2.0 Synopsis

Abbott Endocrine	**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: Leuprolide (LHRH Agonist) to Enhance Immune Function Post-Autologous Stem Cell Transplantation

Coordinating Investigator: Richard Champlin, MD [redacted]

Rationale for Abbreviated Clinical Study Report:

This study was prematurely discontinued on 20 May 2009 due to slow subject enrollment.

Study Sites: Subjects were enrolled at 3 sites in the United States.

Publications: None

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 14 February 2006 Last Subject Last Visit: 05 February 2009	

Objectives:

The objectives of this trial were to:

- assess the rate of immunologic recovery following high-dose chemotherapy and autologous stem cell transplantation as assessed by response to vaccination for subjects receiving 9 months of therapy with either Lupron Depot-3 Month 11.25 mg formulation or placebo.
- obtain safety data on the use of Lupron Depot 3 Month 11.25 mg formulation for luteinizing hormone-releasing hormone (LHRH) blockade as a means of enhancing immunologic recovery following myeloablative therapy and autologous stem cell transplantation.
- assess the rate of infection, disease relapse, and survival.

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Methodology: The L-BT04-093 study was a Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study conducted in subjects with Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or mantle cell lymphoma undergoing hematopoietic stem cell transplantation (HSCT). Approximately 10 total United States and ex-US sites were to be recruited to enroll approximately 80 subjects.

Three intramuscular (IM) injections of a 3 month depot formulation of leuprolide acetate 11.25 mg (hereafter Lupron Depot) or matching placebo were to be administered approximately 3 months apart. Subjects received the first injection of Lupron Depot/placebo at Month –1 (Day –60 to Day –14) prior to HSCT. Although it was recommended that the Lupron Depot injection be administered at least 21 days before the planned HSCT, 14 days prior was the minimum. The second injection was to be administered at approximately 2 months post-HSCT (12 ± 2 weeks from the first injection), and the third at approximately 5 months post-HSCT (12 ± 2 weeks from the second injection).

All subjects received pneumococcal conjugate and tetanus/diphtheria toxoid (Td) vaccines on the same day as the second injection of Lupron Depot/placebo and at Month 6 post-HSCT. Subjects also received hepatitis A vaccine and 1 subcutaneous injection of keyhole limpet hemocyanin (KLH) at the month 6 post-HSCT visit. The primary immune endpoint of the study was in vitro T cell and antibody responses to the KLH vaccination at 6 months post-transplantation. This was measured by enzyme-linked immunosorbent spot-forming cell (ELISpot) for interferon gamma (IFNγ) on the blood sample taken 5 ± 1 weeks post-KLH vaccination.

Thymic function was determined by assessing the output of naïve T cell subsets and the production of T cell (antigen) receptor (TCR) rearrangement excision circles (TRECs) at Screening, and at 1, 2, 3, 5, 6, 7, and 12 months post-HSCT. Other immune parameters (standard immunophenotyping) were assessed at the same time points. Standard immunophenotyping was performed at each clinical site using a standardized monoclonal antibody (MAB) panel. The data were acquired and sent to the Central Core Laboratory [redacted] for analysis. The standard panel consisted of CD3/8/27/45RO, 3/4/27/45RO, 8/16/56/16, and 19/27. Both percentages and absolute number were determined.

All KLH evaluations were performed at [redacted] Serum immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody levels were determined using enzyme linked immunosorbent assay (ELISA) assays. T lymphocyte responses were determined by ELISpot for the cytokine, IFNγ. Results from stimulated leukocytes were compared to control cells.

Measurement of proliferative response to tetanus toxoid antigen was performed. Serum antibody levels for tetanus toxoid, pneumococcus, and hepatitis A were to be determined [redacted] using established ELISA assays.

At specified time points during treatment, subjects underwent the following safety procedures and assessments: blood draws for routine chemistry, hematology, and endocrine safety assessments; physical examination; vital signs; bone density scan for female subjects and male subjects at risk of osteoporosis; and, sexual function assessment. Adverse events and concomitant medications were collected and assessed throughout the study.

Blood samples were collected on Study Day 0 prior to transplant, and 1 and 5 months post-HSCT (prior to the Lupron Depot/placebo injection) for leuprolide pharamacokinetic analyses.

