AstraZeneca

9393IL/0028

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Zoladex™

ACTIVE INGREDIENT: goserelin acetate

Trial title (number): A Randomized Clinical Trial Comparing Goserelin Acetate (ZOLADEX™) 3.6-mg Depot and Goserelin Acetate (ZOLADEX) 10.8-mg Depot in Subjects with Prostate Cancer for Whom Hormonal Therapy Is Indicated (9393IL/0028)

Developmental phase: IV
First subject treated:14 April 2000
Last subject completed: 31 January 2002
Approval date: 09 September 2002

OBJECTIVES

The primary objective was to compare the 1-month goserelin acetate 3.6-mg depot with the 3-month goserelin acetate 10.8-mg depot to determine if simultaneous surges of serum testosterone and luteinizing hormone (LH) levels occur with readministration of either depot formulation. (Surges were defined as increases in LH and testosterone from below the lower limit of the age-specific normal range to above the lower limit of the age-specific normal range that occur simultaneously following readministration of the depot.)

The secondary objective was to assess the safety and tolerability of goserelin acetate (3.6-mg and 10.8-mg depots) in the treatment of subjects with advanced prostate cancer.

METHODS

This was a Phase IV, multicenter (26), randomized, open-label, parallel-group trial comparing the 1-month goserelin acetate 3.6-mg depot with the 3-month goserelin acetate 10.8-mg depot in men with advanced prostate cancer. Subjects randomized to the 3.6-mg group visited the clinic at Baseline and at Day 1 (day of injection), Day 4, and Day 8 of each 28-day cycle for a total of 12 cycles (12 injections). Subjects randomized to the 10.8-mg group visited the clinic at Baseline and at Day 1 (day of injection), Day 4, and Day 8 of each 84-day cycle for a total of 4 cycles (4 injections).

Number of Subjects (planned and analyzed): The protocol stated that 250 subjects (ie, 125 subjects per treatment arm and 10 subjects per center) would be enrolled; in actual study conduct 247 subjects were enrolled (129 received the 3.6-mg depot and 118 received the 10.8-mg depot).

Diagnosis and Main Criteria for Inclusion: Male subjects with advanced stages of prostate cancer who had serum LH and serum testosterone levels above the lower limit of the age-specific normal range.

Test Products, Dose, and Mode of Administration; Batch Numbers:
Goserelin acetate, 3.6-mg injection; Formulation Number: F5589; Batch Number/Lot Number: 983117A,993101, 993142, 2000005433, 2000009525 Goserelin acetate 10.8-mg injection; Formulation Number: F6054; Batch Number/Lot Number: 993148, 2000003824, 2000014976, 993023, 2000024267

Duration of Treatment: 48 weeks
3.6-mg depot: 12 injections, given once every 28 days
10.8-mg depot: 4 injections, given once every 84 days

Statistical Methods: Comparisons of the proportions of surge levels of luteinizing hormone and testosterone between treatment groups were analyzed using Fisher's Exact test.
All subjects randomized to a trial treatment were considered in the safety analysis. The safety endpoints of goserelin acetate 10.8-mg and goserelin acetate 3.6-mg depots were summarized by treatment in frequency tables. The occurrence of adverse events were summarized. Laboratory test results were examined in 3 ways: treatment group means, individual values crossing a threshold of significance, and adverse events. The incidences of adverse events were tabulated by treatment and body system using an in-house dictionary based on COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms). During the treatment or follow-up period, each subject was counted only once for each adverse event. Adverse events were summarized by intensity, outcome leading to death, and investigator-determined causality assessment of the relationship of the event to trial treatment. A separate tabulation was done for serious adverse events and deaths.

RESULTS

Demography: A total of 247 male subjects were recruited from 26 centers and randomized to treatment; 129 were given goserelin acetate 3.6-mg depot at 1 month intervals and 118 were given goserelin acetate 10.8-mg depot at 3 month intervals. Demographic characteristics were generally well balanced among the treatment groups. The majority of the subjects were white between 42 and 88 years of age. The most common reason for withdrawal during randomized treatment was the category "other" which included disease progression, exclusionary medications, and study conduct issues.

*Surge Analysis and Safety Results :*Surges were defined in three ways: 1) a simultaneous elevation in testosterone and luteinizing hormone (LH) after depot readministration from below the lower limit of the age-specific normal range to above the lower limit of the age-specific normal range (Group A); 2) an elevation in testosterone (irrespective of LH) after depot readministration from below the lower limit of the age-specific normal range to above the lower limit of the age-specific normal range (Group B); and 3) an elevation in testosterone after depot readministration from below the castrate level to above the castrate level (Group C). Simultaneous surges (Group A) in both treatment groups were rare and did not represent a significant safety problem for either dose of goserelin acetate. There were only two instances of simultaneous surges (both in the 10.8-mg depot group) and neither subject exhibited adverse events at the time of the surge or experienced any flare reaction. Flare reactions are clinical manifestations of a surge, such as increased bone pain, spinal cord compression, urinary outlet obstruction, and hypercalcemia. Testosterone surges (Group B) occurred in two subjects from each treatment group but one of these subjects was not suppressed to the castrate level on Day 1 and is therefore a treatment failure, not a surge. Thirty-four subjects in the 3.6-mg depot group and 20 subjects in the 10.8-mg depot group had surges of questionable clinical significance (Group C). These subjects had castrate levels of testosterone and upon re-injection of study drug developed testosterone levels above the castrate level. However, the levels did not rise to the subjects' age-specific normal range. These observed surges would be of clinical significance if they were associated with flare reactions. However, no associations were found in any of the 54 surge subjects. Thus, these instances of surges are likely of no importance. All subjects were included in the safety population. Overall, goserelin acetate 3.6-mg depot and 10.8-mg depot were well tolerated. The overall incidence of adverse events was similar for both treatment groups (89.1% and 89.0%, respectively), as were the incidence of adverse events leading to withdrawal (5.4% and 5.9%, respectively) and the incidence of serious adverse events (16.3% and 19.5%, respectively). Adverse events were as expected, with adverse events affecting the cardiovascular system such as vasodilatation and hot flashes predominating. Forty-four subjects had serious adverse events during the randomized treatment period (21 goserelin acetate 3.6-mg depot and 23 goserelin acetate 10.8-mg depot). There were 10 deaths resulting from adverse events reported during the

treatment period in this trial: 4 (3.1%) in the goserelin acetate 3.6-mg depot group and 6 (5.1%) in the goserelin acetate 10.8-mg depot group. Two additional deaths resulting from metastatic cancer were reported in the goserelin acetate 3.6-mg depot group during the safety follow-up period. The number and percentage of subjects with adverse events considered by the investigator to be related to treatment were similar in the two treatment groups: 88 (68.2%) in the goserelin acetate 3.6-mg depot group and 74 (62.7%) in the goserelin acetate 10.8-mg depot group.

Reference:

None at this time

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Zoladex™ (goserelin acetate), Healthcare Professionals should view their specific country information.