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SYNOPSIS

Title of Study:

A phase IIIb randomized study of intermittent versus continuous androgen deprivation therapy using ELIGARD® 22.5 mg 3-month depot in patients with relapsing or locally advanced prostate cancer who are responsive to such therapy

Investigator/Coordinating Investigator:

[redacted] MD, PhD, [redacted] Belgium.

Study Centers:

This was a multi-center study performed in 102 centers in 20 countries (Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Sweden, Spain and United Kingdom).

Publication (reference):

Not applicable.

Study Period:

Date of first enrollment (Study initiation date): 05 April 2006

Date of last evaluation (Study completion date): 08 April 2013

Phase of Development: Phase 3b

Objectives:

The primary objective was to assess prostate-specific antigen (PSA) and testosterone levels after continuous and intermittent androgen-deprivation therapy (ADT) and compare time to PSA progression.

The secondary objectives were:

- To compare the overall survival of patients with relapsing or locally advanced prostate cancer responsive to ADT treated with intermittent androgen deprivation (IAD) vs continuous androgen-deprivation (CAD) therapy
- To compare the effects of these treatment regimens on impotence, libido and vitality/fatigue as well as on the physical and emotional well-being of these patients
- To compare general symptoms, role functioning, global perception of quality of life and social functioning of patients treated with these regimens
- To measure and compare bone turnover and [redacted] in patients treated with these regimens

Methodology:

This was a Phase 3b, open-label, randomized, multi-center study.

Induction Phase (Visits 1-4)
Patients satisfying all selection criteria were treated with Eligard 22.5 mg 3-month depot for 6 months. All

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patients also received bicalutamide (Casodex®) 50 mg once daily (qd) for 1 month from the time of first injection to avoid any flare reaction.

Patients were monitored every 3 months during the induction phase by measurements of total serum PSA and testosterone. Two successive serum PSA levels ≤ 1 ng/mL (at least 2 weeks apart) after 6 months of complete androgen suppression (which defines hormone-responsive prostate cancer) were required for further inclusion of the patients in the randomization procedure. Those patients whose serum PSA level did not meet the definition of hormone responsiveness after 6 months of treatment were withdrawn from the study.

Randomized Phase (Visits 4-16)
Patients with hormone-responsive prostate cancer were then randomly assigned either to the CAD or IAD regimen.

Patients in the CAD group received Eligard 22.5 mg 3-month depot injections without interruption for 36 months and were monitored every 3 months with serum PSA and testosterone measurements.

Patients in the IAD group had their ADT discontinued after the induction therapy phase and entered the off-treatment phase of the first intermittent ADT cycle. They restarted treatment with Eligard if their serum PSA level reached ≥ 2.5 ng/mL during the off-treatment phase. At the time of treatment reintroduction, patients received Eligard 22.5 mg 3-month depot injection plus Casodex (50 mg qd) for 1 month followed by Eligard 22.5 mg every 3 months alone. Medication was again withheld when serum PSA levels were ≤ 1 ng/mL on 2 successive occasions (at least 2 weeks apart). Patients treated with intermittent ADT were monitored every 3 months with serum PSA and testosterone measurements and cycles of intermittent ADT were repeated for a maximum of 36 months.

Long-term Follow-up (Visits 17-19)
After stopping study treatment, all randomized patients continued to be followed up for 18 months to assess overall mortality during the 4.5 years after randomization. During this period, follow-up visits took place every 6 months to record whether the patient was still alive, or, in case of death, to record the exact date when the patient had died.

Number of Patients (planned, enrolled and analyzed):

A total of 700 male patients were planned to be randomized in the study: 350 patients per treatment group.

A total of 1131 patients were screened, of whom 933 entered the induction phase. Of these, 701 patients were randomized (see Figure 1) and 232 patients discontinued before randomization. A total of 131 patients discontinued after randomization.

- The Safety Analysis Set 1 (SAF1) consisted of 932 patients who received at least 1 injection of Eligard. In this study, SAF1 was identical to the Full Analysis Set 1 (FAS1).
- The SAF2 consisted of 690 patients who were randomized and had post-randomization safety data available (353 patients on CAD and 337 patients on IAD). Of these, 602 patients (310 patients on CAD and 292 patients on IAD) entered the follow-up period and 101 patients completed the follow-up period (59 patients on CAD and 42 patients on IAD).
- The FAS2 consisted of 686 patients who entered the study and who were randomized and treated at Visit 4 (352 patients on CAD and 334 patients on IAD). Of these, 599 patients (309 patients on CAD and 290 patients on IAD) entered the follow-up period and 101 patients completed the follow-up period (59 patients on CAD and 42 patients on IAD).
- The Per Protocol Set 1 (PPS1) included 841 patients of the FAS1 who had no major protocol violations during the induction phase, and the PPS2 included 609 patients of the FAS2 who had no protocol violations during the randomized phase (306 patients on CAD and 303 patients on IAD). Of the 609 patients in the

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PPS2, 533 patients (270 patients on CAD and 263 patients on IAD) entered the follow-up period and 85 patients completed the follow-up period (50 patients on CAD and 35 patients on IAD).

Diagnosis and Main Criteria for Inclusion:

Eligible patients were men, aged ≥ 18 years but < 80 years, with histologically or cytologically confirmed adenocarcinoma of the prostate meeting the following criteria:

- Locally advanced (stage T3 or T4) prostate cancer, N0 or N +, M0 with PSA ≥ 5 ng/mL, or
- Relapsing prostate cancer following radical prostatectomy for clinically localized prostate cancer with a serum PSA of ≥ 0.4 ng/mL that had risen on 3 successive occasions (values drawn at least 2 weeks apart) as compared to a previous reference value or,
- Relapsing prostate cancer following radiotherapy with a serum PSA of ≥ 1 ng/mL that had risen on 3 successive occasions (values drawn at least 2 weeks apart) as compared to a previous reference value.