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Number of Subjects (Planned and Analyzed):

Target enrollment was approximately 80 subjects; 25 subjects were enrolled and analyzed for safety, 18 for efficacy, and 10 for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects must have met all of the following main criteria to be eligible for study participation:

1. Female between the age of 18 to 50 or if female > 50 years old had an estradiol concentration level ≥ 30 pg/mL and follicle stimulating hormone level < 40 mIU/mL, or male between the age of 18 to 65 (inclusive).
2. Subject had Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or mantle cell lymphoma and was considered an appropriate candidate for HSCT:
   - Multiple myeloma subjects had a partial or complete response to chemotherapy.
   - Subjects with Hodgkin's disease or non-Hodgkin's lymphoma had achieved a partial response to initial chemotherapy, or first or second chemosensitive relapse, had achieved a complete or partial response to salvage treatment.
   - Subjects in first remission with mantle cell lymphoma, or with intermediate or high grade lymphoma, presented with high intermediate or high IPI (International Prognostic Index) scores.
3. Seronegative for hepatitis C and HIV.
4. Had received prior tetanus immunization.
5. Had not received prior KLH immunization or HSCT.
6. Had an Eastern Collaborative Oncology Group Performance Status (ECOG PS) ≤ 1 or Karnofsky Performance Status ≥ 70%.
7. Had creatinine ≤ 2.0 mg/dL; ejection fraction > 45%; carbon monoxide diffusion in the lungs > 50% of predicted; serum total bilirubin < 1.5 mg/dL times the upper limit normal unless Gilbert's syndrome, serum glutamate pyruvate transaminase (SGPT) < 3 times normal value.
8. Had an absolute neutrophil count ≥ 1,500 μL, platelet count ≥ 100,000/μL, and hemoglobin ≥ 8.0 gm/dL within 21 days prior to randomization.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: All subjects received leuprolide acetate 11.25 mg 3 month depot IM or placebo IM. Each subject was to receive a total of 3 IM injections, which were to be administered approximately 12 weeks apart.

Investigational Product	Formulation	Dosage	Lot Number	Manufacturer and Location
Lupron 11.25 mg 3 Month Depot	11.25-mg depot	11.25 mg IM Q 3 months	Z3043221, Z304F081, Z3043331, Z304F111	[redacted]
Placebo	–	0 mg IM Q 3 months	Z3047021, Z304F081, Z304F101, Z3047041, Z304F111	[redacted]

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Duration of Treatment: Subjects were to receive the first injection on at Month –1 (Day –60 to Day –14) prior to HSCT, the second injection at approximately 2 months post-HSCT (12 ± 2 weeks from the first injection), and the third at approximately 5 months post-HSCT (12 ± 2 weeks from the second injection).

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

None

Criteria for Evaluation

Efficacy:

Evaluable Population for Efficacy Analyses (N = 18): The evaluable subject dataset included all randomized subjects who were followed for at least 7 months and had efficacy assessments.

Pharmacokinetic Population (N = 10): The pharmacokinetic dataset included 10 subjects in the Lupron Depot group who received at least 1 injection of study drug.

Safety Population (N = 25): 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.

Statistical Methods

Efficacy: The primary immune endpoint of the study was in vitro antibody and T cell response to the KLH vaccination post-HSCT. Each of the pairs of ELISA assay outcomes (IgM, IgG1, IgG2, IgG3, and IgG4) and IFNγ at pre-vaccination (6 months) and post-vaccination (7 months) were compared using the Wilcoxon signed rank test. The difference was calculated by subtracting the pre-vaccine measurement from the post-vaccine measurement.

Certain variables (IgM, IgG1, IgG2, IgG3, and IgG4) were dichotomized using pre-specified cutoffs (i.e., 2,000 ng/mL for IgM, 5,000 ng/mL for IgG1, 5,000 ng/mL for IgG2, 2,000 ng/mL for IgG3, 500 ng/mL for IgG4, and > 1:300,000 for IFNγ). The difference was calculated by subtracting the pre-vaccine dichotomized measurement from the post-vaccine dichotomized measurement. Fisher's exact test was used to evaluate the association between the difference in pre- and post-measurement between the placebo and Lupron Depot groups.

Pharmacokinetic: Plasma leuprolide concentrations were summarized with descriptive statistics. Other pharmacokinetic parameters were not calculated due to sparse sampling.

