



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: A-43818 (ABT-818) leuprolide acetate for depot suspension (Lupron Depot)	Volume:	
Name of Active Ingredient: Leuprolide acetate	Page:	
Title of Study: A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6-Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma		
Coordinating Investigator: Jay M. Young, MD [redacted] [redacted] redacted information 03Jul2014		
Study Sites: Subjects were enrolled at 58 sites in the United States (30 sites enrolled subjects treated with Formulation A and subjects treated with Formulation B, 9 sites enrolled only subjects treated with Formulation A, and 19 sites enrolled only subjects treated with Formulation B).		
Publications: None		
Studied Period (Years): First Subject First Visit: 25 February 2008 Last Subject Last Visit (Formulation A): 19 June 2009	Phase of Development: 3	
Objectives: The objectives of this trial were: <ul style="list-style-type: none"> To assess the efficacy and safety of 2 new leuprolide acetate 45-mg 6-month depot formulations over 48 weeks. Each formulation was to be delivered as 2 single injections 24 weeks apart, in subjects with prostate cancer. To establish a pharmacokinetic (PK) profile of serum leuprolide for the 2 new 45-mg 6-month depot formulations in a subset of subjects with prostate cancer. 		
Methodology: The L-PC07-169 study was a Phase 3, open-label, 48-week, multicenter clinical study conducted in men with prostate cancer. This study evaluated the efficacy and safety of 2 leuprolide acetate 45-mg 6-month depot formulations and, in a subset of subjects, plasma leuprolide concentrations to establish the PK profile for these new formulations. Subjects received a total of 2 IM injections, administered 24 weeks apart, both the same formulation (either Formulation A or Formulation B) of leuprolide acetate 45-mg 6-month depot. The first injection was administered on Day 1. The second injection was to be administered on Day 169 (i.e., Month 6 or Week 24). The first 150 subjects enrolled were to receive Formulation A of leuprolide acetate 45-mg 6-month depot. The next 150 subjects enrolled were to receive Formulation B of leuprolide acetate 45-mg 6-month depot. This study included a screening period (up to 28 days), a 12-month treatment period (two 6-month treatment cycles), and a 30-day follow-up period. During the first half of the treatment period, study visits were planned for Days 1, 2, and 8, and at the end of Weeks 2, 4, 8, 14, 20 and 24. During the second half of the treatment period, study visits were planned for Weeks 24 and 25 (on Days 170, 171, and 176), and at the end of Weeks 26, 30, 34, 40, 46 and 48, followed by a 30 day post-treatment follow-up visit.		



<p>Number of Subjects (Planned and Analyzed):</p> <p>Formulation A: Safety and Efficacy: 150 subjects planned; 151 subjects enrolled and analyzed PK: 24 subjects planned; 28 actual (subjects who had at least 1 PK sample); 26 evaluated for PK for both doses; 25 evaluated for PK for the first dose; 25 evaluated for PK for the second dose</p> <p>Formulation B: 150 subjects planned; number of subjects enrolled and analyzed will be reported in a separate clinical study report for Formulation B.</p>					
<p>Diagnosis and Main Criteria for Inclusion: Subjects had to be at least 18 years of age, have serum testosterone level > 150 ng/dL; histologically-confirmed prostatic adenocarcinoma Jewett stage A₂, B, C, or D, or TNM cT_{1b-4}N_{any}M_{any}, or rising PSA following radical prostatectomy (≥ 0.2 ng/dL increase from previous test on 2 consecutive assessments) or rising PSA following prostate irradiation (≥ 2.0 ng/dL increase above the nadir [lowest PSA achieved following radiation therapy]); prostate cancer status and general clinical status was sufficient to warrant at least 48 weeks of continuous androgen deprivation treatment, without concomitant antiandrogen treatment; ECOG performance score of 0, 1, or 2; life expectancy was at least 18 months; no anticipated need for radical prostatectomy or radiotherapy (including conventional electron beam radiation therapy [EBRT], 3-dimensional conformal radiation therapy [3D-CRT], intensity modulated radiation therapy [IMRT], proton beam radiation therapy [PBRT] or brachytherapy) or cryotherapy of local disease within the 48-week treatment period; and no history of bilateral orchiectomy, adrenalectomy, or hypophysectomy.</p>					
<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: All subjects were to receive leuprolide acetate 45-mg 6-month depot IM. Each subject was to receive a total of 2 IM injections that were administered 24 weeks apart, both of the same formulation.</p>					
Investigational Product	Formulation	Formulation Number^a	Dosage	Lot Number	Manufacturer and Location
leuprolide acetate 45-mg 6-month	45-mg	A (IP2)	45 mg IM Q 6 Months	Z3279011	[REDACTED]
leuprolide acetate 45-mg 6-month	45-mg	B (IP1)	45 mg IM Q 6 Months	Z3274011	[REDACTED]
<p>a. Parentheses indicate formulation designations used previously chemistry, manufacturing, and controls (CMC) development [REDACTED]</p>					
<p>Duration of Treatment: Subjects were to receive the first injection on Day 1 and the second injection on Day 169 (i.e., Week 24, Month 6), during the 12-month treatment period (total treatment period = 48 weeks).</p>					
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None</p>					

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Criteria for Evaluation

Efficacy:

ITT Population for Efficacy Endpoints (N = 151): All subjects who received at least 1 dose of study drug, had at least 1 postbaseline measurement of the appropriate parameter, and who did not use prohibited treatment that lowered testosterone levels or blocked its action during the first 32 days following the initiation of study drug.

