Original Article

ELIGANT: a Phase 4, interventional, safety study of leuprorelin acetate (ELIGARD®) in Asian men with prostate cancer

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Background: The incidence and mortality rate of men with prostate cancer have been increasing in Asia. ELIGARD® is a formulation of leuprorelin acetate whose safety and efficacy have been well-established in Western regions. However, limited safety data are available for Asian populations.

Methods: ELIGANT (ELIGard AsiaN sTudy) was a Phase 4, multicenter, prospective, single-arm, interventional study. Men with locally advanced or metastatic prostate cancer without concomitant chemotherapy, or another androgen receptor pathway inhibitor, were enrolled across Asia to receive ELIGARD® (22.5 mg subcutaneous depot injection) every 3 months for 15 months, with a follow-up visit at 18 months. The primary objective was to establish the safety of ELIGARD® in Asian men with hormone-dependent prostate cancer. The secondary objectives were to assess efficacy, via prostate-specific antigen (PSA) progression and testosterone levels, and health-related quality of life (HRQoL).

Results: In total, 106 patients were included in the safety analysis set (SAF). The most common treatment-emergent adverse events (TEAEs) included PSA increase, cough, back pain, hot flush, anemia, and upper respiratory tract infection. TEAEs considered related to ELIGARD® were reported in 13.2% of patients (n=14), two of which were serious. In the full analysis set (FAS) (n=105), 81.2% (n=56) and 68.5% (n=61) of patients achieved a PSA reduction of ≥90% from baseline at 12 and 18 months, respectively. At 18 months, the numbers of patients with testosterone levels <20, 20–50, and >50 ng/dL were 65 (61.9%), 17 (16.2%), and two (1.9%), respectively; 20% had missing testosterone measurements. HRQoL remained stable throughout the study with minimal change from baseline at study completion.

Conclusions: In conclusion, the safety profile of ELIGARD® (22.5 mg) in Asian men with hormone-dependent prostate cancer is comparable to previous studies in Western regions.

Trial Registration: Clinical trial registration number NCT03035032.

Keywords: Depot formulation; leuprolide acetate; prostate cancer; prostate-specific antigen (PSA)

Submitted Apr 13, 2021. Accepted for publication Dec 24, 2021.
doi: 10.21037/tau-21-723
View this article at: https://dx.doi.org/10.21037/tau-21-723

Introduction

While the prevalence of prostate cancer varies by geographic region, incidence rates are generally higher in Western countries and lower in Asian countries (1). However, in recent years, Asian countries have experienced a rapid increase in incidence, with approximately 297,000 cases of prostate cancer in 2018, up from 122,000 in 2008 (1-4). Despite this, age-standardized incidence rates vary heavily throughout the region, from 64.1 per 100,000 in Singapore to 9.1 per 100,000 in China (5). Recent data also suggest a notable disparity in survival prospects across Asia, with 5-year survival estimates ranging from 30–40% in China and Thailand to >85% in Japan, Singapore, and South Korea (3).

Given the prognostic significance of stage at diagnosis, and the advanced state of prostate cancer in many Asian regions (up to ~60%), such observations may be linked to the variable implementation of national screening programs across Asia (6). In particular, Japan, a country with a long-standing national prostate-specific antigen (PSA) screening program, reported a dramatic shift in the proportion of localized prostate cancer diagnoses from 25.9–62.0% between 1993–2014 (7). Similar trends have been observed in South Korea, which reported an increase in incidence and 5-year survival after the advent of national PSA screening (8). However, the value of PSA screening in reducing mortality remains controversial and widespread implementation has been hindered by concerns about cost-effectiveness and the risk of overdiagnosis (9).

Variability in mortality rate may also be linked to treatment access, which can be affected by geographical or financial factors including income and the prevalence of national health care or the need for insurance (10). This may be compounded by the increasing life expectancy of many Asian populations (11). Notably, the proportion of individuals over the age of 60 years is four-fold greater in Asian countries than North America and Europe, indicating that prostate cancer will be a considerable burden for health care systems in the coming decade (11,12). While progress is being made throughout the region, with many countries investigating the utility of nationwide screening programs, the availability of effective treatments across the prostate cancer spectrum will nonetheless remain a significant predictor of mortality.