In addition, the men should have had a Gleason score of ≥ 6, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a life expectancy of at least 5 years. At the randomization (Visit 4), the men should have had 2 successive serum PSA levels ≤ 1 ng/mL (at least 2 weeks apart) after 6 months of complete androgen suppression.

Test Product, Dose and Mode of Administration, Batch Numbers:

Leuprorelin acetate (Eligard®) subcutaneous 3-month depot injection; 22.5 mg.
Batch number: [redacted].

Casodex® 50 mg once daily, white, film-coated tablets.
Batch number: [redacted]

Duration of Treatment (or Duration of Study, if applicable):

- Induction period of 6 months.
- Randomized phase of 36 months
- Long-term follow-up of 18 months, after stopping study treatment.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable

Criteria for Evaluation:

The primary efficacy endpoint was the time to PSA progression defined as 3 consecutive increasing PSA values ≥ 4 ng/mL at least 2 weeks apart. PSA was determined using an immune-assay technique. The date of PSA progression was defined as the date of the first of the 3 increasing PSA values ≥ 4 ng/mL. The time to PSA progression was defined as the number of days from the randomization date (Visit 4 at Month 6) and the date of PSA progression plus 1 day.

Secondary efficacy endpoints were:

- PSA levels and PSA progression-free survival, defined as time from randomization to either PSA progression as defined above or death.
- Overall survival, defined as the time from randomization to either the last available assessment (e.g., follow-up visit) or death, occurring ≤ 60 months after randomization

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- Testosterone levels and testosterone breakthrough, defined as time to serum testosterone > 50 ng/dL or 1.7 nmol/L [conventional], or > 20 ng/dL or 0.7 nmol/L [conservative]
- WHO/ECOG performance status (5-point scale)
- Quality of Life – determined using the European Organization for Research and treatment of Cancer (EORTC)-QLQ-C30 questionnaire and the prostate cancer module QLQ-PR25 summary scales
- Bone turnover and [redacted] (osteoprotegrin [OPG] in serum and bone-specific alkaline phosphatase [BAP] in serum [in a subset of centers only])

Additional, [redacted]

Safety was assessed from the recording of (serious) AEs, clinical laboratory evaluations (biochemistry, hematology and urinalysis), physical examination, vital signs and bone scintigraphy or computerized tomography scans.

Statistical Methods:

Efficacy

The primary analysis, time to PSA progression, was analyzed using Kaplan-Meier techniques, including log-rank tests. Kaplan-Meier curves were presented for the treatment groups. Analyses were presented for the FAS2, which was the primary analysis set, and for the PPS2. Rules for censoring and imputation were applied as specified in the SAP. PSA progression-free survival was analyzed in a similar way, except that death was not a censoring reason but an event. This analysis was used in a sensitivity analysis to support the robustness of the primary efficacy analysis.

Serum PSA levels, testosterone levels and the bone turnover marker values at each visit and change from randomization in these levels were summarized by treatment group and visit by means of descriptive statistics. Time to testosterone breakthrough was summarized descriptively and frequencies of patients with testosterone breakthrough were reported by visit.

The overall survival and time to testosterone breakthrough (> 50 ng/dL or > 20 ng/dL) were also analyzed by Kaplan-Meier analyses including log-rank tests, for the FAS2 and PPS2.

WHO/ECOG performance status, EORTC QLQ-C30 and QLQ-PR25 Quality of life questionnaires were summarized by visit and treatment group by means of descriptive statistics.

For all efficacy variables summaries stratified by primary diagnosis were also provided.

All statistical comparisons were made using 2-sided tests at the $\alpha = 0.05$ significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were 2-sided.

Safety

All AEs were summarized for the induction phase (SAF1) and the randomized phase (SAF2).

The number and percentage of patients with TEAEs, classified by System Organ Class (SOC) and Preferred Term (PT) were summarized for each treatment group. Similar summaries were provided for drug-related

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TEAEs, serious TEAEs and TEAEs that led to study discontinuation. Adverse events were also presented by intensity (worst Common Toxicity Criteria [CTC] grade), severity and by relationship (all TEAEs) to study drugs.

[redacted]

Laboratory test results, vital signs (systolic and diastolic blood pressure, and pulse rate) were summarized descriptively, including changes from baseline, by treatment group and visit.

The number and percentage of patients with no change, no clinically significant change and clinically significant changes for each body system of physical examination was tabulated at screening and at Visit 16. A change from randomization (Visit 4) was calculated for the bone scintigraphy or computerized tomography scan.

Summary of Results/Conclusions:

Population:

In the induction phase, a total of 933 patients were included. Of these, 701 patients were randomized and 232 patients discontinued before randomization (Figure 1). The main reasons for discontinuation after screening (Visit 2) but before randomization (at Visit 4) were 'not fulfilling the in- or exclusion criteria' (n = 176; 18.9%), 'other' (n = 22; 2.4%), and consent withdrawal (n = 13; 1.4%).

A total of 131 patients discontinued after randomization, mainly due to 'other' (n = 45; 6.6%), consent withdrawal (n = 27; 3.9%), death (n = 23; 3.4%) and AE(s) (n = 21; 3.1%) [Figure 1].

The baseline demographics for the SAF1 were well-matched between the treatment groups [Table 1]. Comparable results were found for the other analysis sets.

