analysis, presented in this report, was performed after all patients completed 12 months post-treatment follow-up. Patients will be followed-up for a further 12 months (ie, 24 months in total) after which time a second analysis will be performed and reported.

Population: Approximately 204 patients with endometriosis who completed Trial 9393IL/0026 were anticipated to be eligible for this trial. Sixty patients in each of the 2 treatment groups were required for analysis of the primary efficacy endpoint.

Key inclusion criteria: completed Trial 9393IL/0026; and willing to employ barrier contraception during the trial treatment period unless bilateral tubal ligation had been performed or if their partner had been sterilised.

Key exclusion criteria: pregnancy or breast feeding; sex hormone therapy (including contraceptives) or danazol within 4 months prior to entry to Trial 9393IL/0027; history of hypersensitivity or other severe reactions to a GnRH agonist or other compounds with related structures; treatment with any systemic drugs e.g., glucocorticosteroids, at doses which suppress the hypothalamic-pituitary adrenal axis, or hormone replacement therapy; exhibiting signs of virilisation due to endocrine disorder or hormone therapy; exposure to investigational drugs other than those provided for Trials 9393IL/0026 and 9393IL/0027; clinically significant biochemical or haematological disorders; metabolic bone disease eg, osteoporosis or Cushing's Disease; bone fractures within the 12 months prior to entry to Trial 9393IL/0026; likelihood of the patient commencing menopause during the time-frame of her intended participation in the trial; history of drug or alcohol abuse; considered by the Investigator to be at risk of transmitting acquired-immune deficiency syndrome, other sexually transmitted diseases, or hepatitis; and any medical condition which, in the opinion of the Investigator, would render the patient unsuitable to enter the trial.

Dosage: Patients continued to receive the trial treatment randomly allocated to them in Trial 9393IL/0026: Patients in Group A received 1 ZOLADEX 10.8 mg depot 12 weeks (84 ± 3 days) after administration of the ZOLADEX 10.8 mg depot received in Trial 9393IL/0026; and patients in Group B received 3 ZOLADEX 3.6 mg depots 4-weekly (ie, 1 depot every 28 ± 3 days) commencing 4 weeks (28 ± 3 days) after administration of the third ZOLADEX 3.6 mg depot received in Trial 9393IL/0026.

Key assessments:

Efficacy: The primary efficacy endpoint of this trial was the proportion of patients with return of ovarian function (ie, a rise in serum oestradiol above 100 pmol/l, or return of menses) within 12 weeks (84 days) of the end of the trial treatment period. The end of the trial treatment period in Trial 9393IL/0027 was defined as 28 days after the final (3rd) injection of ZOLADEX 3.6 mg, and 84 days after the injection of ZOLADEX 10.8 mg. The secondary efficacy endpoints of this trial were time to return of ovarian function, time to return of menses, and symptomatology (ie, subjective assessments of pelvic pain, dysmenorrhoea, dyspareunia and vaginal bleeding). Serum oestradiol was measured at Week 0, then during (Weeks 4 and 8) and at the end of the trial treatment period (Week 12), and then at Weeks 15, 18, 21, 24, 36, 48, 60, 84 and 108 or

until menses returned. Subjective symptomatology assessments were performed at the same visits. In this report, data collected at Weeks 84 and 108 are incomplete and are not presented. Safety: Throughout the trial, safety was assessed by regular review of routine clinical laboratory tests and adverse events. In addition, dual electron X-ray absorptiometry (DEXA) scans of the lumbar spine (L2 to L4) and the femoral neck (the same side at all visits) were obtained at Weeks 12, 36, 60, 84 and 108 to assess the effect of the trial treatment on bone mineral density.

