**Document Approval Date**: February 1st, 2018

**Official Title**: A randomized, open-label, parallel-group, active-control study to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of three doses of Leuprolide Oral Tablets (Ovarest™) in comparison to an intramuscular dose of leuprolide acetate (Lupron Depot® 3.75 mg) in healthy female volunteers.

**NCT number**: NCT02807363

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

## 1. TITLE PAGE

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| **TITLE:** | A randomized, open-label, parallel-group, active-control study to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of three doses of Leuprolide Oral Tablets (Ovarest™) in comparison to an intramuscular dose of leuprolide acetate (Lupron Depot® 3.75 mg) in healthy female volunteers |
| **PROTOCOL NO.** | **LOPDT-ENDO-01** |
| **STUDY DRUGS:** | Treatment A: Leuprolide Oral Tablet (Ovarest™), 4 mg, administered daily (qd) for 28 consecutive days<br>Treatment B: Leuprolide Oral Tablet (Ovarest™), 4 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days<br>Treatment C: Leuprolide Acetate intramuscular (IM) injection (Lupron Depot 3.75 mg) administered for one month of therapy<br>**Treatment D**: Leuprolide Oral Tablet (Ovarest™), 10 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days |
| **PRIMARY INVESTIGATOR:** | [redacted] |
| **SPONSOR** | **Enteris BioPharma, Inc.**<br>83 Fulton Street<br>Boonton, New Jersey 07005<br>Tel.: 973-453-3518<br>Fax: 973-588-5966 |
| **CRO** | inVentiv Health<br>2500 rue Einstein<br>Québec (Québec) G1P 0A2 |
| **DATE OF ORIGINAL** | June 22, 2016 |
| **DATE OF VERSION** | February 1, 2018 |
| **VERSION** | Amendment 03 |

**CONFIDENTIAL**

This document is strictly confidential. It was developed by Enteris BioPharma Inc. and should not be disclosed to any party, with the exception of regulatory agencies and study audit personnel without the consent the Sponsor.

## 1. TABLE OF CONTENTS

## 2. PROTOCOL SIGNATURE SHEET

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. LOPDT-ENDO-01 Amendment 03 for issuance.

**Sponsor signature**:

[redacted]

1 FEB 2018
Date

## 3. INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of background information on the test drug, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB)/ethics committee, I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/ethics committee. I will submit the protocol modifications and/or any informed consent modifications to the Sponsor and the IRB/ethics committee, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (current International Conference on Harmonisation [ICH] guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Scotland revision (2000), notes of clarification added in 2002 and 2004, and the most recent version of the Declaration of Helsinki (October, 2013).

[redacted]

13-FEB-2018
**Date**

## 4. PROTOCOL SYNOPSIS

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| **Title of Study** | A randomized, open-label, parallel-group, active-control study to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of three doses of Leuprolide Oral Tablets (Ovarest™) in comparison to an intramuscular (IM) dose of leuprolide acetate (Lupron Depot 3.75 mg) in healthy female volunteers |
| **Protocol Number** | LOPDT-ENDO-01 |
| **Phase** | 2a |
| **Number of Study Centers** | One or two sites, Phase I clinical unit(s) in the North America (US and/or Canada) |
| **Investigational Product, Dosage, and Route of Administration** | Leuprolide Oral Tablets (Ovarest™) utilizing Enteris' Oral Peptide Delivery Technology. The Ovarest™ dosing regimens are selected based upon the results of the PK study LOPD-PH1-01.<br>The Ovarest™ dosing regimens are:<br>**Treatment "A"**: Leuprolide Oral Tablet (Ovarest™), 4 mg, administered daily (qd) for 28 consecutive days<br>**Treatment "B"**: Leuprolide Oral Tablet (Ovarest™), 4 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days<br>**Treatment "D"**: Leuprolide Oral Tablet (Ovarest™), 10 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days |
| **Control Drug (Reference Product)** | **Treatment C**: Leuprolide Acetate intramuscular (IM) injection (Lupron Depot 3.75 mg) administered for one month of therapy |
| **Study Design** | Randomized, Open-Label, Parallel-Group, Active-Control Study for Treatment "A", Treatment "B" and "Treatment "C". Treatment "D" will be evaluated in a Non-Randomized, Open-Label, Single-Group Study design setting. |
| **Study Objectives** | The objectives are to determine the safety, PK profile, and PD effects of the three doses of Ovarest™ in healthy female volunteers in comparison to a marketed dose of leuprolide acetate administered IM (Lupron Depot 3.75 mg). Note: For the third Ovarest dose (Treatment "D"), a complete PK profile will not be evaluated.<br>This trial will serve as a bridging PK/PD study between the 4 mg Leuprolide Oral Tablet administered over 28 days as qd or bid regimens, the 10 mg Leuprolide Oral Tablet administered over 28 days as a bid regimen, and a marketed IM injection of leuprolide acetate (Lupron Depot 3.75 mg) designed for one month of therapy. This trial will also be a bridging study to historical |

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| | PK/PD data for Lupron Depot® 3.75-mg and Lupron Depot® 11.25-mg (3-month) formulations.<br><br>The most important objective of this study is to provide adequate PD assessments to support development of the Leuprolide Oral Tablet with estradiol ($E_2$) suppression similar to those reported for the Lupron Depot® and other $E_2$-inhibiting hormonal therapies. Another reason for this trial is to describe the PK/PD dose-proportionality of the 4-mg and 10-mg Leuprolide Oral Tablet administered as qd and/or bid regimens.<br><br>Thus, the **Primary Study Objectives** are:<br><br>1) To determine the safety and to provide comparative evaluation of the PK and PD profiles of the 4-mg Leuprolide Oral Tablets following qd and bid administration and the 10-mg Leuprolide Oral Tablets following bid administration in healthy, premenopausal female volunteers over 28 days *vs* a marketed formulation of leuprolide acetate administered IM for one month of therapy.<br><br>2) To evaluate the PK properties of Leuprolide Oral Tablets after multiple dosing (*ie*, 28 days of dosing)<br><br>3) To assess the PK/PD dose-proportionality of the Leuprolide Oral Tablets administered as 4 mg qd, 4 mg bid and 10 mg bid dosing regimens<br><br>4) To evaluate the PK and/or PD properties of the Leuprolide Oral Tablets (*eg*, $E_2$ suppression rates) *vs* other hormonal therapies for the treatment of reproductive disorders, including endometriosis.<br><br>**Secondary Study Objective**:<br><br>To evaluate safety and tolerability of the long-term administration of leuprolide in healthy female volunteers. |
| **Number of Subjects** | Up to thirty-two (32) subjects (12 subjects in each of the two Ovarest™ treatment groups and 8 subjects in the Lupron Depot group) were to be enrolled in the study. Eligible subjects were to be randomly assigned to one of three treatment groups in a Treatment“A”:Treatment“B”:Treatment“C” ratio of 3:3:2. The randomization schedule was prepared prior to the study and will be balanced by using permuted blocks. The randomization schedule could be further stratified by the study site, if necessary.<br><br>Twenty-three subjects were initially enrolled in this study (9 subjects in each of Ovarest treatment groups and 5 subjects in the Lupron Depot group). At the time of the current protocol Amendment, all initially enrolled subjects had completed the study, except for one subject who was withdrawn on post–dose Day 1 (due to vomiting). After interim PK and safety evaluations, it was decided not to enroll any new subjects in Treatment Groups “A”, “B” and “C”. Instead, up to twelve (12) subjects will be enrolled in a new Treatment Group D” (Leuprolide Oral |

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| | Tablet, Ovarest, 10 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days). |
| **Dose Justification of Treatment "D"** | Pharmacodynamic data, specifically the suppression of estradiol, showed that both the 4 mg QD and BID regimens (Treatments "A" and "B") fell substantially short of the suppression demonstrated by Lupron Depot®. Interim safety results from this study were also evaluated. Overall, Leuprolide Oral Tablets within a 4 mg to 8 mg daily dosing range were safe and reasonably well tolerated. The study results support a further dose increase in planned clinical evaluations.<br><br>Leuprolide Oral Tablets were shown to be safe and well tolerated in the Phase 1 study LOPDT-PH1-01, at doses of 1 and 4 mg in normal healthy volunteers. The absolute bioavailability was 2.2% and 3.0% for the 1 and 4 mg doses, respectively, compared to subcutaneous injection. The 4-mg Leuprolide Oral Tablet generated an overall drug exposure (a 24-hour AUC=19338 h*pg/mL) that was less than 12% of the drug exposure (163021 h*pg/mL) reported for a marketed 1-mg SC injection. A projected AUC for the 10 mg tablet administered twice daily (Treatment "D") will be less than 60% of the 1-mg SC drug exposure. Projected Cmax of Treatment "D" will also be lower than Cmax reported for the 1-mg SC injection. These estimates clearly support the safety of the 10 mg tablet administered twice daily (Treatment "D").<br><br>There is a further safety margin for the Treatment "D" dose of 10 mg bid: the Lupron Depot® 3.75 mg label contains the statement, "In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose." Given the low bioavailability of the oral dose, about 3%, a substantial safety margin is assured. |
| **Inclusion Criteria** | Subjects enrolled in this study will be members of the community at large. The recruitment advertisements may use various media types (*eg*, radio, newspaper). Subjects must meet all of the following criteria to be included in the study:<br><br>1) Healthy premenopausal female volunteers, aged 18 to 49 years<br><br>2) Body mass index (BMI) ≥18 and ≤32 kg/m$^2$, and weight ≥110 lb (≈50 kg)<br><br>3) Regular menstrual cycles with a usual length ranging from 21 days to 35 days. If subject has recently used hormonal birth control, historical data prior to use will be used to determine qualification and must also meet this criterion.<br><br>4) If of childbearing potential and sexually active with a risk of pregnancy, willing to use one of the following acceptable methods of contraception throughout the study and for at least 30 days after the last drug administration:<br><br>a) intrauterine contraceptive device without hormone release system placed at least 4 weeks prior to the first study drug administration with |

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| | simultaneous use of condom for the male partner<br>b) simultaneous use of diaphragm with intravaginally applied spermicide and condom for the male partner starting at least 14 days prior to drug administration<br>c) sterile male partner (vasectomized for at least 6 months)<br>d) Note: Surgically sterile subjects who have had tubal ligation are considered of non-childbearing potential and are not required to use contraception<br>5) Willing to refrain from excessive use of alcohol during the entire study and willing to refrain from use of alcohol 24 hours prior to any PK blood draw taken during the study<br>6) Willing to refrain from use of prescription medications, over-the-counter medications and natural health products during the entire study<br>7) Willing and capable to give informed consent to participate in study |
| **Exclusion Criteria** | Subjects to whom any of the following applies will be excluded from the study:<br>1) Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, similar nonapeptides or any of the excipients in LUPRON DEPOT. ***Note: This is a contraindication from the Lupron Depot label.***<br>2) Undiagnosed abnormal vaginal bleeding. ***Note: This is a contraindication from the Lupron Depot label.***<br>3) Known or suspected pregnancy, or subjects who are considering becoming pregnant prior to the conclusion of this study. ***Note: LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug.*** *LUPRON DEPOT may cause fetal harm when administered to a pregnant woman…. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.*<br>4) Breastfeeding or within 2 months after stopping breastfeeding (relative to the screening visit). ***Note: Use of LUPRON DEPOT is contraindicated in women who are breastfeeding.***<br>*5)* Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.***<br>**6)** Markedly impaired liver function or liver disease. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with markedly impaired liver function or liver*** |

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| | ***disease.*** |
| | 7) Known or suspected carcinoma of the breast. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with known or suspected carcinoma of the breast.*** |
| | 8) Status postpartum or postabortion within a period of 2 months prior to the screening visit |
| | 9) A cervical cytology smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low grade squamous intraepithelial lesions or greater (Pap smear results within last 12 months are acceptable if properly documented) |
| | 10) Use of any tobacco products (including electronic cigarettes) in the 3 months preceding the screening visit or positive urine cotinine test at screening |
| | 11) History of significant alcohol or drug abuse within one year prior to the screening visit |
| | 12) Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mm Hg, diastolic blood pressure lower than 50 or over 90 mm Hg, or heart rate less than 50 or over 100 bpm) at screening |
| | 13) Any clinically significant history or presence of neurologic, endocrinologic, pulmonary, hematologic, immunologic, or metabolic disease |
| | 14) History of severe respiratory depression or pulmonary insufficiency |
| | 15) Diabetes mellitus requiring insulin |
| | 16) History of headaches with focal neurological symptoms |
| | 17) Uncontrolled thyroid disorder |
| | 18) Sickle cell anemia |
| | 19) Current or history of clinically significant depression in the last year |
| | 20) Known disturbance of lipid metabolism |
| | 21) Hepatic adenoma or carcinoma |
| | 22) Known or suspected endometrial carcinoma or estrogen-dependent neoplasia |
| | 23) Clinically significant history or presence of any gastrointestinal pathology (*eg*, chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (*eg*, diarrhea, vomiting) or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug |
| | 24) Difficulty in swallowing study medication |
| | 25) Any food allergy, intolerance, restriction or special diet that, in the opinion of |

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| | the Investigator, could contraindicate the subject's participation in this study<br>26) Positive test for hepatitis B, hepatitis C, or human immunodeficiency virus at screening<br>27) Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit<br>28) Administration of any biologics within 90 days prior to the screening visit<br>29) Clinically significant finding on the electrocardiogram (ECG) suggesting participation in the study could pose a risk to the subject<br>30) A depot injection or an implant of any drug within 6 months prior to the screening visit<br>31) Use of oral contraceptives or other sex steroid hormones within 3 months prior to the screening visit<br>32) Any clinically significant physical or gynecological abnormality at the screening visit<br>33) Any clinically significant abnormal laboratory test result at the screening visit<br>34) Hemoglobin <115 g/L and/or hematocrit <0.32 L/L<br>35) Use of prescription medication within 14 days prior to the first administration of study medication or over-the-counter products (including natural health products; *eg*, food supplements, vitamins, herbal supplements) within 7 days prior to the first administration of study medication, except for topical products without significant systemic absorption<br>36) Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing<br>37) Deemed by the Investigator to have questionable ability to comply with the study protocol<br>38) History of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors;<br>39) Significant risk factors for decreased bone mineral content and/or bone mass, such as family history (in a first degree relative) of osteoporosis, personal history of chronic use of corticosteroids or anticonvulsants. |
| **Treatment and Duration** | Approximately one month of dosing ( either 28 consecutive days of daily oral dosing, or a single IM injection on day 1) and approximately 1 month (28 days) of post-dosing PK/PD evaluations. The total study duration, from screening to the final study visit will be up to approximately 3.5 months. |
| **Study** | Subjects meeting the eligibility criteria will be randomized to receive one of the two doses of Ovarest™ for 28 days or a monthly IM dose of Lupron |

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| **Methodology and Evaluations** | Depot. Newly enrolled subjects will receive the third Ovarest dose (Treatment "D") that will be administered in the same fashion as Treatment "B". Assessments of the PD profile of treatment "D" will also mimic evaluations of Treatment "B". However, unlike other Ovarest groups, Treatment "D" will not have comprehensive assessments of the PK profile. The subjects that have already participated in this study may be invited to receive Treatment "D" if they are eligible per the study inclusion and exclusion criteria. The subjects in Treatments "A", "B", and "C" will start dosing (Treatment Day 1) on either Day 1 up to Day 4 of their menstrual cycle, or within the last 11 days of their menstrual cycle. (Note: onset of menstrual period is considered as day 1 of the menstrual cycle.) Please see Appendix G for a table of acceptable days for initiation of dosing in relation to cycle length. Permissible time windows for the start of the dosing will be determined based on the onset of menstrual period prior to the screening visit or a projected start of the next menstrual cycle. The projected start of the next menstrual cycle will be based on the date of onset of menses during the screening period and the typical length of the normal menstrual cycle for each subject as reported by each subject during the screening visit. Subjects enrolled to the third oral dose (Treatment "D") will have a dosing initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began. The 4-mg qd oral dose will be administered once daily, in the morning, on an empty stomach; the 4-mg and 10-mg bid oral doses will be administered twice daily, in the morning and in the evening, 12 hours apart and on an empty stomach. Note: On an empty stomach means that the oral doses are administered at least 2 hours before or at least 2 hours after the meal. Oral administration instructions are applicable to both on-site and at-home dosing. For at-home dosing, each subject will take the oral dose with approximately 240 mL of water. Subjects randomized to the two oral doses (Treatments "A" and "B") will have twenty-four (24) serial serum samples drawn on Treatment Days 1 and 28 immediately prior to dosing (0 time), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 20, and 24 hours following oral dosing. For the IM injection (Treatment "C"), serial serum samples will also be drawn on Treatment Day 1, prior to dosing (0 time), at 0.5, 1, 2, 6, 12, 18, and 24 hours postdosing. Blood samples for the IM injection will also be taken in the morning on Day 29. Additional blood samples for all subjects will be taken in the morning (in the oral groups, just prior to dosing) on Treatment Days 8, 15, and 22. Samples will be appropriately stored until they can be assayed for leuprolide and hormonal levels. Serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and plasma concentrations of $E_2$ and progesterone will be measured (immediately prior to dosing) on Treatment Days 1, 8, 15, 22, and in the morning of Day 29.<br><br>Subjects enrolled to the third oral dose (Treatment "D") will have a dosing |

