

CLINICAL REVIEW

NDA 21-343

The mean LH concentration at Baseline was 8.0 (± 0.7) MIU/mL, with the middle quartile ranging from _____ MIU/mL. Concentrations increased until a maximum mean concentration of 42.9 (± 3.8) MIU/mL was reached at Hour 8 post-Baseline. By Day 10, the mean concentration (4.8 MIU/mL) had decreased below the Baseline concentration, and concentrations then dropped consistently throughout the remainder of the month.

A straight line interpolation of the mean data (using Days 7 and 14 for Baseline threshold, and Days 7, 14, 21, 28, and 35 for the 1 MIU/mL threshold) suggest that the Baseline threshold was crossed as early as Day 8 and the 1 MIU/mL threshold was crossed by Day 25.

Concentrations increased slightly from 0.7 MIU/mL following the Day 28 injection and peaked at Hour 8 post-Day 28 following this second dose, with a mean concentration of 1.2 (± 0.1) MIU/mL. Concentrations decreased steadily throughout the rest of the month and by Day 49 the mean concentration was 0.15 MIU/mL.

Following the third leuprolide injection, mean concentrations increased slightly from 0.13 MIU/mL on Day 56 to 0.26 (± 0.02) MIU/mL at Day 57, and then continued to decrease to 0.09 (± 0.01) MIU/mL at Month 6. At Month 6, LH concentrations ranged from _____ MIU/mL. Results were similar across centers.

8.6.9 Changes in serum leuprolide concentrations

The pharmacokinetics of leuprolide in serum during monthly treatment with ELIGARD™ 7.5 mg were multiphasic. Serum concentrations rose rapidly after the first dose (C_{max} : 25.3 \pm 11.3 ng/mL at 4-8 hr), and then declined over the next several days.

During the majority of each dosing interval (the "plateau" phases from Days 2-28, 31-56 and 59-84), serum levels remained relatively constant. Mean leuprolide serum levels during the plateau phases ranged from 0.28 – 1.9, 0.45 – 1.67, and 0.45 – 1.55 ng/mL for the three dose intervals, respectively.

Serum leuprolide did not fall below 0.1 ng/mL in any patient during the study.

Based on the AUC reported for a 1 mg intravenous injection of leuprolide acetate (126 ng hr mL⁻¹), the bioavailability of the first ELIGARD™ 7.5 mg injection was 93 \pm 24%.

The average serum concentration of leuprolide during the plateau phase was 0.70 ng/mL, suggesting that leuprolide was delivered at a rate of approximately 140 μ g/day during this period.

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There was no evidence of significant accumulation during repeated dosing with ELIGARD™ 7.5 mg in this study.

Mean serum leuprolide levels measured 28 days after each dose (0.42, 0.45, 0.45 ng/mL, respectively) did not differ ($P > 0.05$). The apparent decrease in C_{max} values after the second and third doses is a result of the reduced number of sampling timepoints. Values of C_{max} , C_{min} and AUC during the plateau phase were similar after each of the three doses.

The mean pharmacokinetic parameters after the first dose in this Phase 3 study were nearly identical to those observed in the single-dose Phase 1 study (Atrix Clinical Study Report - AGL9802, dated September 23, 1999), with burst phase C_{max} values of 25.3 and 26.3 ng/mL, plateau phase C_{max} values of 2.69 and 2.68 ng/mL, plateau phase C_{min} values of 0.175 and 0.169 ng/mL, and $AUC_{0-day28}$ values of 873 and 866 ng hr mL⁻¹, respectively.

Medical officer's comments:

1. The pivotal study showed that ELIGARD™ achieved constant suppression of testosterone secretion by maintaining serum leuprolide exposures at levels above the minimum required for complete inhibition of gonadotropic hormone release.
2. Clinically insignificant and minor weight-related variation in response were noted. This should not impact approvability since ELIAGR was shown to be effective in producing sustained castrate testosterone suppression in patients with advanced prostate cancer weighing up to 130 kg (287 lbs).

8.6.10 Patient performance status

At Baseline, Days 28, 56, 84, and Months 4, 5, and 6, patient performance status was evaluated using a WHO performance scale. The scale consisted of three categories, ranging from 0 to 2 with the following definitions: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = Ambulatory and capable of self-care but unable to carry out any work activities.

Very little change was observed throughout the study in terms of performance status. At Baseline, 88% of patients were classified as fully active (Status = 0). By Month 6 this percentage remained at 88%. The percentage of patients with a score of 1 at Baseline was 11%, as was the percentage at Month 6. Only one patient (<1%) had a performance score of 2 at Baseline, while no patients had a score greater than 1 at Month 6. Results were consistent across centers.

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8.6.11 Patient assessments of bone pain and urinary symptoms

Bone pain, urinary symptoms, and "urinary pain" were assessed by patient scales ranging from 1 to 10 and collected at Baseline, Days 1, 2, 3, 4, 7, 10, 14, 28, 56, 77, 84, Months 4, 5, and 6, and are summarized in Table 13.

Both bone pain and "urinary pain" were assessed on a scale ranging from 1 (no pain) to 10 (worst pain possible). Symptoms on urination were also assessed on a scale ranging from 1 to 10 with 1 defined as "no difficulty" and 10 defined as "very difficult".

At Baseline, patients experienced little bone pain, with a mean score of 1.22 and ranging from 1 to 9. This score remained low throughout the study and was 1.26 at Month 6, with a range of 1-7. Urinary pain was similarly low, with a mean of 1.12 at Baseline (range: 1-5) decreasing to 1.07 at Month 6 (range: 1-8). Likewise, urinary symptoms were low throughout the study. At Baseline, the mean symptom score was 1.62 (range: 1-10), decreasing at Month 6 to 1.38 (range: 1-9).

8.6.12 Changes in serum PSA concentrations

Mean PSA was grossly elevated above the upper normal limit at Baseline (>800%). Mean values were reduced 94% from Baseline to Month 6. Of 107 patients with PSA scores above the limit of detection at Baseline, 79 (74%) had reductions of $\geq 90\%$ at Month 6. Mean total acid phosphatase was markedly increased above the upper normal limit (140%) at Baseline. Mean values declined steadily over the duration of the study, achieving the normal range from Day 42 onwards. There was a 39% decrease in total acid phosphatase from Baseline to Month 6.

Medical officer's comment:

The secondary efficacy assessments demonstrate changes similar to those reported following long-term administration of other superactive GnRH agonists. This finding reflects the fact that majority of patients in this population have hormone-sensitive tumors.

8.7 Conclusions regarding demonstrated efficacy

8.7.1 Achievement of protocol defined primary efficacy endpoints

Following six, once-monthly doses of [redacted] 7.5 mg, 100% of patients who continued in the study through at least Day 14 reached castrate suppression of testosterone concentration, defined as testosterone concentration of ≤ 50 ng/dL for two consecutive timepoints approximately one week apart. By Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and by Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all of those patients who achieved castrate testosterone suppression (≤ 50 ng/dL) remained suppressed throughout their participation in the study. That is, no castrate suppression breakthroughs (defined as a testosterone concentration of > 50 ng/dL after achieving suppression) were observed during the study. The

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median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days.

8.7.2 Medical officer's overall assessment of efficacy

The efficacy results from pivotal Study AGL 9904 indicated that the clinical and statistical efficacy objectives of the trial were successfully met. The sponsor's study successfully achieved the principal criteria that DRUDP has used to evaluate the efficacy of superactive GnRH analogs in the palliative management of prostate cancer.

8.7.3 Support of efficacy claims in proposed label

The results of Study AGL 9904 support the sponsor's proposed label indication (the palliative treatment of advanced prostate cancer). The reviewer believes that this novel monthly formulation of leuprolide offers another resource for the medical community in treating these unfortunate cancer patients.