RESULTS

Demography: A total of 270 patients from 33 centres entered Trial 9393IL/0027 between 12 March 1997 and 29 April 1998, inclusive. Of these, 135 received treatment with ZOLADEX 10.8 mg, and 133 received treatment with ZOLADEX 3.6 mg.; the remaining two patients were withdrawn before having received randomised treatment with ZOLADEX 3.6 mg depot. Demographic characteristics were similar between the two treatment groups. Mean ages and ranges were 29 years (18 to 44 years) and 31 years (18 to 41 years) for the 10.8 mg and 3.6-mg groups respectively. One-hundred-and-ninety-three patients completed 12 months follow-up (102 who received ZOLADEX 10.8 mg and 91 who received ZOLADEX 3.6 mg). Protocol deviations were observed in both treatment groups, resulting in reduced populations for the per-protocol analyses of the primary and secondary endpoints. Many of these deviations were a consequence of over-restrictive time windows and definitions originally given in the protocol.
Efficacy: The proportion of patients with return of ovarian function in each treatment group is presented in Table I.

Table I Proportion of patients with return of ovarian function within 84 days of the end of the treatment period

Treatment group	n	Proportion with return of ovarian function within 84 days
ZOLADEX 10.8 mg	30	0.50
ZOLADEX 3.6 mg	49	1.00

	Difference in proportions	95% confidence interval for difference in proportions
10.8 mg - 3.6 mg	- 0.50	-0.68 to -0.32

Since the 95% confidence interval for the difference in proportions was not contained within the interval -0.2 to +0.2, equivalence could not be concluded for this endpoint.
A large number of patients showed episodic ovarian activity during the treatment period which fell within the over-restrictive protocol definition of a return of ovarian function. Consequently, the number of patients in the per-protocol analysis for the primary endpoint was less than that required to achieve the 90% power to demonstrate equivalence using the 95% confidence interval. The secondary efficacy endpoint of time to return of ovarian function could not be analysed due to the numbers of patients with return of ovarian function during the treatment period. An estimate of the median time to return of menses for the two treatment groups gave

135 days for the 10.8-mg group and 32 days for the 3.6-mg group. The hazard ratio was 0.14 and the upper and lower 95% confidence intervals 0.09 and 0.20.

For the symptomatology analysis, both depots were effective in reducing symptoms by the end of the treatment period, with over 90% of patients in both treatment groups reporting an absence of dysmenorrhoea compared with <5% at trial entry. At the same time point, for dyspareunia and pelvic pain, >65% of patients were symptom-free compared with ≤35% and <20%, respectively, at trial entry. Post-treatment, prolonged control of dysmenorrhoea and pelvic pain were seen for patients in the ZOLADEX 10.8-mg group, as shown by the following odds ratios (defined as the estimated odds of not experiencing symptoms in the ZOLADEX 10.8-mg group divided by the odds in the ZOLADEX 3.6-mg group); 9.8 at Week 36 and 2.2 at Week 60 for dysmenorrhoea, and 1.9 and 1.6 for pelvic pain. For control of dyspareunia, the 10.8-mg depot was as effective as the 3.6-mg depot, the odds ratios being 1.3 and 1.1 for Weeks 36 and 60.

Safety: There were no deaths in this trial. Of the 135 patients who received ZOLADEX 10.8 mg, 133 (98.5%) reported at least one adverse event and 22 (16.3%) had at least one serious adverse event, compared with 128 out of 133 (96.2%) patients reporting an adverse event and 15 (11.1%) suffering at least one serious adverse event in the ZOLADEX 3.6-mg group. In general, the incidence and type of adverse events were similar for the two treatment groups, with the most commonly reported events, namely vasodilatation and headache, being recognised pharmacological effects of ZOLADEX. Clinical laboratory data showed that there were no differences between the treatment groups. In the 11 cases where significant haematological abnormalities were identified according to the protocolled definitions, none was considered to be of ongoing clinical significance. For biochemistry, 22 patients (15 in the 10.8-mg group and 7 in the 3.6-mg group) had significant abnormalities according to the protocolled definitions, mainly for alkaline phosphatase, and was a consequence of the increase bone mineral loss in the 10.8-mg group. None was considered to be of ongoing clinical significance.

Loss of bone mineral density (BMD) was seen in both ZOLADEX treatment groups at all time points. However, these were larger in the 10.8 mg treatment group. The mean treatment difference for femoral neck BMD at the end of the treatment period was -0.009 g/cm^2, increasing to -0.017 g/cm^2 at Week 36 and -0.025 g/cm^2 at Week 60. Both treatment groups showed an increase of bone mineral density towards baseline values at Week 60, although this was greater for the 3.6 mg treatment group.