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| | initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began. During the visit, just prior to the first dosing, baseline blood samples will be taken for leuprolide and hormonal levels. The same blood draws will be performed immediately prior to the first dose of the day on Treatment Days 8, 15, 22, and in the morning of Day 29.<br><br>On Day 29, after the 24-hour blood draws in the oral groups (Treatments "A", and "B") and after the PK/PD blood draws in the Treatment "D" and the IM injection group (Treatment "C"), physical, gynecological, and safety laboratory evaluations will be performed.<br><br>Note: Throughout the text, Treatment Day 29 may be used interchangeably with Postdosing Day 1.<br><br>Four follow-up visits will be scheduled at 7, 14, 21 and 28 days after the last dose (Treatments "A", "B", and "D") or the last day of the 28-day dosing cycle (Treatment "C"). During each follow-up visit, blood samples will be drawn to assess leuprolide (via a single blood draw) and LH, FSH, $E_2$, and progesterone concentrations. During each follow-up visit, subjects will be asked about onset (or absence) of menstrual period.<br><br>Safety laboratory evaluations will also be performed during the 28-day postdosing visit. The 28-day postdosing visit will be considered the Final Study Visit. In addition, to the PK/PD and safety laboratory assessments, ECG, physical and gynecological examinations will also be performed.<br><br>A total of 55 PK blood samples will be taken from subjects in the two oral groups (Treatments "A" and "B") for the evaluation of the leuprolide serum concentrations. A total of 11 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The blood volume for each PK sample is assumed to be approximately 3 mL for leuprolide analysis, and the volume for each PD sample is assumed to be approximately 16 mL (10 mL for progesterone and estradiol analysis, and 6 mL for FSH and LH analysis). The total amount of blood volume for all PK and PD draws is 341 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn should not exceed 407 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.<br><br>In the Treatment group "D" a total number of samples for PK evaluations will be reduced by 46 when compared to other oral groups. The total amount of |

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| | blood drawn will be reduced by 138 mL (46 x 3 mL) and should not exceed 269 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.<br><br>A total of 16 PK blood samples will be taken from subjects in the Lupron group (Treatment "C") for the evaluation of the leuprolide serum concentrations. A total of 10 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The total amount of blood volume for all PK and PD draws is 208 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn in the Lupron group should not exceed 274 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.<br><br>Serum concentrations of leuprolide and concentrations of PD parameters will be determined via validated bioanalytical methods. Sensitivity and specificity of the employed bioanalytical methods will be described in the study report.<br><br>During both the 28-day dosing period and the post-dosing 28-day follow-up, subjects will record vaginal (menstrual) bleeding on diary cards. |
| **Pharmacokinetic (PK) Parameters** | The following PK parameters will be evaluated for each subject for each evaluation period (*ie*, Treatment Days 1 and 28 for the two oral groups (Treatments "A" and "B") and day 1 for the Lupron Depot group):<br>- Maximum concentration level ($C_{max}$);<br>- Time to maximum concentration level ($T_{max}$);<br>- Area under the concentration versus time curve from 0 hours to 24 hours ($AUC_{0-24}$)<br>- Area under the concentration versus time curve from 0 hours to last available observation ($AUC_{0-t}$).<br>- Area under the concentration versus time curve from 0 hours to infinity ($AUC_{0-inf}$).<br><br>In addition, in the two oral groups (Treatments "A" and "B") steady-state concentration levels (Css) will be calculated at the end of the fourth treatment week (Days 28-29) as the 24-hour AUCs divided by the duration of the dosing interval. This parameter will be considered as the primary PK endpoint for Treatments "A" and "B." A comparable primary endpoint for the Lupron group (Treatment "C") will be an average concentration during the fourth treatment week (calculated as a mean of leuprolide concentration levels on Days 22 and 29).<br><br>Other PK parameters may be calculated if necessary. |

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| | Summaries of the leuprolide concentrations will also be reported for each follow-up visit. |
| **Pharmaco-dynamic (PD) Parameters** | As noted earlier, PD assessments include LH, FSH, $E_2$, and progesterone.<br><br>Blood draws for the PD assessments will be performed immediately prior to dosing on Treatment Days 1, 8, 15, 22, and Postdosing Day 1.<br><br>Additional PD assessments will be performed during the follow-up visits (postdosing Days 7, 14, 21 and 28).<br><br>The primary PD metric - suppression of $E_2$ level - will be assessed at each on-treatment evaluation timepoint. Treatment Day 22 and Treatment Day 28 evaluations (separately and combined) will be considered as most important. In addition to a primary $E_2$ suppression threshold ($E_2 \leq$ 40pg/mL), a suppression of $E_2$ below 20 pg/mL may also be assessed, if considered necessary. The suppression of ovulation (as evidenced by progesterone levels <3 ng/mL) will be evaluated with Treatment Day 22 and Postdosing Day 1 assessments positioned as primary.<br><br>Similar summaries will be provided for the follow-up visits (postdosing Days 7, 14, 21, and 28). In addition, time to return to prestudy baseline hormonal levels could be estimated.<br><br>Number of vaginal (menstrual) bleeding days will be summarized by treatment group for 28 days of therapy and for 28 days of poststudy follow-up. The subject incidence of the onset of menstrual period after completion of therapy will be reported for each treatment group.<br><br>Summaries of PD metrics may be further stratified by the cycle period (days) of the start of dosing. |
| **Safety Evaluations and Adverse Events** | Safety evaluations will be based on the discontinuations due to treatment-emergent adverse events (TEAEs), changes from screening to last assessment (poststudy) in physical and gynecological examinations, clinical laboratory test results (hematology, serum chemistry, and urinalysis), treatment-induced changes in vital signs, and by the incidence and severity of TEAEs reported. TEAEs will be reported for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period). Clinically notable events (including possible flare-up symptoms) may also be recorded on diary cards. |
| **Statistical Methods** | The primary statistical analyses of PK data (Treatments "A" and "B" only) will be conducted on the population of subjects completing 28 days of dosing. Supporting evaluations will be performed for the cohort of subjects who received |

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| | at least one dose of study medication and provided any PK data.<br><br>Similarly, the primary statistical analyses of PD data (all Treatment groups) will be conducted on the population of subjects completing 28 days of dosing. Supporting evaluations will be performed for the cohort of subjects who received at least one dose of study medication and provided any PD data.<br><br>The safety analysis will be performed on all subjects who received at least one dose of study medication.<br><br>Incidence of subjects with suppressed $E_2$ levels will be reported for each study period by treatment group. The incidence of subjects with suppressed $E_2$ levels for the fourth treatment week (Day 22 and Day 29 combined) will be considered as a primary efficacy endpoint. The incidence of suppressed ovulation during the same period will also be reported. The FSH, LH, $E_2$ and progesterone levels will be reported by treatment group for each evaluation period by using summary statistics. Changes in these parameters from prestudy baseline will also be summarized by treatment group.<br><br>The summaries will be provided for the PK parameters with a focus on steady-state concentration levels. PD and PK parameters will be graphed by treatment group for each evaluation period. Correlations between leuprolide concentration levels and PD parameters will be assessed.<br><br>Safety endpoints, study discontinuation information, changes in the physical and gynecological examination findings, and treatment-emergent changes in vital signs and clinical laboratory test results will be summarized. The subject incidence of TEAEs will be reported by the treatment received.<br><br>A detailed Statistical Analysis Plan will be developed prior to the database lock. |
| **Sample Size** | The sample size for this study is not based on the statistical power considerations. This sample size is considered as adequate for a pilot PK/PD "proof-of-concept" study. Since a formal proof of the PK bioequivalence across the treatment arms and/or formal across-treatment statistical comparisons of the PD endpoints are not objectives of this proof-of-concept study, the sample size is not based on the power considerations. With the proposed sample size, we expect reliable estimates of the PK and PD parameters for leuprolide oral tablets and a general validation of related historical data for Lupron Depot therapy. The safety and tolerability assessments of the qd and bid regimens of the 4-mg oral tablet and bid regimen of the 10-mg oral tablet should also be robust enough to support the dosing selection and instructions in subsequent clinical studies. |
| **Manufacturer of the Investigational Product** | Enteris BioPharma Inc. |

## 5. BACKGROUND

Enteris BioPharma has developed a proprietary Oral Peptide Delivery Technology to enable, for the first time, the oral administration of the widely-prescribed gonadotropin-releasing hormone agonist leuprolide, a synthetic nonapeptide.

Various formulations of leuprolide at several different dose levels have been previously approved by the FDA for treatment of prostate cancer, endometriosis, uterine fibroids, and central precocious puberty. Specifically, approval of leuprolide for the treatment of endometriosis has been granted for both 3.75 mg q 1 month and 11.25 mg q 3 months as intramuscular (IM) injections (Lupron Depot® and Lupaneta®, the latter including co-packaging of leuprolide with daily oral norethindrone acetate 5 mg).

Enteris now develops a daily oral form of leuprolide (Leuprolide Oral Tablet) for the treatment of endometriosis. The prospect of delivering this drug orally would allow the elimination of IM injections associated with disturbing side effects. In addition, an oral route of delivery may offer a number of other potential clinical benefits (*eg*, a possibility of immediate termination of therapy for medical or any other reasons).

The name of the product (Leuprolide Oral Tablet) contains the name of the active moiety (Leuprolide), and not the name of the salt (Leuprolide Acetate), as stipulated by the USP Salt Policy and FDA Guidance for Industry titled, "Naming of Drug Products Containing Salt Drug Substances." The strength is also expressed in terms of the active moiety (e.g., "4 mg Leuprolide Oral Tablets") rather than the salt strength equivalent (e.g., "4.46 mg Leuprolide Acetate Oral Tablets).

Because of the well-documented pharmacology, clinical efficacy and safety of leuprolide for this and other indications, the clinical development of this new oral dosage form will be ultimately linked to pharmacokinetic (PK) and pharmacodynamic (PD) properties of marketed leuprolide formulations, including but not limited to IM depot form ("Lupron Depot") which will serve as reference product(s) in the Enteris BioPharma' 505(b)(2) NDA. Particularly, the PK exposure and safety profile of Leuprolide Oral Tablets will be evaluated against the marketed 1-mg subcutaneous (SC) injection. Extensive nonclinical safety data, and clinical safety and efficacy data exist from publicly available sources.

Leuprolide Oral Tablets were shown to be safe and well tolerated in the Phase 1 study LOPDT-PH1-01, at doses of 1 and 4 mg in normal healthy volunteers. The absolute bioavailability was 2.2% and 3.0% for the 1 and 4 mg doses, respectively, compared to subcutaneous injection. The 4-mg Leuprolide Oral Tablet generated an overall drug exposure (a 24-hour AUC=19338 h*pg/mL) that was less than 12% of the drug exposure (163021 h*pg/mL) reported for a marketed 1-mg SC injection. A projected AUC for the 10 mg tablet administered twice daily (Treatment "D") will be less than 60% of the 1-mg SC drug exposure. Projected Cmax of Treatment "D" will also be lower than Cmax reported for the 1-mg SC injection. These estimates clearly support the safety of the 10 mg tablet administered twice daily (Treatment "D").

Following the conclusion of LOPDT-PH1-01, Leuprolide Oral Tablets were reformulated in an effort to increase bioavailability. Reformulated tablets were administered to beagle dogs and the bioavailability was compared to the 4 mg dose from LOPDT-PH1-01. An increase in bioavailability was seen, from 2.2% for the Phase 1 tablet to 7.3% for the reformulated tablet. The reformulated 4 mg tablet (LEU-

012-17002) was then tested in this study, with 28 days of dosing in QD and BID regimens (Treatments "A" and "B", respectively), and Lupron Depot 3.75 mg as an active comparator (Treatment "C"). Interim PK/PD results from this study were recently evaluated, which showed that the bioavailability of the reformulated tablet, rather than increase as predicted by testing in the dog, actually decreased to approximately 1.5%. Pharmacodynamic data, specifically the suppression of estradiol, showed that both the 4 mg QD and BID regimens fell substantially short of the suppression demonstrated by Lupron Depot®. Interim safety results from this study were also evaluated. Overall, Leuprolide Oral Tablets within a 4 mg to 8 mg daily dosing range were safe and reasonably well tolerated. The study results support a further dose increase in planned clinical evaluations.

This protocol amendment include a fourth arm, which will be a 10 mg Leuprolide Oral Tablet administered BID for 28 days (Treatment "D"). As with the previous arms of the study, PD markers will be evaluated weekly during the 28 days of dosing and for a 28 day wash out period. The tablet formulation will revert to the more successful formulation used in the Phase 1 study, where the bioavailability was 3.0%. The amount of leuprolide projected to be absorbed into the circulation is 0.6 mg per day (3% of 20 mg). This is roughly equivalent to the 0.5 mg per day delivered by daily subcutaneous injection that was effective in treating uterine fibroids, and is approximately 60% of the 1 mg approved SC dose administered in the Phase 1 study. There is a further safety margin for the Treatment "D" dose of 10 mg bid: the Lupron Depot® 3.75 mg label contains the statement, "In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose." Given the low bioavailability of the oral dose, about 3%, a substantial safety margin is assured.

The comparative PK/PD evaluations will form important bridges between different routes of leuprolide administration using both the company's proprietary data and relevant published findings.

Additional information on Leuprolide Oral Tablet can be found in the Investigator's Brochure.

## 6. STUDY OBJECTIVES

The objectives are to determine the safety, PK profile, and PD effects of the three doses of Ovarest™ in healthy female volunteers in comparison to a marketed dose of leuprolide acetate administered IM (Lupron Depot 3.75 mg). Note: For the third Ovarest dose (Treatment "D"), a complete PK profile will not be evaluated.

This trial will serve as a bridging PK/PD study between the 4 mg Leuprolide Oral Tablet administered over 28 days as qd or bid regimens and the 10 mg Leuprolide Oral Tablet administered over 28 days as a bid regimen and a marketed IM injection of leuprolide acetate (Lupron Depot 3.75 mg) designed for one month of therapy. This trial will also be a bridging study to historical PK/PD data for Lupron Depot® 3.75 mg and Lupron Depot® 11.25 mg (3-month) formulations.

The most important objective of this study is to provide adequate PD assessments to support development of the Leuprolide Oral Tablet with $E_2$ suppression similar to those reported for Lupron Depot® and other $E_2$-inhibiting hormonal therapies. Another reason for this trial is to describe the PK/PD dose-proportionality of the 4-mg and 10-mg Leuprolide Oral Tablet administered as qd and/or bid regimens.

Thus, the **Primary Study Objectives** are:

5) To determine the safety and to provide comparative evaluation of the PK and PD profiles of the 4 mg Leuprolide Oral Tablets in healthy, premenopausal female volunteers following qd and bid administration and the 10-mg Leuprolide Oral Tablets following bid administration in healthy, premenopausal female volunteers over 28 days *vs* a marketed formulation of leuprolide acetate administered IM for one month of therapy

1) To evaluate the PK properties of Leuprolide Oral Tablets after multiple dosing (*ie*, 28 days of dosing)

2) To assess the PK/PD dose-proportionality of the Leuprolide Oral Tablets administered as 4 mg qd, 4 mg bid and 10 mg bid dosing regimens

3) To evaluate the PK and/or PD properties of the Leuprolide Oral Tablets (*eg*, $E_2$ suppression rates) *vs* other hormonal therapies for the treatment of reproductive disorders, including endometriosis

**Secondary Study Objective**:

To evaluate safety and tolerability of the long-term administration of leuprolide in healthy female volunteers.