- ITT Population for the Primary Efficacy Endpoint (N = 150): The ITT population with the following subjects excluded:
 - prematurely discontinued subjects whose final testosterone value was before Day 19 and was not suppressed (i.e., excluded subjects whose final testosterone value was > 50 ng/dL and before Day 19), or
 - subjects who were suppressed through Week 48 with no escapes but had no testosterone values at Week 4 (Days 20 to 32, inclusive) by which to determine suppression by Day 32.

Other subjects who prematurely discontinued from the trial were included and censored at the time of their last testosterone measurements according to the Kaplan-Meier methodology.

One subject (145) was excluded from the ITT population for the primary efficacy endpoint because he had no testosterone value for Week 4. Serum testosterone for this subject was suppressed (13 ng/dL) at the next study visit (Day 57). The subject completed the study and his serum testosterone levels remained suppressed throughout the treatment period.

- Completer Population (N = 135): Subjects in the ITT population for the primary endpoint who had 2 injections of study drug and a testosterone determination for the Week 48 window (Days 324 to 344, inclusive) were included in the completer population. The completer population was used for a sensitivity analysis of the primary efficacy endpoint.

Safety Population (N = 151): All subjects who received at least 1 dose of study drug were included in all safety summaries and analyses.

PK Population (Evaluated for PK for Both Doses: N = 26): Evaluated for PK for First Dose: 25; Evaluated for PK for Second Dose: 25. The data from all subjects with samples collected for plasma leuprolide determinations were included in the PK analysis with the following exceptions: 2 subjects were not evaluated for either dose because of sparse sampling, 1 subject was excluded from the PK calculations for the first dose because of unexpectedly low leuprolide plasma concentrations, 1 subject was excluded from PK calculations for the second dose because he discontinued from the study after the first dose, and 2 subjects were excluded from the AUC_t calculation after the first dose because of missing samples.



Statistical Methods

Efficacy: The percentage of subjects whose serum testosterone concentrations were suppressed (≤ 50 ng/dL) from Week 4 through Week 48 was calculated using the Kaplan-Meier method for right-censored observations. The 2-sided 90% lower confidence bound for this percentage was also calculated using the standard error from the Kaplan-Meier method. Seven supportive sensitivity analyses were performed to evaluate the effects of different assumptions on the primary endpoint analysis. As secondary endpoint analyses, the change from baseline in serum PSA levels at each treatment visit, mean serum testosterone concentrations at each treatment visit, and acute-on-chronic changes in testosterone and LH concentrations (i.e., changes from just prior to the second injection through 14 days after the second injection) were summarized. In addition, time to testosterone suppression, duration of suppression, the proportion of subjects who escaped from suppression, serum LH and PSA concentrations at each study visit, acute-on-chronic changes in serum PSA concentrations, change from baseline in ECOG performance status, change in subject symptom assessments, and change from baseline in serum PAP concentrations were also summarized with appropriate statistics. *P* values were provided for all mean changes using paired t-tests.

Pharmacokinetic: Plasma leuprolide concentrations were summarized with descriptive statistics. In addition, mean plasma concentration versus time profiles were plotted. The following PK parameters for leuprolide were estimated by noncompartmental methods and summarized with descriptive statistics: the mean plasma concentration versus time profile, AUC (area under the plasma concentration time curve), C_{\max} (maximum plasma concentration), t_{\max} (time to maximum plasma concentration), C_{trough} (trough plasma concentration), and C_{ss} (steady-state concentration).

Safety: The number and percentage of subjects with treatment emergent adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and were further summarized by maximum severity and maximum investigator-assigned relationship to study drug. Adverse events of special interest, which included injection site reaction, anemia, bone fracture, diabetes, and cardiac events, were also summarized. Clinical laboratory and vital sign measurements were summarized for mean changes to each study visit, by shifts relative to the laboratory normal ranges (clinical laboratory measurements only), and by the number and percentage of subjects with values that met the predefined criteria for potentially clinically significant (PCS) values.

Summary/Conclusions

Demographic and Other Baseline Characteristic Results:

Approximately 79% of subjects were White and 20% of subjects were Black or African-American. Subjects ranged from 48 to 92 years of age, with a mean of 74.9 years. The majority of subjects were at least 65 years of age (88.1%). The average time since subjects had their first histological diagnosis of prostate cancer was 4.6 years. Fifty-six subjects (37.6%) had their first histological diagnosis within 1 year prior to study enrollment and 23 subjects (15.4%) had their first histological diagnosis 10 to up to 20 years prior to enrollment. The NCI grade based on TNM classification was stage II for 103 subjects (71.5%), stage III for 20 subjects (13.9%), and stage IV for 21 subjects (14.6%). The majority of subjects (65.3% [94/144]) had a Gleason score of 7 or higher, and the majority of subjects (82.0%) had an ECOG score of 0. The mean baseline testosterone level was 433.1 ng/dL and the mean baseline PSA level was 35.3 ng/mL.



Efficacy Results:

Overall, testosterone suppression with this new 45-mg, 6-month depot formulation was rapid and was sustained throughout the 12 month treatment period. The primary endpoint of serum testosterone suppression to values ≤ 50 ng/dL from Week 4 through Week 48 was met with a suppression rate of 93.7%. The lower bound of the 2-sided 90% confidence interval of 90.3% using the Kaplan-Meier method exceeded the prespecified minimum requirement of 87% for the formulation to be successful.