Androgen deprivation therapy (ADT) remains a mainstay for the treatment of advanced prostate cancer worldwide. However, preference for surgical *vs.* medical ADT varies by region (13,14). Medical ADT options, including the luteinizing hormone-releasing hormone (LHRH) agonist leuprolide acetate, the LHRH antagonist degarelix, the androgen receptor antagonist enzalutamide, and the androgen synthesis inhibitor abiraterone acetate, are approved for the treatment of prostate cancer across Asia (15).

In the last two decades, depot formulations of LHRH agonists have increased in popularity due to the reduction in treatment burden for patients (16). ELIGARD® (Astellas Pharma Inc./BV, Tokyo, Japan) is a subcutaneous formulation of leuprolide acetate that uses the ATRIGEL® delivery system and provides controlled release over a 1-, 3-, 4- or 6-month treatment period (17). The safety and efficacy of ELIGARD® have been established in clinical trials. However, these trials have been predominantly focused in Western regions (18-20). While ELIGARD® is currently approved in a number of Asian countries, and the 3-month formulation has been in use for many years, safety data are currently lacking for this population. There is also a notable paucity of quality-of-life data for patients with prostate cancer in Asian regions.

The ELIGANT (ELIGard AsiaN sTudy) study was designed to bridge this knowledge gap by establishing the safety profile of ELIGARD® in Asian men with locally advanced or metastatic prostate cancer.

We present the following article in accordance with the TREND reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-21-723/rc).

Methods

Study design and conduct

ELIGANT was a Phase 4, multicenter, prospective, single-arm, open-label interventional study conducted at 20 centers throughout Asia, including sites in Hong Kong, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam.

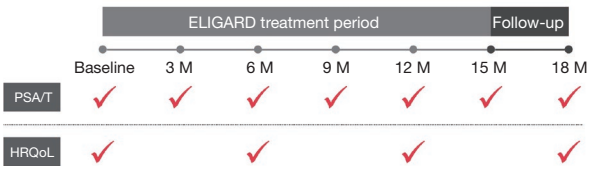

Figure 1 Study design overview. PSA, prostate-specific antigen; T, testosterone; HRQoL, health-related quality of life.

The patient population included males diagnosed with locally advanced or metastatic prostate cancer whose physician had initiated treatment with the 3-month ELIGARD® (22.5 mg) formulation. The 3-month formulation was selected due to its frequency of use in this region, but it is not associated with a lower safety profile. Patients with castration-resistant disease, history of prostate cancer therapy, including LHRH agonists, abiraterone, enzalutamide, and chemotherapy agents, or prior bilateral orchiectomy, were excluded. Prior or concomitant bicalutamide (50 mg once daily) and other antiandrogens were permitted for flare prevention only. Additional administration of an appropriate anti-androgen was considered beginning at least 3 days to 4 weeks prior to the first ELIGARD® injection and continuing for the first 2 to 3 weeks of treatment to avoid any flare reaction. Use of bicalutamide or similar anti-androgen beyond 3 weeks after starting ELIGARD® therapy and for reasons other than flare prevention was not allowed. Eligible patients were approached for enrollment in this study and access to ADT (medical or surgical) was confirmed as part of the prescreening process prior to obtaining informed consent. Patients received subcutaneous injections of ELIGARD® every 3 months for 15 months and attended a follow-up visit 3 months after the final dose (*Figure 1*). The study drug was administered by qualified study personnel at the research site during each study visit. If treatment compliance was 80%, patients received counseling and support to improve compliance and adherence to the study schedule. Patients who were <80% compliant with the treatment regimen for 2 consecutive visit periods were withdrawn.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), Good Clinical Practice, International Council for Harmonisation guidelines, and applicable local laws and regulations. The study was approved by an independent ethics committee or institutional review board at each location (see Table S1 for full information for each site) and all patients were required to provide written informed consent prior to participating in the study.

Endpoints

The primary endpoint was safety, assessed via collection of adverse events throughout the study at 3, 6, 9, 12, 15, and 18 months. Adverse events were graded using the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Event (CTCAE) guidelines (Version 4.03). Secondary endpoints included efficacy outcomes of clinical response based on PSA and testosterone levels, and the impact of ELIGARD® on health-related quality of life (HRQoL) utilizing the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer module (EORTC QLQ-PR25) (21) and European Quality of Life 5-Dimension, 5-Level scale (EQ-5D-5L) questionnaire (22). PSA and testosterone levels were recorded at baseline and at 3, 6, 9, 12, 15, and 18 months, while HRQoL was assessed at baseline and at 6, 12, and 18 months. All other tests (including imaging assessments) were optional and were performed at the investigator's discretion.