The prostate cancer characteristics for the SAF1 at baseline were comparable between the treatment groups, with exception of the time since diagnosis, which was slightly longer in the IAD group vs the CAD group (median value: 88 vs. 74 days)[Table 2].

Around 37% of all SAF1 patients had a Gleason score ≤ 6, and another 37% of patients had a Gleason score of 7. A Gleason score of ≥ 8 was recorded for 26.0% of patients. None of the patients included in the SAF1 had a Gleason < 6.

The TNM classification at baseline for the SAF1 showed that over 75% of patients had a palpable tumor confined within the prostate (T2; 11.4%) or extending through prostate capsule and/or seminal vesicles (T3; 66.3%). The regional lymph nodes could either not be assessed (NX) in 33.4% of patients and did not show any metastasis (N0) in 61.4% of patients. Distant metastasis were absent (M0) in 99.8% of patients.

The overall primary diagnosis (reported for FAS2 only) was locally advanced prostate cancer in 58.0% of patients (CAD: 59.9%; IAD: 56.0%), relapsing prostate cancer after radical prostatectomy in 26.7% of patients (CAD: 25.0%; IAD: 28.4%), and relapsing prostate cancer after other therapies in 15.3% of patients (CAD: 15.1%; IAD: 15.6%).

All patients in the CAD and IAD group received 2 Eligard injections during the induction phase. The mean (SD) number of days between injections was 89.5 (6.6) and 89.8 (7.8), respectively (FAS1).

The mean (SD) number of Eligard injections during the randomized period was 10.8 (2.8) in the CAD group, and 3.1 (1.8) in the IAD group. The mean (SD) number of days between injections was 88.5 (4.4) and 327.5 (189.7), respectively [FAS2; Table 3].

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Efficacy Results:

Primary Efficacy Variable

The primary endpoint was the time to PSA progression. A summary of the results from the Kaplan-Meier analysis for the FAS2 is presented in Table 4 and Figure 2.

The primary endpoint, time to PSA progression, did not differ significantly between treatment groups (P = 0.718), with a similar number of events recorded in each group (34 [9.7%] events in the CAD group and 30 [9.0%] events in the IAD group). The results for the PPS2 were similar (P = 0.621).

Secondary Efficacy Variables – Serum PSA Levels and PSA Progression-free Survival

During the induction phase, mean PSA levels decreased from 16.1 ng/mL before the start of treatment (Visit 2) to 0.32 ng/mL at randomization for patients in the CAD group, and from 18.7 to 0.26 ng/mL for patients in the IAD group (FAS1). The mean PSA levels of the non-randomized patients (those whose serum PSA level did not meet the definition of hormone responsiveness) decreased from 56.3 to 5.04 ng/mL (FAS1). The results for the PPS1 were similar to that of the FAS1.

For patients who were randomized at Visit 4 (FAS2), the mean PSA level was 0.28 ng/mL at randomization for patients in the CAD group and these values remained between 0.28 and 3.00 ng/mL for the remainder of the treatment period. The mean PSA level for patients in the IAD group was 0.27 ng/mL at randomization and fluctuated between 0.58 and 3.37 ng/mL for the remainder of the treatment period. Whilst the range of PSA levels which were recorded in the CAD and IAD group were similar across the treatment period, from Visit 6 there was a general trend of slightly higher levels being recorded in the IAD group.

Stratification by primary diagnosis for the FAS2, showed for patients with locally advanced prostate cancer that their mean PSA levels were approximately 23-30 ng/mL before initiation of therapy, but subsequently decreased to levels comparable to levels observed in patients with relapsing prostate cancer after radical prostatectomy and in patients with relapsing prostate cancer who had undergone other therapies.

The mean time to PSA < 4 ng/mL during the induction phase (FAS1) was around 100 days for patients with locally advanced cancer, and between 41 and 59 days for patients with relapsing cancer.

The time to PSA progression or death in the FAS2 did not differ significantly between treatment groups (P = 0.865), with a similar number of events recorded in each group (43 [12.2%] events in the CAD group and 41 [12.3%] events in the IAD group) [Table 5]. The results from the PPS2 were similar (P = 0.676).

Secondary Efficacy Variables – Overall Survival

The results from the Kaplan-Meier analysis for overall survival (until 4.5 years after randomization) for FAS2 are summarized in Table 6. The time to death did not significantly differ between treatment groups (P = 0.969), with a similar number of events recorded in each treatment group (44 [12.5%] events in the CAD group and 42 [12.6%] events in the IAD group). The results for the PPS2 were similar (P = 0.781).

Secondary Efficacy Variables – Testosterone Levels and Breakthrough

During the induction phase, mean testosterone levels decreased from 411.5 ng/dL before the start of treatment (Visit 2) to 24.5 ng/dL at Visit 3 for patients in the CAD group, and from 412.9 to 20.7 ng/dL for patients in the IAD group. Mean testosterone levels in patients who were not randomized decreased from 379.4 ng/dL to 57.7 ng/dL (FAS1). The results for the PPS1 were similar.

The mean testosterone level for patients in the IAD group (those that had their Eligard dosing halted) at randomization was similar to the levels observed in the CAD group (11.4 ng/dL vs 12.9 ng/dL), but then

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increased thereafter (range between 61.0 and 268.0 ng/dL). It should however be noted that these are mean values and that no analysis was done of testosterone levels against timing of Eligard cessation in individual patients. The results for the PPS2 were similar to that of the FAS2.