9. Integrated review of safety

9.1. Data sources

As previously noted, the sponsor submitted safety data from 3 clinical studies:

- a. AGQ 9706 (assessment of local tolerability of delivery system).
- b. AGL 9802 (8 orchiectomized patients)
- c. AGL 9904 (pivotal Phase 3 trial)

9.2. Description of patient exposure

To date, 128 patients with a medical history of advanced carcinoma of the prostate have been exposed to at least a single SC injection of study drug.

In a 56-day pharmacokinetic trial (AGL9802), eight patients received a single injection of ELIGARD™ 7.5 mg. In the pivotal efficacy study (AGL9904), 120 patients received at least one injection of study drug. Of these, 117 patients received six injections of study drug. Three patients discontinued during the study. One patient (#2007) withdrew voluntary consent due to changes in the number of blood draws and a subsequent reduction in his study compensation. He received three monthly injections. A second patient (#2416), who received two monthly injections, discontinued due to transportation difficulties after moving from the area of the study center. A third patient (#2801), who received a single injection, discontinued 14 days later because his insurance provider refused to reimburse study-related costs.

Table 5 summarizes the total number of patients enrolled and the total study duration for each trial.

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Table 5: Number of Subjects Exposed to ELIGARD™ in NDA 21-343.

Study	Number of Patients	Number of Doses	Study Duration
AGL9802	8	1	56 Days (2 months)
AGL9904	117	6	184 Days (6 Months)
	1	3	
	1	2	
	1	1	
Total	128	716	

Medical officer's comment:

The number of patients exposed to the monthly formulation of ELIGARD™, and the duration of its exposure, in conjunction with the historical information relevant to other 28-day formulations, is considered adequate to assess the general safety of ELIGARD™ for the indication of management of advanced prostate cancer.

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9.3. Safety assessments conducted in the primary safety study

9.3.1. Procedures for collecting safety data

At each clinical visit, patients were to be assessed for potential adverse events. At each visit, adverse events were recorded on a visit-specific adverse event case report form (CRF). The severity of the adverse event was to be graded in accordance with the World Health Organization (WHO) toxicity scales as provided in the study protocol. Additional information about serious adverse events was provided to the sponsor on a separate serious adverse event (SAE) form.

Local tolerance to the study drug (assessed as "swelling", "redness", "bruising", "pain" and "induration") was recorded separately.

9.3.2. Analysis and reporting of safety data.

9.3.2.1. Adverse events

Adverse events were classified into body system categories. Adverse events were coded into preferred terms using the World Health Organization (WHO) Adverse Reaction Dictionary (ARD)/ECOG. Adverse events were summarized by the number of patients reporting an event and the percentage of patients with that event.

9.3.2.2. Vital signs

Vital signs including heart rate, blood pressure, respiratory rate and temperature were documented at Screening, Baseline, and Days 7, 14, 28, 56, 84, and Months 4, 5, and 6.

9.3.2.3. Clinical laboratory tests

Individual laboratory values were listed by patient and by visit. Laboratory parameters before treatment, at each visit, and the change from pretreatment values to each on-treatment assessment were presented as summary statistics. Shift tables (change from baseline value to on treatment values) based on laboratory normal ranges were presented for each laboratory measurement and each assessment time. Incidence rates of new on-treatment abnormal laboratory values, based on the shift tables, were calculated and listed by laboratory test and visit.

Blood samples for hematology, coagulation, and blood chemistry were collected at screening and at all visits through Day 14, and then at Days 28,

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42, 56, 70, 84, Month 4, Week 18, and Month 6 for all patients. The specific assessments were:

- a. Hematology: hemoglobin, red blood cell count, and total leukocytes
- b. Coagulation: prothrombin time
- c. Blood chemistry: Glucose, BUN, creatinine, SGOT/AST, SGPT/ALT, alkaline phosphatase, and bilirubin.

Medical officer's comment:

Safety assessments listed are adequate for this product.

9.4. Demographics (for Pivotal Study AGL 9904 and Study AGL9802)

One hundred twenty-eight (128) men with a history of carcinoma of the prostate have received at least one SC injection of ELIGARD 7.5 mg. The majority of these patients were white, older males in their seventies.

In terms of disease stage and severity, 74% were classified as Jewett's stage C and 26% were classified as stage D. Almost 70% had a history of urinary tract symptomatology at baseline.

Please also refer to section 8.6.1 of this review.

9.5. Adverse events

9.5.1. Overview of adverse events (Data from AGL 9904 and AGL 9802)

- a. There were no deaths reported.
- b. There were no premature discontinuations due to an adverse event reported.
- c. There were a total of nine serious adverse events (SAEs) across both studies; none were considered related to study drug.
- d. Overall, there were 880 all-causality adverse events (AEs).
- e. Overall, there were 494 treatment-related AEs reported by a total of 97 patients.

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Most treatment-related AEs (e.g., hot flashes, testicular discomfort, dizziness, diminished libido, impotence, etc.) were those that are typically associated with testosterone suppression and consequent to medical castration.

- f. Across both studies and for both all-causality and treatment-related events, the majority of adverse events were reported as "mild" in severity. Of the 494 treatment-related events, 400 were reported as "mild".
- g. Thirty-one AEs were considered to be "severe" (3 for AGL9802, 28 for AGL9904) by the investigator. Only eleven of these 31 (all in Study AGL9904) were reported to be possibly or probably related to treatment. These events were listed as: five (5) reports of "burning at injection site" and one report each of hot flashes, night sweats, decreased libido, low hemoglobin and hematocrit, and tremors.
- h. Adverse events common to both trials were: hot flashes (flushing), localized ecchymosis and bruising, and "disturbances of skin sensation" (e.g., injection site burning or pain immediately following injection).
- i. Injection site reactions (including stinging, burning, erythema, bruising/ecchymoses, pruritis and induration) were reported commonly. However, most events were brief in duration, mild in severity, and sporadic in nature. No patient discontinued due to a local reaction. All local reactions resolved without sequelae. There were no trends for an increase in intensity, frequency or duration of injection site AEs with subsequent injections.
- j. There were no clinically significant changes observed in vital sign measurements (temperature, heart rate, blood pressure and respiratory rate) for either clinical trial.

9.5.2. Deaths

There were no deaths reported in NDA 21-343.

9.5.3. Serious adverse events

There were nine (9) reported serious adverse events (SAEs). None were attributed to drug by investigator. All were considered "serious" by the need for hospitalization criterion. These events are described individually below.

AGL9802 (N=1)

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One patient (#0202) required hospitalization for bradycardia. The event resolved and was not considered related to study treatment.

AGL9904 (N=8)

Two patients (#0502, #1411) reported serious cardiovascular events that required hospitalization. Patient #0502 reported a blocked artery and subsequently required cardiac bypass surgery. Patient #1411 reported a worsening of arteriosclerosis (originally recorded in the baseline medical history) and a cardiac stent was placed. Both events resolved and neither was considered to be related to study drug.

Two patients reported digestive system events that required hospitalization. Patient #1104 reported hematemesis and was admitted to the hospital for endoscopy, gastric lavage and blood transfusion. The event was not deemed to be related to study treatment by the investigator. Patient #1406 required hospitalization for an inguinal hernia repair. The existence of an inguinal hernia was reported in the baseline medical history. Repair was deemed necessary during the study and therefore the patient was hospitalized.

Patient #2008 reported a worsening of osteoarthritis and underwent a hip replacement procedure. The event was not related to study drug and was considered to be ongoing at the end of the study.

Patient #0807 was diagnosed with squamous cell carcinoma of the floor of the mouth that required resection. The event was not related to study treatment.