Statistical analysis

Statistical analysis was performed using SAS®, version 9.4. The sample size (n=107) was based on the percentage of ELIGARD®-related adverse events observed over a 6-month period in previous studies (~50%), with an assumed drop-out rate of 10%. The study was powered to accomplish its primary objective of establishing a safety profile for ELIGARD® in Asian men with locally advanced or metastatic prostate cancer.

Descriptive statistics were used to assess the primary and secondary endpoints for this patient population. For continuous variables, this included the number of patients (n), mean (for observed values and absolute changes from baseline), standard deviation (SD), median, minimum, and maximum. For categorical variables, frequency and percentage were presented. Analyses of secondary endpoints (PSA control, testosterone control, and HRQoL) were conducted using data from the full analysis set (FAS) and the per-protocol set (PPS).

In accordance with International Council for Harmonisation recommendations, the analysis sets included: a safety analysis set (SAF), consisting of patients

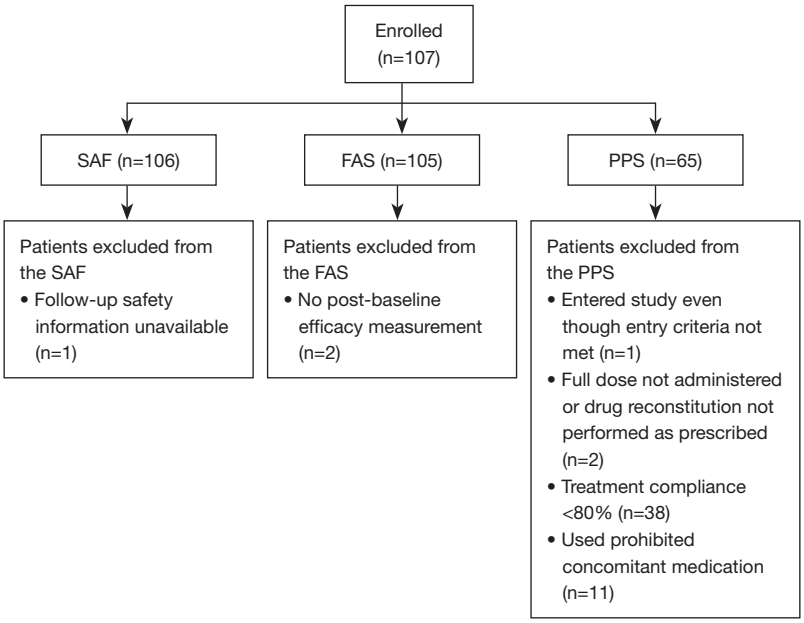

Figure 2 CONSORT diagram. SAF, safety analysis set; FAS, full analysis set; PPS, per-protocol set.

who received at least one dose of ELIGARD® and had follow-up safety information available; an FAS, consisting of patients who received at least one dose of ELIGARD® and had at least one post-baseline measurement of PSA and testosterone levels; and a PPS, consisting of patients in the FAS who did not meet select criteria for exclusion per the study protocol. These criteria were intended to capture non-adherence to the protocol and included the following reasons for exclusion; entering into the study but not satisfying entry criteria, developing withdrawal criteria during the study but not being withdrawn, not receiving a full dose or drug reconstitution not being performed as prescribed, or having a treatment compliance <80%, or using prohibited concomitant medications.

In general, missing data were not imputed. However, if >10% of data were missing for one or more key data categories (e.g., safety data), the impact of missing data on the analysis was discussed and the pattern of missing data was explored. If there was evidence of bias in the pattern of missing data, and data categories that were considered good predictors of the missing data were available, the multiple imputation method at the study level may have been used to replace missing values as secondary exploratory analyses. If the multiple imputation method was used, a sensitivity analysis was also performed to compare data from the complete case analysis where records with missing data were excluded and the full set analysis with imputed data.

Protocol deviations

Critical protocol deviations occurred in 3.7% of patients. These included failures by site staff to perform lab tests, inclusion of a patient who had received prior treatment with LHRH analogues, and administration of the study drug by a physician who was not delegated in the study. Protocol deviations did not impact patient safety or affect overall study results.

Results

Baseline demographics and disease characteristics

Overall, 107 patients were enrolled at 20 centers across Asia between Q2 2017 and Q3 2018. The SAF, FAS, and PPS analysis sets comprised 106, 105, and 65 patients, respectively, with reasons for exclusion listed in *Figure 2*.