Results of the primary analysis were supported by the sensitivity analyses, with similar results when no Week 48 window was applied, when final suppression was considered to have occurred at the end of the 21-day Week 48 window, when late failures were considered to have occurred at the start of the 21-day Week 48 window. In the very conservative analysis where subjects who prematurely discontinued with their last testosterone result being still suppressed were considered as failures, the percentage suppressed was 84.7%. When a simple percentage was created among the 135 subjects who completed the trial, including subjects having a testosterone result in the 21-day Week 48 window, 94.1% (127/135) of subject were successfully suppressed. Most subjects were not suppressed by Week 2 and the Kaplan-Meier estimate of percentage of subjects suppressed from Week 2 through Week 48 was 10.8%. There was no Week 3 visit in this study so suppression at this time point could not be assessed. One additional subject suppressed after Week 4 and the Kaplan-Meier estimate of the percentage of subjects suppressed from Week 8 to Week 48 was 94.3%.

Subgroup analyses for the primary endpoint included age, race, NCI prostate cancer staging based on TNM, BMI, and baseline testosterone level. No differences were observed for age or BMI. The testosterone suppression rate was numerically higher for the 118 subjects who were Caucasian (95.5%) compared with the 30 subjects who were Black or African-American (86.5%), but the difference was not statistically significant. Similarly, subjects with higher baseline testosterone levels (top tertile: > 481 ng/dL) had a numerically lower testosterone suppression rate (89%) compared with subjects who had baseline testosterone levels in the middle (95.9%) and lower (95.9%) tertiles, but the difference did not reach statistical significance. The testosterone suppression rate for the 21 subjects with stage IV prostate cancer (100%) was statistically significantly greater than for the 103 subjects with stage II prostate cancer (92.0%).

Nine subjects were considered treatment failures. Of these, only 1 subject failed to suppress by Day 32 and 8 subjects escaped testosterone suppression after Week 4. The escapes from testosterone suppression were not associated with increases in PSA for any subject, and the escapes were transient for 5 of the 8 subjects.

As expected, an initial stimulation of the hypothalamic-pituitary-gonadal axis (flare effect) was observed following the first dose of leuprolide acetate 45-mg with an increase in mean LH levels from 7.2 mIU/mL at baseline to 29.7 mIU/L on Day 8 and an initial increase in mean serum testosterone levels from 432.9 ng/dL at baseline to 468.2 ng/mL on Day 8. Suppression of LH and testosterone was well maintained through each 24-week treatment interval, with LH means less than or equal to 0.2 mIU/mL for each injections, and testosterone means at the end of the interval less than 11 ng/dL for both injections. After Week 4, mean LH levels were maintained at levels ≤ 0.4 mIU/mL and mean testosterone levels were maintained at levels ≤ 14.3 ng/dL throughout the remainder of the treatment period.



Efficacy Results (Continued):

Clinically, the acute-on-chronic effect on the hypothalamic-pituitary-gonadal axis appears to be negligible with the second injection. However, small statistically significant mean increases (0.1 to 0.2 mIU/mL) in LH were observed from just prior to the second injection to the serial time points after the second injection. These increases were not associated with any increases in testosterone (mean decreases were observed) or PSA (mean change of 0.1 ng/mL).

The mean PSA levels initially increased from 35.0 ng/mL at baseline to 40.4 ng/mL on Day 8 (flare effect) and subsequently decreased to levels ≤ 2.9 ng/mL throughout the remainder of the treatment period. After Day 8, only 3 subjects had increases from baseline at any given visit and these PSA increases were not correlated with increases in testosterone. At Week 14 and following, PSA levels in the majority of subjects decreased at least 50% from baseline, and most subjects ($> 85\%$ at each visit) with high PSA levels at baseline shifted to normal. There was no increase in PSA level during the acute-on-chronic phase of the study as indicated by minimal mean change (+0.1 ng/mL).

Although the mean baseline scores, on a scale of 1 (no pain/no difficulty) to 10 (worst possible pain/very difficult), were low for bone pain (1.6), urination pain (1.4), and urination difficulty (1.6), there were small mean improvements for each of these assessments at every visit. The mean improvements were statistically significant for 4 of the 11 assessment times for urination pain and 5 of the 11 assessment times and the Final Visit for urination difficulty.

The majority of subjects (82.0%) had a baseline ECOG score of 0 (best performance), and 27 subjects had a baseline ECOG score of either 1 ($n = 25$) or 2 ($n = 2$) at baseline. At each study visit, the majority of subjects ($> 82\%$) had no change or had improvements in their performance status.

Pharmacokinetic Results:

After dosing, an initial rapid increase in plasma leuprolide concentration (burst) was observed, followed by a rapid decline over the first 7 days postdose. The maximum leuprolide concentration occurred at approximately 2 hours after each injection. The mean C_{max} values for the first and second doses were 6.7 and 7.4 ng/mL, respectively.

After the rapid decline of leuprolide concentration at the end of the burst phase, the mean leuprolide concentrations rose between Weeks 2 and 4, where it started to decline slowly from Week 4 to Week 24. Because of the decreasing trend of leuprolide concentration in the sustained release phase of the PK profile, a steady state concentration (C_{ss}) was not reported.

Among 25 subjects who had plasma leuprolide samples assayed at the end of the first dosing period prior to the second injection (24 weeks after the first injection), 24 subjects had quantifiable leuprolide concentrations (LLOQ = 0.025 ng/mL). Among 25 subjects who had plasma leuprolide samples assayed at the end of the second dosing period at Week 48 (24 weeks after the second injection), 22 subjects had quantifiable leuprolide concentrations. The mean trough leuprolide concentration at the end of first and second dosing period were 0.073 and 0.057 ng/mL, respectively.