Patient #2701 was noted to have elevated plasma calcium and during a medical work-up, a computerized tomography scan of the lungs revealed malignancy for which the person received radiation therapy in the hospital. The event was not related to study treatment or to their original prostate cancer diagnosis and was ongoing as of the end of the study.

Patient #2705 experienced dizziness and muscle weakness on his left side. He was subsequently transported to the hospital by paramedics, who reported his blood pressure as being low (actual BP not documented) and the event was reported as "hypotension". When the patient arrived at the hospital the event was diagnosed as a seizure. He was given a maintenance dose of phenytoin sodium (Dilantin). There has been no recurrence of seizure. Use of Dilantin was ongoing at study completion. The event was considered not related to study treatment and was ongoing at the end of the study.

Medical officer's comment:

The reviewer agrees that none of these SAEs appeared to be related to treatment with ELIGARD 7.5 mg.

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9.5.4. Premature discontinuations due to adverse events

There were no reported premature discontinuations due to adverse events.

9.5.5 Reported Adverse Events

9.5.5.1 Overall adverse events: In Study AGL 9802

Eight patients (100% of those enrolled) reported a total of 37 all-causality adverse events.

One patient (12.5%) reported a serious adverse reaction. That patient required hospitalization for bradycardia. The investigator considered the event to be not related to study drug.

Three adverse reactions in 2 patients (25%) were reported as "severe". Patient #0201 reported severe gastroenteritis and Patient #0204 reported both severe gastroenteritis and severe cramp of limb. None of these events were considered drug-related.

Seven treatment-related events were reported by 5 patients (62.5%). These included stinging and burning at injection site (N=3), hot flashes (N=2), and erythema at the site (N=1). These events were generally mild and brief (one minute or less) in duration.

Medical officer's comment:

It should be noted that in AGL9802, seven of the eight patients (87.5%) reported a "disturbance of skin sensation", described as pain, stinging, or burning at the injection site. In addition, three patients (37.5%) also reported "bruising". It is unclear why some of these particular events were not considered at least possibly drug-related by the investigator.

9.5.5.2. All-causality adverse events : Study AGL 9904

A total of 850 all-causality adverse events were reported by 120 patients (100% of total enrolled). See Table 6 below.

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Table 6: Incidence (%) of All-Causality Systemic Adverse Events Reported by at least 3 Patients (n = 120) Treated with ELIGARD in Study AGL9904

Body System	Adverse Event	Number	Percent
Body as a Whole	Malaise/Fatigue	22	(18.3%)
	Dizziness/giddiness	10	(8.3%)
	Insomnia	5	(4.2%)
	Headache	5	(4.2%)
	Non-specified pain	5	(4.2%)
	Abnormal blood chemistry*	5	(4.2%)
	Edema	4	(3.3%)
	Abnormal lab-other**	4	(3.3%)
	Pyrexia	3	(2.5%)
	Musculoskeletal	Shoulder pain	10
Lumbago		7	(5.8%)
Pelvis/thigh pain		6	(5.0%)
Limb pain		6	(5.0%)
Backache		4	(3.3%)
Myalgia		3	(2.5%)
Cardiovascular	Hot Flashes/Flushing	69	(57.5%)
Genitourinary	Atrophy of Testes	6	(5.0%)
	Dysuria	7	(5.8%)
	Nocturia	6	(5.0%)
	Hematuria	4	(3.3%)
	Urge incontinence	3	(2.5%)
	Urinary frequency	3	(2.5%)
Digestive	Gastroenteritis	8	(6.7%)
	Constipation	5	(4.2%)
	Flatulence	3	(2.5%)
	Dyspepsia	3	(2.5%)
Respiratory	Cough	10	(8.3%)
	Sinusitis	9	(7.5%)
	Common cold	8	(6.7%)
	Acute pharyngitis	5	(4.2%)
	Influenza	3	(2.5%)
Injury	Contusion of elbow	4	(3.3%)
Infections	Herpes simplex infections	3	(2.5%)
Skin and appendages	Burning, stinging, pain at injection site	65	(54.2%)
	Ecchymoses	24	(20.0%)
	Erythema	18	(15.0%)
	Pruritis	13	(10.8%)
	Rash	8	(6.7%)

*Abnormal blood chemistry included hyperglycemia, elevated triglycerides, and elevated creatinine.

** other non-specific findings on examination of blood included decreased number of red blood cells, decreased hemoglobin or hematocrit, increased aspartate aminotransferase, or increased alanine aminotransferase levels.)

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Eight serious adverse events (SAEs) were reported by a total of eight patients. These included squamous cell carcinoma (#0707), worsening of arteriosclerosis (#1406), blocked artery (#0502), inguinal hernia (#1406), vomiting blood (#1104), osteoarthritis (#2008), abnormal computerized tomography scan of lungs (#2701), and hypotension (#2705). None of these was considered treatment-related.

No patient in AGL9904 discontinued prematurely due to an adverse event.

9.5.5.3 Treatment-related adverse events : Study AGL9904

A total of 487 treatment-related adverse events were reported by 92 patients (76.7% of total enrolled). Overall, the most commonly reported treatment-related adverse events were hot flushes (56.7%); pain, burning or stinging at the injection site (53.3%); malaise/fatigue (17.5%); erythema at the injection site (12.5%); pruritis (10%); testicular discomfort/atrophy (5.0%); dizziness/giddiness (3.3%); and gastroenteritis (2.5%). See Table 7 below.

Body System	Adverse Event	Number	Percent
Body as a Whole	Malaise and Fatigue	21	(17.5%)
	Dizziness/giddiness	4	(3.3%)
Cardiovascular	Hot Flashes/Flushing*	68	(56.7%)
Genitourinary	Atrophy of Testes*	6	(5.0%)
Digestive	Gastroenteritis/Colitis	3	(2.5%)
Skin and appendages	Burning, stinging, pain at injection site	64	(53.3%)
	Erythema at injection site	17	(14.2%)
	Pruritis	12	(10.0%)

*Expected pharmacological consequences of testosterone suppression.

The following possibly or probably related adverse events were reported by fewer than 2% of all patients: insomnia, sweating, syncope, flatulence, constipation, tremor, backache, joint pain, depression, vertigo, disturbance of smell or taste, alopecia, testicular soreness, decreased libido, gynecomastia, breast soreness.

In terms of severity, 98% of treatment-related adverse reactions were reported as "mild" or "moderate". For example, hot flashes were reported as mild in 56 (80.0%) patients, moderate in 13 (18.6%) patients and severe in one (1.4%) patient.

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The severity and duration of local site reactions is discussed in a separate section later in this review (9.5.6.). However, in general, these events were generally reported as mild in intensity, transient in duration and non-recurrent. In one patient; a single recurrence of pruritus occurred at a single subsequent injection (#0703). Two patients had a single recurrence of erythema (Patient #0703, injections #3 and #4; Patient #2404, injections #1 and #6). There was no increase in the intensity or duration of local site reactions at the time of the recurrent event.

Eleven treatment-related "severe" adverse events were reported by 10 patients (8.3%). These events included burning at injection site, decrease in libido, decrease in hematocrit and hemoglobin, night sweats, hot flashes, and tremors.

Medical officer's comments

Hot flashes and testicular atrophy are frequently reported adverse events following androgen withdrawal. These are well-recognized pharmacological consequences of medical castration.

Overall, the types of adverse events reported and their frequencies are not unexpected considering the study population (e.g. older men with advanced prostate cancer). Such event terms would include skeletal pain, back pain, malaise, fatigue, and testicular atrophy.

9.5.5.4 Adverse events by race, age, weight, disease stage

9.5.5.4.1. RACE

In terms of race, Study 9802 had all white patients. AGL 9904 Ninety-two patients were white, 15 were black, and 13 were Hispanic. Only two categories of adverse event were different in reported incidences between races: "disturbance of skin sensation" and "malaise/fatigue".