## 7. STUDY DESIGN

### 7.1 Overall Study Design and Plan – Description

This study will evaluate the safety, PK profile and PD effects of the three Ovarest™ dosing regimens: Leuprolide Oral Tablet, 4 mg, administered qd for 28 consecutive days (Treatment "A"), Leuprolide Oral Tablet, 4 mg, administered bid for 28 consecutive days (Treatment "B"), and Leuprolide Oral Tablet, 10 mg, administered bid for 28 consecutive days (Treatment "D"), in comparison to leuprolide acetate administered IM, Lupron Depot 3.75 mg (Treatment "C").

The study was originally designed as a randomized, open-label, parallel-group active-control trial. Up to thirty-two (32) subjects (12 subjects in each Ovarest™ treatment group and 8 subjects in the Lupron Depot group) were to be randomly assigned to the study drug in a Treatment "A":Treatment"B":Treatment"C" ratio of 3:3:2. The randomization schedule was to be balanced by using permuted blocks. The randomization schedule could be further stratified by the study site, if necessary.

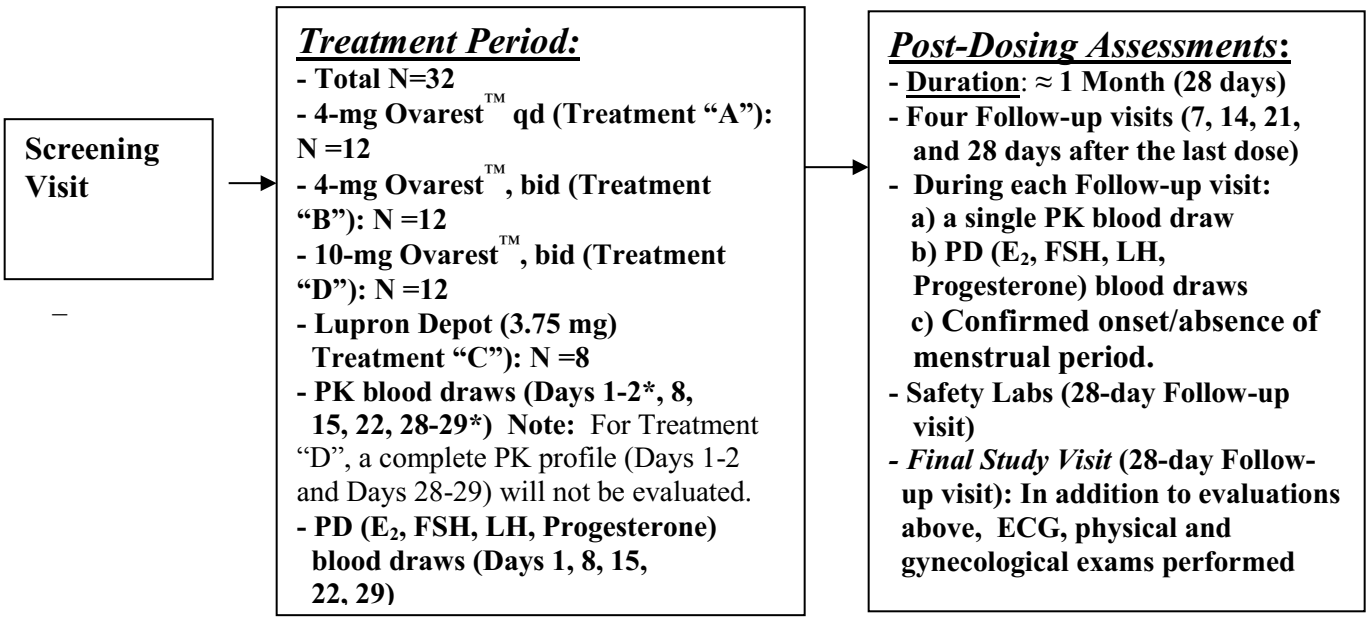
Twenty-three subjects were initially enrolled in this study (9 subjects in each of Ovarest treatment groups and 5 subjects in the Lupron Depot group). At the time of the current protocol Amendment, all initially enrolled subjects had completed the study, except for one subject who was withdrawn on post–dose Day 1 (due to vomiting). After interim PK and safety evaluations, it was decided not to enroll any new subjects in Treatment Groups "A", "B" and "C". Instead, up to twelve (12) subjects will be enrolled in a new Treatment Group D" (Leuprolide Oral Tablet, Ovarest, 10 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days).

The study consists of two major periods: approximately one month of dosing ( either 28 consecutive days of daily oral dosing, or a single IM injection on Treatment Day 1) and approximately 1 month (28

days) of postdosing PK/PD evaluations. The total study duration from screening to the final study visit will be up to approximately 3.5 months.

Study design schematic is displayed in Figure 1 below. A detailed "Times and Events Schedule" is presented in APPENDIX B.

**Figure 1 Study Design Schematic**




Subjects meeting the eligibility criteria will be randomized to receive one of the two doses of Ovarest™ for 28 days or a monthly IM dose of Lupron Depot. Newly enrolled subjects will receive the third Ovarest dose (Treatment "D") that will be administered in the same fashion as Treatment "B". Assessments of the PD profile of treatment "D" will also mimic evaluations of Treatment "B". However, unlike other Ovarest groups, Treatment "D" will not have comprehensive assessments of the PK profile. The subjects that have already participated in this study may be invited to receive Treatment "D" if they are eligible per the study inclusion and exclusion criteria The subjects in Treatments "A", "B", and "C" will start dosing (Treatment Day 1) on either days 1-4 or days 18-28 of their menstrual cycle. (Note: onset of menstrual period is considered as day 1 of the menstrual cycle.) Permissible time windows for the start of the dosing will be determined based on the onset of menstrual period prior to the screening visit or a projected start of the next menstrual cycle. The projected start of the next menstrual cycle will be based on the date of onset of menses during the screening period and the typical length of the normal menstrual cycle for each subject as reported by each subject during the screening visit. Subjects enrolled to the third oral dose (Treatment "D") will have a dosing initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began. The 4-mg qd oral dose will be administered once daily, in the morning, on an empty stomach; the 4-mg and 10-mg bid oral doses will be administered twice daily, in the morning and in the evening, 12 hours apart and on an

empty stomach. Note: On an empty stomach means that the oral doses are administered at least 2 hours before and at least 2 hours after the meal. For clarity, all oral doses have to be taken on an empty stomach except for the morning doses of Days 1 and 28, for which the fasting period is -10h to +4h. Subjects randomized to the two oral doses (Treatments "A" and "B") will have twenty-four (24) serial serum samples drawn on Treatment Days 1 and 28 immediately prior to dosing (0 time), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 20, and 24 hours following oral dosing. For Treatment "B", the PK blood draws will be drawn for the morning dose. For the IM injection (Treatment "C"), serial serum samples will also be drawn on Treatment Day 1, prior to dosing (0 time), at 0.5, 1, 2, 6, 12, 18, and 24 hours postdosing. Blood samples for the IM injection will also be taken in the morning on Postdosing Day 1. Additional blood samples for all subjects will be taken in the morning (in the oral groups, just prior to dosing) on Treatment Days 8, 15, and 22. Samples will be appropriately stored until they can be assayed for leuprolide and hormonal levels. Serum concentrations of LH, FSH, $E_2$, and progesterone will be measured (immediately prior to dosing) on Treatment Days 1, 8, 15, 22, and in the morning of Day 29.

Subjects enrolled to the third oral dose (Treatment "D") will have a dosing initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began. During the visit, just prior to the first dosing, baseline blood samples will be taken for leuprolide and hormonal levels. The same blood draws will be performed immediately prior to the first dose of the day on Treatment Days 8, 15, 22, and in the morning of Day 29.

On Day 29, after the 24-hour blood draws in the oral groups (Treatments "A" and "B") and after the PK/PD blood draws in the Treatment "D" and the IM injection group (Treatment "C"), physical, gynecological, and safety laboratory evaluations will be performed.

Note: throughout the text, Treatment Day 29 may be used interchangeably with Postdosing Day 1.

After the 28-day dosing period, four follow-up visits will be scheduled at 7, 14, 21, and 28 days after the last dose. During each follow-up visit, blood samples will be drawn to assess leuprolide (via a single blood draw) and LH, FSH, $E_2$, and progesterone concentrations. During each follow-up visit, subjects will be asked about onset (or absence) of menstrual period.

Safety laboratory evaluations will also be performed during the 28-day postdosing visit. The 28-day postdosing visit will be considered the Final Study Visit. In addition to the PK/PD and safety laboratory assessments, ECG, physical and gynecological examinations will also be performed.

A total of 55 PK blood samples will be taken from subjects in the oral groups (Treatments "A",and "B") for the evaluation of the leuprolide serum concentrations. A total of 11 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The blood volume for each PK sample is assumed to be approximately 3 mL for leuprolide analysis, and the volume for each PD sample is assumed to be approximately 16 mL (10 mL for progesterone and estradiol analysis, and 6 mL for FSH and LH analysis). The total amount of blood volume for all PK and PD draws is 341 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An

additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn should not exceed 407 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

In the Treatment group "D" the total number of samples for PK evaluations will be reduced by 46 when compared to other oral groups. The total amount of blood drawn will be reduced by 138 mL (46 x 3 mL) and should not exceed 269 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

A total of 16 PK blood samples will be taken from subjects in the Lupron group (Treatment "C") for the evaluation of the leuprolide serum concentrations. A total of 10 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The total amount of blood volume for all PK and PD draws is 208 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn in the Lupron group should not exceed 274 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

Serum concentrations of leuprolide and concentrations of PD parameters will be determined via validated bioanalytical methods. Sensitivity and specificity of the employed bioanalytical methods will be described in the study report.

A number of PK parameters will be evaluated for each subject for each evaluation period (*ie*, Treatment Days 1 and 28 for the two oral groups (Treatments "A" and "B") and day 1 for the Lupron Depot group (*eg*, $C_{max}$, $T_{max}$, $AUC_{0-24}$, $AUC_{0-t}$, $C_{ss}$, etc). PD parameters will include values of the hormones measured (LH, FSH, $E_2$, and progesterone) in relation to the baseline values and/or prespecified thresholds). See Section 12.2 and Section 12.3 for the detailed description of the PK and PD parameters and planned statistical analyses.

During both the 28-day dosing period and postdosing 28-day follow-up, subjects will record vaginal (menstrual) bleeding on diary cards. Clinically notable events (including possible flare-up symptoms) may also be recorded. See APPENDIX F for a sample diary card.

The evaluation of safety will be based on the incidence of TEAEs, discontinuations due to TEAEs, treatment-induced changes in vital signs, body weight, physical and gynecological examinations, and laboratory test results.

### 7.1.1 Discussion of the Study Design

With the weekly measurements of leuprolide and hormonal concentration levels, the study design is generally consistent with published PK/PD studies of Lupron Depot (Enteris BioPharma. Data on file).

Interim analysis of the PK portion of this study for Treatments "A" and "B" showed that the leuprolide exposure was approximately 6% and 12% of the exposure of a marketed 1 mg subcutaneous injection of

leuprolide. By returning to the formulation used in the phase 1 study (LOPDT-PH1-01), and by increasing the dose to 10 mg bid (Treatment "D"), the projected systemic exposure will is still less 60% of the exposure of a marketed 1-mg subcutaneous injection of leuprolide. These estimates clearly support the safety of the 10 mg tablet administered twice daily (Treatment "D"). Further support for the safety of the 10 mg tablet administered twice daily is found in the Lupron Depot® 3.75 mg label, which contains the statement, "In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose."

Additional information on PK properties of Leuprolide Oral Tablet can be found in the Investigator's Brochure.

The blood PK sampling schedule in this study for oral tablets is generally similar to that implemented in the study LOPDT-PH1-01. Since leuprolide oral tablets have a "peak-and-trough" PK pattern, their sampling schedule will be different from that of the Lupron Depot with its continuous drug release.

A once-weekly schedule of PD evaluations mimics a number of published $E_2$ inhibition and ovulation suppression trials.

The following precautions are incorporated into the study to minimize bias:

- Subjects are sequentially assigned to randomly ordered treatment arm.
- Subject enrollment is dependent on satisfactory fulfillment of the inclusion/exclusion criteria with particular attention to contraindications to the leuprolide therapy as noted in (LUPRON DEPOT 3.75 mg, leuprolide for depot suspension. Full prescribing information).
- The person performing the PK/PD assays will be blinded to the oral treatment arms.

Since a formal proof of the PK bioequivalence across the treatment arms and/or formal across-treatment statistical comparisons of the PD endpoints are not objectives of this proof-of-concept study, the sample size is not based on the power considerations. With the proposed sample size, we expect reliable estimates of the PK and PD parameters for leuprolide oral tablets and a general validation of related historical data for Lupron Depot therapy. The safety and tolerability assessments of the qd and bid regimens of the 4-mg oral tablet and a bid regimen of the 10-mg oral tablet should also be robust enough to support the dosing selection and instructions in subsequent clinical studies.

### 7.2 Study Procedures

Unless otherwise specified, procedures, data collection, and evaluation will be conducted as per the clinical site Standard Operating Procedures.

## Screening Visit

Subjects will be assessed for eligibility within 40 days prior to the start of study medication. Written informed consent must be obtained prior to the performance of any study procedures. For eligibility purposes, abnormal laboratory or vital signs results may be repeated once if abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements.

The following procedures will be performed and information collected at the Screening Visit:

- Informed Consent Form signed. Demographic data (race, age), information regarding smoking habits and alcohol consumption
- Baseline characteristics and vital signs (height, body weight, body mass index [BMI], temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure)
- Relevant medical history with focus on reproductive history (number of pregnancies and deliveries), gynecological history, menstrual pattern (typical duration of a menstrual cycle and typical duration of a menstrual period), and use of contraceptives.
- Date of onset of the last menstrual period (LMP)
- Cervical cytology Papanicolaou (Pap) smear. The cervical smear may be waived if done within last 12 months and a report is available.
- Clinical laboratory tests (hematology, clinical chemistry, serology and urinalysis – see APPENDIX E for details)
- Serum pregnancy test (β-human chorionic gonadotropin [β-hCG]). Subjects with positive results are not eligible for the study.
- Alcohol breath test
- Obtain baseline PD blood sample (LH, FSH, $E_2$, and progesterone)
- Urine drug screen and urine cotinine. Subjects with positive results are not eligible for the study.
- Physical examination
- Gynecological examination (including manual breast exam)
- 12-lead ECG
- Check of inclusion/exclusion criteria

## Treatment Period (28-Day Dosing Cycle)

### Treatment Day – 1 (Check-in) – Treatments "A", "B" and "C"

This visit will take place within 40 days of the Screening Visit.

Subjects will report to the investigational clinic at least 11 hours before next-day dosing and will remain domiciled until the completion of all study procedures on Treatment Day 2.

- Collect information on changes in medical history/current medical conditions and concomitant medication since the Screening Visit, to confirm that excluded medications have not been taken or have appropriately been discontinued and washed out.
- Collect information on the date of onset of the LMP if it took place after the Screening Visit.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure).
- Collect samples for urine drug screen and urine cotinine tests.

- Perform serum pregnancy test (β-hCG) for all subjects; subjects with positive results are not eligible for the study.
- Perform alcohol breath test.
- Review inclusion and exclusion criteria to confirm eligibility.
- The subjects will undergo a supervised overnight fast of at least 10 hours in duration. A light snack will be served on the evening of admission the clinical facility. No liquid or food intake is allowed during the fast, except water, which is permitted up until 1 hour prior to study drug administration.