The mean AUC_t values were 1282 and 1142 ng•h/mL for the first and second doses, respectively. The mean total AUC_t value for the both doses was 2483 ng•h/mL. Leuprolide plasma concentration-time profile of leuprolide acetate 6-month depot appeared to be reproducible as the mean PK profile after the first dose was similar to that after the second dose.



Safety Results:

Treatment-emergent adverse events were reported for 143 of the 151 subjects (94.7%) for the 48-week treatment period. The most common adverse events reported for at least 10% of subjects included hot flush (58.3% [88/151]), injection site pain (17.9% [27/151]), and fatigue (11.9% [18/151]). The majority of these events were mild to moderate in severity. The most common adverse events that were treatment-related (i.e., considered possibly or definitely related to study drug by the investigator) were also hot flush (57.6%), injection site pain (9.9%), and fatigue (9.9%). All other treatment-related adverse events were reported for no more than 5 subjects (3.3%).

One death, considered not related to study drug, was reported. The subject was 92 years of age with a history of chronic obstructive pulmonary disease (COPD) and died because of aspiration pneumonia that began 11 days after he completed the study.

Serious adverse events were reported for 31 subjects (20.5%), including 2 subjects who discontinued from the study because of serious adverse events (coronary artery disease, asthenia, and hyperkalemia for Subject [REDACTED]; non-Hodgkin's lymphoma stage IV for Subject [REDACTED]). Two subjects had serious adverse events that were considered possibly related to study drug by the investigator (colonic pseudo-obstruction for Subject [REDACTED] and angina pectoris for Subject [REDACTED]); the events for both subjects resolved and the subjects completed the study.

Seven subjects had adverse events that led to discontinuation from the study. The events for 4 of these subjects were considered at least possibly related to study drug by the investigator: fatigue and sleep disorder for Subject [REDACTED], constipation for Subject [REDACTED], fatigue and hot flush for Subject [REDACTED] and hot flush for Subject [REDACTED].

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Hematology laboratory data revealed small mean decreases in hemoglobin, hematocrit, and red blood cell count that are consistent with the known side effects of androgen deprivation therapy. The mean decrease in hemoglobin concentration from baseline (142.4 g/L) to Final Visit (131.9 g/L) was -10.5 g/L, representing a less than 10% mean decrease over the 48-week treatment period. The percentage of subjects with at least 1 hemoglobin value < 105 g/L was 7.3%. Adverse events associated with anemia and low hemoglobin were reported in 10 subjects, 4 of whom required blood transfusions. Only 2 subjects had hemoglobin values as low as 90 g/L: 1 subject had an associated serious adverse event of anemia that the investigator attributed to metastatic cancer and 1 subject had a transient unexplained decreased value that returned to normal at the next visit.

Four subjects experienced transaminase levels that exceeded $3 \times \text{ULN}$ and the values for 3 of these subjects returned to near baseline levels or decreased towards the normal range during the treatment period. The elevations for the remaining subject were observed at Final Visit. No clinically significant changes affecting renal function were noted. Small mean decreases were observed for uric acid and creatinine, while small mean increases were observed for BUN, inorganic phosphorus and bicarbonate. None of these changes were of clinical concern.

The mean glucose concentration for this study population was above normal at baseline (5.784 mmol/L) and further increased by 0.399 mmol/L at the Final Visit. Only 1 subject had a high PCS glucose value (≥ 16.555 mmol/L) during the study; this subject had a history of type 2 diabetes.

Small mean increases from baseline were observed for the lipid parameters cholesterol (+0.148 mmol/L at Final Visit), HDL cholesterol (+0.074 mmol/L at Final Visit), and triglycerides (+0.156 mmol/L at Final Visit), but not for LDL cholesterol (-0.013 mmol/L at Final Visit), but the percentage of subjects with high PCS values at any time during the study was small (cholesterol [0.7%]; triglycerides [3.3%]).



Safety Results (Continued):

No clinically important trends were observed for urinalysis or vital signs. A small increase in mean weight was observed in this study (+1.76 kg at Final Visit).

Conclusions:

The efficacy and safety data of this new 45 mg, 6-month depot formulation of leuprolide acetate presented in this clinical study report are consistent with the efficacy and safety of Lupron Depot formulations that are currently marketed in the US. Testosterone suppression was rapid and was sustained throughout the 12-month treatment period. Overall, 93.7% of subjects met the primary endpoint of serum testosterone suppression to values ≤ 50 ng/dL from Week 4 through Week 48 using the Kaplan-Meier method for right-censored observations. Sensitivity analyses of the primary endpoint support the primary analysis. Subgroup analyses did not reveal any meaningful difference in response to treatment or unexpected safety concerns.

The hormonal (testosterone and LH) and clinical responses to treatment with this formulation reflect a favorable performance profile after transient initial increases in testosterone and LH with a rapid decrease in testosterone to castrate levels by Week 4; negligible acute-on-chronic responses following the second injection; and excellent suppression through the end of each treatment cycle. These hormonal results are comparable to those observed for the approved 3-month and 4-month Lupron Depot formulations.

Adverse event and laboratory findings were consistent with those observed in previous leuprolide acetate clinical trials and no new safety signals were observed.

In summary, this 45-mg, 6-month formulation of leuprolide acetate achieved the prespecified efficacy requirement, resulted in no new safety signals compared with the established Lupron Depot safety profile, and will provide enhanced convenience for patients by reducing the number of injections per year.