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. 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, Other Baseline Characteristic Characteristics, and Exposure:

A total of 25 eligible subjects with multiple myeloma (n = 18), non-Hodgkin's lymphoma (n = 4), or Hodgkin's disease (n = 3) were enrolled and treated in this Phase 2, double-blind, randomized, parallel-group, placebo-controlled, multicenter study of Lupron 11.25 mg 3 Month Depot (Lupron Depot). The majority of subjects were white (76%) and male (76%). The overall mean (±SD) age was 48.2 (8.53) years. All randomized subjects had an ECOG Performance Status grade ≤ 1 at baseline.

The study was prematurely discontinued due to slow subject enrollment. Overall, mean (SD) duration of exposure to Lupron Depot was 217 (76) days (median: 249 days), with a range of 85 to 287 days. Mean exposure to placebo was 221 (71) days (median: 253 days), with a range of 85 to 275 days.

Efficacy Results:

Of the 18 subjects (9 Lupron Depot, 9 placebo) in the evaluable dataset, 13 subjects (8 Lupron Depot and 5 placebo) had complete (pre- and post-vaccination) immunoglobulin data; primary efficacy analyses were conducted using their data. Out of 9 subjects in each treatment group who were included in the evaluable dataset, 11 subjects (6 Lupron Depot and 5 placebo) had complete (pre- and post-vaccination) T lymphocyte responses to KLH determined by ELISpot for IFNγ. Primary efficacy analyses were conducted using their data.

Among the evaluable subjects, disease progression occurred in 11.1% of subjects (1 of 9) in the Lupron Depot group and 33% of subjects (3 of 9) in the placebo group.

There is evidence that the difference in IgM pre- and post-measurements is significantly different from 0 in the Lupron Depot group. There is also evidence that the difference between IgG1 pre- and post-measurements is significantly larger than 0 in the Lupron Depot group. That is, both IgM and IgG1 appear to increase with the administration of Lupron Depot. There is marginal evidence ($P = 0.06$) that the difference between IFNγ pre- and post-measurements is significantly larger than 0 in the placebo group, but no other effects were seen.

Certain variables in the data were dichotomized using pre-specified cutoffs (i.e., 2,000 ng/mL for IgM, 5,000 ng/mL for IgG1, 5,000 ng/mL for IgG2, 2,000 ng/mL for IgG3, 500 ng/mL for IgG4, and > 1:300,000 for IFNγ). There is no evidence of a significant difference in the proportion between the groups. However, the evidence is marginally significant ($P = 0.08$) for both IgG1 and IgG3, which increased with Lupron Depot. The rates of increase were 62% (5/8) for both of these variables in the Lupron Depot-treated subjects, compared to no increases seen in the 5 placebo subjects for whom there were data.

An increase in CD4 over time was observed in both treatment groups, beginning 1 to 2 months earlier with Lupron Depot than with placebo. The TREC data based on TREC/100,000 cells show that there is an increase in naïve CD4+ T cells (peak at 6 months) consistent with renewed thymus function.

The data presented this way are a proportion of the number of CD4 + cells, indicating thymus activation causing a surge of new naïve cells into the total CD4+ cell pool, not seen in the control group. It is anticipated that if the data were to be expressed as a total number of TREC+ CD4+ cells that an increase in their levels in the blood may be seen earlier. No such increase was observed with the CD8+ cells, because these cells are often derived extra-thymically and may not be mainstream CD8*ab* chain T cells

Pharmacokinetic Results:

The mean leuprolide plasma concentration on Study Day 0 prior to transplant and 1 and 5 months post-HSCT was 0.068 ng/mL (n = 9), 0.077 ng/mL (n = 10), and 0.065 ng/mL (n = 8), respectively. Other leuprolide pharmacokinetic parameters were not calculated due to sparse sampling.

Safety Results:

The safety profile of Lupron 11.25 mg 3 Month Depot observed in this study was consistent with the known safety profile of approved formulations of Lupron Depot and a population undergoing bone marrow transplant. Treatment-emergent adverse events were reported for 10 of 12 subjects (83%) in the Lupron Depot group and 8 of 13 subjects (61.5%) in the placebo group ($P > 0.10$). The incidence of specific treatment-emergent adverse events (other than those described in the Package Inserts) in the Lupron Depot group was low, with none reported for more than 1 subject (8.3%). The majority of treatment-emergent adverse events were mild or moderate in severity, as assessed by the investigator. Treatment-related adverse events were reported for a minority of study subjects (25.0% Lupron Depot and 7.7% placebo).

One subject (in the Lupron Depot group) died during the study due to a treatment-emergent adverse event of respiratory failure following (possible pseudomonal) pneumonia, which the investigator assessed as not related to study drug.