**Treatment Day 1 – Treatments "A", "B", and "C"**

- Verify no change in subject's health status before dosing.
- Assign randomization number.
- Obtain baseline PK blood sample immediately (within 10 minutes) prior to dosing.
- Obtain baseline PD blood sample (LH, FSH, $E_2$, and progesterone) immediately (within 30 minutes) prior to dosing.
- Do not allow any food or liquid during the fasting period, except water, which is permitted up until 1 hour prior to study drug administration.
- Administer study drug in the morning according to the randomization schedule. Oral tablets will be administered with 240 mL of water. Perform mouth check following oral tablet dosing to ensure compliance.
- Subjects will remain seated or semireclined and will be required to avoid lying down or sleeping (unless medically necessary or procedurally required) for the first 1 hour after drug administration.
- Obtain serial blood samples for the PK evaluations at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, and 15 hours following single oral dosing in Treatment group "A" or the first oral dosing in Treatment group "B" (16, 17, 18, 20, and 24 hour samples to be obtained on Treatment Day 2). Note: A 12-hour sample in Treatment group "B" will be obtained within 10 minutes before the second oral dose.
- Obtain serial blood samples for the PK evaluations at 0.5, 1, 2, 6, and 12 hours following an IM injection (Treatment "C") (18 and 24 hour samples to be obtained on Treatment Day 2).
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) predose (within 2 hours prior to dosing). Note: The vital signs will be assessed prior to the single oral dosing in Treatment group "A", prior to the first oral dosing in Treatment group "B" and prior to the IM injection in Treatment group "C".
- Record adverse events (AEs) and concomitant medication use.
- The fasting period will be -10h to +4h for Treatment groups "A" and "C.", and -10h to +4h for the first dose in Treatment group "B", and -2h to +2h for the second dose in Treatment "B". All meal times will be recorded and entered into the clinical database.
- Water will not be permitted until 1 hour after dosing.

**Treatment Day 1 – Treatment "D"**

This visit will take place within 40 days of the Screening Visit. Subjects enrolled to the third oral dose (Treatment "D") will have a dosing initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began.

- Verify no change in subject's health status before dosing.
- Perform urine pregnancy test; subjects with positive results cannot be enrolled in the study.
- Collect samples for urine drug screen and urine cotinine tests.
- Perform alcohol breath test.
- Assign randomization number.
- Obtain baseline PK blood sample immediately (within 10 minutes) prior to dosing.
- The fasting period will be -2h to +2h for the first administered dose.
- Obtain baseline PD blood sample (LH, FSH, E2, and progesterone) immediately (within 30 minutes) prior to dosing.
- Administer study drug in the morning. Oral tablets will be administered with 240 mL of water. Perform mouth check following oral tablet dosing to ensure compliance.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) predose (within 2 hours prior to dosing). Note: The vital signs will be assessed prior to the first oral dosing
- Record adverse events (AEs) and concomitant medication use.
- Release subject from the clinical site 2 hours after dosing.

**Treatment Day 2– Treatments "A", "B", and "C"**

- Obtain PK blood samples at 16, 17, 18, 20, and 24 hours following single oral dosing in Treatment group "A" or the first oral dosing in Treatment groups "B" and "D". Obtain PK blood samples at 18 and 24 hours following an IM injection (Treatment group "C").
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) at approximately 24 hours after the previous dose (just prior to the Day 2 single oral dosing in Treatment group "A" and prior to the first oral dosing in Day 2 in Treatment groups "B" and"D").
- Record AEs and concomitant medication use.
- Release subject from the clinical site after the 24-hour blood draw. Provide diary before check-out.

**Treatment Days 8, 15, 22– Treatments "A", "B", "C" and "D"**

- Verify no change in subject's health status before the scheduled oral dosing (single oral dosing in Treatment group "A" or the first oral dosing in Treatment groups "B" and "D").

- Collect samples for urine drug screen and urine cotinine tests. Potential cases of subjects with positive drug screen, cotinine or alcohol results will be evaluated on a case-by-case basis for discontinuation in the study.
- ***On Treatment Day 15 only:*** Perform urine pregnancy test; subjects with positive results must be discontinued from study.
- Perform alcohol breath test.
- Obtain PK blood sample immediately (within 10 minutes) prior to scheduled oral dosing or any time for Treatment group "C."
- Obtain PD blood sample (LH, FSH, $E_2$, and progesterone) immediately (within 30 minutes) prior to scheduled oral dosing or any time for Treatment group "C."
- Oral dosing will be done in the clinic
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) within 1 hour prior to schedule oral dosing or any time for Treatment group "C."
- Record AEs and concomitant medication use.
- Review subject's diaries.
- Subjects will be asked to take their breakfast at least 2 hours before dosing time (for example, at 6AM if dosing time is 8AM), and to verify upon arrival at the clinic if they respected the requirement.
- Release subject from the clinical site after dosing.

**Treatment Day 27 (Check-in):** ***Treatment "A" and Treatment "B" groups only***

Subjects from Treatment groups "A" and "B" will report to the investigational clinic at least 11 hours before next-day morning oral dosing and will remain domiciled until the completion of all study procedures on Postdosing Day 1.

- Verify no change in subject's health status.
- Record AEs and concomitant medication use.
- Review subject's diaries.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure).
- Collect samples for urine drug screen and urine cotinine tests.
- Perform urine pregnancy test; subjects with positive results must be discontinued from study.
- Perform alcohol breath test.

- The subjects will undergo a supervised overnight fast of at least 10 hours in duration. A light snack will be served on the evening of admission the clinical facility. No liquid or food intake is allowed during the fast, except water, which is permitted up until 1 hour prior to study drug administration.
- Oral dosing will be done in the clinic for the evening dose in Treatment group "B".

**Treatment Day 28:** ***Treatment "A" and Treatment "B" groups only***

- Verify no change in subject's health status before dosing.
- Obtain baseline PK blood sample immediately (within 10 minutes) prior to scheduled oral dosing (single oral dosing in Treatment group "A" or first oral dosing in Treatment group "B").
- Obtain baseline PD blood sample (LH, FSH, $E_2$, and progesterone) immediately (within 30 minutes) prior to the scheduled oral dosing.
- Do not allow any food or liquid during the fasting period except water, which is permitted up until 1 hour prior to study drug administration.
- Administer oral tablets in the morning with 240 mL of water. Perform mouth check following oral tablet dosing to ensure compliance.
- Subjects will remain seated or semireclined and will be required to avoid lying down or sleeping (unless medically necessary or procedurally required) for the first 1 hour after drug administration.
- Obtain serial blood samples for the PK evaluations at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, and 15 hours following single oral dosing in Treatment group "A" or the first oral dosing in Treatment group "B" (16, 17, 18, 20, and 24 hour samples to be obtained on Postdosing Day 1). Note: A 12-hour sample in Treatment group "B" will be obtained just prior to the second oral dose.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) predose (within 1 hour prior to dosing). Note: The vital signs will be assessed prior to the single oral dosing in Treatment group "A" and prior to the first oral dosing in Treatment group "B."
- Record AEs and concomitant medication use.
- The fasting period will be -10h to +4h for Treatment group "A", and -10h to +4h for the first dose in Treatment group "B", and -2h to +2h for the second dose in Treatment "B". All meal times will be recorded and entered into the clinical database.
- Water will not be permitted until 1 hour after dosing (Treatment "A" and both doses of Treatment "B").

## Postdosing Period

**Postdosing Day 1:**

***Treatment "A" and Treatment "B" groups only***

- Obtain PK blood sample at 16, 17, 18, 20, and 24 hours following single oral dosing in Treatment group "A" or the first oral dosing in Treatment group "B."
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) at approximately 24 hours after the last dose for Treatment group "A: and 12 hours after the last dose for Treatment group "B".

***Treatment "C" and Treatment "D" groups only***

- Treatment "C" and Treatment "D" volunteers are not confined on day 28, but rather shall be present in the morning of postdosing day 1 only following on overnight fast for 12h because of the lipid panel clinical laboratory test.
- Obtain PK blood sample any time in the morning.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) any time in the morning.
- Review subject's diaries.
- Collect samples for urine drug screen and urine cotinine tests.
- Perform urine pregnancy test; subjects with positive results must be discontinued from study.
- Perform alcohol breath test.

***All Treatment groups***

- Obtain PD blood sample (LH, FSH, $E_2$, and progesterone) any time in the morning.
- Record AEs and concomitant medication use.
- Clinical laboratory tests (hematology and clinical chemistry – see – See APPENDIX E for details).
- Physical examination
- Gynecological examination (including manual breast exam)
- Release subject from the clinical site after all scheduled evaluations.

**Postdosing Days 7, 14, 21**

- Collect samples for urine drug screen and urine cotinine tests.
- Perform alcohol breath test.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) any time in the morning.
- Obtain PK blood sample any time in the morning.
- Obtain PD blood sample (LH, FSH, $E_2$, and progesterone) any time in the morning.

- Record AEs and concomitant medication use.
- Review subject's diaries.
- Release subject from the clinical site after the PK and PD blood samples.

## Final Study Visit (Postdosing Day 28)

- Obtain PK blood sample any time in the morning.
- Obtain PD blood sample (LH, FSH, $E_2$, and progesterone) any time in the morning.
- Assess body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) any time in the morning.
- Perform urine pregnancy test.
- Record AEs and concomitant medication use.
- Review subject's diaries.
- Clinical laboratory tests (hematology, clinical chemistry and urinalysis - see– See APPENDIX E for details).
- Physical examination
- Gynecological examination (including manual breast exam)
- 12-lead ECG
- Release subject from the clinical site after all scheduled evaluations.

Note: the same procedures will be performed for subjects who prematurely discontinue from the study.

Throughout the study, abnormal safety measurements will be repeated as per the clinical site SOPs or upon physician request. Any abnormal repeated measurement will be evaluated by a physician and repeated again if judged necessary

# 8. ELIGIBILITY CRITERIA

## 8.1 Inclusion Criteria

Subjects enrolled in this study will be members of the community at large. The recruitment advertisements may use various media types (*eg*, radio, newspaper). Subjects must meet all of the following criteria to be included in the study:

1) Healthy premenopausal female volunteers, aged 18 to 49 years
2) BMI ≥18 and ≤32 kg/m$^2$, and weight ≥110 lb (≈50 kg).
3) Regular menstrual cycles with a usual length ranging from 21 days to 35 days. If subject has recently used hormonal birth control, historical data prior to use will be used to determine qualification and must also meet this criterion.

4) If of childbearing potential and sexually active with a risk of pregnancy, willing to use one of the following acceptable methods of contraception throughout the study and for at least 30 days after the last drug administration:
   a) intrauterine contraceptive device without hormone release system placed at least 4 weeks prior to the first study drug administration with simultaneous use of condom for the male partner
   b) simultaneous use of diaphragm with intravaginally applied spermicide and condom for the male partner starting at least 14 days prior to drug administration.
   c) sterile male partner (vasectomized for at least 6 months)
   d) Note: Surgically sterile subjects who have had a tubal ligation are considered of non-childbearing potential and are not required to use contraception
5) Willing to refrain from excessive use of alcohol during the entire study and willing to refrain from use of alcohol 24 hours prior to any PK blood draw taken during the study
6) Willing to refrain from use of prescription medications, over-the-counter medications and natural health products during the entire study
7) Willing and capable to give informed consent to participate in study

### 8.2 Exclusion Criteria

Subjects to whom any of the following applies will be excluded from the study:

1) Hypersensitivity to GnRH, GnRH agonist analogs, similar nonapeptides, or any of the excipients in LUPRON DEPOT. ***Note: This is a contraindication from the Lupron Depot label.***
2) Undiagnosed abnormal vaginal bleeding. ***Note: This is a contraindication from the Lupron Depot label.***
3) Known or suspected pregnancy, or subjects who are considering becoming pregnant prior to the conclusion of this study. ***Note: LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug.*** *LUPRON DEPOT may cause fetal harm when administered to a pregnant woman…. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.*
4) Breastfeeding or within 2 months after stopping breastfeeding (relative to the screening visit). ***Note: Use of LUPRON DEPOT is contraindicated in women who are breastfeeding.***
5) Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.***
6) Markedly impaired liver function or liver disease. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with markedly impaired liver function or liver disease.***

7) Known or suspected carcinoma of the breast. ***Note: Per the LUPRON DEPOT label, a possible coadministration of norethindrone acetate is contraindicated in women with known or suspected carcinoma of the breast.***
8) Status postpartum or postabortion within a period of 2 months prior to the screening visit
9) A cervical cytology smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low grade squamous intraepithelial lesions (SIL) or greater (Pap smear results within last 12 months are acceptable if properly documented)
10) Use of any tobacco products (including electronic cigarettes) in the 3 months preceding the screening visit or positive urine cotinine test at screening
11) History of significant alcohol or drug abuse within one year prior to the screening visit
12) Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mm Hg, diastolic blood pressure lower than 50 or over 90 mm Hg, or heart rate less than 50 or over 100 bpm) at screening
13) Any clinically significant history or presence of neurologic, endocrinologic, pulmonary, hematologic, immunologic, or metabolic disease
14) History of severe respiratory depression or pulmonary insufficiency.
15) Diabetes mellitus requiring insulin
16) History of headaches with focal neurological symptoms
17) Uncontrolled thyroid disorder
18) Sickle cell anemia
19) Current or history of clinically significant depression in the last year
20) Known disturbance of lipid metabolism
21) Hepatic adenoma or carcinoma
22) Known or suspected endometrial carcinoma or estrogen-dependent neoplasia
23) Clinically significant history or presence of any gastrointestinal pathology (*eg*, chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (*eg*, diarrhea, vomiting) or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of the drug.
24) Difficulty in swallowing study medication
25) Any food allergy, intolerance, restriction or special diet that, in the opinion of the Investigator, could contraindicate the subject's participation in this study
26) Positive test for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening
27) Administration of any investigational drug and/or experimental device within 30 days prior to the screening visit
28) Administration of any biologics within 90 days prior to the screening visit

29) Clinically significant finding on the ECG suggesting participation in the study could pose a risk to the subject

30) A depot injection or an implant of any drug within 6 months prior to the screening visit

31) Use of oral contraceptives or other sex steroid hormones within 3 months prior to the screening visit

32) Any clinically significant physical or gynecological abnormality at the screening visit

33) Any clinically significant abnormal laboratory test result at the screening visit

34) Hemoglobin <115 g/L and/or hematocrit <0.32 L/L

35) Use of prescription medication within 14 days prior to the first administration of study medication or over-the-counter products (including natural health products; *eg*, food supplements, vitamins, herbal supplements) within 7 days prior to the first administration of study medication, except for topical products without significant systemic absorption

36) Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing

37) Deemed by the Investigator to have questionable ability to comply with the study protocol

38) History of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors;

39) Significant risk factors for decreased bone mineral content and/or bone mass, such as family history (in a first degree relative) of osteoporosis, personal history of chronic use of corticosteroids or anticonvulsants.

### 8.3 Contraindications, Warnings and Other Notes

Leuprolide is contraindicated in:

1) Women with hypersensitivity to GnRH and GnRH agonist analogs.

2) Women with undiagnosed abnormal vaginal bleeding.

3) Women who are or may become pregnant while receiving the drug. Leuprolide may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide. There was increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

4) Women who are breastfeeding

The following are warnings from the approved product label of a marketed formulation of leuprolide (Lupron Depot®, 3.75 mg)

- Safe use of leuprolide in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.
- When used monthly at the recommended dose, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT.
- Therefore, patients should use nonhormonal methods of contraception.
- Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.
- During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.
- Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post marketing.

Per leuprolide (Lupron Depot®, 3.75 mg) prescribing information, patients should be aware of the following information:

1) Since menstruation usually stops with effective doses of LUPRON DEPOT, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT may experience breakthrough bleeding.
2) Patients should not use LUPRON DEPOT if they are pregnant, breastfeeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.
3) Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
4) Adverse events occurring in clinical studies with LUPRON DEPOT that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels returned to normal after treatment was discontinued.
5) Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6) The induced hypoestrogenic state also results in a loss in bone density over the course of treatment, some of which may not be reversible. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.)
7) If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed

before retreatment begins to ensure that values are within normal limits. Retreatment with LUPRON DEPOT alone is not recommended.

8) In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content**.**

### 8.4 Withdrawal of Subjects

Every subject has the right to refuse further participation in the study at any time and without providing reasons for this decision and without prejudice to further treatment. A subject's participation is to be terminated immediately upon their request. The Investigator should record the appropriate reason in the case report form (CRF) and in the source document.

The subject may be withdrawn from the study at any time at the discretion of the Investigator; the reason should be fully documented in the CRF. Should the subject, during the course of the study, develop conditions that would prevent the subject from being dosed as per Investigator's judgment (*eg*, absolute contraindications, prohibited concomitant medications) or would be considered as potentially dangerous AEs, they must be withdrawn immediately. The reasons are to be fully documented in the CRF.

