

Clinical Trial Results Summary
Study EN3330-301

Study Number: EN3330-301	
Title of Study: Phase III, Open-Label Study to Evaluate Efficacy and Safety of Histrelin Subdermal Implant in Patients With Advanced Prostate Cancer (Protocol 301)	
Investigators Name and Address: Twenty-seven (27) study sites in the U.S. and Canada.	
Publication (reference): None	
Study Period (years): Date of First Enrollment: 21-Apr-2000 Date Last Patient Completed: 27-Aug-2003	Phase of Development: III
Objectives: <i>Primary Objective:</i> To evaluate the efficacy and safety of the 50-mg histrelin acetate subdermal implant in patients with advanced prostate cancer.	
<p>Methodology: It was the intent of the original protocol, submitted by a previous sponsor, to evaluate the efficacy and safety of the histrelin acetate subdermal implant versus Lupron-Depot[®]-3 Month. The current sponsor, Valera Pharmaceuticals, Inc. (VPI) (formerly Hydro Med Sciences), assumed responsibility for the study after the initiation of the Phase III trial. In order to develop a product more compatible with the sponsor's clinical development plan, VPI applied for and received FDA acceptance of a modification of the study design in December 2001. The updated study design eliminated the Lupron-Depot[®]-3 Month comparator arm and continued the study as an open-label nonrandomized study to evaluate the efficacy and safety of the histrelin acetate implant. A separate report was prepared for full disclosure practices on the Lupron-Depot[®]-3 month patients who were enrolled in the original protocol.</p> <p>The methodology discussed in this clinical study report is of the modified study design of December 2001: Within 21 days prior to implant insertion, all prospective enrollees were screened to provide medical history, demographic information, physical examination, laboratory evaluations, 12-lead ECG, bone scan, concomitant medications and procedures, prior cancer medications and surgeries, 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.</p> <p>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 [FACT-P]) were obtained prior to implant insertion on Day 1 [Visit 1]. At selected study sites, serum testosterone, LH, and histrelin were drawn prior to and after insertion. This PK/PD subgroup had blood samples obtained before implant insertion and at 5, 15, 30, and 45 minutes and 1, 2, 4, 6, 8, 12, 24, 48, and 96 hours post-insertion including standard and subsequent visits to determine PK parameters.</p> <p>Patients were evaluated at Week 1 and 2 [Visits 2 and 3] post-implant insertion for testosterone and prostate-specific antigen (PSA) concentrations, vital signs, adverse events, and concomitant medications and procedures. The insertion site was inspected by the Investigator with inquiry to the patient regarding the implant and discomfort at the site. Testosterone was determined for all patients. Histrelin and LH concentrations were determined for all patients in the PK/PD subgroup.</p> <p>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. Histrelin, testosterone, and PSA were determined at selected study sites for the PK/PD subgroup. All patients were evaluated for insertion site adverse events and discomfort at the insertion site. LH was analyzed at all visits for PK/PD patients, and periodically for non-PK/PD patients.</p>	