Patients in the SAF had a median age of 71.5 years, a median PSA at diagnosis of 59.6 ng/mL, and a median duration of prostate cancer of 24.8 months. The majority of patients had a clinical tumor stage of T2 or T3 (28.3%; n=30 and 35.8%; n=38, respectively), with 67.9% of patients diagnosed with stage M1 metastasis. Approximately one-fifth (20.8%; n=22) of patients had received prior cancer treatment, including prostatectomy (14.2%), transurethral resection of the prostate (1.9%), pelvic lymph node dissection (0.9%), and other treatments (4.7%). Similarly,

Table 1 Baseline characteristics of the SAF (n=106)

Characteristics	Patients
Age, median (range), years	71.5 (50–90)
Median PSA at diagnosis[†,‡] (range), ng/mL	59.6 (0.1–7,161.0)
Median duration of prostate cancer[†] (range), months	24.8 (19.2–168.5)
Gleason score at initial diagnosis, n (%)	
<7	17 (16.0)
7	25 (23.6)
8	27 (25.5)
9	28 (26.4)
10	9 (8.5)
Clinical tumor stage, n (%)	
Tx	3 (2.8)
T0	0
T1	9 (8.5)
T2	30 (28.3)
T3	38 (35.8)
T4	21 (19.8)
ECOG performance status[§], n (%)	62 (60.8)
0	33 (32.4)
1	62 (60.8)
Prior cancer treatment[¶], n (%)	22 (20.8)
Prostatectomy	15 (14.2)
Transurethral resection of the prostate	2 (1.9)
Pelvic lymph node dissection	1 (0.9)
Other	5 (4.7)
Prior radiation therapy	5 (4.7)

[†], n=103; [‡], 6.6% of participants (n=7) had received prior prostate cancer therapy; [§], n=102; [¶], each patient may have >1 treatment history. SAF, safety analysis set; PSA, prostate-specific antigen; ECOG, Eastern Cooperative Oncology Group.

57.5% of patients (n=61) received concomitant bicalutamide for flare prevention in the SAF. The baseline characteristics for the SAF are summarized in *Table 1*.

Primary endpoint: safety

During the study, 75.5% of patients (n=80) experienced at least one treatment-emergent adverse event (TEAE)

Table 2 TEAEs, SAF (n=106)

Characteristic	No. patients (%); No. of events
AEs	82 (77.4); 286
SAEs	31 (29.2); 59
TEAEs	80 (75.5); 283
Serious TEAEs	31 (29.2); 59
Drug-related AEs	15 (14.2); 26
Drug-related SAEs	2 (1.9); 2
Drug-related TEAEs	14 (13.2); 25
Any TEAE leading to drug withdrawal	11 (10.4); 12
Any TEAE leading to drug interruption	1 (0.9); 2
Any TEAE leading to death[†]	8 (7.5); 8
TEAE grade[‡]	
1	58 (54.7); 122
2	40 (37.7); 96
3	27 (25.5); 54
4	2 (1.9); 2
5	8 (7.5); 8
Missing	1 (0.9); 1

[†], one additional patient died due to disease progression; however, disease progression events were not to be reported as AEs; [‡], one patient who had missing severity was included in the number of patients with grade 3 or higher TEAEs. TEAE, treatment-emergent adverse event; SAF, safety analysis set; AE, adverse event; SAE, serious adverse event.

(*Table 2*). Of these, the most frequently reported were PSA increased (17%; n=18), cough (9.4%; n=10), back pain (8.5%; n=9), hot flush (7.5%; n=8), anemia (6.6%; n=7), and upper respiratory tract infection (5.7%; n=6) (*Table 3*). At least one drug-related TEAE was experienced by 13.2% (n=14) of patients, the most common of which was hot flush (n=5). Only one patient (0.9%) experienced a cardiac disorder (congestive heart failure). In total, 35.8% (38/106) of patients experienced grade ≥3 TEAEs. The majority of drug-related TEAEs were mild or moderate in severity (9.4% and 5.7%, respectively, for grade 1 or grade 2). Severe drug-related TEAEs were reported in 1.9% of patients (n=2); grade 3 musculoskeletal chest pain and grade 3 femur fracture.