Disturbance of skin sensation (all-causality) was reported by 56 of 92 white patients (60.9%); six of 15 black patients (40%), and three of 13 Hispanic patients (23.1%). The difference between whites and Hispanics was found to be statistically significant ($p < 0.05$). Ecchymosis was reported only by white patients (23.9%).

Malaise and fatigue were reported by 21 whites (22.8%), no blacks (0%), and no Hispanics (0%). This difference was statistically significant ($p < 0.05$).

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Medical officer's comment:

The conclusions that can be drawn from this data are limited due to few patients in the non-white categories.

9.5.5.4.2. WEIGHT

No statistically significant associations were discovered between adverse event rates and weight.

9.5.5.4.3. DISEASE STAGE

There were also no statistically significant associations noted between adverse events and baseline disease stage by Jewett's classification system.

9.5.5.5 Localized injection site adverse events

9.5.5.5.1. STUDY AGQ 9706:

In this randomized, controlled Phase 1 study, 8 normal volunteers received a single injection of the Atrigel delivery system alone, while 4 received only saline. The site of injection was evaluated for erythema, edema, induration, and bruising immediately after each injection and at 15 and 30 minutes, 1, 2, 6, 24, and 48 hours post-injection, and 30 days post-injection (i.e., Day 30, Day 60, Day 90).

All local site reaction adverse events reported in this trial were "mild" in severity and all resolved without treatment. All reports of pain, burning, erythema, bruising, and pruritis were of a "short duration". The sponsor believes that none of these were clinically significant.

Medical officer's comment:

Despite the sponsor's contention that all adverse events in this trial were of a "short duration" and none were "clinically meaningful", induration was reported in the Atrigel group only. Induration lasted greater than 48 hours. This information should be made available to prescribers and patients in the package insert.

9.5.5.5.2. STUDY AGL9802

Mild burning on injection was reported by three of eight total patients. Burning on injection was reported lasting less than 20 seconds by one patient, 41 to 60 seconds by one patient, and 3 to 5 minutes by another patient. Mild

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erythema was reported by one patient, which lasted more than five minutes but less than 24 hours.

Medical officer's comment:

These appear to be events that were judged to be "treatment-related" by the investigator.

It is notable that in AGL9802, seven of the eight patients (87.5%) reported a "disturbance of skin sensation", described as pain, stinging, or burning at the injection site. In fact, one of these events (pain) was reported as lasting >5 days. In addition, three patients (37.5%) also reported "bruising". It is unclear why some of these events were not considered at least possibly drug-related by the investigator.

9.5.5.5.3. STUDY AGL9904

In Study AGL9904, a total of 708 injections were administered to a total of 120 patients. In their analysis of local adverse events, the sponsor chose to analyze this data in two ways: by total number of injections and by total number of patients.

9.5.5.5.4 ANALYSIS BY TOTAL NUMBER OF INJECTIONS

Table 8 below describes the frequency and severity of local site reactions (by total injection count). Table 9 below describes the duration of local site reactions (by total injection count).

Table 8: Frequency and severity of local site reactions (by total injection count)*												
Adverse Event	Total number of study injections	Number of injection site AEs (% total injections)		Mild			Moderate			Severe		
				N (% total injection site AEs)		(% total injections)	N (% total injection site AEs)		(% total injections)	N (% total injection site AEs)		(% total injections)
Burning	708	245	(34.6)	207	(84)	(29)	33	(13)	(4.6)	5	(2)	(0.7)
Pain	708	31	(4.4)	25	(76)	(3.5)	6	(19)	(0.8)	0	(0)	(0)
Erythema	708	18	(2.5)	18	(100)	(2.5)	0	(0)	(0)	0	(0)	(0)
Bruising	708	18	(2.5)	17	(94)	(2.4)	1	(6)	(0.1)	0	(0)	(0)
Pruritus	708	13	(1.8)	11	(85)	(1.6)	2	(15)	(0.3)	0	(0)	(0)
Induration	708	3	(0.4)	3	(100)	(0.4)	0	(0)	(0)	0	(0)	(0)
Ulceration	708	1	(0.1)	1	(100)	(0.1)	0	(0)	(0)	0	(0)	(0)

*Source: ISS Table 21C.

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Table 9: Duration of local injection site adverse events by maximum severity recorded*

(Total injections in 120 patients = 708)

	Mild								
	0-20 Sec	21-40 Sec	41-60 Sec	1-3 Min.	3-5 Min.	> 5 Min	1-2 Days	3-5 Days	> 5 Days
Burning (n=207)	75 (36%)	38 (18%)	47 (23%)	37 (18%)	7 (3.4%)	3 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Pain (n=25)	1 (4%)	0 (0%)	2 (8%)	1 (4%)	0 (0%)	3 (12%)	6 (24%)	6 (24%)	6 (24%)
Erythema (n=18)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (44%)	10 (56%)
Bruise (n=17)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	16 (94%)
Itching (n=11)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18%)	1 (9%)	4 (36%)	4 (36%)
Induration(n=3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	2 (67%)
Ulceration (n=1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
	Moderate								
	0-20 Sec	21-40 Sec	41-60 Sec	1-3 Min.	3-5 Min.	> 5 Min	1-2 Days	3-5 Days	> 5 Days
Burning (n=33)	8 (24%)	5 (15%)	10 (30%)	9 (27%)	0 (0%)	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Pain (n=6)	1 (17%)	0 (0%)	0 (0%)	4 (67%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)
Erythema (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bruise (n=1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Itching (n=2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)
Induration (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ulceration (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Severe								
	0-20 Sec	21-40 Sec	41-60 Sec	1-3 Min.	3-5 Min.	> 5 Min	1-2 Days	3-5 Days	> 5 Days
Burning (n=5)	2 (40%)	0 (0%)	2 (40%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Pain (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Erythema (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Bruise (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Itching (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Induration (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Ulceration (n=0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)

*Source: ISS Table 22C.

Data presented in table 8 and 9 above are described in greater detail in the following text:

Burning (or "stinging") on injection was reported after 245 of the 708 injections (34.6% of study injections). Severity was reported as "mild" in 207 of 245 events (84%). This represents 29% of the total injections given in the study. Severity was reported as moderate in 33 of 245 events (4.6% of total study injections). Severity was reported as severe in five (2%) of 245 reported events. Thus, severe burning upon injection was reported for 0.7% of total study injections.

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Duration of burning was generally brief with 76% of all events lasting one minute or less. Of the 33 reported moderate events, duration was less than one minute for 23 events, from one to three minutes for nine events, and three to five minutes for one event. Of the five severe events, four lasted one minute or less and one lasted from one to three minutes. The longest duration of burning was 15 minutes (reported in 3 events). No patients reported recurrent severe burning at a subsequent injection.

Pain at the injection site was reported after 31 of 708 injections (4.1% of study injections). Severity was reported as mild in 25 (76%) of 31 reported events representing 3.5% of total study injections. Severity was reported as moderate in six (19%) of the 31 reported events, representing 0.8% of study injections. There were no reports of severe pain.

Duration of pain events was generally brief. In the moderate group, five of six events resolving within three minutes, and one event lasting longer than 5 minutes but not longer than 2 days.

Erythema was reported following 18 injections (2.5% of study injections). All of these events were documented as mild. Eight of these events were resolved in three to five days. Ten of the events were resolved in greater than five days.

Of note, only two patients (Patient #0703, injections #3 and #4; Patient #2404, injections #1 and #6) had more than one event in this category, e.g., reported erythema occurring at more than a single administered injection. In these patients, the second event was neither more severe nor more persistent than the first. And, there were no additional reports of erythema in those two patients.

