Study Number: EN3330-302

Title of Study: Phase III, Open-Label, Randomized, Parallel, Active-Control Study to Evaluate Efficacy and Safety of Histrelin Subdermal Implant in Patients With Metastatic Prostate Cancer

Investigator Name and Address:

Publication (reference): None

Study Period (years):		**Phase of Development**: III
Date of First Enrollment:	25-May-2000	
Date Last Patient Completed:	18-Dec-2001	

Objectives:

Primary Objective: To evaluate the efficacy and safety of a 50-mg histrelin acetate subdermal implant compared with Zoladex® 3-Month (10.8 mg goserelin acetate implant) in patients with metastatic prostate cancer.

Methodology: This trial was an open-label, randomized, parallel treatment, active-control multicenter study in adult males with documented metastatic prostate cancer disease who were judged to be candidates for hormone therapy.

Within 21 days prior to implant insertion, all prospective enrollees were entered into a screening period to provide medical history, demographic information, physical examination, laboratory evaluations, 12-lead ECG, bone scan, chest x-ray, liver ultrasound, concomitant medications and procedures, and a physician assessment including pain level and WHO performance scale in order to assess eligibility for the study. Written informed consent was obtained before any procedures were undertaken.

Once inclusion/exclusion criteria were met, baseline evaluations (physical assessment and examination, vital signs and weight, clinical laboratory evaluations, concomitant medications and procedures, adverse events, and a Quality of Life questionnaire) were obtained prior to implant insertion on Day 1 [Visit 1]. All appropriately screened patients were to then receive either histrelin acetate 50-mg or Zoladex® 3-Month 10.8 mg implant based on 1:1 randomization at Day 1 [Visit 1). Patients with implants were evaluated at Week 1 and 2 [Visits 2 and 3] post-insertion for testosterone and PSA concentrations, vital signs, adverse events, and concomitant medications and procedures. The Zoladex® implants were replaced at Weeks 12, 24, 36, and 48 [Visits 6, 9, 12, and 15], while the histrelin acetate implants were replaced at Week 52 [Visit 16], respectively. Patients were followed monthly from Weeks 4 to 60 [Visits 4 to 18] to evaluate testosterone and PSA concentrations, adverse events, concomitant medications and procedures, disease progression, and urine and serum histrelin in the renal/hepatic impairment subgroup. Periodic clinical and subjective assessments were completed for all patients.

Number of Patients (Planned and Analyzed): A total of 135 patients were planned for inclusion into the study. Final enrollment was 59 patients: 33 in the histrelin acetate implant treatment group and 26 in the Zoladex® 3-Month 10.8 mg implant treatment group. Of the 33 patients in the histrelin implant group, 25 completed 52 weeks of the study while 8 discontinued. Twenty-five (25) patients in the Zoladex® group received the first treatment. One patient (10/902) was randomized to the Zoladex® group, but he died before receiving drug.

Diagnosis and Main Criteria for Inclusion: Study participants were men, forty-five (45) years of age or older, with histologically confirmed adenocarcinoma of the prostate, disease staging Ml or an apparent failure of initial definitive therapy suggested by an elevated PSA or rising PSA values. Serum testosterone levels were required to be 150 ng/dL (5.25 nmol/L) or greater at screening. All patients were otherwise expected to be in good health, be able to understand the nature of the study, and be willing to undergo the procedures required by the protocol.

Test Product, Dose and Mode of Administration, Lot Number: Histrelin hydrogel implant, 3 cm x 3.5 mm, containing 50 mg of histrelin acetate; 50 mg surgically placed subdermally into the inner aspect of the upper arm. Lot number: 508B.

Duration of Treatment: 60 weeks

Reference Therapy, Dose and Mode of Administration, Lot Numbers: Zoladex® goserelin implant: D, L-lactic and glycolic acids copolymer impregnated with 10.8 mg of goserelin acetate, injected subcutaneously into the upper abdominal wall. Lot numbers: PM557D, PM559D, IM537C, DM540D, LM543D, IM537C, PM553A, IM536A, PM551B, PM5590, AM516C, IM533D, PI583D, 1278-480, NM851J, 99F11Nl1851J, GGE06HM572B, 00B07V1559B, 00B07Ul559B, 99C08IM536A, 99E06HM572B, 99E06MM572B, 00D13/2P1892C, 99627NM856C, HM585B, NM509D, NM509C, HM583B, LI577A, NM520D, NM508A, NM514B, NM518B, MM520C, AM514A, AM514D, AM518B, NM505A, U1564B, HM575C, 41564B