In total, 11 (10.4%) patients discontinued treatment with ELIGARD® due to experiencing at least one TEAE

Table 3 TEAEs reported in ≥3% patients, SAF (n=106)

TEAEs	All grades, n (%)	Grade ≥3, n (%)
PSA increased	18 (17.0)	3 (2.8)
Cough	10 (9.4)	0
Back pain	9 (8.5)	1 (0.9)
Hot flush	8 (7.5)	0
Anemia	7 (6.6)	3 (2.8)
Upper respiratory tract infection	6 (5.7)	1 (0.9)
Arthralgia	5 (4.7)	2 (1.9)
Constipation	5 (4.7)	0
Insomnia	5 (4.7)	0
Headache	4 (3.8)	1 (0.9)
Nausea	4 (3.8)	0
Pain in extremity	4 (3.8)	1 (0.9)
Pneumonia	4 (3.8)	4 (3.8)
Urinary retention	4 (3.8)	0

TEAE, treatment-emergent adverse event; SAF, safety analysis set; PSA, prostate-specific antigen.

(12 events in total) and one patient had their dosing interrupted. TEAEs that led to treatment discontinuation included death (2.8%; n=3), multiple organ dysfunction syndrome (0.9%; n=1), septic shock (0.9%; n=1), PSA increased (2.8%; n=3), blood testosterone decreased with a concurrent PSA increase (0.9%; n=1), prostate cancer metastatic (0.9%; n=1), intracranial hemorrhage (0.9%; n=1), and chronic obstructive pulmonary disease (0.9%; n=1); none of which were related to ELIGARD®. Overall, eight (7.5%) patients experienced a TEAE that resulted in death; however, none was considered treatment related.

Secondary endpoints

PSA control

PSA control was assessed using time to PSA progression, which was calculated from the first administration of ELIGARD® to the date of progression. PSA progression was defined as a ≥25% increase and an absolute increase of ≥2 ng/mL from nadir and confirmed by a second value ≥3 weeks later. By study completion, PSA progression had been observed in 23.8% of patients (n=25), with a median time to progression of 8.8 (range, 5.6–16.0) months in the FAS. In the PPS, PSA progression was observed in 15.4% of patients (n=10), with a median time to progression of 10.45 (range, 9.0–16.0) months.

Table 4 PSA reductions at 3, 12, and 18 months for FAS and PPS

Time point, months	≥30%, n (%)	≥50%, n (%)	≥90%, n (%)
FAS† (n=105)			
3	98 (96.1)	91 (89.2)	71 (69.6)
12	67 (97.1)	65 (94.2)	56 (81.2)
18	81 (91.0)	79 (88.8)	61 (68.5)
PPS‡ (n=65)			
3	63 (98.4)	61 (95.3)	49 (76.6)
12	63 (96.9)	62 (95.4)	53 (81.5)
18	61 (96.8)	59 (93.7)	47 (74.6)

†, total number of patients with PSA assessment at 3, 12, and 18 months was n=102, n=69, and n=89, respectively; ‡, total number of patients with PSA assessment at 3, 12, and 18 months was n=64, n=65, and n=63, respectively. PSA, prostate-specific antigen; FAS, full analysis set; PPS, per-protocol set.

In addition to PSA progression, the percentage of patients with ≥30%, ≥50%, and ≥90% reductions in PSA from baseline were recorded for the FAS and PPS (*Table 4*). In the FAS, the majority of patients experienced a PSA reduction of ≥90% at both the 12- (81.2%; n=56) and 18-month (68.5%; n=61) time points. Similarly, in the PPS, 81.5% (n=53) and 74.6% (n=47) experienced a PSA reduction of ≥90% at 12 and 18 months, respectively.

Testosterone

Evaluation of testosterone control was achieved using the percentage of patients with testosterone levels <20, 20–50, and >50 ng/dL throughout the study. After receiving ELIGARD® for 12 months, 51.4% of patients (n=54) had testosterone levels <20 ng/dL in the FAS, which increased to 61.9% after 18 months of treatment (*Table 5*). At both 12 and 18 months, 1.9% of patients (n=2) had testosterone levels >50 ng/mL. In the PPS, 80.0% of patients had achieved testosterone levels <20 ng/dL after 12 months of treatment, which remained constant at 18 months. Comparatively, 1.5% of patients (n=1) had testosterone levels >50 ng/mL at 12 months *vs.* none at 18 months.