Bruising was reported following 18 injections (2.5% of study injections). Seventeen of these events were characterized as mild and one as moderate. One of these events resolved in three to five days and sixteen took greater than five days to resolve.

Of note, none of the patients on anticoagulant (warfarin) therapy in the study experienced any bruising at the injection site following any of the study injections.

Pruritus was reported following 13 injections (1.8% of study injections). Eleven of these events were documented as mild (85% of the reported events, 0.2% of total study injections). Two patients reported moderate events (15% of the reported events, 0.13% of study injections). Duration of the events was variable with two of the 18 events lasting greater than five minutes; one lasting one to three days; four lasting three to five days; and four lasting greater than five days.

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Of note, only one patient (Patient #0703, injections #3 and #4) had more than one event in this category. The event recurred only once. In this patient, the second event was neither more severe nor more persistent than the first events.

Induration was reported following three injections (0.4% of study injections). All of these events were categorized as mild. While one of these events resolved within 5 days, two of these events were reported as lasting 43 and 80 days, respectively.

Ulceration at the injection site was reported following one injection (0.1% of all injections). The severity of that event was reported as "mild" and resolved 110 days after onset and ulceration did not occur with additional injections.

There were no recurrent events of induration or ulceration upon repeat injection in any patient.

9.5.5.5 ANALYSIS BY TOTAL NUMBER OF PATIENTS

Burning: Burning upon injection was the most commonly reported localized injection site adverse event. In terms of severity, it was reported by 55 patients (45.8% of all patients) as a mild event, by 5 patients (12.5%) as a moderate event, and by five patients (4.2%) as a severe event. In terms of duration, burning lasted for less than five minutes in all but three patients, who reported burning lasting for 15 minutes.

Pain: Pain on injection was reported by 18 patients (15.0% of all patients) as a mild event, and by 4 patients (3.3%) as a moderate event. Pain generally resolved within 2 days of injection and often within 5 minutes. One patient reported pain lasting up to 5 days, and five patients reported pain lasting up to 10 days.

Erythema: Erythema was reported as a mild event by 15 patients (12.5% of all patients). Erythema resolved within five days in 6 patients. Nine patients reported erythema lasting more than 5 days. In one patient, erythema lasted for 14 days and in one patient, erythema was ongoing at 66 days following injection.

Bruising: Bruising at the injection site was reported as a mild event by 13 patients (10.8% of all patients), and as a moderate event by 1 patient (0.8%). Bruising generally lasted for more than 5 days, and resolved within fourteen days in 10 patients. In the remaining three patients, bruising resolved within 3 weeks.

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Itching: Itching at the injection site was reported by 10 patients as mild (8.3% of all patients) and as moderate by 2 patients (1.7%). Itching resolved within five days in 8 patients. Itching resolved within eleven days in 3 patients, and within ninety-six days in 1 patient.

Induration: Mild induration at the site was reported by three patients (2.5%). Induration resolved within five days in 1 patient, within forty-three days in 1 patient, and within eighty days in 1 patient. Induration was not reported after subsequent injections in these patients.

Ulceration: Mild ulceration at the injection site was reported by one patient (0.8%) two days after his third injection. The event resolved within 110 days after onset and did not recur with subsequent injections in this patient.

Medical officer's comments:

With the exception of 3 notable events (two patients reported induration that continued for 43 and 80 days, respectively, and one patient reported ulceration at the injection site two days after the third injection that resolved after 110 days), the local adverse events were all mild and of short duration. All events resolved spontaneously, and none was associated with irreversible injury.

Given the demonstrated efficacy benefits of this product for advanced prostate cancer, this reviewer believes that all these local events don't add up to "overwhelm" the product's efficacy profile and preclude its approval.

Nevertheless, the package insert should be revised to accurately describe the frequency, severity, and duration of the local adverse events.

9.6 Laboratory assessments

9.6.1 Routine laboratory assessments

Mean values for hematology, clinical chemistry, and coagulation parameters were generally within normal limit ranges for all study timepoints for both trials. No clinically significant excursions or trends were noted.

Hematology assessments included total WBCs, total RBCs, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and platelets.

Clinical chemistry assessments included serum glucose, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphorous, sodium, potassium, chloride, bicarbonate, triglycerides, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatine kinase, and lactate dehydrogenase.

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Coagulation parameters included international normalized ratio for anticoagulant monitoring, protime and partial thromboplastin time.

9.6.2. Special laboratory assessments

9.6.2.1. Prostate cancer markers

For serum PSA and total acid phosphatase, there were progressive decreases in mean values over the course of the Study 9904. Mean serum PSA declined by greater than 90% over the study period. Total acid phosphatase declined from 7.86 μ L at baseline to 4.88 μ L at Month 6; a decrease of 39%.

9.6.2.2. Serum cholesterol

For serum cholesterol, mean values at Day 28 were modestly elevated over baseline. These elevations fluctuated from 3.5% to 7% over the upper normal limit.

9.6.2.3. International normalized ratio for coagulation monitoring

Mean INR values remained within normal limit range throughout the study with less than 6% increase from baseline to Month 6. The proportion of patients with very minor elevations of INR increased from one of 117 (< 1%) patients at baseline to eight of 112 (7%) at Month 6, however, the incidence of this finding at intervening timepoints varied widely. Other coagulation studies were without notable findings.

9.7. "Marked" laboratory abnormalities

Clinical laboratory safety tests were performed at centralized facilities. These facilities provided normal ranges for each analyte. Additional limits for each parameter that would indicate larger and potentially more serious deviations from normal were referred to as the "alert range". Further limits were identified for each parameter that represented substantial deviations from the normal range and were referred to as the "panic range".

The sponsor defined any value in the "panic range" as "markedly abnormal". No marked abnormalities were noted in study AGL9802.

Table 10 below displays all "markedly abnormal" laboratory parameters by patient and time point within Study AGL9904.

Patient #	Timepoint	Test	Value	Normal Range
0502	Day 84	Potassium		3.3 - 5.5 MEQ/L
	Month 6	INR		0.5 - 1.5
0803	Day 3	Creatine Kinase		24 - 195 IU/L

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	Day 70	Creatine Kinase	24 – 195 IU/L
	Day 84	Creatine Kinase	24 – 195 IU/L
1201	Month 5	INR	0.5 – 1.5
1302	Day 56	Basophils, ABS	0.0 – 0.17 x10E3/UL
	Baseline	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
1406	Day 1	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 3	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 14	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 56	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 70	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 84	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
1411	Day 70	Creatine Kinase	24 – 195 IU/L
2401	Day 3	INR	0.5 – 1.5
	Day 7	INR	0.5 – 1.5
	Day 28	INR	0.5 – 1.5
	Day 56	INR	0.5 – 1.5
2402	Baseline	Creatine Kinase	24 –195 IU/L
	Day 1	Creatine Kinase	24 – 195 IU/L
	Day 3	Creatine Kinase	24 – 195 IU/L
	Day 7	Creatine Kinase	24 – 195 IU/L
	Day 14	Creatine Kinase	24 – 195 IU/L
	Day 28	Creatine Kinase	24 – 195 IU/L
	Day 42	Creatine Kinase	24 – 195 IU/L
2405	Baseline	Creatine Kinase	24 – 195 IU/L
	Day 1	Creatine Kinase	24 – 195 IU/L
	Day 42	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
2701	Day 70	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Day 84	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Month 4	Eosinophils, ABS	0.0 – 0.56 x10E3/UL
	Month 5	Eosinophils, ABS	0.0 – 0.56 x10E3/UL

Medical officer's comments:

1. A review of these patients' clinical outcomes revealed no irregular or outstanding clinical adverse events. Thus, while these lab values may be "markedly" elevated, they did not appear to translate into meaningful clinical adverse outcome. In addition, the incidence of such lab values was very low. Finally, these lab values might reflect the effects of other illnesses or background variables.
2. The data submitted describing "shifts" in laboratory values to (a) values below the lower limit of the normal range ("shift to low") or (b) to values above the upper limit of the normal range ("shift to high") were not notable for any clinically important drug-related changes.
3. Overall, all available laboratory data do not raise concerns about significant drug-induced toxicity associated with the use of the ELIGARD™ for the treatment of advanced prostate cancer.