Criteria for Evaluation:

Efficacy: Primary efficacy was evaluated by the demonstration of the suppression of testosterone as assessed by the proportion of patients whose serum testosterone indicated chemical castration levels (≤50ng/dL [1.75 nmol/L]) at Weeks 4 through 52 [Visits 4 through 16]. Secondary efficacy was assessed by biochemical determination of serum LH, PSA, and PAP. Additional secondary efficacy evaluation criteria included: the WHO Performance Status, Pain Level assessment, the National Prostatic Cancer Project (NPCP) assessment for objective clinical status, PSA status, time to disease progression, and Quality of Life Questionnaires (FACT-P).

Safety: Safety data were evaluated utilizing spontaneously reported adverse events (AEs), vital signs, clinical laboratory results, physical examinations, and ECGs collected at screening, at per-protocol defined times throughout the study, and at the time of final evaluation or premature discontinuation.

To assess the safety of the histrelin acetate implant in patients with renal or hepatic impairment at insertion, or in those patients who may develop renal or hepatic impairment secondary to disease progression, a renal/hepatic impairment subgroup was included in the safety evaluation.

Statistical Methods:

Efficacy: Statistical analyses were provided for the intent-to-treat (ITT) safety population with subset analyses performed based on characterization of metastatic disease for each treatment group and renal and hepatic impairment for the histrelin acetate treatment group. The co-primary efficacy variable, testosterone, recorded at Weeks 4 through 52 [Visits 4 through 16] was used to calculate the proportion of patients attaining castrate levels (≤50ng/dL [1.75 nmol/L]) per treatment group. Ninety-five (95%) confidence intervals (CI) for the proportion of successes were calculated. The number of patients who failed (>50ng/dL at any visit from Weeks 4 to 52) was also summarized per treatment group. Testosterone, LH, PSA, and PAP values were summarized by descriptive statistics at each assessment time and change from baseline was provided for each treatment group. A t-test was utilized to compare the mean change from baseline between the two treatment groups. The objective clinical status utilized the NPCP criteria and the numbers and proportions of patients in each response category were summarized. Differences in the distribution of responses between the treatment groups were tested utilizing a Cochran-Mantel-Haenszel (CMH) test. A similar analysis for PSA was also performed. Summaries were provided for the number of patients meeting efficacy criterion, number of patients with disease progression, physician assessment of patient activity based on the WHO performance scale, patient pain level and quality of life. The difference in time to disease progression between treatment groups was evaluated.

Safety: Vital signs and body weight were summarized per treatment group utilizing descriptive statistics. Clinical laboratory data was summarized and mean change from baseline was evaluated for each treatment group. A t-test was utilized to compare the mean change from baseline between the two

treatment groups at each assessment time. The number of patients with adverse events was summarized by preferred term and body system and further summarized by intensity and relationship to study drug by treatment group. The patients prematurely terminated the study due to drug related adverse events who were summarized. Patients with renal and hepatic impairment were classified by severity and analyzed in respect to adverse events and changes from baseline in renal and liver function laboratory values.

SUMMARY:

Efficacy Results: This study confirms the efficacy and reliability of the LHRH agonist histrelin as equally efficacious as the Zoladex® 3-Month depot injection. Most patients (with the exception of three individual patient visits) achieved chemical castration by Week 4 and maintained testosterone suppression (defined as a serum testosterone level ≤50 ng/dL) through Week 52. Levels of LH and PSA showed the same pattern. The results confirm that the daily dose of histrelin acetate delivered throughout the 52 weeks was sufficient to maintain chemical castration equivalent to repeated depot injections of Zoladex® 3-Month depot.

Safety Results: Patients were in the upper age group and had at least one underlying, longstanding disease for which they were receiving treatment. It was, therefore, to be expected that many patients would report adverse events, have random fluctuations in the biochemical and hematological values, and that a number would have serious adverse events that might result in death. Investigators' reports that identified causal relationships of events to study drugs and underlying disease showed no consistent association or pattern, which suggests that both histrelin acetate and Zoladex® treatment posed no significant risk in these patients.