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: A-43818 (ABT-818) leuprolide acetate for depot suspension (Lupron Depot)	Volume:	
Name of Active Ingredient: Leuprolide acetate	Page:	
Title of Study: A Phase 3 Multi-Center, Open-Label, Trial to Evaluate the Efficacy, Safety and Pharmacokinetics of Two 6-Month Leuprolide Formulations in Subjects with Prostatic Adenocarcinoma (Formulation B)		
Coordinating Investigator: Jay M. Young, MD [redacted] redacted information 03Jul2014		
Study Sites: Subjects were enrolled at 58 sites in the United States (30 sites enrolled subjects treated with Formulation A and subjects treated with Formulation B, 9 sites enrolled only subjects treated with Formulation A, and 19 sites enrolled only subjects treated with Formulation B).		
Publications: None		
Studied Period (Years): First Subject First Visit (Formulation B): 28 April 2008 Last Subject Last Visit (Formulation B): 18 September 2009		Phase of Development: 3
Objectives: The objectives of this trial were: <ul style="list-style-type: none">To assess the efficacy and safety of 2 new leuprolide acetate 45 mg 6-month depot formulations over 48 weeks. Each formulation was to be delivered as 2 single injections, 24 weeks apart, in subjects with prostate cancer.To establish a pharmacokinetic (PK) profile of plasma leuprolide for the two new 45 mg 6-month depot formulations in a subset of subjects with prostate cancer.		



Methodology: The L-PC07-169 study was a Phase 3, open-label, 48-week, multicenter clinical study conducted in men with prostate cancer. This study evaluated the efficacy and safety of 2 leuprolide acetate 45 mg 6-month depot formulations and, in a subset of subjects, plasma leuprolide concentrations to establish the PK profile for these new formulations. Subjects received a total of 2 IM injections, administered 24 weeks apart, both the same formulation (either Formulation A or Formulation B) of leuprolide acetate 45 mg 6-month depot. The first injection was administered on Day 1. The second injection was to be administered on Day 169 (i.e., Month 6 or Week 24).

The first 150 subjects enrolled were to receive Formulation A of leuprolide acetate 45 mg 6-month depot. The next 150 subjects enrolled were to receive Formulation B of leuprolide acetate 45 mg 6-month depot. This study included a screening period (up to 28 days), a 12-month treatment period (two 6-month treatment cycles), and a 30-day follow-up period. During the first half of the treatment period, study visits were planned for Days 1, 2, and 8, and at the end of Weeks 2, 4, 8, 14, 20 and 24. During the second half of the treatment period, study visits were planned for Weeks 24 and 25 (on Days 170, 171, and 176), and at the end of Weeks 26, 30, 34, 40, 46 and 48, followed by a 30-day post-treatment follow-up visit.

Number of Subjects (Planned and Analyzed):

Formulation A:

Safety and Efficacy: 150 subjects planned; 151 subjects enrolled and analyzed

PK: 24 subjects planned; 28 actual (subjects who had at least 1 PK sample); 26 evaluated for PK for both doses; 25 evaluated for PK for first dose; 25 evaluated for PK for second dose

Formulation B:

Safety and Efficacy: 150 subjects planned; 159 subjects enrolled and analyzed

PK: 24 subjects planned; 29 actual (subjects who had at least 1 PK sample); 28 evaluated for PK for both doses; 27 evaluated for PK for first dose; 24 evaluated for PK for second dose

Diagnosis and Main Criteria for Inclusion: Subjects had to be at least 18 years of age, have serum testosterone level > 150 ng/dL; histologically-confirmed prostatic adenocarcinoma Jewett stage A₂, B, C, or D, or TNM cT_{1b-4}N_{any}M_{any}, or rising PSA following radical prostatectomy (≥ 0.2 ng/dL increase from previous test on 2 consecutive assessments) or rising PSA following prostate irradiation (≥ 2.0 ng/dL increase above the nadir [lowest PSA achieved following radiation therapy]); prostate cancer status and general clinical status was sufficient to warrant at least 48 weeks of continuous androgen-deprivation treatment, without concomitant antiandrogen treatment; ECOG performance status was grade 0, 1, or 2; life expectancy was at least 18 months; no anticipated need for radical prostatectomy or radiotherapy (including conventional electron beam radiation therapy [EBRT], 3-dimensional conformal radiation therapy [3D-CRT], intensity modulated radiation therapy [IMRT], proton beam radiation therapy [PBRT] or brachytherapy) or cryotherapy of local disease within the 48-week study period; and no history of bilateral orchiectomy, adrenalectomy, or hypophysectomy.



Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: All subjects were to receive leuprolide acetate 45 mg 6-month depot IM. Each subject was to receive a total of 2 IM injections that were administered 24 weeks apart, both of the same formulation.					
Investigational Product	Formulation	Formulation Number^a	Dosage	Lot Number	Manufacturer and Location
leuprolide acetate 45 mg 6-month	45 mg	A (IP2)	45 mg IM Q 6 Months	Z3279011	[REDACTED]
leuprolide acetate 45 mg 6-month	45 mg	B (IP1)	45 mg IM Q 6 Months	Z3274011	[REDACTED]
a. Parentheses indicate formulation designations used previously for chemistry, manufacturing, and controls (CMC) development [REDACTED]					
Duration of Treatment: Subjects were to receive the first injection on Day 1 and the second injection on Day 169 (i.e., Week 24, Month 6), during the 12-month treatment period (total treatment period = 48 weeks).					
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None					

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Criteria for Evaluation

Efficacy:

ITT Population for Efficacy Endpoints (N = 157): All subjects who received at least 1 dose of study drug, had at least 1 postbaseline measurement of the appropriate parameter, and who did not use prohibited treatment that lowered testosterone levels or blocked its action during the first 32 days following the initiation of study drug. Two subjects [REDACTED] were excluded from the ITT population for any efficacy endpoint due to taking prohibited medication (finasteride [Proscar®] and testosterone undecionate [Nebido®], respectively) during the first 32 days following the initiation of study drug.