9.8 Safety issues of special concern

There are no safety issues of "special concern". As a class, clinical experience has shown that superactive GnRH agonists are generally safe and well tolerated in the treatment of advanced prostate cancer.

TOXICOLOGY:

Toxicology of Leuprolide acetate: Leuprolide acetate is an approved drug substance for several malignant and benign indications and its toxicity has been extensively investigated and safety is well established.

Toxicology of N-methyl-2-pyrrolidone: N-methyl-2-pyrrolidone (NMP) is an approved excipient for drug product, Atridox under NDA 50-751 as Atridox for the treatment of periodontal disease. Since it has not been approved for any indication by the parenteral route of administration, literature is reviewed briefly for its toxicological profile.

NMP Acute toxicity:

Reports of the acute toxicity LD₅₀ of NMP in several species have been summarized by Akesson (Arbete och Hals, 40:1-24, 1994) and as shown in table 5 below data suggests low degree of toxicity:

Table 5

Species	Route of Administration	LD ₅₀ (mg/kg body weight)
Rat	Intravenous	2300
Mouse	Intravenous	3600
Rat	Intraperitoneal	2500
Mouse	Intraperitoneal	4400
Rat	Oral	3900
Mouse	Oral	4100
Rabbit	Oral	3500
Guinea pig	Oral	4400
Rat	Dermal	2500-10,000
Rabbit	Dermal	4000-8000
Rabbit	Dermal, abraded skin	2000-40000

NMP repeated dose toxicity:**Subchronic oral toxicity: 28-day feeding study in rats with n-methylpyrrolidone (NMP)**

This study was conducted in compliance with GLP regulations by [REDACTED]

in

1994. DuPont HLR 92-94.

5 groups of 5 rats/sex were fed diets containing 0, 2000, 6000, 18000 and 30000 ppm for 28 days. The overall daily mean intake of NMP in the diets was 0, 149, 429, 1234 and 2019 mg/kg in males and 0, 161, 493, 1548 and 2268 mg/kg body weight in females.

These dose levels were selected based on 2 week study where dose of 0, 20000 and 30000 ppm were used and with both dose levels significant body weight was significantly lower compared to controls.

Results

Mortality: There was no compound-related mortality

Clinical observations: No adverse clinical observations were reported. The incidence of dark yellow stained cage boards was increased in both male and female rats at 18000 and 30000 ppm diet. This was attributed to one or more metabolites of NMP. Alopecia was noted in high dose male rats.

Body weight and body weight gains for the 2000 ppm dose group was similar to controls but decreases in body weight for 6000, 18000 and 30000 ppm dose groups were 6%, 17% and 33% in males and 6%, 8% and 14% in females. Overall (day 0-28) decrements in mean body weight gain were 15%, 40% and 72% in males and 15%, 19% and 52% respectively in females.

Food consumption was decreased in both males and females.

Clinical pathology changes consisted of decreased lymphocyte count and increased neutrophil count in the highest dose group. In this group, serum cholesterol was increased and total protein and albumin concentrations decreased in both male and female rats. Mean glucose concentration was decreased in 18000 and 30000 ppm dosed males.

The increase in urobilinogen and bilirubinuria in the 30000 ppm males was attributed to urine color interfering in the assays.

Gross observations related to compound administration included small testes in 3/5 rats at 30000 ppm and small thymus in 2/5 females at this dose level.

Compound related changes seen on histological examination of tissues revealed centrilobular hepatocellular hypertrophy in all males at 18000 and 30000 ppm and in all females at 30000 ppm and 3/5 at 18000 ppm. Hypocellular bone marrow was seen in all rats administered 30000 ppm. Testicular degeneration was reported in all 30000 ppm males and in one male at 18000 ppm. Thymic atrophy was seen in 3/5 females at 30000 ppm. No target organ was identified. Based on changes in body weight, food consumption, serum glucose, albumin, protein and cholesterol, which occurred at 18000 and 30000 ppm in males and 30000 ppm in females, NOAEL was considered 6000 ppm in males and 18000 ppm in females.

Sponsor stated that oral toxicity studies of 90 days duration have been conducted in compliance with GLP the mouse, rat and beagle dog. However, only summary reports are submitted.

In the mice 90-day toxicity study ([redacted] 60C0225/93053 report of 11-13-1995), dose of 1000, 2500 of 7500 ppm i.e, approximately 277, 619 and 1931 mg/kg/day were used. Results showed that the no-observed adverse effect level (NOAEL) was 1000 ppm/day i.e. 277 mg/kg/day but no direct target organ toxicity occurred at any dose.

In the 90-day rat toxicity study ([redacted] October 31, 1995), doses of 90, 225 and 540 mg/kg/day were used via diet. The study included a neurobehavioral battery of tests, conducted pre-dose and at 4, 8, and 13 weeks, consisting of motor activity and functional observational battery assessments. At week 13, a subset of animals was whole body perfused for histopathology of the brain, spinal cord, peripheral nerves and muscle. Groups were similarly treated after a one-month off-dose period.

Results showed that at mid and high doses, body weight and food consumption was decreased. No deaths or adverse effects including in neurohistopathology were observed. In the

neurobehavioral tests, increased foot splay occurred at both doses, while at the higher dose there was higher incidence of low arousal and slight palpebral closure, later suggesting a sedative effect. The NOAEL was 90 mg/kg/day

In the 90-day oral toxicity study in dogs [redacted] (1980), doses of 25, 79 and 250 mg/kg/day in corn oil were used. It was reported that there were no statistically significant treatment-related effects on standard range of parameters including histopathology except for intermittent reductions in serum cholesterol, albumin and total protein at the mid and high doses. Apart from these the NOAEL was 250 mg/kg/day.

Inhalation toxicity of NMP following repeat exposure has been studied in rats and mice. A 10-day study in rats at 1.5 mg/L had no toxic effects (no reference cited).

Lee et al (Fundamental Appl. Toxicol. 9:222-235, 1987) exposed rats to NMP at 0.1, 0.5, and 1 mg/kg for 6 hours/day, 5 days/week for 4 weeks. Deaths occurred at the high dose within 10 days. There was suppression of hematopoiesis in the bone marrow and of lymphoid activity, both were reversible. Pneumonitis was seen in the high dose but not in the mid dose rats (no reference cited).

In a 20-day dermal toxicity study in rabbits using intact and abraded skin at doses of 0.4, 0.8 and 1.6 ul/kg/day, resulted only in mild skin irritation in the low and mid dose groups (no reference cited).

Toxicity studies with the proposed formulation:

Study title: ATLS-84: A four month subchronic toxicity in rats following parenteral dosing.

Key study findings: The incidence of pyelonephritis with urinary bladder inflammation and calculi could be due to the vehicle, NMP. The vehicle caused testicular tubular degeneration in 5/9 rats.