The time to conventional as well as conservative testosterone breakthrough did significantly differ between the treatment groups (both $P < 0.001$), with a higher number of events recorded in the IAD vs the CAD group (conventional: 327 events [97.9%] vs 22 events [6.25%], respectively; and conservative: 330 events [98.8%] vs 105 events [29.8%], respectively)[FAS2: Table 7]. In the IAD group, median time to conventional testosterone breakthrough was 176.0 days and median time to conservative testosterone breakthrough was 174.0 days. Due to the low number of events, these figures could not be determined for the CAD group.

Secondary Efficacy Variables – WHO/ECOG Performance Status

The patients' WHO/ECOG status tended to slightly deteriorate towards the end of the treatment period. There were no notable differences between treatment groups. Throughout the study, including at baseline, patients with relapsing prostate cancer, most notably those who underwent radical prostatectomy, had a less severe WHO/ECOG status than patients with locally advanced cancer. Results of FAS2 and PPS2 were similar.

Secondary Efficacy Variables – Quality of Life

Results of the EORTC QLQ-C30 showed no relevant differences between the treatment groups in the functional scales (i.e., physical, role, emotional, cognitive and social functioning) of which mean scores were all > 80 at randomization up to end of the treatment. The mean global health status worsened during treatment, with nausea, vomiting and appetite loss being the most distressing symptoms, in both groups. Changes over time were small, probably not clinically relevant and similar for patients in the CAD and IAD group.

The QLQ-PR25 summary scales at randomization and at end of treatment indicated small mean increases (indicating a worse quality of life) for incontinence aid and sexual function, and small mean decreases for urinary symptoms, hormonal treatment related symptoms and the sexual active summary scale. No consistent pattern was observed for bowel symptoms. There were some differences between treatment groups, in particular for use of incontinence aid and sexual activity. For sexual activity, patients in the CAD group showed a small improvement at Visit 16 compared to baseline, whereas no relevant change was observed for patients in the IAD group. The difference in use of incontinence aid was already present at baseline.

Secondary Efficacy Variables – Bone Turnover Markers

OPG and BAP in serum were measured at a subset of centers only. There was a small decrease (-0.7 pmol/L) in mean OPG levels from randomization to the end of the treatment period, with no differences between the CAD and IAD group. Due to stability problems, only a limited number of samples were analyzed for BAP. Therefore, no relevant conclusions could be drawn.

Safety Results:

Adverse Events

Induction Phase

Overall, 509 (54.6%) patients had 1 or more AEs during the induction phase [Table 8]. The most common AE (preferred term) was hot flush (reported by 327 patients; 35.1%). Other AEs reported by ≥ 2% of patients overall in the induction phase were hypertension (32 patients; 3.4%), erectile dysfunction (23 patients; 2.5%) and insomnia (19 patients; 2.0%). Most events of hot flush (322 patients; 34.5%) and all events of erectile dysfunction were considered related to treatment by the investigator.

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Most AEs were grade 1 (mild) or grade 2 (moderate). Eight AEs in 76 patients were grade 4 or grade 5 in severity. All events were in the non-randomized treatment group and none of the AEs were considered related to treatment by the investigator.

Six (0.6%) patients died during the induction phase and 48 (5.2%) patients had 1 or more AEs during the induction phase that were considered serious. All deaths and most SAEs (61 out of 72 events; 84.7%) were considered unrelated to treatment by the investigator.

Eighteen (1.9%) patients discontinued from the induction phase due to AEs. For 8 (0.9%) patients, the AEs leading to discontinuation were considered related to treatment by the investigator.

Randomized Phase

Overall, 510 (73.9%) patients had ≥ 1 AEs during the randomized phase, with no clinically relevant difference between the CAD (256 patients; 72.5%) and IAD (254 patients; 75.4%) group [Table 9]. The most common AEs (preferred terms) were hot flush, reported by 68 (19.3%) patients in the CAD group and by 72 (21.4%) patients in the IAD group, and hypertension, reported by 45 (12.7%) patients in the CAD group and by 37 (11.0%) patients in the IAD group. Most events of hot flush were considered related to treatment by the investigator: 66 (18.7%) patients in the CAD group and 70 (20.8%) patients in the IAD group.

Most AEs were grade 1 (mild) or grade 2 (moderate). There were 85 AEs of grade 4 (life-threatening or disabling) or grade 5 (death) in severity, but only 2 events were considered related to treatment by the investigator. These events were grade 4 acute renal failure in the IAD group, and grade 4 acute myocardial infarction in the CAD group.

Twenty-four (3.5%) patients died during the randomized phase, as reported in Table 9. An additional 6 patients also died during the randomized phase, but for these patients no AE with outcome 'fatal' was reported and therefore they are not included in Table 9. Overall, cardiac disorders and cancer were the most commonly reported causes of death.

A total of 178 (25.8%) patients had 1 or more AEs during the randomized phase that were considered serious (88 patients [24.9%] in the CAD group and 90 patients [26.7%] in the IAD group). Myocardial infarction was more frequent in the IAD group than in the CAD group, but all but 1 event was considered not related to treatment by the investigator. Most SAEs were considered unrelated to treatment by the investigator (380 out of 392 events; 96.9%).

Forty-two (6.1%) patients discontinued from the randomized phase due to AEs (42 patients [4.8%] in the CAD group and 25 patients [7.4%] in the IAD group). For 4 (0.6%) patients (all in the CAD group), the AEs leading to discontinuation were considered related to treatment by the investigator.

Follow-up Phase

Sixty patients died during follow-up (36 on CAD and 24 on IAD).

<u>Other Safety Parameters</u>

[redacted]

A small decrease in mean hemoglobin, hematocrit and erythrocytes values was observed in the CAD group compared to IAD. In consistence, shifts from normal at randomization to below the laboratory reference range at the end of the treatment period were most frequently observed for hemoglobin, hematocrit and erythrocytes,

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with a slightly more pronounced effect in the CAD group. There were no notable differences between treatment groups or trends from randomization to the end of the treatment period for other hematology, or biochemistry parameters. All mean values for all parameters were well contained within laboratory reference ranges.