A positive alcohol breath test, urine drug screen, or cotinine test will also be grounds for subject withdrawal, to be handled on a case-by-case basis. If pregnancy occurs or is suspected during study drug treatment, the subject must be discontinued immediately. The outcome of the pregnancy must be followed and a Pregnancy Follow-up form completed.

The termination of an individual's participation should be considered in case of a serious adverse event (SAE) (see Section 11.3 for details) or considerable worsening of the subject's clinical conditions.

At the discretion of Enteris BioPharma, the entire study or part of the study may be canceled for medical or other reasons. In case of premature termination or suspension of the study or part of the study, the Sponsor will promptly inform the Investigator/institutions, regulatory authorities and Institutional Review Boards (IRBs) of the termination or suspension and the reason for the measure.

In addition, Enteris BioPharma retains the right to end the study at any time if the study cannot be carried out as agreed upon in the protocol.

The reasons for discontinuation include:

- AE
- Death
- Pregnancy
- Protocol violation

- Lost to follow-up
- Study terminated by Sponsor
- Noncompliance with study drug (to be handled on a case-by-case basis)
- Withdrawal by subject decision (appropriate details must be provided on the CRF)
- Physician decision (appropriate details must be provided on the CRF)
- Other

If, by the time of discontinuation, a dose of the investigational product has been administered, the subject must be advised to agree to the study evaluation described for the Early Discontinuation Visit.

If a randomized subject misses a scheduled appointment, she should be immediately contacted by phone to reschedule office visit. After waiting 2 weeks for the subject to respond, a certified letter with request for an end-of-study visit must be sent. The certified letter receipt will be filed with the Investigator's copy of the subject's case record form. If the subject fails to return after use of these methods, they will be considered lost to follow-up.

Subjects discontinued early after having received at least one dose of study drug will not be replaced. Study drug assigned to the withdrawn subject may not be given to another subject.

Data generated from screening failures (subjects not admitted to the study after the screening phase and not assigned a randomization number) may be listed according to main reason for not being admitted into the treatment phase.

# 9 STUDY TREATMENT

## 9.1 Description

The active ingredient in both Leuprolide Oral Tablet and LUPRON DEPOT is leuprolide acetate [5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide, acetate salt], which has the following molecular formula: $C_{59}H_{84}N_{16}O_{12} \cdot {}_{1\text{-}2}C_2H_4O_2$.

Enteris BioPharma will supply the Leuprolide Oral Tablet study drug. Each 4 mg tablet contains 4 mg of leuprolide active moiety as the acetate salt (4.46 mg of leuprolide acetate salt), plus inactive ingredients as follows: [redacted],

[redacted].

LUPRON DEPOT is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a monthly IM injection. The front chamber of LUPRON DEPOT 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH. During the manufacture of LUPRON DEPOT 3.75 mg, acetic acid is lost, leaving the peptide.

### 9.1.1 Drug Administration and Return

**Oral Tablet.** Leuprolide Oral Tablet will be administered to each subject with 240 mL of water. The 4-mg qd oral dose (Treatment "A") will be administered once daily, in the morning, on an empty stomach; the 4-mg and 10-mg bid oral doses (Treatments "B" and "D") will be administered twice daily, in the morning and in the evening, 12 hours apart and on an empty stomach. Note: On an empty stomach means that the oral doses are administered at least 2 hours before and at least 2 hours after the meal. Oral administration instructions are applicable to both on-site and at-home dosing. For at-home dosing, each subject will take the oral dose with approximately 240 mL of water.

**Intramuscular Injection**. As is noted earlier, LUPRON DEPOT is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a monthly IM injection. The dual-chamber syringe contains leuprolide acetate (3.75 mg), See APPENDIX D. "Lupron Depot® 3.75 mg" for additional details.

### 9.1.2 Dispensing

Study drug will be shipped directly to the study site. Each oral medication kit is labeled with the following information: drug description (leuprolide, lot number, protocol number, route of administration, storage conditions, Sponsor's identification and address, and the statement, "Investigational Drug". The subject number and the date of study drug administration will be recorded in the CRF. As this study is an open-label study, study drug will not be blinded.

The composition and pharmaceutical quality of the investigational products can be traced back via the lot number. Further details of the investigational product can be found in the Investigator's Brochure.

### 9.1.3 Storage

Leuprolide Oral Tablet must be stored refrigerated between 2° and 8°C (36° and 46°F). The container must be kept tightly closed and protected from light and moisture.

Leuprolide acetate IM injection must be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

A clinical site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

### 9.1.4 Method of Assigning Subjects to Treatments

Eligible subjects were to be given study drug according to the randomization schedule. Initially enrolled subjects were randomly assigned to one of three treatment groups in a Treatment"A":Treatment"B":Treatment"C" ratio of 3:3:2. The randomization schedule was prepared prior to the study and was to be balanced by using permuted blocks (SAS®, PROC PLAN will be employed). Subjects will be assigned a subject number (randomization number) with 2 digits (*e.g.*, 01-32). The subject numbers was to be linked to a specific treatment (Treatment "A," Treatment "B," or Treatment "C"). The randomization schedule could be further stratified by the study site, if necessary.

Newly enrolled subjects will also receive a number linked to a specific treatment (Treatment "D").

Subjects that have already participated in this study will receive a new unique subject number that will be linked exclusively to protocol-specified procedures for Treatment "D".

### 9.1.5 Restrictions

Subjects will be required to abstain from:

- use of prescription medications, over-the-counter medications, and natural health products during the entire study
- using soft or hard drugs or any tobacco products during the study
- excessive use of alcohol during the entire study and willing to refrain from use of alcohol for 24 hours prior to any PK blood draw taken during the study
- products containing xanthines, energy drinks, and grapefruit for 24 hours prior to any PK blood draw taken during the study
- food containing poppy seeds prior to any PK blood draw taken during the study

A urine drug screen, a urine cotinine test, and an alcohol breath test will be performed for all subjects at scheduled study visits.

### 9.1.6 Physical Activity

For safety reasons, subjects will be required to remain seated or semireclined and will be required to avoid lying down or sleeping (unless medically necessary, procedurally required, or to go to the bathroom) for the first 1 hour after on-site drug administration. When subjects will be ambulated during this interval, they will be accompanied by the study site personnel. Vigorous physical activity will be prohibited at all times during the confinements. These restrictions are not applicable to subjects receiving Treatment "D".

## 9.2 Prior and Concomitant Medications

With the exception of concomitant drug therapy required for the medical management of an AE, there will be no other scheduled prior or concomitant therapy permitted during this study.

Seasonal flu vaccine will be allowed during the study; however, subjects will be advised that receiving vaccination within 3 days prior to admission to the clinic could result in vaccine-related side effects that could appear while on study. Any subject presenting with side effects associated with vaccination or

who has been vaccinated within 3 days prior to the admission will be evaluated by the study physician and could be judged ineligible or withdrawn from the study.

All concomitant medications, whether prescription or nonprescription (including pharmacological doses of vitamins), are to be recorded in the CRF using the brand name and stating dosage, indication, and duration of intake.

### 9.3 Drug Accountability

Accurate records must be kept regarding administration of study drug to each individual participant in the study. Reasons for departure from the expected drug administration must be recorded.

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), the Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study drugs according to accepted medical and pharmaceutical practice. All details of study drug receipt, storage, administration, and return will be recorded and the records must be retained in the Investigator's site file. Accurate site records of drug inventory and dispensing must be maintained. All records must be made available to Enteris BioPharma, the clinical research organization, and appropriate regulatory agencies upon request. Study drug must be administered exclusively to study participants during the course of the study.

At the end of the study or as directed during the course of the study, all leuprolide study supplies (including partial and empty containers) will be returned to drug supplier, Sponsor or to the local warehouses for future destruction. A final reconciliation statement will be completed at the end of the study.

### 9.4 Treatment Compliance

For the on-site dosing days, measurements of treatment compliance will be performed by the study site personnel. The subject identification will be verified and cross-checked with the predispensed medication and a mouth (using a tongue depressor and a flash light) and hand check will be performed to ensure subjects have swallowed the study medication (applicable to oral leuprolide tablets only). During off-site dosing days, subjects will record the oral tablets intake on their diary cards. Proper instructions will be given to subjects when compliance issues are identified.

## 10. PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY EVALUATIONS

### 10.1 Pharmacokinetic and Pharmacodynamic Evaluations

Subjects randomized to the the two oral doses (Treatments "A" and "B") will have twenty-four (24) serial blood samples drawn on Treatment Days 1 and 28 immediately prior to dosing (0 time), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 20, and 24 hours following oral dosing. For the IM injection (Treatment "C"), serial blood samples will also be drawn on Treatment Day 1, prior to dosing (0 time), at 0.5, 1, 2, 6, 12, 18, and 24 hours postdosing. Blood samples for the IM injection will also be taken in the morning on Postdosing Day 1. Additional blood samples for all subjects will be taken in the morning (in the oral groups, just prior to dosing) on Treatment Days 8, 15, and 22. Samples will be appropriately stored until they can be assayed for

leuprolide and hormonal levels. Serum concentrations of LH and FSH, and plasma concentrations of $E_2$ and progesterone, will be measured (immediately prior to dosing) on Treatment Days 1, 8, 15, 22, and in the morning of Day 29 (postdosing day 1).

After the 28-day dosing period, four follow-up visits will be scheduled at 7, 14, 21, and 28 days after the last dose. During each follow-up visit, blood samples will be drawn to assess leuprolide (via a single blood draw) and LH, FSH, $E_2$, and progesterone concentrations. During each follow-up visit, subjects will be asked about onset (or absence) of menstrual period.

A total of 55 PK blood samples will be taken from subjects in the oral groups (Treatments "A" and "B") for the evaluation of the leuprolide serum concentrations. A total of 11 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The blood volume for each PK sample is assumed to be approximately 3 mL for leuprolide analysis, and the volume for each PD sample is assumed to be approximately 16 mL (10 mL for progesterone and estradiol analysis, and 6 mL for FSH and LH analysis). The total amount of blood volume for all PK and PD draws is 341 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn should not exceed 407 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

In the Treatment group "D" a total number of samples for PK evaluations will be reduced by 46 when compared to other oral groups. The total amount of blood drawn will be reduced by 138 mL (46 x 3 mL) and should not exceed 269 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

A total of 16 PK blood samples will be taken from subjects in the Lupron group (Treatment "C") for the evaluation of the leuprolide serum concentrations. A total of 10 PD blood samples will also be taken for the determination of LH, FSH, $E_2$, and progesterone levels. The total amount of blood volume for all PK and PD draws is 208 mL. Four safety blood draws will be performed during the study with a volume of 8 mL per draw. An additional 34 mL of blood may be drawn during the study to allow for repeat draws and/or additional safety tests and for the screening pregnancy test. The total amount of blood drawn in the Lupron group should not exceed 274 mL over 3 months, including all samples collected for PK and PD analyses and eligibility and safety purposes.

Serum concentrations of leuprolide and concentrations of PD parameters will be determined via validated bioanalytical methods. Sensitivity and specificity of the employed bioanalytical methods will be described in the study report.

During the both 28-day dosing period and post-dosing 28-day follow-up, subjects will record vaginal (menstrual) bleeding on diary cards. Clinically notable events (including possible flare-up symptoms) may also be recorded on diary cards.

See Section 12.2 and Section 12.3 for the detailed description of the PK and PD parameters and planned statistical analyses.

### 10.2 Safety Evaluations

AEs and concomitant therapies will be reported during the scheduled office visits. At each treatment office visit, the body weight and vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) will be assessed.

Complete physical and gynecological examinations and routine laboratory evaluations will be repeated at the end of dosing period (Postdosing Day 1) and at the Final Visit and also in case of early discontinuation.

Safety evaluations will be based on the discontinuations due to TEAEs, treatment-induced changes in physical and gynecological examinations, in clinical laboratory test results, in body weight and vital signs, as well as by the incidence and severity of TEAEs reported. TEAEs will be evaluated for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

## 11. ADVERSE EVENT REPORTING

The most important part of the safety evaluations is analysis of TEAEs and SAEs as well discontinuations due to AEs. The following sections describe procedures related to AEs monitoring and reporting.

### 11.1 Definition of Adverse Events

AEs or adverse experiences are defined in the (ICH) Guidance for Industry E6: Good Clinical Practice as follows:

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH April 1996).

Any medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration is considered to be preexisting, and should be documented in the CRF.

Any AE (*ie*, a new event or an exacerbation of a preexisting condition) with an onset date after study drug administration up to the last day on study (including the follow-up, off-study medication period of the study), should be recorded as an AE on the appropriate CRF page(s) (see Section 11.2 for details).

An AE does not include:

- Medical or surgical procedures (*eg*, surgery, endoscopy, tooth extraction, transfusion); the condition leading to the procedure is an AE
- Preexisting diseases or conditions present or detected prior to start of study drug administration if they do not worsen
- Situations where an untoward medical occurrence has not occurred (*eg*, hospitalization for elective surgery, social and/or convenience admissions)

- Overdose of either study drug or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation

The period of observation for AEs starts at first dose of study drug and continues until the subject undergoes a final examination as part of the study. The period will also include 30 days following the final examination during which time SAEs must be reported. AEs occurring after the completion of the study must be reported if the Investigator considers that there is a causal relationship with the study medication.

All patients experiencing AEs – whether the events are considered to be associated with any study procedure and/or study medication and/or devices or not – must be monitored as much as possible at least until symptoms subside, any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death. In the latter instance, a full pathologist's report must be supplied as soon as possible. All findings must be reported in the Adverse Event CRF and documented in the patient's medical records. The Sponsor will provide Investigators involved in this clinical study with periodic updates on clinically relevant AEs according to legal requirements.

### 11.2 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded electronically and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be collected in the source data and populated in the CRF will include:

- The date of onset of any new AE or the worsening of a previously observed AE.
- The specific type of reaction in standard medical terminology
- The resolution status of the AE ("Resolved" or "Ongoing")
- For the resolved AEs, stop date
- The severity of the adverse categorized using the following definitions:

  **Mild:** discomfort noted, but no disruption of normal daily activity

  **Moderate**: discomfort noted of sufficient severity to reduce or adversely affect normal activity

  **Severe**: incapacitating, with inability to work or perform normal daily activity

- The relationship of the AE to the study drug, according to the following definitions:

  **Unrelated**: There is evidence that the AE definitely has an etiology other than the assigned study drug.

  **Possibly Related**: The AE has a temporal relationship to study drug administration. However, an alternative etiology may be responsible for the AE. Information on drug/product withdrawal may be lacking or unclear.

  **Probably Related**: The AE has a temporal relationship to study drug administration. The event is unlikely to be related to an alternative etiology. There is a reasonable response on withdrawal. Rechallenge information is not required.

**Definitely Related**: The AE has a temporal relationship to study drug administration and resolves when the drug is discontinued. An alternative etiology is not apparent. If the subject is rechallenged with the assigned study drug, the AE recurs. Rechallenge is not necessarily required.

- Description of action taken in treating the AE ("Dose not Changed" and "Drug Withdrawn" – to be specified on the CRF)

### 11.3 Reporting of Serious Adverse Drug Experiences, Including Deaths

A serious adverse drug experience (SAE), as defined in 21 CFR 312.32 is:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Serious adverse experiences, including death due to any cause, which occur during this study or within 30 days following the final examination, whether or not related to the administration of study drug, must be reported immediately (within 24 hours of learning of the event) to the Medical Monitor.

| | |
|---|---|
| Contact: | Dr. Paul Shields |
| Phone: | 973-453-3520 |
| Back up phone: | 973-641-5807 |
| Fax: | 973-588-5966 |

### 11.4 Withdrawal from Study Treatment Due to Adverse Event

Subjects withdrawn from receiving additional study drug due to an AE will be followed by the Investigator until the outcome is determined. Additional reports will be provided to the Sponsor or regulatory authorities when requested. Every effort will be made to follow the subject for the full study period as per the schedule of study visits.

# 12. STATISTICAL METHODS

## 12.1 Populations and General Considerations

The primary statistical analyses of PK data will be conducted on the population of subjects completing 28 days of dosing. Supporting evaluations will be performed for the cohort of subjects who received at least one dose of study medication and provided any PK data.

Similarly, the primary statistical analyses of PD data will be conducted on the population of subjects completing 28 days of dosing. Supporting evaluations will be performed for the cohort of subjects who received at least one dose of study medication and provided any PD data.