- ITT Population for the Primary Efficacy Endpoint (N = 154): The ITT population with the following subjects excluded:
 - prematurely discontinued subjects whose final testosterone value was before Day 19 and was not suppressed (i.e., excluded subjects whose final testosterone value was > 50 ng/dL and before Day 19), or
 - subjects who were suppressed through Week 48 with no escapes from testosterone suppression but had no testosterone values at Week 4 (Days 20 to 32, inclusive) by which to determine suppression by Day 32.

Three subjects [REDACTED] did not have testosterone data at Week 4 or subsequent escapes and were excluded from the ITT population for the primary endpoint. Other subjects who prematurely discontinued from the trial were included and censored at the time of their last serum testosterone measurements according to the Kaplan-Meier methodology.

- Completer Population (N = 112): Subjects in the ITT population for the primary endpoint who had a Week 48 visit (Days 324 to 344, inclusive) and received 2 depot injections of study drug were included in the completer population. The completer population was used for a sensitivity analysis of the primary efficacy endpoint.

PK Population (N = 28): The data from all subjects with samples collected for plasma leuprolide determinations were included in the PK analysis with the following exceptions: Subjects [REDACTED] were not planned to be included in the original PK cohort. However, these subjects had plasma samples collected. All 4 subjects received the first dose, and only 3 subjects [REDACTED] received the second dose. PK parameters were calculated for Subjects [REDACTED] for the first dose but were not calculated for Subjects [REDACTED] because of the sparse sampling after the second dose. No PK parameters were calculated for Subject [REDACTED] because of the sparse sampling after the first dose. PK parameters were not calculated for plasma PK profiles for Subject [REDACTED] because of sparse sampling after the first dose. Although PK parameters were calculated for the first dose, Subjects [REDACTED] terminated early from the study before the second dose of Formulation B. The PK parameter, AUC_t , was not determined for Subject [REDACTED] because of missing samples between 1344 and 3360 hours after the first dose. The PK parameter, AUC_t , was not determined for Subject [REDACTED] because of missing samples between 4040 and 8046 hours after the second dose.

Safety Population (N = 159): All subjects who received at least 1 dose of study drug were included in all safety summaries and analyses. All subjects in the database received at least 1 dose of study drug.

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Statistical Methods

Efficacy: The percentage of subjects whose serum testosterone levels were suppressed (≤ 50 ng/dL) from Week 4 through Week 48 was calculated according to the Kaplan-Meier method for right-censored observations. The 2-sided 90% lower confidence bound for this percentage was also calculated using the standard error from the Kaplan-Meier method. Seven supportive sensitivity analyses were performed to evaluate the effects of different assumptions on the primary endpoint analysis. As secondary endpoint analyses, the change from baseline in serum PSA levels at each treatment visit, mean serum testosterone concentrations at each treatment visit, and acute-on-chronic changes in testosterone and LH concentrations (i.e., changes from just before the second injection through 14 days after the second injection). In addition, time to testosterone suppression, duration of suppression, the proportion of subjects who escaped from suppression, serum LH and PSA concentrations at each study visit, acute-on-chronic changes in serum PSA concentrations, change from baseline in ECOG performance status, change in subject symptom assessments, and change from baseline in serum PAP concentrations were also summarized with appropriate statistics. *P* values were provided for all mean changes using paired t-tests.

Pharmacokinetic: Plasma leuprolide concentrations were summarized with descriptive statistics. In addition, mean plasma concentration versus time profiles were plotted. The following PK parameters for leuprolide were estimated by noncompartmental methods and summarized with descriptive statistics: the mean plasma concentration versus time profile, AUC (area under the plasma concentration time curve), C_{\max} (maximum plasma concentration), t_{\max} (time to maximum plasma concentration), and C_{trough} (trough plasma concentration).

Safety: The number and percentage of subjects with treatment emergent adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and were further summarized by maximum severity and maximum investigator-assigned relationship to study drug. Adverse events of special interest, which included injection site reaction, anemia, bone fracture, diabetes, and cardiac events, were also summarized. Clinical laboratory and vital sign measurements were summarized for mean changes to each study visit, by shifts relative to the laboratory normal ranges (clinical laboratory measurements only), and by the number and percentage of subjects with values that met the predefined criteria for potentially clinically significant (PCS) values.

Summary/Conclusions

Demographic and Other Baseline Characteristic Results:

Approximately 66% (105/159) of subjects were White and 30% (47/159) of subjects were Black or African-American. Subjects ranged from 46 to 94 years of age, with a mean of 73.1 years. The majority of subjects were at least 65 years of age (79.2%). The average time from first histological diagnosis of prostate cancer was 4.8 years. Forty-nine subjects (31.8%) had their first histological diagnosis within 1 year prior to study enrollment whereas 28 subjects (18.2%) had their first histological diagnosis at least 10 years prior to enrollment. The NCI stage based on TNM classification was stage II for 113 subjects (76.4%), stage III for 11 subjects (7.4%), and stage IV for 24 subjects (16.2%). The majority of subjects (73.3% [110/150]) had a Gleason score of 6 or 7, and the majority of subjects (81.8%) had an ECOG score of 0. The mean baseline serum testosterone level was 412.3 ng/dL and the mean baseline serum PSA level was 17.4 ng/mL.