There were no relevant changes from baseline to the end of treatment visit in vital signs. There were also no relevant differences between treatment groups.

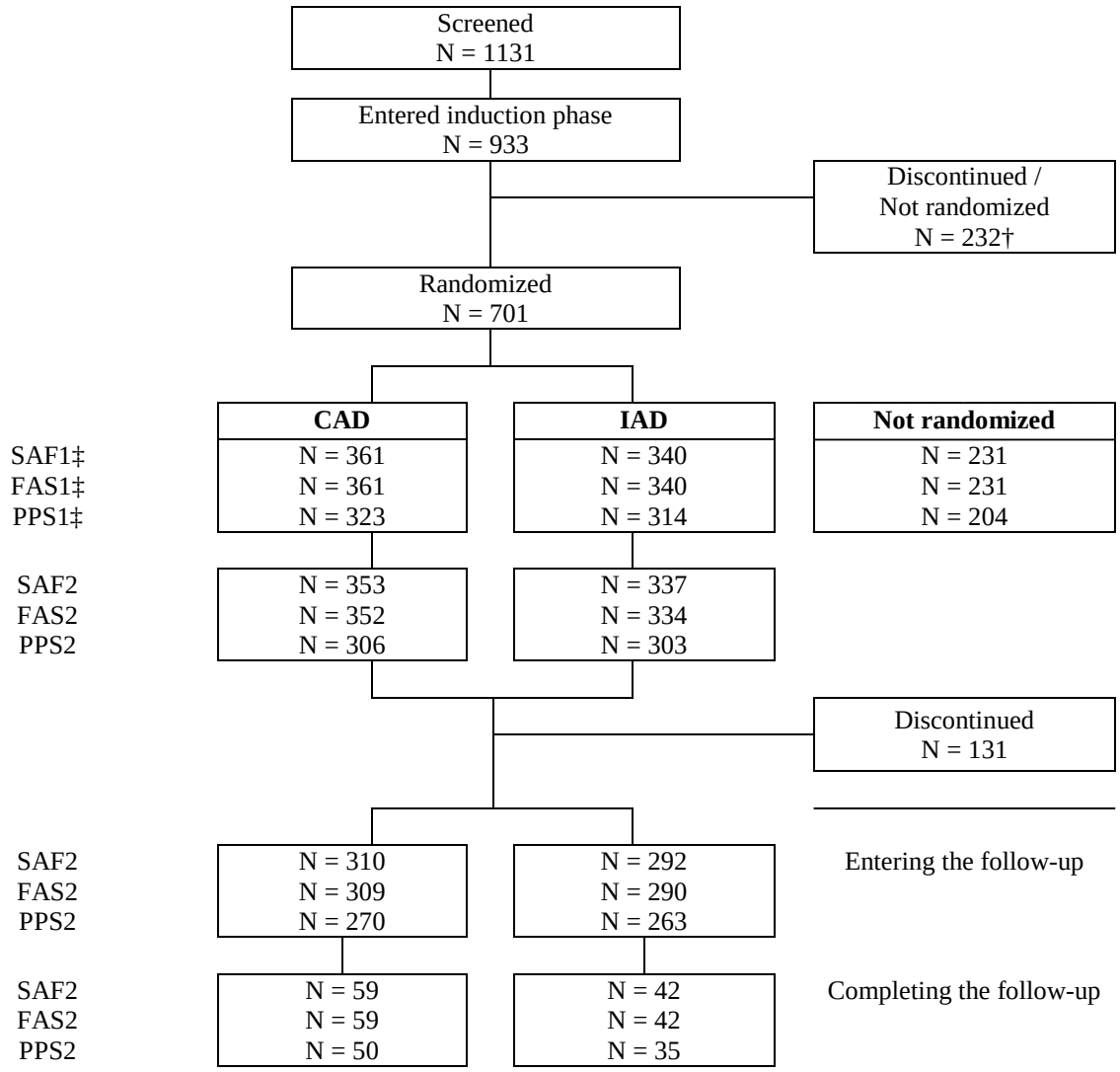
Abnormalities at the physical examination were frequent at all visits, including at study entry (Visit 1), and most of these abnormalities were findings related to the prostate, as expected in this population. There were no relevant differences between groups. The number of patients with a bone scintigraphy or computerized tomography scan at Visit 16 was low, i.e., 73 out of 932 patients; and of these, more than 75% had no clinically significant findings (SAF1).

CONCLUSIONS:

- There were no statistically significant differences between continuous and intermittent Eligard therapy with respect to the primary efficacy endpoint time to PSA progression (FAS2). This was confirmed by the results of the same analysis run on the PPS2, the sensitivity analyses and the analyses which stratified by primary diagnosis.
- The time to PSA progression-free survival until 3 years after randomization, and the overall survival until 4.5 years after randomization were also not statistically significantly different between treatment regimens.
- Most patients in the CAD group maintained castrate levels of testosterone throughout the treatment period, and the proportion of patients with conventional and conservative breakthrough events was low. As expected, mean levels of testosterone in the IAD group were higher. Whilst no analysis of testosterone levels against timing of Eligard cessation for individual patients was performed, most of the patients in the IAD group had an increase of testosterone to above castrate levels at some point during the study.
- Overall, there was no difference of intermittent vs continuous ADT on WHO/ECOG status and quality of life. Patients in the CAD group showed a small improvement from baseline for sexual activity, whereas no such change was observed for patients in the IAD group.
- A small decrease in OPG was observed in both treatment groups. Due to stability problems limited data was available for BAP and no relevant conclusions could be drawn.
- Both treatment regimens were generally well tolerated, with no differences between continuous and intermittent ADT in the incidence, type or severity of AEs. The most commonly reported events were in line with the Eligard SPC (hot flush and hypertension). Most AEs were grade 1 (mild) or grade 2 (moderate).
- There were no treatment-related deaths.
- Treatment-related SAEs and treatment-related AEs that led to discontinuation were infrequent.
- [redacted]
- There were no clinically relevant changes in laboratory parameters and vital signs over time. The most frequently reported abnormalities at the physical examination were findings related to the prostate, as expected in this population. There were no differences between treatment groups.