Treatment-emergent, non-fatal, serious adverse events were reported for 6 subjects (50.0%) in the Lupron Depot group and 4 subjects (30.8%) in the placebo group. The investigator considered all serious adverse events to be not related to study drug, and none of the non-fatal serious adverse events led to premature discontinuation of study drug.

One subject in the Lupron Depot group with a history of psoriasis had a treatment-emergent adverse event of mild psoriasis (unrelated to study drug) that led to the premature discontinuation of study drug. No subject in the placebo group had a treatment-emergent adverse event that led to the premature discontinuation of study drug.

Hematology laboratory data revealed small mean decreases in hemoglobin, hematocrit, and RBC count that are consistent with the known side effects of androgen deprivation therapy. The mean decrease in hemoglobin concentration from baseline (126.8 to 131.1 g/L) to each visit ranged from –1.7 to –17.6 g/L in the Lupron Depot group, representing a 13% mean decrease over the 13 month study period. Nine and 6 (of 10 subjects each) in the Lupron Depot and placebo groups had 1 or more hemoglobin values measured during the study that met the criterion for PCS low value (i.e., ≤ 95 g/L for female, ≤ 115 g/L for male, or ≥ 20 g/L decrease). There was 1 adverse event of decreased hemoglobin in the placebo group and none in the Lupron Depot group. There were no reports of anemia as an adverse event.

Safety Results (Continued):

Median time to engraftment was 11 days for both the Lupron Depot and placebo groups for neutrophils (absolute neutrophil count of ≥ 500/μL) and platelet count (≥ 20,000/μL). Median times to lymphocyte count thresholds of > 500/μL and > 1000/μL were shorter with Lupron Depot (2 days and 5 days, respectively). This increase in lymphocytes is again consistent with improved thymus and bone marrow function and also the reduction in immunosuppression caused by sex steroids.

Mean increases in liver function test values (AST, ALT, LDH, and alkaline phosphatase) were observed in the Lupron Depot group at 1 or more evaluation timepoints, although there were no consistent trends after month 3 in the mean between-group changes from baseline. One subject (8.3%) in the Lupron Depot group experienced transaminase levels that exceeded 2 × ULN at 1 on-treatment timepoint (AST and ALT on Study Day 57), with these values returning to below baseline levels at their final measurement (4 days post-treatment). Adverse events of liver enzyme abnormalities were reported in 1 subject in the placebo group and no subjects in the Lupron Depot group.

A mean increase from baseline glucose was observed in the Lupron Depot group at the Months 6, 7, and 12 visits (placebo-subtracted mean increase was 1.04 to 1.74 mmol/L at these visits).

No clinically significant changes affecting renal function were noted with Lupron Depot, with the exception of 1 subject who had an isolated serum creatinine (PCS high) and BUN values above the reference range on Study Day 50, with all other values, measured both before and after, within the reference range. The elevated serum creatinine value was reported as an adverse event.

Shifts from baseline to the final value for chemistry variables in the Lupron Depot group were similar to that in the placebo group, or not in the direction of concern, with the exception of glucose: 4 of 11 (36%) Lupron Depot treated subjects with a normal baseline glucose developed hyperglycemia. No subject had a high PCS glucose value. An increase in glucose is understandable because androgen deprivation therapy can be associated with impaired glucose tolerance and insulin resistance, and corticosteroid use was common in this study.

As expected, subjects in the Lupron Depot group experienced decreases in gonadotropins and sex steroids during the treatment period of the study.

No clinically important trends were observed for vital signs. No Lupron Depot-treated subject had a vital sign that met the PCS low or high criteria.

There were no clinically significant differences in incidence or types of infections between the groups.

The study demonstrated that Lupron 11.25 mg 3 Month Depot – up to 3 injections administered 3 months apart – was generally well tolerated, with a safety profile consistent with the known safety of approved depot formulations of leuprolide acetate and other GnRH agonists. No new or unexpected safety concerns were identified.

Conclusions:

In summary, an increase in immunoglobulins (IgM, IgG1, IgG2, IgG3, IgG4) and possibly decreased IFNγ, compared to placebo, was observed although only selected differences between treatment groups reached the level of statistical significance. The TREC data show that there is an increase in naïve CD4+ T cells consistent with renewed thymus function. Although a signal of efficacy was observed in this study, the small sample size limits clinical conclusions from the data. Lupron Depot was safe and generally well tolerated by study subjects.