Study no: ATLS-84. [redacted] No. 98T-09729-00

Volume #, and page #: 1.17 of 1.55, page 1

Conducting laboratory and location: [redacted]

Date of study initiation: 8-4-1998

GLP compliance: yes

QA report: yes (*) no ()

Drug, lot #, radiolabel, and % purity: Identification No. DM603156, not radiolabeled, purity not given

Formulation/vehicle: solution/ not mentioned although clinical formulation LA 2500 contains PLGH in NMP

Methods (unique aspects):

Dosing:

Species/strain: Rat/Crl:CD (SD)BR

./#/sex/group or time point (main study): only male rats used as shown in table 6 below:

Table 6

Group	# of animals	treatment	Dose (mg/kg)	Route of Administration	Termination (day)		
					61	91/92	123
1	20	Vehicle control	100 ul	Subcutaneous	5 rat	10 rats	5 rats
2	15	LA 2500 (low dose) (10X)	10 ul (1 mg/kg)	Subcutaneous	5 rats	10 rats	--
3	15	LA 2500 (mid dose) (30X)	30 ul (3 mg/kg)	Subcutaneous	5 rats	10 rats	--
4	20	LA 2500 (high dose) (100 X)	100 ul (10 mg/kg)	Subcutaneous	5 rats	10 rats	5 rats
5	15	Lupron Depot Control	400 ul (10 mg/kg)	Intramuscular	5 rats	10 rats	--

Satellite groups used for toxicokinetics or recovery: none

Age: 10-12 weeks

Weight: 360 –435 g

Doses in administered units: as shown in table

Route, form, volume, and infusion rate: as shown in table. Dosed biweekly i.e. on days 14, 28, 42, 60,74 and 90 or 91.

Observations and times:

Mortality and overt signs of toxicity: daily

Clinical signs: daily for first 14 days then weekly thereafter

Body weights: prior to treatment, weekly for the first 4 weeks and monthly thereafter and then before termination

Food consumption: not recorded

Ophthalmoscopy: not conducted

EKG: not performed

Hematology: at termination on days 61, 91/92 and 123

Clinical chemistry: same times as hematology

Urinalysis: not mentioned

Gross pathology: at necropsy

Organs weighed: liver, brain, spleen, kidneys, testes, prostate, and seminal vesicles

Histopathology: on organs shown in histopathology inventory table

Toxicokinetics: none

Other:

Results:

Mortality: one vehicle control animal died on day 12. This rat was dehydrated and had bloody urine. An other high dose rat died on day 90. This animal was also dehydrated and red substance was observed around the animal's penis.

Clinical signs: No significant behavioral changes or signs of toxicity were observed. On dermal observations, slight to moderate excoriation and scabbing was observed at various injection sites on animals in groups 1, 2, 3 and 4 following the day 0, 14, 28, 42 and 74 injection procedures. The severity appeared to the amount of dose injected, remained apparent throughout the study and was greater in the high dose group. No dermal lesions were observed on any animals in the Lupron Depot control group. Edema was also seen at injection sites and it was stated to be proportional to volume of injection and subsided over time.

Body weights: no statistical differences were noted for any treatment group.

Food consumption: not recorded

Ophthalmoscopy:-

Electrocardiography:-

Hematology: No consistent, biologically significant differences were reported between the control and treated groups. All values were reported to be within a normal expected range. Parameters showing significant differences were a decrease in RBC count in groups 2 and 3, increase in MCV in groups 2, 3 and 5 and decrease in MCHC in group 3.

Clinical chemistry: as for hematology, no consistent significant differences between control and treated groups were observed. Scattered significant differences for treated compared to vehicle controls were: a decrease in sodium in group 5, LDH in groups 3 and 5, and increase in cholesterol, bilirubin and GGT in groups 4 and 5.

Urinalysis: -

Organ weights: absolute weight as well as organ/body weight ratios were statistically lower for treated groups compared to vehicle controls for testes, seminal vesicles and prostate. In group 5, weight of the kidneys was lower on day 60 and that of liver on day 91. The kidney weight was lower for group 4 on day 123.

Gross pathology: the findings in the vehicle control animal that died during the study had cloudy urine and granular material with stones in the urinary bladder. The trigone area appeared thickened, edematous and hemorrhagic. Kidney cortex had yellow and white multi-focal areas of discoloration. The cause of death was ascribed to spontaneous pyelonephritis with urinary calculi and obstruction.

The high dose animal that died on day 91, had kidney lesions as seen in the vehicle control animal, had inflammation of the bladder which had multiple renal calculi. The death was attributed to pyelonephritis with urinary calculi. Sponsor suggested these findings to be unrelated to treatment. The possibility of vehicle causing these changes was speculated.

Histopathology: Treatment-related microscopic changes were observed in injection sites, reproductive organs, pituitary glands, mammary glands and lungs in animals assigned to both 91/92 and 123 sacrifice periods.

On day 91/92, SC injection site findings in vehicle control group consisted of mild to marked inflammation and mild to moderate fibrosis. Reactive changes were slightly less severe with 10 mg/kg LA-2500. With both the vehicle control and LA 2500, reactive changes on day 123 were regarded as mild suggesting resolution.

On sacrifice days 91/92 and day 123, treatment related changes in reproductive organs and male mammary glands in animals given 10 mg/kg; LA 2500 and Lupron Depot consisted of degeneration of the seminiferous tubules and atrophy of interstitial (Leydig) cells in testes, atrophy of accessory sex glands (prostate and seminal vesicles), involution of the glandular epithelium in male mammary glands and epididymal hypospermia. Tubular degenerative changes were more severe in Lupron treated group. Tubular degeneration was also reported in 5/9 vehicle control animals.

Treatment related changes in prostate and seminal vesicles or male mammary glands consisted of atrophy and involution of glandular epithelium with reduction in secretory materials. These changes were similar in 10 mg/kg LA-2500 and Lupron Depot treated groups but not observed in any vehicle control rat.

Pituitary chromophobe hyperplasia was observed in 4/10 Lupron treated rats on day 91/92 and in 4/5 animals given 10 mg/kg LA-2500 terminated on day 123. This was not observed in vehicle control animals.

Microscopic findings in pulmonary tissues consisted of perivascular inflammation. It was minimal to moderate in all groups sacrificed at the 91/92 day interval but was reported to be slightly more severe in rats given Lupron Depot when compared to other test groups. Pulmonary inflammation was attributed to the release of inflammatory mediators or mobilization of test materials from SC or IM injection sites.

No microscopic hepatic or renal changes were reported.

Toxicokinetics: -

Serum testosterone levels: The effect of treatment on serum testosterone concentration (pg/ml) for rats sacrificed on days 61, 91/92 and 123 compared to their respective vehicle controls is shown in table 7 below:

Table 7

Group	61 day termination		91/92 day termination		123 day termination	
	Control group 1	Treated	Control group 1	treated	Control group 1	treated
2	2506	2351	3111	2748		
3	2506	782*	3111	699*		
4	2506	528*	3111	478*		
5	2506	626*	3111	441*	4047	729*

* statistically significantly different compared to control (p<0.05)

Conclusion: At the dose levels used treatment with LA-2500 or Lupron Depot did not produced any overt toxicity. Both leuprolide-containing formulations had the expected testosterone lowering effect. The treatment thus had pharmacological but no toxicological effects.

Toxicology summary: Since pyelonephritis with urinary bladder inflammation and calculi was observed in both deceased control and high dose rats, it seems possibly due to vehicle, NMP. Slight to moderate excoriation and scabbing also seems to be due to the excipient since it occurred in the Atrigel and vehicle treated groups but not in Lupron treated rats. Testicular atrophy was also seen in 5/9 vehicle treated rats.

Toxicology conclusions: Treatment had the expected pharmacological effects with minimal overt toxicity.

ATLS-79: Systemic toxicity in the rat following 4 and 13 weeks of subcutaneous implantation-final report

This study was conducted by [redacted] in accordance with FDA's GLP Regulations.

The purpose of this study was to evaluate the potential systemic toxicity of Atrisite (PLGH in NMP, 0% polymer, 1% NMP lot # 1042) following SC implantation in the rat.