Date of Report: 23 Jan 2014

Figure 1 Disposition of Patients



† There is a discrepancy in the nonrandomized group due to Patient [redacted] who was not documented as a Screening failure, whereas [redacted] should have been, based on the fact that inclusion criterion 3 was not met (locally advanced but TNM missing); no Eligard was administered.

‡ Population additionally included patients who were not randomized.

CAD: Continuous Androgen Deprivation; IAD: Intermittent Androgen Deprivation

FAS: Full Analysis Set; SAF: Safety Analysis Set; PPS: Per Protocol Set

Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3, 12.1.1.4, 12.1.1.5, 12.1.1.7.1, 12.1.1.7.2, 12.1.1.7.3

Table 1 Demographic Characteristics at Baseline (SAF1)

		CAD (N = 361)	IAD (N = 340)	Not Randomized (N = 231)	Total (N = 932)
Race (n, %)	Caucasian	360 (99.7)	339 (99.7)	230 (99.6)	929 (99.7)
	Black	1 (0.3)	1 (0.3)	0	2 (0.2)
	Asian	0	0	1 (0.4)	1 (0.1)
	Other	0	0	0	0
Age: years	Mean (SD)	70.6 (6.49)	71.1 (6.00)	69.5 (6.95)	70.5 (6.46)
	Median (range)	71.0 (50-82)	72.0 (47-81)	70.0 (42-84)	71.0 (42-84)
	< 65 (n, %)	62 (17.2)	43 (12.6)	51 (22.1)	156 (16.7)
	≥ 65 (n, %)	299 (82.8)	297 (87.4)	180 (77.9)	776 (83.3)
Weight: kg	Mean (SD)	80.1 (11.83)	81.1 (12.02)	82.4 (12.13)	81.0 (11.99)
	Median (range)	80.0 (48127)	80.0 (45-130)	82.0 (56-120)	80.0 (45-130)
Height: cm	Mean (SD)	172.3 (6.83)	172.5 (6.42)	172.7 (6.98)	172.5 (6.72)
	Median (range)	172.0 (152-198)	172.0 (156-192)	172.0 (156-193)	172.0 (152-198)
BMI: kg/m^2	Mean (SD)	27.0 (3.50)	27.2 (3.54)	27.6 (3.48)	27.2 (3.52)
	Median (range)	26.4 (18.5-44.6)	26.9 (17.8-44.5)	27.2 (20.3-38.5)	26.8 (17.8-44.6)

Source: Table 12.1.2.1

Table 2 Summary of Prostate Cancer History (SAF1)

		CAD (N = 361)	IAD (N = 340)	Not Randomized (N = 231)	Total (N = 932)
Time since diagnosis (days)	N	351	323	223	897
	Mean (SD)	659.5 (956.15)	712.1 (986.39)	365.2 (828.65)	605.3 (946.85)
	Median (range)	74 (0-4401)	88 (0-4185)	43 (0-5470)	66 (0-5470)
Any surgery (n, %)	No	241 (66.8)	225 (66.2)	196 (84.8)	662 (71.0)
	Yes	120 (33.2)	115 (33.8)	35 (15.2)	270 (29.0)
Reason for therapy (n, %)	Primary cancer	113 (93.4)	108 (92.3)	30 (85.7)	251 (91.9)
	Metastases	1 (0.8)	1 (0.9)	1 (2.9)	3 (1.1)
	Other	7 (5.8)	8 (6.8)	4 (11.4)	19 (7.0)
Any radiation (n, %)	No	301 (83.4)	274 (80.6)	201 (87.0)	776 (83.3)
	Yes	60 (16.6)	66 (19.4)	30 (13.0)	156 (16.7)
Reason for therapy (n, %)	Primary cancer	51 (82.3)	58 (87.9)	26 (76.5)	135 (83.3)
	Metastases	1 (1.6)	0	1 (2.9)	2 (1.2)
	Other	10 (16.1)	8 (12.1)	7 (20.6)	25 (15.4)
Any chemotherapy (n, %)	No	361 (100)	337 (99.1)	230 (99.6)	928 (99.6)
	Yes	0	3 (0.9)	1 (0.4)	4 (0.4)
Reason for therapy (n, %)	Primary cancer	0	3 (100)	1 (100)	4 (100)
	Metastases	0	0	0	0
	Other	0	0	0	0
Any other therapy (n, %)	No	305 (84.5)	285 (83.8)	207 (89.6)	797 (85.5)
	Yes	56 (15.5)	55 (16.2)	24 (10.4)	135 (14.5)
Reason for therapy (n, %)	Primary cancer	42 (72.4)	45 (77.6)	20 (76.9)	107 (75.4)
	Metastases	1 (1.7)	0	0	1 (0.7)
	Other	15 (25.9)	13 (22.4)	6 (23.1)	34 (23.9)