Efficacy Results:

Serum testosterone was suppressed to values ≤ 50 ng/dL from Week 4 through Week 48 in 86.9% of subjects in the ITT population for the primary endpoint according to the Kaplan-Meier method for right-censored observations. The lower limit of the 2-sided 90% confidence interval was 82.2%, which was below the prespecified minimum requirement of 87% for the leuprolide acetate 45 mg 6-month depot Formulation B to be successful.

Eighteen subjects (11.7%) in the ITT population for the primary endpoint did not have successful testosterone suppression from Week 4 through Week 48 using the primary analysis. Seven subjects escaped suppression at the blood collection time just before the second study drug injection and 9 subjects escaped suppression after the second leuprolide acetate injection. Of the remaining 2 subjects counted as failures for the primary endpoint, 1 subject was not suppressed by Day 32 and also escaped suppression after the second injection and was counted as a failure to suppress by Day 32 according to the Kaplan-Meier method. Another subject had no Week 4 result and then had an acute-on-chronic escape from testosterone suppression after a delayed second injection. This subject was conservatively counted as a failure to suppress testosterone by Day 32, according to the method specified in the protocol. The increases in testosterone for 17 of 18 subjects who escaped suppression were not associated with increases in PSA.

The sensitivity analyses supported the findings of the primary analysis.

Since the prespecified goal for the primary endpoint was not met, the analysis does not proceed to the secondary endpoints according to the closed testing procedure specified in the protocol. The results of the secondary and additional endpoints are presented in the clinical study report for completeness, but no claims are made for efficacy of Formulation B.

Pharmacokinetic Results:

After dosing, an initial rapid increase in plasma leuprolide concentration (burst) was observed, followed by a rapid decline over the first 7 days postdose. The maximum leuprolide concentration occurred at approximately 2 hours after injection. The mean C_{max} values for the first and second doses were 14.74 and 13.15 ng/mL, respectively.

After the rapid decline of leuprolide concentration at the end of the burst phase, the mean leuprolide concentrations increased between Weeks 1 to 2 and declined slowly from Week 2 to Week 24. Because of the decreasing leuprolide concentration over time in the sustained-release phase of the PK profile, a steady state concentration (C_{ss}) was not reported.

Among 25 subjects who had plasma leuprolide samples assayed at the end of the first dosing period before the second injection (24 weeks after the first injection), only 11 subjects had quantifiable leuprolide concentrations (lower limit of quantitation = 0.025 ng/mL). Among 19 subjects who had plasma leuprolide samples assayed at the end of the second dosing period at Week 48 (24 weeks after the second injection), only 12 subjects had quantifiable leuprolide concentrations. The mean trough leuprolide concentration at the end of first and second dosing period was 0.017 and 0.029 ng/mL, respectively.

The mean AUC_t values were 1225 and 980 ng•h/mL for the first and second doses, respectively. The mean total AUC_t value for the both doses was 2246 ng•h/mL. Leuprolide plasma concentration-time profile of leuprolide 6-month depot appeared to be reproducible as the mean PK profile after the first dose was similar to that after the second dose.



Safety Results:

Treatment emergent adverse events were reported for 144 of the 159 subjects (90.6%). With the exception of hot flush, injection site pain, arthralgia, and constipation, the type and incidence of adverse events during this study are consistent with the age (median: 74 years) and disease status of this subject population (i.e., organ-confined, locally-advanced or metastatic prostate cancer). The most common adverse events reported for at least 10% of subjects were hot flush (44.7%), injection site pain (16.4%), arthralgia (13.8%), and constipation (10.1%). The majority of these adverse events were mild in severity, as assessed by the investigator. The most common adverse events that were treatment-related (i.e., considered possibly or definitely related to study drug by the investigator) were hot flush (44.0%), injection site pain (11.3%), and fatigue (6.3%). These events reflect some of the most common reported side effects observed in patients receiving androgen-deprivation therapy. All other treatment-related adverse events were reported for no more than 7 subjects each (4.4%).

Six subjects died during the study because of a treatment-emergent adverse event and all of these events were considered not related to study drug. The adverse events with an outcome of death were hepatic neoplasm malignant, cerebrovascular disorder, dementia, suicide, multi-organ failure, and urosepsis. Of the 41 subjects (25.8%) who experienced serious adverse events, 2 subjects had serious adverse events that were considered possibly related to study drug by the investigator (acute myocardial infarction and deep vein thrombosis). All other serious adverse events were considered not related to study drug. There were 10 subjects with serious cardiac adverse events and all 10 subjects had significant cardiac risk factors. Of the 12 subjects who discontinued from the study at least in part due to adverse events, the events were considered at least possibly related to study drug for 3 subjects (hot flush for 2 subjects and worsening anxiety and worsening panic attack).

None of the adverse events of injection site pain were severe, reported as a serious adverse event, or led to premature discontinuation from the study. Adverse events associated with anemia, glucose metabolism, osteoporosis (bone fractures), and cardiovascular disease represent adverse events of interest since they are either known or suspected side effects of androgen-deprivation therapy. These events occurred in a small number of patients and did not lead to discontinuation. All bone fractures were the result of trauma and were considered not related to study drug, except for a femur fracture that was considered possibly related to study drug by the investigator, with an alternative etiology of fall. The cardiovascular adverse event profile suggests trends or patterns that are consistent with findings in this patient population.