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<p>All active patients were to receive new histrelin acetate implants at Week 52 [Visit 16]. An Acute-on-Chronic (AOC) subgroup had blood samples obtained before implant insertion 48 to 72 hours post-insertion [Visit 16A], at Week 53 [Visit 16B], at Week 56 [Visit 17], and at Week 60 [Visit 18] to determine dynamics of suppression and to observe whether escape from suppression had occurred.</p>
<p>Number of Patients: One hundred thirty-eight (138) patients were enrolled into the study.</p>
<p>Diagnosis and Main Criteria for Inclusion: Study participants were males, forty-five (45) years of age or older, with histologically confirmed adenocarcinoma of the prostate, disease staging III or IV 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 with a life expectancy of at least one year, be able to understand the nature of the study, and be willing to undergo the procedures required by the protocol.</p>
<p>Test Product, Dose and Mode of Administration, Lot Number(s): Histrelin acetate hydrogel implant, 3 cm x 3.5 mm, 50 mg of histrelin acetate, surgically placed subdermally into the inner aspect of the upper arm. Lot numbers: 508A, 508B, 510 and 511</p>
<p>Duration of Treatment: 60 weeks</p>
<p>Reference Therapy, Dose and Mode of Administration, Lot Number(s): None</p>
<p>Criteria for Evaluation:</p> <p>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]) Week 4 through Week 52 [Visits 4 through 16]. Secondary efficacy was assessed by measurement of serum levels of LH, PSA, and prostatic acid phosphatase (PAP). Additional secondary efficacy evaluation criteria included non-clinical assessments: the WHO Performance Status, Pain Level assessment, the National Prostatic Cancer Project (NPCP) assessment for objective clinical status, PSA status, and Quality of Life Questionnaire (FACT-P). An assessment of the dynamics of suppression were obtained utilizing two subgroups, a PK/PD subgroup from Day 1 to Week 52 [Visits 1 to 16] and an AOC subgroup from Weeks 52 to 60 [Visits 16A to 18].</p> <p>Safety: Safety data were evaluated from spontaneously reported adverse events (AEs), vital signs measurements, clinical laboratory results, physical examination results, and ECGs collected at screening, at per-protocol defined times throughout the study, and at the time of final evaluation or premature withdrawal.</p> <p>Tolerability data were evaluated by visual inspection of the insertion site by the Investigator and by active inquiry to the patient regarding the implant and discomfort at the site at all clinical visits. To assess the safety of the histrelin acetate implant in patients with renal or hepatic impairment at baseline or in those patients who may have developed renal or hepatic impairment secondary to disease progression, a renal/hepatic impairment subgroup was included in the safety evaluation.</p>
<p>Statistical Methods:</p> <p>Efficacy:</p> <p>Primary: Statistical analyses were provided for the intent-to-treat (ITT) safety population with subset analyses performed based on cancer stage, age, race, and renal and hepatic impairment. The efficacy variable, testosterone, recorded through Weeks 4 to 52 [Visits 4 through 16] was used to calculate the proportion of patients attaining castrate levels (≤ 50ng/dL [1.75 nmol/L]). 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) and the number of patients with spontaneous expulsions of the histrelin acetate implant were also calculated.</p>

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Secondary: LH, PSA, and PAP values were summarized by descriptive statistics at each assessment time and change from baseline. The objective clinical status utilized the National Prostatic Cancer Project (NPCP) criteria and the numbers and proportions of patients in each response category was summarized. 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.

Safety: Vital signs and body weight, clinical laboratory data, and adverse events were summarized utilizing descriptive statistics. The number of patients prematurely terminating the study due to adverse events and the number of adverse events was 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.

Pharmacokinetics:

PK/PD subgroup: Serum histrelin acetate, serum testosterone, and LH, were summarized by descriptive statistics. Histrelin acetate concentrations for C_{max}, T_{max}, AUC, and C_{pav} were summarized.

Acute-On-Chronic subgroup: Serum testosterone histrelin acetate and LH levels post-insertion Implant #2 were examined utilizing the paired t-test. The presence of an AOC effect (serum testosterone >50ng/dL at 48 hours and/or 7 days post-insertion in a patient with a previous testosterone level ≤50ng/dL) was evaluated by summary of testosterone at Weeks 52, 53, 56, and 60 [Visits 16, 16A, 16B, 17, and 18].

SUMMARY:

Efficacy Results: This study confirms the efficacy and consistency of the LHRH agonist histrelin acetate and the implant delivery device. All patients achieved chemical castration (defined as a serum testosterone level ≤50 ng/dL) by Week 4, and maintained chemical castration through 52 weeks of treatment. Levels of LH and PSA showed the same pattern. Suppression of testosterone and LH acts as a surrogate marker for evaluation of the implant delivery device, complementing the measurement of serum histrelin acetate concentration. The PSA acts as a surrogate marker of progression of disease. The results confirm that the device consistently and reliably delivers histrelin acetate as predicted, over 52 weeks. The daily dose of histrelin acetate delivered throughout the 52 weeks was sufficient to maintain chemical castration at all measurement time points.

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 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 the implant posed no significant risk in these patients.