The experimental design was as follows:

Table 8

Group	# of animals implanted	Implantation days	Termination intervals
Control	5 male, 5 female	Day 0	Day 28
Control	5 male, 5 female	Day 0	Day 91
Test	5 male, 5 female	Day 0	Day 28
Test	5 male, 5 female	Day 0, 30, 60	Day 91

0.08 ml of test article (i.e. 48 ug NMP) was injected SC. strips were similar implanted in rats, which served as controls. Animals were observed daily for mortality and overt signs of toxicity. Clinical signs were recorded daily for the first 14 days and then weekly thereafter. Animals were weighed before implantation and weekly thereafter.

On day 28, 10 animals from control and treated group were euthenized and blood collected for hematology and clinical chemistry. At necropsy thymus, liver, spleen, kidneys, adrenal glands for both males and females were weighed and preserved for histopathological examination. Also testes in males and ovaries in females were weighed and preserved.

On day 30 and 60 all remaining animals were re-injected with the test article. All remaining animals were euthanatized on day 91.

Results:

Clinical observations revealed no significant behavioral changes or signs of toxicity.

Body weight was comparable for the treated and controls gropes.

At necropsy all animals macroscopically appeared normal.

Organ weights and organ to body weight ratios were similar between test and control groups.

Microscopic examination of selected tissues revealed no evidence of treatment-related response.

Microscopic examination of the SC tissue indicated no significant difference in the cellular reaction at the implant sites between the negative control and the test article. Reinjection of the test article produced no notable reaction.

There were no consistent treatment-related changes in hematology and clinical chemistry parameters.

Conclusion: It was concluded that under the conditions of this study, there was no evidence of systemic toxicity from Atrisite following SC implantation.

Histopathology Inventory for NDA # 21-343

Study	ATL	ATR		
	S-84	S-79		
Species	Rat	Rat		
Adrenals	*	*		
Aorta	*			
Bone Marrow smear	*			
Bone (femur)	*			
Brain	*			
Cecum	*			

Cervix				
Colon	*			
Duodenum	*			
Epididymis	*			
Esophagus	*			
Eye	*			
Fallopian tube				
Gall bladder				
Gross lesions	*			
Harderian gland				
Heart	*			
Ileum	*			
Injection site	*			
Jejunum	*			
Kidneys	*	*		
Lachrymal gland				
Larynx	*			
Liver	*	*		
Lungs	*			
Lymph nodes, cervical	*			
Lymph nodes mandibular	*			
Lymph nodes, mesenteric	*			
Mammary Gland	*			
Nasal cavity				
Optic nerves				
Ovaries		*		
Pancreas	*			
Parathyroid	*			
Peripheral nerve				
Pharynx	*			
Pituitary	*			
Prostate	*			
Rectum	*			
Salivary gland	*			
Sciatic nerve	*			
Seminal vesicles	*			
Skeletal muscle	*			
Skin	*			
Spinal cord	*			
Spleen	*	*		
Sternum				
Stomach	*			
Testes	*	*		
Thymus	*			

Thyroid	*			
Tongue				
Trachea	*			
Urinary bladder	*			
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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As noted previously, prescribers must be aware of the rare potential for "clinical flare" upon initiating therapy. In addition, serious systemic allergy has been reported to occur rarely.

In the particular case of ELIGARD, it appears that local site reactions were reported frequently but in general, these were mild in severity, brief in duration, and appeared to resolve without incident. In a small percentage of patients, subcutaneous induration or erythema may persist.

9.9 Safety consultations

No safety consultations were obtained.

9.10 Safety findings and proposed labeling

The ADVERSE REACTIONS section was revised by this reviewer to accomplish the following objectives:

1. To separately describe the results of Studies 9802 and 9904.
2. To more accurately and objectively describe the local injection site reactions.

In addition, safety issues in other sections of the PI were revised as necessary to maintain consistency in the drug class. Labeling negotiations were undertaken with the sponsor following which the sponsor submitted an acceptable PI on January 16, 2002.

10. Package insert

The proposed package insert was reviewed in great detail. Overall, the PI was accurate and clear. However, some modification of the clinical information was deemed necessary. These proposed changes in the PI were forwarded to sponsor. Following extensive negotiation the sponsor submitted an acceptable PI on January 16, 2002.

11. Use in special populations

Women and children were not studied for this indication (treatment of advanced prostate cancer). These groups are contraindicated in the package insert.

The pharmacokinetics of ELIGARD in patients with renal or hepatic insufficiency were not studied for this NDA. While this fact is noted in the package insert, it is

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not considered a safety issue because clinical experience has revealed leuprolide to be very safe even at high concentrations and because leuprolide is rapidly metabolized by enzymes that break down proteins.

12. Conclusions and recommendations

12.1. Overall risk/benefit assessment

The reader is also referred to the Executive Summary section of this review.

Benefits: Surgical castration is the standard against which hormonal therapies for the palliative management of advanced prostate cancer have been compared. The goal of androgen suppression therapy is to reduce serum testosterone concentrations to levels comparable to those observed following orchiectomy (≤ 50 ng/dL). Superactive GnRH agonists that suppress serum testosterone to castrate levels have been shown to have comparable long-term efficacy as orchiectomy, as assessed by time to disease progression and survival. Achievement of castrate levels of serum testosterone is generally obtained by 1 month after the start of therapy with a superactive GnRH agonist.

The results of Study AGL 9904, the principal efficacy and safety study supporting this NDA indicate that the 28-day formulation of ELIGARD™ is effective in suppressing serum testosterone to ≤ 50 ng within 28 days of first dosing and in maintaining serum testosterone at ≤ 50 ng through 6 dosing cycles (168 days) in greater than 90% of patients. In addition, there was no clinically meaningful acute-on-chronic phenomenon seen during the course of the studies. These findings are considered sufficient to support the efficacy of the ELIGARD™ for the palliative treatment of advanced prostate cancer.

Risks: In contrast to surgical castration, treatment with a superactive GnRH agonist initially results in a temporary (1-2 weeks) increase in gonadal androgen secretion before reducing serum testosterone to castrate levels. The initial rise in serum testosterone may cause a temporary worsening of symptoms referred to as "a flare." Most commonly, the androgen-induced flare consists of an increase in bone pain in patients with advanced prostate cancer. Less frequently, more serious complications such as compression of the spinal cord with motor impairment can occur. This potential complication is a labeled warning for all superactive GnRH agonists. The likelihood of such serious complications is diminished with earlier diagnosis of prostate cancer, as is occurring today in the United States. The risk of a clinically serious complication resulting from the initial surge of testosterone at the onset of treatment with ELIGARD™ should be no different than that associated with the use of other presently approved superactive GnRH analogs.

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Vast clinical experience had shown that GnRH agonists are safe and well tolerated for the treatment of prostate cancer.

Since GnRH analogs are small peptides, they have the potential to induce antibody formation and hypersensitivity reactions. Rare reports of systemic allergic reaction have been noted in the literature.

In addition, this new formulation has demonstrated the potential for local induration, erythema, and pruritis. The majority of these events were mild in severity, short in duration, and non-recurrent. On the basis of the overall safety data submitted this issue should not preclude approval.

In summary, based on safety and efficacy information submitted in NDA 21-343, this reviewer believes that ELIGARD™ is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

12.2. Recommendations

It is recommended that the monthly formulation of ELIGARD™ should be approved for the proposed indication of "*palliative treatment of advanced prostate cancer*".

/S/

1/23/02

Ashok Batra, MD

Medical Officer
Division of Reproductive and Urologic Drug Products
Arch NDA 21-343
cc: HFD-580/Div File
HFD-580/DShames/MHirsch/JBest
HFD-870/KimMJ

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Eligard™ (leuprolide acetate for injectable suspension)

ATRIX Laboratories, Inc.

The Safety Update Review was included in the Integrated Review of Safety in the Medical Officer's Review (see Section 9).

TS/

11/11/02