A review of adverse events by age (< 65 years versus ≥ 65 years) indicated a similar percentage of subjects younger than 65 years of age (93.9% [31/33]) compared with subjects at least 65 years of age (89.7% [113/126]) with any treatment-related adverse event. Adverse events by race indicated a greater incidence of any treatment-related adverse event for Caucasian (95.2% [100/105]) than for subjects who were Black or African American (83.0% [39/47]) or of other races (71.4% [5/7]).

Hematology laboratory data revealed small mean decreases in hemoglobin, hematocrit, and red blood cell count that are consistent with the known side effects of androgen-deprivation therapy. The mean decrease in hemoglobin concentration from baseline (140.6 g/L) to Final Visit (130.7 g/L) was -9.9 g/L, representing an approximate 10% mean decrease over the 48-week treatment period. Approximately 25% of subjects experienced a shift to hemoglobin values below the normal range (< 125 g/L) at the Final Visit. The percentage of subjects with at least 1 hemoglobin value < 105 g/L was 6.9% (11 of 159 subjects). Adverse events of anemia were reported in 9 subjects, 2 of whom required blood transfusions.



Safety Results (Continued):

Small mean increases in liver enzymes (AST, ALT, GGT, LDH and alkaline phosphatase) were observed. Six subjects experienced transaminase (AST and ALT) levels that exceeded $3 \times$ upper limit of normal (ULN) and the values for 3 of these subjects returned to near baseline levels at the Final Visit. One subject had elevated AST and ALT levels at baseline that increased to a maximum of $4 \times$ ULN on Day 239 and remained elevated at the Final Visit. Two other subjects had elevated transaminase levels ($> 3 \times$ ULN) during the study and 1 of the 2 enzymes remained elevated at the Final Visit. Three of six subjects with transaminase levels that exceeded $3 \times$ ULN also had an increase in total bilirubin ≥ 34.2 $\mu\text{mol/L}$. At the Final Visit, the transaminase and total bilirubin had returned to baseline levels. Adverse events of liver enzyme abnormalities were reported in 5 subjects and these adverse events did not lead to discontinuation. Because leuprolide acetate is not metabolized by the liver, it is unlikely that these changes are associated with treatment.

No clinically significant changes affecting renal function were noted. Mean decreases in uric acid and creatinine and increases in BUN were observed. Shifts in BUN to values above the normal range at the end of treatment (Final Visit) were observed in 8.8% of subjects and 3.8% of subjects had high PCS BUN values (≥ 14.28 mmol/L) during the study. An increase in BUN has been reported for Lupron Depot 3 Month-22.5 mg and Lupron Depot 4 Month 30 mg. Similar to the increase in inorganic phosphorus observed with Lupron Depot 3 Month 22.5 mg and Lupron Depot 4 Month 30 mg, mean increases in serum inorganic phosphorus (+0.157 mmol/L at Final Visit) were also observed in this study. At the end of the treatment period, 7 subjects had shifts to values above the normal range. Although there was a small mean increase in bicarbonate (+2.0 mmol/L at Final Visit), only 1 subject had a shift to a value above the normal range at Final Visit. There is no known mechanism of action with androgen-deprivation therapy causing increases in bicarbonate.

The mean glucose concentration for this study population was above normal at baseline (5.98 mmol/L) and further increased by 0.39 mmol/L at the Final Visit. Approximately 36.4% of subjects had shifts in glucose to values above the normal range at the end of treatment, and 5 subjects had a high PCS glucose value. This is not unexpected because androgen-deprivation therapy can be associated with impaired glucose tolerance and insulin resistance.

Small mean increases from baseline were observed for the lipid parameters cholesterol (+0.110 mmol/L at Final Visit), HDL cholesterol (+0.037 mmol/L at Final Visit), triglycerides (+0.111 mmol/L at Final Visit), and LDL cholesterol (+0.024 mmol/L at Final Visit). This effect has been observed in other studies of leuprolide acetate in men with prostate cancer. More than 20% of subjects had shifts to values above the normal range at the Final Visit for cholesterol (21.6%), LDL cholesterol (28.2%), and triglycerides (21.5%). A shift to values above the normal range at the Final Visit for HDL cholesterol (10.5%) was also observed. The percentage of subjects with high PCS values at any time during the study was small (triglycerides [3.8%]).

No clinically important trends were observed for vital signs. A small percentage of subjects met the PCS criteria for low and high systolic blood pressure (3.1% each) and the PCS criteria for low diastolic blood pressure (1.9%). A small mean increase in weight was observed in this study (0.98 kg increase from baseline to Final Visit). Weight increase has been reported previously in men on androgen-deprivation therapy.



Conclusions:

Formulation B did not meet the prespecified efficacy criteria. Serum testosterone was suppressed to values ≤ 50 ng/dL in 86.9% with a lower confidence bound of 82.2%, which did not meet the prespecified minimum requirement of 87% for the formulation to be successful.

The study demonstrated that 2 injections of leuprolide acetate 45 mg 6-month depot Formulation B administered 6 months apart was generally well tolerated with a safety profile consistent with the known safety of approved depot formulations of leuprolide acetate and other gonadotropin-releasing hormone agonists. No new or unexpected safety signals were identified.