Source: Table 12.1.3.2.1

Table 3 Summary of Study Drug Exposure During the Randomized Phase (FAS2)

		CAD (N = 352)	IAD (N = 334)
Time from randomization to last visit in the randomized phase (days)	N	352	334
	Mean (SD)	940.1 (246.17)	965.0 (238.55)
	Median (range)	1022.0 (1-1203)	1033.5 (85-1248)
Mean time between Eligard injections during randomized phase (days)	N	352	273
	Mean (SD)	88.48 (4.403)	327.45 (189.654)
	Median (range)	87.40 (73.8-127.0)	276.70 (85.0-1063.0)
Number of Eligard doses during randomized phase	N	352	273
	Mean (SD)	10.8 (2.75)	3.1 (1.82)
	Median (range)	12.0 (1-12)	3.0 (1-10)
Number of Eligard doses during randomized phase	0 (n, %)	0	0
	1 - 3 (n, %)	18 (5.1)	184 (67.4)
	4 - 6 (n, %)	17 (4.8)	76 (27.8)
	7 - 9 (n, %)	20 (5.7)	8 (2.9)
	10 - 12 (n, %)	297 (84.4)	5 (1.8)
	> 12 (n, %)	0	0

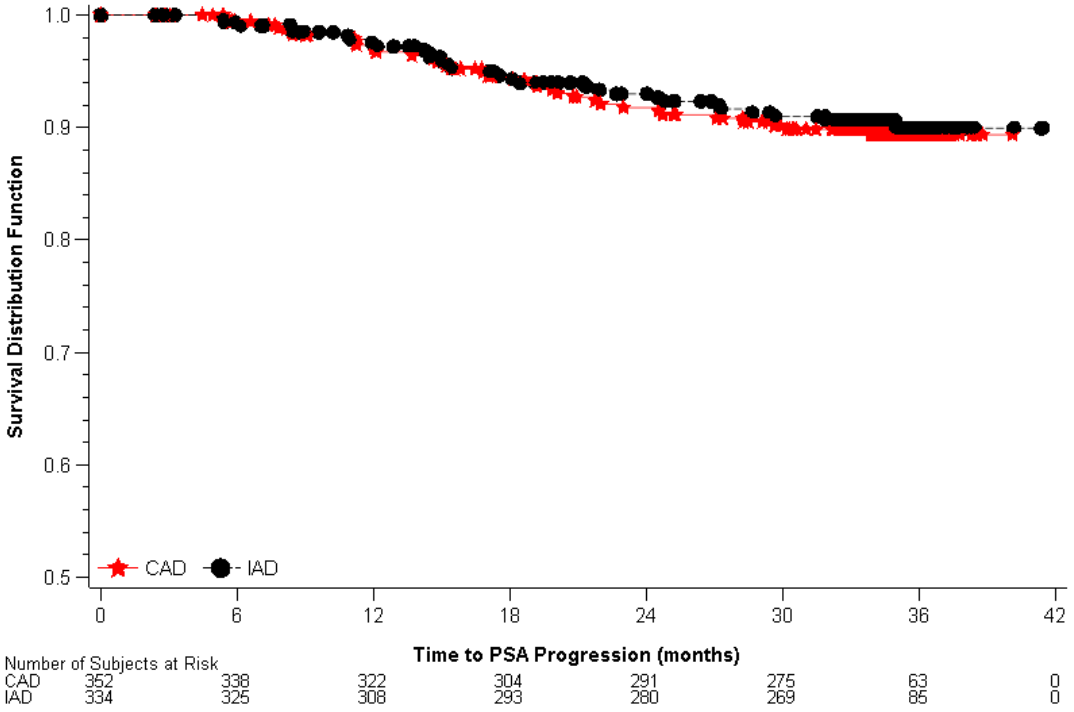
Source: Table 12.2.1.1.2

Table 4 Summary of Survival Analysis of Time to PSA Progression (FAS2)

	CAD (N = 352)	IAD (N = 334)
Events (n, %)	34 (9.66)	30 (8.98)
3 PSA ≥ 4 ng/mL	21 (5.97)	20 (5.99)
1 PSA ≥ 4 ng/mL at discontinuation	13 (3.69)	10 (2.99)
Censored (n, %)	318 (90.34)	304 (91.02)
Completed randomized phase	272 (77.27)	263 (78.74)
Discontinued without event	37 (10.51)	30 (8.98)
Death	9 (2.56)	11 (3.29)
P-value of logrank test	0.718	
Kaplan-Meier-estimate progressed at 3 years (%)	10.64	10.06
95% CI	7.70, 14.60	7.08, 14.18

Source: Table 12.3.1.2.1

Figure 2 **Kaplan-Meier Plot for Time to PSA Progression (FAS2)**



Source: Figure 12.3.1.1

Table 5 **Summary of Survival Analysis of Time to PSA Progression-free Survival (FAS2)**

	CAD (N = 352)	**IAD (N = 334)**
Events (n, %)	43 (12.22)	41 (12.28)
Censored (n, %)	309 (87.78)	293 (87.72)
P-value of logrank test	0.865	
Kaplan-Meier-estimate progressed at 3 years (%) 95% CI	13.24 9.98, 17.46	13.08 9.72, 17.50

Source: Table 12.3.3.1.1

Table 6 **Summary of Survival Analysis of Time to Overall Survival (FAS2)**

	CAD (N = 352)	**IAD (N = 334)**
Events (n, %)	44 (12.50)	42 (12.57)
Censored (n, %)	308 (87.50)	292 (87.43)
P-value of logrank test	0.969	
Kaplan-Meier-estimate survived at 60 months (%) 95% CI	84.98 80.02, 88.80	81.84 74.67, 87.15