The safety analysis will be performed on all subjects who received at least one dose of study medication.

Compliance with the oral dosing regimens will be assessed, and criteria for the subject's evaluability for PK and/or PD analyses will be specified in the Statistical Analysis Plan (SAP).

Unless otherwise noted, the summaries for quantitative variables (*eg*, continuous PK and PD parameters) will include the sample size, mean, median, standard deviation, coefficient of variation, minimum, and maximum. For qualitative (categorical) variables (*eg*,, suppression of $E_2$ below a specified threshold), the summaries will include the number and percent of subjects in each category.

A detailed SAP will be developed prior to the database lock.

## 12.2 Pharmacokinetic Parameters and Analyses

The following PK parameters will be calculated from the individual serum drug concentration versus time profiles for each subject from Treatment groups "A", "B" and "C" and for each treatment period**:**

**Table 1 Description of the Pharmacokinetic Parameters**

| Parameter | Description |
|---|---|
| **$C_{max}$** | Maximum concentration level |
| **$T_{max}$** | Time to maximum concentration level |
| **$AUC_{0-24}$** | Area under the drug concentration versus time curve calculated using the linear trapezoidal method from 0 hours to 24 hours |
| **$AUC_{0-t}$** | Area under the drug concentration versus time curve calculated using the linear trapezoidal method from 0 hours to t, where t is the time of the last available observation ($C_t$) |
| **$AUC_{0-inf}$** | Area under the drug concentration versus time curve from 0 hours to infinity, $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/K_{el}$ |
| **Css_oral** | Steady state concentration level calculated for oral tablets at the end of the fourth treatment week (Treatment Days 28-29) as the 24-hour AUCs divided by the duration of the dosing interval. |
| **Css_im** | Steady state concentration level calculated for IM injection at the fourth treatment week (a mean of leuprolide levels on Days 22 and 29). |

| | |
|---|---|
| **$K_{el}$** | The apparent elimination rate constant, calculated by linear regression of log concentration *vs* time during the elimination phase |
| **$T_{1/2}$** | Terminal half-life calculated as ln(2)/ $K_{el}$ |

PK parameters will be derived using a non-compartmental PK model. Scheduled sampling time points will be used for the calculations. To derive the PK parameters, the serum concentrations below limit of quantification in early timepoints will be treated as zero and serum levels below limit of quantification appearing in the elimination phase will be omitted from the calculations of $K_{el}$.

The summaries will be provided for all PK parameters with steady-state concentration levels (Css) considered as most important. No formal statistical between-treatment comparisons will be conducted. PK parameters will be graphed by treatment group for each evaluation period.

### 12.3 Pharmacodynamic Parameters and Analyses

As noted earlier, PD assessments (LH, FSH, $E_2$, and progesterone) will be performed during the Screening Visit and immediately prior to dosing on Treatment Days 1, 8, 15, 22, and 29. Additional PD assessments will be performed during the follow-up visits (postdosing Days 7, 14, 21 and 28).

The primary PD metric - suppression of $E_2$ level - will be assessed at each on-treatment evaluation timepoint. Treatment Day 22 and Treatment Day 28 evaluations (separately and combined) will be considered as most important. The summaries will also be provided across the entire dosing period and the entire postdosing period, separately and combined. The summaries of PD metrics may be further stratified by the cycle period (days) of the start of dosing.

In addition to a primary $E_2$ suppression threshold ($E_2 \leq 40$ pg/mL), a suppression of $E_2$ below 20 pg/mL may also be assessed, if considered necessary. The suppression of ovulation (as evidenced by progesterone levels <3 ng/mL) will be evaluated with Treatment Day 22 and Postdosing Day 1 assessments positioned as primary. Changes from predosing baseline in $E_2$ and progesterone levels will also be summarized at each on-treatment evaluation timepoint. Predosing baseline for all PD metrics is the highest value across two observations: (a) screening measurement and (b) measurement taken just prior to the first dose of the study drug. Similar summaries will be provided for the follow-up visits (postdosing Days 7, 14, 21, and 28). In addition, time to return to prestudy baseline hormonal levels could be estimated.

PD parameters will be graphed by treatment group for each evaluation period.

Additionally, correlations between leuprolide concentration levels and PD parameters will be examined.

Number of vaginal (menstrual) bleeding days will be summarized by treatment group for 28 days of therapy and for 28 days of poststudy follow-up. The subject incidence of the onset of menstrual period after completion of therapy will be reported for each treatment group.

Further details of the PD data analysis will be disclosed in the SAP.

### 12.4 Safety Endpoints and Analyses

Safety summaries will be provided for the discontinuations due to TEAEs, treatment-induced changes in physical and gynecological examinations, in clinical laboratory test results (hematology, serum chemistry, and urinalysis), in vital signs and body weight, and by the incidence and severity of TEAEs reported. The TEAEs will be summarized for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period). Clinically notable events (recorded on diary cards) may also be summarized by treatment group. A listing of SAEs will be compiled.

### 12.5 Sample Size

The sample size for this study is not based on the statistical power considerations. This sample size is considered as adequate for a pilot PK/PD "proof-of-concept" study. Since a formal proof of the PK bioequivalence across the treatment arms and/or formal across-treatment statistical comparisons of the PD endpoints are not objectives of this proof-of-concept study, the sample size is not based on the power considerations. With the proposed sample size, we expect reliable estimates of the PK and PD parameters for leuprolide oral tablets and a general validation of related historical data for Lupron Depot therapy. The safety and tolerability assessments of the qd and bid regimens of the 4-mg oral tablet and a bid regimens of the 10-mg oral tablet should also be robust enough to support the dosing selection and instructions in subsequent clinical studies.

## 13. ACCESS TO SOURCE DOCUMENTS

The Investigator will make the source documents for this trial available to the Sponsor or its representatives, or to the regulatory authority or health authority inspectors.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study medication and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical investigators, to other pharmaceutical companies, to the FDA and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an ICH region (*ie*, United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

## 14. QUALITY CONTROL AND QUALITY ASSURANCE

Study monitors will periodically audit, at mutually convenient times during and after the study, all electronic source data and corresponding office and clinical laboratory records for each subject. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of the source data, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

## 15. ETHICS

### 15.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the Scotland revision (2000) and notes of clarification added in 2002 and 2004 as described in APPENDIX C.

### 15.2 Institutional Review Board

The protocol, informed consent form, and any materials (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/ethical committee.

The Investigator will ensure that all aspects of the IRB review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB approval will be provided to the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates that the IRB may require, including any final close out reports. The Investigator will inform the IRB of any reportable adverse events.

### 15.3 Informed Consent

Each subject will be provided with oral and written information describing the nature and duration of the study, in a language they can understand, and must consent in writing to participate before undergoing screening. The date of the consent shall be entered by the subject. The original signed

consent form will be retained with the study center's records. Each subject will also be given a copy of his/her signed consent form.

## 16. DATA HANDLING AND RECORDING

The Investigator is responsible for the completeness and accuracy of information collected in the CRFs for each individual enrolled. The CRFs will be signed and dated by the Investigator.

All clinical raw data will be recorded promptly, accurately, and legibly; either directly into the Initiator™ Clinical Trial Management System as e-source data or indelibly on paper (*eg*, ECG readings). A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. When recorded electronically using Initiator™, CRFs will be electronically generated afterwards. All raw data will be conserved in order to maintain data integrity. A physician and/or the clinical staff will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

The sponsor or designee will conduct data processing. Source data will be reviewed carefully for accuracy and completeness. If necessary, the study site will be contacted for corrections and/or clarifications. All data will be entered into a study database for analysis and reporting. Any data captured electronically (such as laboratory data) will be transferred electronically to the database. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

## 17. PUBLICATION POLICY

The result of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

## 18. PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Sponsor is responsible for all protocol amendments and modifications, except those intended to reduce immediate risk to subjects. The Sponsor is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB or ethical committee. Approval by the IRB will be obtained before changes are implemented.

As per the Canadian regulatory agency, a Clinical Trial Application will be submitted before the beginning of the study and a No Objection Letter must be received prior to dosing.

## 19. REFERENCES

1. Sennello LT et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. J Pharm Sci 1986; 75(2): 158-160.
2. LUPRON DEPOT 3.75 mg (leuprolide for depot suspension). Full prescribing information. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019943s032,020011s039lbl.pdf

   (last accessed 23 May 2016).

## 20. APPENDIX A: LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate Aminotransferase |
| AUC | area under the serum concentration-time curve |
| ß-HCG | beta-human chorionic gonadotropin |
| bid | twice daily |
| BMI | body mass index |
| bpm | beats per minute |
| BUN | Blood Urea Nitrogen |
| Cmax | maximum observed concentration |
| CRF | case report form |
| CRO | clinical research organization |
| $E_2$ | estradiol |
| ECG | electrocardiogram |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GnRH | gonadotropin-releasing hormone |
| ICH | International Conference on Harmonization |
| HbsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| IM | intramuscular |
| Inc | incorporated |
| IRB | Institutional Review Board |
| IV | intravenous |
| kg | kilogram(s) |
| L | liter(s) |
| lb | pound(s) |
| LH | luteinizing hormone |
| LMP | last menstrual period |
| m | meter |
| mg | milligram(s) |
| MD | medical doctor |
| mL | milliliter(s) |
| mm Hg | millimeters of mercury |
| NDA | New Drug Application |
| PD | pharmacodynamic |
| pg | picogram(s) |
| pH | negative logarithm of the activity of H+ |
| PK | pharmacokinetic |

| | |
|---|---|
| QA | quality assurance |
| qd | daily |
| RBC | red blood cells |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| $T_{1/2}$ | elimination half-life |
| TEAE | Treatment-emergent adverse event |
| Tmax | time to maximum concentration |
| WBC | white blood cells |

## 21. APPENDIX B: TIME AND EVENTS SCHEDULE

| Evaluation/Event | Screening Visit [a] | Treatment Period (28-Day Dosing Cycle) | | | | | | | Post-Dosing Period | | | | | Final Study Visit (PD Day[d] 28) (or Early Discontinuation Visit) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day[b, n] -1 | Day[b] 1 | Day[b, n] 2 | Day[b] 8 | Day[b] 15 | Day[b] 22 | Day[b,c] 27 | Day[b,c] 28 | PD Day[d] 1 | PD Day[d] 7 | PD Day[d] 14 | PD Day[d] 21 | |
| **Treatment Groups** | ABCD | ABC | ABCD | ABC | ABCD | ABCD | ABCD | AB | AB | ABCD | ABCD | ABCD | ABCD | ABCD |
| **Informed consent** | X | | | | | | | | | | | | | |
| **Relevant medical history** | X | X[n] | X[o] | | | | | | | | | | | |
| **Randomization** | | | X | | | | | | | | | | | |
| **Demographic and baseline characteristics** | X[e] | X[e,n] | X[e] | X[e,,n] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] |
| **Physical examination** | X | | | | | | | | | X[f] | | | | X[f] |
| **Gynecological examination** | X | | | | | | | | | X[f] | | | | X |
| **Vital signs** | X[g] | X[g,n] | X[g] | X[g,n] | X[g] | X[g] | X[g] | X[g] | X[g] | X[g] | X[g] | X[g] | X[g] | X[g] |
| **12-lead ECG** | X | | | | | | | | | | | | | X |
| **Laboratory Evaluations (chemistry, hematology)** | X | | | | | | | | | X[f] | | | | X |
| **Urinalysis** | X | | | | | | | | | | | | | X |
| **Pap smear** | X[h] | | | | | | | | | | | | | |
| **Serum (β-hCG) pregnancy test** | X[i] | X[i,n] | | | | | | | | | | | | |
| **Urine pregnancy test** | | | X[o] | | | X | | X[f] | | X[f] | | | | X |
| **Urine drug screen/ Urine cotinine Test** | X | X[n] | X[o] | | X | X | X | X | | X | X | X | X | |
| **Serology tests** | X[j] | | | | | | | | | | | | | |
| **Alcohol breath test** | X | X[n] | X[o] | | X | X | X | X | | X | X | X | X | |
| **Confinement** | | X[n] | X[n] | X[n] | | | | X[c] | X[c] | X[c] | | | | |
| **Drug administration by site personnel** | | | X [k] | | X[k] | X[k] | X[k] | X[k] | X[k] | | | | | |
| **Leuprolide (PK) Blood Draws** | | | X[l] | X[l,n] | X[l] | X[l] | X[l] | | X[l] | X[l] | X[l] | X[l] | X[l] | X[l] |
| **(PD) blood draws (LH, FSH, $E_2$, progesterone)** | X[m] | | X[m] | | X[m] | X[m] | X[m] | | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] |
| **Review of AEs, concomitant meds, diaries** | | | X | X[,n] | X | X | X | X | X | X | X | X | X | X |

[a] Screening visit may take place up to 40 days prior to start of the study drug administration

[b] Days relative to the start of the study drug administration

[c] Day 27 Confinement is for Ovarest groups (Treatment "A" and Treatment "B") only

[d] PD (Postdosing) days relative to the last day of the study drug administration (the last day of the 28-day dosing cycle). PD Day 1 is used interchangeably with Treatment Day 29 throughout the text.

[e] Demographic information (eg, race, age) will be recorded at Screening Visit only. Height, body weight, BMI (Screening Visit), body weight (Treatment Days -1, 1, 2, 8, 15, 22, 27, 28 and 29; PD Days 7, 14, 21 and 28 (Final Visit)) or Early Discontinuation Visit.

[f] Post-dosing evaluations on Day 29, after the PD blood draws: Physical and gynecological examinations, laboratory evaluations (chemistry, hematology), urine pregnancy test (Treatment groups "C" and "D"), Urine drug and cotinine Test (Treatments "C" and "D"), alcohol breath test (Treatment "C" and "D"). Note: For Treatment Groups "A", and "B", urine pregnancy test, urine drug and cotinine test, and alcohol breath test are performed on Treatment Day 27.

[g] Temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure: Taken in the morning (in the Ovarest groups, just prior to oral dosing on Treatment Days 1, 2, 8, 15, 22)

[h] Pap smear taken within 12 months prior to the screening will be acceptable if properly documented

[i] Serum (β-hCG) pregnancy test at Screening Visit and on Day - 1. Negative results must be obtained prior to randomization and dosing.

[j] Serology tests at Screening visit only (include HIV antibody test, hepatitis B and C tests).

[k] Day 1 - Treatment "A", both doses of Treatment "B", first dose of Treatment "D", and Treatment "C"; Days 8, 15 and 22 – Treatment "A" and first dose of Treatments "B" and "D"; Day 27 – second dose of Treatments "B"; Day 28 – Treatment "A" and both doses of Treatment "B".

[l] PK blood draws: Subjects randomized to the Ovarest doses (Treatments "A", and "B") will have twenty-four (24) serial blood samples drawn on Treatment Days 1 and 28 immediately prior to dosing (0 time), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 20, and 24 hours following oral dosing. For the IM injection (Treatment "C"), serial blood samples will also be drawn on Treatment Day 1, prior to dosing (0 time), at 0.5, 1, 2, 6, 12, 18, and 24 hours post-dosing. Subjects from Treatment group "D will have PK sample drawn on Day 1, just prior to the first dosing. Additional blood samples for all subjects will be taken in the morning (in the oral groups, just prior to dosing) on Treatment Days 8, 15 and 22, and postdosing day 1, as well as during four follow-up visits (PD Days 7, 14, 21, and 28).

[m] PD blood draws: Taken at screening and in the morning (in the Ovarest groups, just prior to oral dosing) on Treatment Days 1, 8, 15, 22 and 28 (Day 28 - for Treatments "A" and "B" only, and in the morning of Postdosing Days 1, 7, 14, 21 and 28.

[n] Treatments "A", "B" and "C" only

[o] Treatment "D" only

## 22. APPENDIX C: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

### Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
And amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.".
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best

proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

**B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14 The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the

consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

## C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and

therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

[1] Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

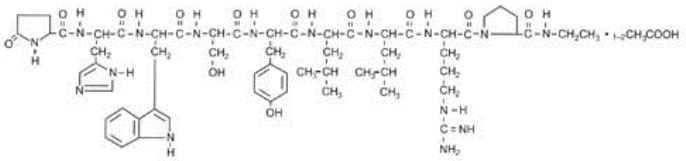
# 23. APPENDIX D: LUPRON DEPOT® 3.75 mg (Full Prescribing Information)

**LUPRON DEPOT® 3.75 mg**
**(leuprolide acetate for depot suspension)**

**Rx only**

## DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON DEPOT is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a monthly intramuscular injection.