Source: Table 12.3.9.1.1

Table 7 Summary of Survival Analysis of Time to Conventional and Conservative Testosterone Breakthrough (FAS2)

	Conventional Testosterone breakthrough		Conservative Testosterone Breakthrough	
	CAD (N = 352)	IAD (N = 334)	CAD (N = 352)	IAD (N = 334)
Patients with breakthrough event(s) (n, %)	22 (6.25)	327 (97.90)	105 (29.83)	330 (98.80)
Censored (n, %)	330 (93.75)	7 (2.10)	247 (70.17)	4 (1.20)
P-value of logrank test	< 0.001		<0.001	
Kaplan-Meier-estimate progressed at 3 years (%) 95% CI	7.57 4.90, 11.61	99.09 97.52, 99.75	31.68 26.85, 37.14	100.00 --

Time to conventional breakthrough was defined as the time from randomization to serum testosterone > 50 ng/dL.

Time to conservative breakthrough was defined as the time from randomization to serum testosterone > 20 ng/dL.

Source: Table 12.3.2.2.1 and Table 12.3.2.5.1

Table 8 Summary Table of Adverse Events – Induction Phase (SAF1)

		CAD (N = 361)	IAD (N = 340)	Not Randomized (N = 231)	Total (N = 932)
N (%) with any TEAE		197 (54.6%)	196 (57.6%)	116 (50.2%)	509 (54.6%)
Total TEAEs		388	367	257	1012
N (%) with treatment-related[#] TEAEs		149 (41.3%)	150 (44.1%)	87 (37.7%)	386 (41.4%)
Total treatment-related TEAEs		232	218	137	587
N (%) deaths†¶		--	--	--	6 (0.6%)
N (%) with serious TEAEs		15 (4.2%)	11 (3.2%)	22 (9.5%)	48 (5.2%)
Total serious TEAEs		--	--	--	72
N (%) with treatment-related§ serious TEAEs		4 (1.1%)	2 (0.6%)	1 (0.4%)	7 (0.8%)
Total treatment-related§ serious TEAEs		6	3	2	11
N (%) discontinued due to TEAE‡		5 (1.4%)	0	13 (5.6%)	18 (1.9%)
N (%) discontinued due to treatment-related[#] TEAE‡		5 (1.4%)	0	3 (1.3%)	8 (0.9%)
N (%) with TEAE by severity	Grade 1	77 (21.3%)	71 (20.9%)	35 (15.2%)	183 (19.6%)
	Grade 2	94 (26.0%)	100 (29.4%)	48 (20.8%)	242 (26.0%)
	Grade 3	26 (7.2%)	25 (7.4%)	26 (11.3%)	77 (8.3%)
	Grade 4	0	0	2 (0.9%)	2 (0.2%)
	Grade 5	0	0	4 (1.7%)	4 (0.4%)[^]
	Missing	0	0	1 (0.4%)	1 (0.1%)

TEAE: treatment-emergent adverse event

Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-Threatening or Disabling, Grade 5 = Death

† Only AEs with outcome 'fatal' are counted

‡ Only AEs that were the primary reason for discontinuation are taken into account.

§ Adverse events that are possibly or probably treatment-related, or for which the relationship is missing.

¶ Patients [redacted] but had no grade 5 AE recorded.

Source: Tables 12.6.1.1.1, 12.6.1.2.1, 12.6.1.3.1, 12.6.1.4.1, 12.6.1.6.1, 12.6.1.7.1, 12.6.1.8.1, 12.6.1.9.1 and 12.6.1.10.1

Table 9 Summary Table of Adverse Events – Randomized Phase (SAF2)

		CAD (N = 353)	IAD (N = 337)	Total (N = 690)
N (%) with any TEAE		256 (72.5%)	254 (75.4%)	510 (73.9%)
Total TEAEs		1204	1187	2391
N (%) with treatment-related§ TEAEs		145 (41.1%)	124 (36.8%)	269 (39.0%)
Total treatment-related§ TEAEs		274	222	496
N (%) deaths†		9 (2.5%)	15 (4.5%)	24 (3.5%)
N (%) with serious TEAEs		88 (24.9%)	90 (26.7%)	178 (25.8%)
Total serious TEAEs		179	213	392
N (%) with treatment-related§ serious TEAEs		4 (1.1%)	4 (1.2%)	8 (1.2%)
Total treatment-related§ serious TEAEs		7	5	12
N (%) discontinued due to TEAE‡		17 (4.8%)	25 (7.4%)	42 (6.1%)
N (%) discontinued due to treatment-related[#] TEAE‡		4 (1.1%)	0	4 (0.6%)
N (%) with TEAE by severity	Grade 1	47 (13.3%)	53 (15.7%)	100 (14.5%)
	Grade 2	109 (30.9%)	107 (31.8%)	216 (31.3%)
	Grade 3	73 (20.7%)	63 (18.7%)	136 (19.7%)
	Grade 4	17 (4.8%)	16 (4.7%)	33 (4.8%)
	Grade 5	9 (2.5%)	14 (4.2%) ¶	23 (3.3%)
	Missing	1 (0.3%)	1 (0.3%)	2 (0.3%)

TEAE: treatment-emergent adverse event

Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-Threatening or Disabling, Grade 5 = Death

† Only AEs with outcome 'fatal' are counted

‡ Only AEs that were the primary reason for discontinuation are taken into account.

§ Adverse events that are possibly or probably treatment-related, or for which the relationship is missing.

¶ Patient [redacted] but the [redacted] was not recorded as a grade 5 AE.

Source: Table 12.6.1.1.2 and Table 12.6.1.4.2