The front chamber of LUPRON DEPOT 3.75 mg prefilled dual-chamber syringe contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 3.75 mg, acetic acid is lost, leaving the peptide.

## CLINICAL PHARMACOLOGY

Leuprolide acetate is a long-acting GnRH analog. A single monthly injection of LUPRON DEPOT 3.75 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins.

Reference ID: 3398785

Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally. Intramuscular injection of the depot formulation provides plasma concentrations of leuprolide over a period of one month.

**Pharmacokinetics**

**Absorption**

A single dose of LUPRON DEPOT 3.75 mg was administered by intramuscular injection to healthy female volunteers. The absorption of leuprolide was characterized by an initial increase in plasma concentration, with peak concentration ranging from 4.6 to 10.2 ng/mL at four hours postdosing. However, intact leuprolide and an inactive metabolite could not be distinguished by the assay used in the study. Following the initial rise, leuprolide concentrations started to plateau within two days after dosing and remained relatively stable for about four to five weeks with plasma concentrations of about 0.30 ng/mL.

**Distribution**

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

**Metabolism**

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of $^{14}C$-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

**Excretion**

Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

**Special Populations**

The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

**Drug Interactions**

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

**CLINICAL STUDIES**

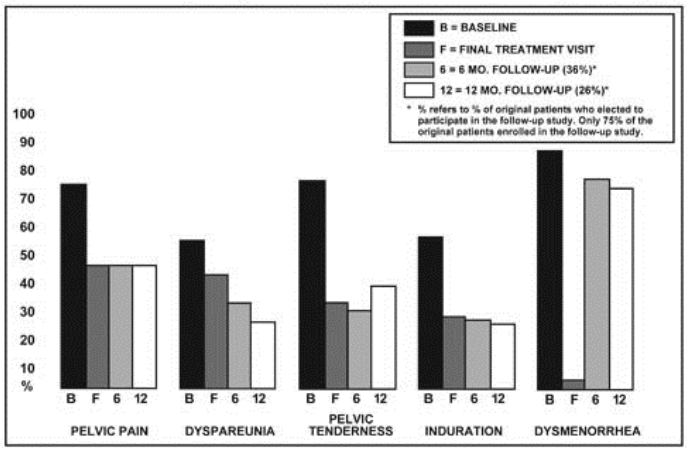
**Endometriosis**

In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time, and in addition laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of patients, respectively, excluding those who became pregnant.

Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during two controlled clinical studies. This included all patients at end of treatment and those who elected to participate in the follow-up period. This might provide a slight bias in the results at follow-up as 75% of the original patients entered the follow-up study, and 36% were evaluated at 6 months and 26% at 12 months.

**FIGURE 1–PERCENT OF PATIENTS WITH SIGN/SYMPTOMS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP**

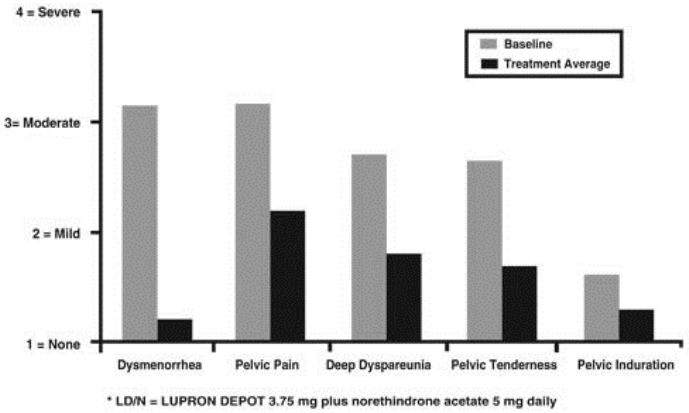



**Hormonal replacement therapy**

Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in significantly reducing the loss of bone mineral density associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium). One controlled, randomized and double-blind study included 51 women treated with LUPRON DEPOT alone and 55 women treated with LUPRON plus norethindrone acetate 5 mg daily. The second study was an open label study in which 136 women were treated with LUPRON plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study. Suppression of menses was maintained throughout treatment in 84% and 73% of patients receiving LD/N in the controlled study and open label study, respectively. The median time for menses resumption after treatment with LD/N was 8 weeks.

Figure 2 illustrates the mean pain scores for the LD/N group from the controlled study.

**Figure 2**
**Treatment Period Mean Pain Scores For LD/N* Patients**




* LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily

**Uterine Leiomyomata (Fibroids)**

In controlled clinical trials, administration of LUPRON DEPOT 3.75 mg for a period of three or six months was shown to decrease uterine and fibroid volume, thus allowing for relief of clinical symptoms (abdominal bloating, pelvic pain, and pressure). Excessive vaginal bleeding (menorrhagia and menometrorrhagia) decreased, resulting in improvement in hematologic parameters.

In three clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Benefit occurred by three months of therapy, but additional gain was observed with an additional three months of LUPRON DEPOT 3.75 mg. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

Post-treatment follow-up was carried out for a small percentage of LUPRON DEPOT 3.75 mg patients among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

In another controlled clinical study, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At three months, 75% of patients met this criterion.

At three months, 80% of patients experienced relief from either menorrhagia or menometrorrhagia. As with the previous studies, episodes of spotting and menstrual-like bleeding were noted in some patients.

In this same study, a decrease of ≥ 25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT 3.75 mg.

**INDICATIONS AND USAGE**

**Endometriosis**

LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. (Refer also to norethindrone acetate prescribing information for WARNINGS, PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of initial treatment or retreatment should be limited to 6 months.

**Uterine Leiomyomata (Fibroids)**

LUPRON DEPOT 3.75 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. (See Table 1.) LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to** three months.

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older.

**Table 1 PERCENT OF PATIENTS ACHIEVING HEMOGLOBIN ≥ 12 GM/DL**

| Treatment Group | Week 4 | Week 8 | Week 12 |
|---|---|---|---|
| LUPRON DEPOT 3.75 mg with Iron | 41* | 71† | 79* |
| Iron Alone | 17 | 40 | 56 |
| * P-Value < 0.01 | | | |
| † P-Value < 0.001 | | | |

**CONTRAINDICATIONS**

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. (See **Pregnancy** section.) The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
4. Use in women who are breast-feeding. (See **Nursing Mothers** section.)
5. Norethindrone acetate is contraindicated in women with the following conditions:
    - Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions
    - Markedly impaired liver function or liver disease
    - Known or suspected carcinoma of the breast

**WARNINGS**

Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.

When used monthly at the recommended dose, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT. Therefore, patients should use non-hormonal methods of contraception.

Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.

The following applies to co-treatment with LUPRON and norethindrone acetate:

Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.

Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caution in women with risk factors, including lipid abnormalities or cigarette smoking.

**PRECAUTIONS**

**Information for Patients**

Patients should be aware of the following information:

1. Since menstruation usually stops with effective doses of LUPRON DEPOT, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT may experience breakthrough bleeding.
2. Patients should not use LUPRON DEPOT if they are pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.

3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a non-hormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.
4. Adverse events occurring in clinical studies with LUPRON DEPOT that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels returned to normal after treatment was discontinued.
5. Patients should be counseled on the possibility of the development or worsening of depression and the occurrence of memory disorders.
6. The induced hypoestrogenic state **also** results in a loss in bone density over the course of treatment, some of which may not be reversible. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received calcium supplementation with 1000 mg elemental calcium.) (See ***Changes in Bone Density*** section).
7. If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Retreatment with LUPRON DEPOT alone is not recommended.
8. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin-releasing hormone analogs, including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.
9. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
10. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.

**Convulsions**

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

**Laboratory Tests**

See **ADVERSE REACTIONS** section.

**Drug Interactions**

See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**

**Drug/Laboratory Test Interactions**

Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be misleading.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks. Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies

(prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery.

**Pregnancy**

**Teratogenic Effects**

Pregnancy Category X (see **CONTRAINDICATIONS** section).

When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, LUPRON DEPOT produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

**Nursing Mothers**

It is not known whether LUPRON DEPOT is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of LUPRON DEPOT on lactation and/or the breast-fed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

**Pediatric Use**

Experience with LUPRON DEPOT 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older. See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.

**Geriatric Use**

This product has not been studied in women over 65 years of age and is not indicated in this population.

**ADVERSE REACTIONS**

**Clinical Trials**

Estradiol levels may increase during the first weeks following the initial injection of LUPRON, but then decline to menopausal levels. This transient increase in estradiol can be associated with a temporary worsening of signs and symptoms (see **WARNINGS** section).

As would be expected with a drug that lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

The **monthly formulation of LUPRON DEPOT 3.75 mg** was utilized in controlled clinical trials that studied the drug in 166 endometriosis and 166 uterine fibroids patients. Adverse events reported in ≥5% of patients in either of these populations and thought to be potentially related to drug are noted in the following table.

**Table 2 ADVERSE EVENTS REPORTED TO BE CAUSALLY RELATED TO DRUG IN ≥ 5% OF PATIENTS**

| | Endometriosis (2 Studies) | | | | | | Uterine Fibroids (4 Studies) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | LUPRON DEPOT 3.75 mg N=166 | | Danazol N=136 | | Placebo N=31 | | LUPRON DEPOT 3.75 mg N=166 | | Placebo N=163 | |
| | N | (%) | N | (%) | N | (%) | N | (%) | N | (%) |
| Body as a Whole | | | | | | | | | | |
| Asthenia | 5 | (3) | 9 | (7) | 0 | (0) | 14 | (8.4) | 8 | (4.9) |
| General pain | 31 | (19) | 22 | (16) | 1 | (3) | 14 | (8.4) | 10 | (6.1) |
| Headache* | 53 | (32) | 30 | (22) | 2 | (6) | 43 | (25.9) | 29 | (17.8) |
| Cardiovascular System | | | | | | | | | | |
| Hot flashes/sweats* | 139 | (84) | 77 | (57) | 9 | (29) | 121 | (72.9) | 29 | (17.8) |
| Gastrointestinal System | | | | | | | | | | |
| Nausea/vomiting | 21 | (13) | 17 | (13) | 1 | (3) | 8 | (4.8) | 6 | (3.7) |
| GI disturbances* | 11 | (7) | 8 | (6) | 1 | (3) | 5 | (3.0) | 2 | (1.2) |
| Metabolic and Nutritional Disorders | | | | | | | | | | |
| Edema | 12 | (7) | 17 | (13) | 1 | (3) | 9 | (5.4) | 2 | (1.2) |
| Weight gain/loss | 22 | (13) | 36 | (26) | 0 | (0) | 5 | (3.0) | 2 | (1.2) |
| Endocrine System | | | | | | | | | | |
| Acne | 17 | (10) | 27 | (20) | 0 | (0) | 0 | (0) | 0 | (0) |
| Hirsutism | 2 | (1) | 9 | (7) | 1 | (3) | 1 | (0.6) | 0 | (0) |
| Musculoskeletal System | | | | | | | | | | |
| Joint disorder* | 14 | (8) | 11 | (8) | 0 | (0) | 13 | (7.8) | 5 | (3.1) |
| Myalgia* | 1 | (1) | 7 | (5) | 0 | (0) | 1 | (0.6) | 0 | (0) |
| Nervous System | | | | | | | | | | |
| Decreased libido* | 19 | (11) | 6 | (4) | 0 | (0) | 3 | (1.8) | 0 | (0) |
| Depression/emotional lability* | 36 | (22) | 27 | (20) | 1 | (3) | 18 | (10.8) | 7 | (4.3) |
| Dizziness | 19 | (11) | 4 | (3) | 0 | (0) | 3 | (1.8) | 6 | (3.7) |
| Nervousness* | 8 | (5) | 11 | (8) | 0 | (0) | 8 | (4.8) | 1 | (0.6) |
| Neuromuscular disorders* | 11 | (7) | 17 | (13) | 0 | (0) | 3 | (1.8) | 0 | (0) |
| Paresthesias | 12 | (7) | 11 | (8) | 0 | (0) | 2 | (1.2) | 1 | (0.6) |
| Skin and Appendages | | | | | | | | | | |
| Skin reactions | 17 | (10) | 20 | (15) | 1 | (3) | 5 | (3.0) | 2 | (1.2) |
| Urogenital System | | | | | | | | | | |
| Breast changes/tenderness/pain* | 10 | (6) | 12 | (9) | 0 | (0) | 3 | (1.8) | 7 | (4.3) |
| Vaginitis* | 46 | (28) | 23 | (17) | 0 | (0) | 19 | (11.4) | 3 | (1.8) |
| In these same studies, symptoms reported in <5% of patients included: *Body as a Whole* - Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* - Palpitations, Syncope, Tachycardia; *Digestive System* - Appetite changes, Dry mouth, Thirst; *Endocrine System* - Androgen-like effects; *Hemic and Lymphatic System* - Ecchymosis, Lymphadenopathy; *Nervous System* – Anxiety*, Insomnia/Sleep disorders*, Delusions, Memory disorder, Personality disorder; *Respiratory System* - Rhinitis; *Skin and Appendages* - Alopecia, Hair disorder, Nail disorder; | | | | | | | | | | |

| |
|---|
| *Special Senses* - Conjunctivitis, Ophthalmologic disorders*, Taste perversion; *Urogenital System* - Dysuria*, Lactation, Menstrual disorders. |
| * = Possible effect of decreased estrogen. |

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT, patients diagnosed with uterine fibroids received a higher dose (7.5 mg) of LUPRON DEPOT. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included glossitis, hypesthesia, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

Table 3 lists the potentially drug-related adverse events observed in at least 5% of patients in any treatment group during the first 6 months of treatment in the add-back clinical studies.

In the controlled clinical trial, 50 of 51 (98%) patients in the LD group and 48 of 55 (87%) patients in the LD/N group reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 37 (86%) patients in the LD group and 22 of 38 (58%) patients in the LD/N group reported having experienced hot flashes. The mean number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups, respectively.

**Table 3 TREATMENT-RELATED ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS**

| | **Controlled Study** | | | | **Open Label Study** | |
|---|---|---|---|---|---|---|
| | **LD - Only* N=51** | | **LD/N† N=55** | | **LD/N† N=136** | |
| **Adverse Events** | **N** | **(%)** | **N** | **(%)** | **N** | **(%)** |
| *Any Adverse Event* | 50 | (98) | 53 | (96) | 126 | (93) |
| Body as a Whole | | | | | | |
| Asthenia | 9 | (18) | 10 | (18) | 15 | (11) |
| Headache/Migraine | 33 | (65) | 28 | (51) | 63 | (46) |
| Injection Site Reaction | 1 | (2) | 5 | (9) | 4 | (3) |
| Pain | 12 | (24) | 16 | (29) | 29 | (21) |
| Cardiovascular System | | | | | | |
| Hot flashes/sweats | 50 | (98) | 48 | (87) | 78 | (57) |
| Digestive System | | | | | | |
| Altered Bowel Function | 7 | (14) | 8 | (15) | 14 | (10) |
| Changes in Appetite | 2 | (4) | 0 | (0) | 8 | (6) |
| GI Disturbance | 2 | (4) | 4 | (7) | 6 | (4) |
| Nausea/Vomiting | 13 | (25) | 16 | (29) | 17 | (13) |
| Metabolic and Nutritional Disorders | | | | | | |
| Edema | 0 | (0) | 5 | (9) | 9 | (7) |
| Weight Changes | 6 | (12) | 7 | (13) | 6 | (4) |
| Nervous System | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Anxiety | 3 | (6) | 0 | (0) | 11 | (8) |
| Depression/Emotional Lability | 16 | (31) | 15 | (27) | 46 | (34) |
| Dizziness/Vertigo | 8 | (16) | 6 | (11) | 10 | (7) |
| Insomnia/Sleep Disorder | 16 | (31) | 7 | (13) | 20 | (15) |
| Libido Changes | 5 | (10) | 2 | (4) | 10 | (7) |
| Memory Disorder | 3 | (6) | 1 | (2) | 6 | (4) |
| Nervousness | 4 | (8) | 2 | (4) | 15 | (11) |
| Neuromuscular Disorder | 1 | (2) | 5 | (9) | 4 | (3) |
| Skin and Appendages | | | | | | |
| Alopecia | 0 | (0) | 5 | (9) | 4 | (3) |
| Androgen-Like Effects | 2 | (4) | 3 | (5) | 24 | (18) |
| Skin/Mucous Membrane Reaction | 2 | (4) | 5 | (9) | 15 | (11) |
| Urogenital System | | | | | | |
| Breast Changes/Pain/Tenderness | 3 | (6) | 7 | (13) | 11 | (8) |
| Menstrual Disorders | 1 | (2) | 0 | (0) | 7 | (5) |
| Vaginitis | 10 | (20) | 8 | (15) | 11 | (8) |
| * LD-Only = LUPRON DEPOT 3.75 mg | | | | | | |
| † LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg | | | | | | |

**Changes in Bone Density**

In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) and calcium supplementation is effective in significantly reducing the loss of bone mineral density that occurs with LUPRON treatment, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis.

LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data of the lumbar spine from these two studies are presented in Table 4.

**Table 4 MEAN PERCENT CHANGE FROM BASELINE IN BONE MINERAL DENSITY OF LUMBAR SPINE**

| | **LUPRON DEPOT 3.75mg** | | **LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily** | | | |
|---|---|---|---|---|---|---|
| | **Controlled Study** | | **Controlled Study** | | **Open Label Study** | |
| | **N** | **Change (Mean, 95% CI)#** | **N** | **Change (Mean, 95% CI)#** | **N** | **Change (Mean, 95% CI)#** |
| Week 24* | 41 | -3.2% (-3.8, -2.6) | 42 | -0.3% (-0.8, 0.3) | 115 | -0.2% (-0.6, 0.2) |
| Week 52† | 29 | -6.3% (-7.1, -5.4) | 32 | -1.0% (-1.9, -0.1) | 84 | -1.1% (-1.6, -0.5) |
| * Includes on-treatment measurements that fell within 2–252 days after the first day of treatment. | | | | | | |

| |
|---|
| † Includes on-treatment measurements >252 days after the first day of treatment. |
| # 95% CI: 95% Confidence Interval |

When LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LUPRON DEPOT for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended**.

**Changes in Laboratory Values During Treatment**

**Plasma Enzymes**

**Endometriosis**

During early clinical trials with LUPRON DEPOT 3.75 mg, regular laboratory monitoring revealed that AST levels were more than twice the upper limit of normal in only one patient. There was no clinical or other laboratory evidence of abnormal liver function.

In two other clinical trials, 6 of 191 patients receiving LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Five of the 6 increases were observed beyond 6 months of treatment. None were associated with elevated bilirubin concentration.

**Uterine Leiomyomata (Fibroids)**

In clinical trials with LUPRON DEPOT 3.75 mg, five (3%) patients had a post-treatment transaminase value that was at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

**Lipids**

**Endometriosis**

In earlier clinical studies, 4% of the LUPRON DEPOT 3.75 mg patients and 1% of the danazol patients had total cholesterol values above the normal range at enrollment. These patients also had cholesterol values above the normal range at the end of treatment.

Of those patients whose pretreatment cholesterol values were in the normal range, 7% of the LUPRON DEPOT 3.75 mg patients and 9% of the danazol patients had post-treatment values above the normal range.

The mean (±SEM) pretreatment values for total cholesterol from all patients were 178.8 (2.9) mg/dL in the LUPRON DEPOT 3.75 mg groups and 175.3 (3.0) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 193.3 mg/dL in the LUPRON DEPOT 3.75 mg group and 194.4 mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.03$) in both groups.

Triglycerides were increased above the upper limit of normal in 12% of the patients who received LUPRON DEPOT 3.75 mg and in 6% of the patients who received danazol.

At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT 3.75 mg patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT 3.75 mg compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT 3.75 mg but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables below.

**Table 5 SERUM LIPIDS: MEAN PERCENT CHANGES FROM BASELINE VALUES AT TREATMENT WEEK 24**

| | LUPRON | | LUPRON plus norethindrone acetate 5 mg daily | | | |
|---|---|---|---|---|---|---|
| | Controlled Study (n=39) | | Controlled Study (n=41) | | Open Label Study (n=117) | |
| | Baseline Value* | Wk 24 % Change | Baseline Value* | Wk 24 % Change | Baseline Value* | Wk 24 % Change |
| Total Cholesterol | 170.5 | 9.2% | 179.3 | 0.2% | 181.2 | 2.8% |
| HDL Cholesterol | 52.4 | 7.4% | 51.8 | -18.8% | 51.0 | -14.6% |
| LDL Cholesterol | 96.6 | 10.9% | 101.5 | 14.1% | 109.1 | 13.1% |
| LDL/HDL Ratio | 2.0† | 5.0% | 2.1† | 43.4% | 2.3† | 39.4% |
| Triglycerides | 107.8 | 17.5% | 130.2 | 9.5% | 105.4 | 13.8% |
| * mg/dL | | | | | | |
| † ratio | | | | | | |

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data returned to pretreatment values.

**Table 6 PERCENTAGE OF PATIENTS WITH SERUM LIPID VALUES OUTSIDE OF THE NORMAL RANGE**

| | LUPRON | LUPRON plus norethindrone acetate 5 mg daily |
|---|---|---|

| | Controlled Study (n=39) | | Controlled Study (n=41) | | Open Label Study (n=117) | |
|---|---|---|---|---|---|---|
| | Wk 0 | Wk 24* | Wk 0 | Wk 24* | Wk 0 | Wk 24* |
| Total Cholesterol (>240 mg/dL) | 15% | 23% | 15% | 20% | 6% | 7% |
| HDL Cholesterol (<40 mg/dL) | 15% | 10% | 15% | 44% | 15% | 41% |
| LDL Cholesterol (>160 mg/dL) | 0% | 8% | 5% | 7% | 9% | 11% |
| LDL/HDL Ratio (>4.0) | 0% | 3% | 2% | 15% | 7% | 21% |
| Triglycerides (>200 mg/dL) | 13% | 13% | 12% | 10% | 5% | 9% |
| * Includes all patients regardless of baseline value. | | | | | | |

Low HDL-cholesterol (<40 mg/dL) and elevated LDL-cholesterol (>160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with LUPRON and norethindrone acetate.

**Uterine Leiomyomata (Fibroids)**

In patients receiving LUPRON DEPOT 3.75 mg, mean changes in cholesterol (+11 mg/dL to +29 mg/dL), LDL cholesterol (+8 mg/dL to +22 mg/dL), HDL cholesterol (0 to +6 mg/dL), and the LDL/HDL ratio (-0.1 to +0.5) were observed across studies. In the one study in which triglycerides were determined, the mean increase from baseline was 32 mg/dL.

### Other Changes

**Endometriosis**

The following changes were seen in approximately 5% to 8% of patients. In the earlier comparative studies, LUPRON DEPOT 3.75 mg was associated with elevations of LDH and phosphorus, and decreases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH. In the hormonal add-back studies LUPRON DEPOT in combination with norethindrone acetate was associated with elevations of GGT and SGPT.

**Uterine Leiomyomata (Fibroids)**

Hematology: (see **CLINICAL STUDIES** section) In LUPRON DEPOT 3.75 mg treated patients, although there were statistically significant mean decreases in platelet counts from baseline to final visit, the last mean platelet counts were within the normal range. Decreases in total WBC count and neutrophils were observed, but were not clinically significant.

Chemistry: Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant.

**Postmarketing**

The following adverse reactions have been identified during postapproval use of LUPRON DEPOT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported. There have been rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of development or worsening of depression during treatment with LUPRON.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection. Symptoms consistent with fibromyalgia (eg: joint and muscle pain, headaches, sleep disorder, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Other events reported are:

*Hepato-biliary disorder*: Rarely reported serious liver injury

*Injury, poisoning and procedural complications:* Spinal fracture

*Investigations*: Decreased WBC

*Musculoskeletal and Connective tissue disorder*: Tenosynovitis-like symptoms

*Nervous System Disorder*: Convulsion, peripheral neuropathy, paralysis

*Vascular Disorder*: Hypotension

Cases of serious venous and arterial thromboembolism have been reported, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack.

Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is unknown if there is a causal association between the use of GnRH analogs and these events.

**Pituitary apoplexy**

During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in different patient populations.

**OVERDOSAGE**

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

**DOSAGE AND ADMINISTRATION**

*LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.*

**Endometriosis**

The recommended duration of treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate is six months. The choice of LUPRON DEPOT alone or LUPRON DEPOT plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to LUPRON DEPOT alone.

If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT administered monthly and norethindrone acetate 5 mg daily may be

considered. Retreatment beyond this one six-month course cannot be recommended. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. LUPRON DEPOT alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.

An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with LUPRON DEPOT and norethindrone acetate.

**Uterine Leiomyomata (Fibroids)**

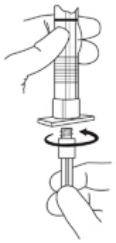
*Recommended duration of therapy with LUPRON DEPOT 3.75 mg is* ***up to*** *3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.*

The recommended dose of LUPRON DEPOT is 3.75 mg, incorporated in a depot formulation. *For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions*:

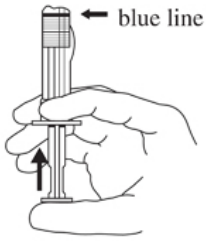
Reconstitution and Administration Instructions

- The lyophilized microspheres are to be reconstituted and administered as a single intramuscular injection.
- Since LUPRON DEPOT does not contain a preservative, the suspension should be injected immediately or discarded if not used within two hours.
- As with other drugs administered by injection, the injection site should be varied periodically.

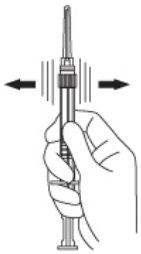
1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.



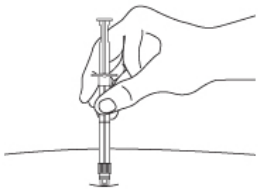

4. Keep the syringe UPRIGHT. Mix the microspheres (powder) thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.



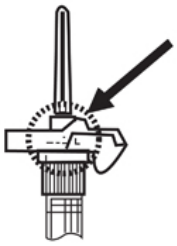
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.

Reference ID: 3398785

6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe. Now the syringe is ready for injection.
7. After cleaning the injection site with an alcohol swab, the intramuscular injection should be performed by inserting the needle at a 90 degree angle into the gluteal area, anterior thigh, or deltoid; injection sites should be alternated.



NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication.



8. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

**AFTER INJECTION**

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip

with the thumb or finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a CLICK is heard or felt.


**ADDITIONAL INFORMATION**

- Dispose of the syringe according to local regulations/procedures.

**HOW SUPPLIED**

Each LUPRON DEPOT 3.75 mg kit (NDC 0074-3641-03) contains:

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs
- a complete prescribing information enclosure

Each syringe contains sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT 3.75 mg is administered as a single monthly IM injection.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

**REFERENCES**

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2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

Reference ID: 3398785

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63; 1172-1193.
4. Polovich, M., White, J.M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. Ed.) Pittsburgh, PA: Oncology Nursing Society.

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AbbVie Inc.
North Chicago, IL 60064
by Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

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## 23. APPENDIX E: CLINICAL LABORATORY TESTS

| **CLINICAL CHEMISTRY** | **HEMATOLOGY** |
|---|---|
| ***The following clinical chemistry tests will be performed at the Screening Visit, at Postdosing Days 1, and at the Final Visit*** | ***The following hematology tests will be performed at the Screening Visit, at Postdosing Day 1, and at the Final Visit*** |
| Calcium | Hemoglobin |
| Chloride | Hematocrit |
| Creatinine | RBC count |
| Glucose | WBC count with differential |
| Alkaline phosphatase | Platelet count |
| Potassium | **URINALYSIS** |
| Sodium | ***The following urinalysis tests will be performed at the Screening Visit and the Final Visit*** |
| Aspartate aminotransferase (AST) | pH |
| Alanine aminotransferase (ALT) | Specific gravity |
| Blood urea nitrogen (BUN) | Glucose |
| Phosphorus | Protein |
| Protein total | RBC |
| Albumin | WBC |
| Bilirubin total | Ketones |
| **LIPID PANEL** | Bilirubin |
| Cholesterol | Nitrite |
| Triglycerides | Urobilinogen |
| LDL | Microscopic examination (performed on abnormal findings unless otherwise specified) |
| HDL | Macroscopic examination |
| **SEROLOGY** | |
| ***The following serology tests will be performed at the Screening Visit*** | |
| HIV antibody test | |
| HbsAg Hepatitis B test | |
| Hepatitis C (HCV) antibody test | ***The following test will be performed at Screening Visit and at Treatment Day -1*** |
| ***The following tests will be performed at the Screening Visit, at Treatment Days -1*, 8, 15, 22, 27** (Treatments "A", "B", and "D"), Treatment Day 29 (Treatments "C" and "D"), and at Post-Treatment Days 7, 14, 21.***<br>****Day – 1 for Treatments "A", "B" and "C", Day 1 for Treatment "D"***<br>***** Day 27 for Treatments "A" and" B"only*** | Serum pregnancy (β-hCG) test (Treament "A", "B" and "C") |
| Urine drug screen test | ***The following test will be performed at*** |

| | |
|---|---|
| | ***Treatment Days 1* (*Treatment D) 15, 27** (**Treatments "A", and, "B"), Postdosing Day 1*** (***Treatment "C" and "D") and Postdosing Day 28 (Final Visit)*** |
| Urine cotinine test | Urine pregnancy test |

## 24. APPENDIX F: SUBJECT DIARY CARD

**Subject Number:_____ Subject initials: _____**

***PART 1: 28-Day Treatment (Dosing) Period***

| Date (MM/DD)[2] | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Day → | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
| ***Pills Taken[1]*** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Time of first dose | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fasting rules followed (1st dose) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Time of second dose | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fasting rules followed (2nd dose) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ***Bleeding Diary*** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if NO BLEEDING/SPOTTING | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if SPOTTING | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if LIGHT bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if NORMAL bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if HEAVY bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | |

**Principal Investigator or Designee Signature: _____ Date: _____**

[1]This section is shown for Treatment Groups "B" and "D" subjects; for Treatment Group "A" subjects, remove reference to second dose; For Treatment Group "C" subjects, remove entire "Pills Taken" section.

**Subject Number:_____ Subject initials: _____**

## ***PART 2: 28-Day Post-Dosing Evaluation Period***

| Date (MM/DD) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Post-dosing Day → | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** |
| ***Bleeding Diary*** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if NO BLEEDING/SPOTTING | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if SPOTTING | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if LIGHT bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if NORMAL bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Check if HEAVY bleeding | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

**Principal Investigator or Designee Signature: _____ Date: _____**

## 25. APPENDIX G: ACCEPTABLE DAYS FOR INITIATION OF DOSING IN RELATION TO CYCLE LENGTH

| Cycle Length (days) | Acceptable days for initiation of dosing | | |
|---|---|---|---|
| 21 | Day 1 – Day 4 | -or- | Day 11 to Day 21 |
| 22 | Day 1 – Day 4 | -or- | Day 12 to Day 22 |
| 23 | Day 1 – Day 4 | -or- | Day 13 to Day 23 |
| 24 | Day 1 – Day 4 | -or- | Day 14 to Day 24 |
| 25 | Day 1 – Day 4 | -or- | Day 15 to Day 25 |
| 26 | Day 1 – Day 4 | -or- | Day 16 to Day 26 |
| 27 | Day 1 – Day 4 | -or- | Day 17 to Day 27 |
| 28 | Day 1 – Day 4 | -or- | Day 18 to Day 28 |
| 29 | Day 1 – Day 4 | -or- | Day 19 to Day 29 |
| 30 | Day 1 – Day 4 | -or- | Day 20 to Day 30 |
| 31 | Day 1 – Day 4 | -or- | Day 21 to Day 31 |
| 32 | Day 1 – Day 4 | -or- | Day 22 to Day 32 |
| 33 | Day 1 – Day 4 | -or- | Day 23 to Day 33 |
| 34 | Day 1 – Day 4 | -or- | Day 24 to Day 34 |
| 35 | Day 1 – Day 4 | -or- | Day 25 to Day 35 |

Note: Subjects enrolled to the third oral dose (Treatment "D") will have a dosing initiation visit scheduled 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began.