HRQoL

Patients had a high baseline quality of life with mean (SD)

Table 5 Testosterone levels at 12 and 18 months for FAS and PPS

Analysis set	Patients†, n (%)	
	FAS (n=105)	PPS (n=65)
Testosterone level at 12 months‡		
<20 ng/dL	54 (51.4)	52 (80.0)
20–50 ng/dL	13 (12.4)	12 (18.5)
>50 ng/dL	2 (1.9)	1 (1.5)
Missing	36 (34.3)	0
Testosterone level at 18 months§		
<20 ng/dL	65 (61.9)	52 (80.0)
20–50 ng/dL	17 (16.2)	8 (12.3)
>50 ng/dL	2 (1.9)	0
Missing	21 (20.0)	5 (7.7)

†, percentage of patients may be <100% because not all patients in the FAS had a testosterone levels measured at 12 and 18 months post-baseline; ‡, total number of patients in the FAS with testosterone measurements at 12 and 18 months was n=69 and n=84, respectively; §, total number of patients in the PPS with testosterone measurements at 12 and 18 months was n=65 and n=60, respectively. FAS, full analysis set; PPS, per-protocol set.

EQ-5D visual analog scale (VAS) scores in the FAS of 78.8 (13.04). Minimal change from baseline with a mean (SD) score of 81.5 (15.76) was observed at study completion, with quality of life remaining stable throughout the study (*Figure 3*, Table S2). Deterioration in Japan EQ-5D-5L index and EQ-5D VAS scores was observed in 33.3% and 30.5% of patients, respectively, at 18 months in the FAS. Similarly, in the PPS, deterioration in Japan EQ-5D-5L index and EQ-5D VAS scores was observed in 35.4% and 36.9%, of patients, respectively, at 18 months.

At 18 months, mean (SD) improvements from baseline were observed in EORTC QLQ-PR25 scores across all patients for urinary symptoms [–4.06 (15.370)]. Mean (SD) increases from baseline scores were observed for bowel symptoms [0.31 (9.036)], incontinence [1.67 (31.484)], and hormonal treatment-related symptoms [4.68 (11.604)]. In the FAS, 33.3% of patients reported a deterioration in urinary symptoms, 3.8% in incontinence symptoms, 17.1% in bowel symptoms, 24.8% in hormone treatment-related symptoms, 9.5% in sexual activity, and 5.7% in sexual function. Similar values were observed in the PPS.

Discussion

The results of the ELIGANT study demonstrate that ELIGARD® 22.5 mg has an acceptable safety profile in men with hormone-dependent prostate cancer in Asia. There was a low incidence of drug-related TEAEs in this population [25 TEAEs reported in 14 patients (13.2%)], with only two serious TEAEs considered related to ELIGARD® treatment. Several of the most frequently reported TEAEs can likely be attributed to the pharmacological mechanism of action of ELIGARD®, as sex hormone suppression is typically associated with adverse events such as hot flush, cough, and back pain (17,23). These events are frequently observed with many ADT treatment options, including LHRH agonists goserelin and triptorelin (24,25). Overall, the safety profile was consistent with previous trials of 22.5 mg ELIGARD® in Europe, Asia, and the United States, with no new safety signals reported (18,19,26,27). In these trials, the most common TEAEs reported included hot flush, hypertension, and constipation in the European ICELAND study; hot flush, fatigue, and nausea in the United States; and hot flush, pain, and infection in Asian men with prostate cancer (18,19,26,27). In particular, the Phase 3 ICELAND study, which enrolled 933 men across Europe, reported both a similar frequency of TEAEs overall (72.5% *vs.* 75.5% for ELIGANT) and a comparable proportion of TEAEs with grade ≥3 severity (27.3% *vs.* 35.9%) with 22.5 mg ELIGARD® in prostate cancer (19). Nevertheless, the comparison of safety profiles between these two studies must be interpreted with caution due to the different study designs, sample sizes, and baseline characteristics. However, there are no significant safety concerns with regards to the use of ELIGARD® in Asian men with prostate cancer.

In addition, the results of the ELIGANT study suggest that ELIGARD® 22.5 mg has an acceptable efficacy profile in Asian men with hormone-dependent prostate cancer. Reductions in PSA and testosterone levels occurred up to 18 months for the majority of patients in each analysis set. These trends correspond with previous studies of ELIGARD® in prostate cancer, wherein PSA and testosterone control were sustained over treatment periods up to 36 months, and the majority of patients achieved testosterone levels of ≤20 ng/dL (27-30). Accordingly, very few participants (1.9%; n=2) in the ELIGANT study (FAS) demonstrated testosterone levels >50 ng/mL after treatment, at both 12 and 18 months. These observations

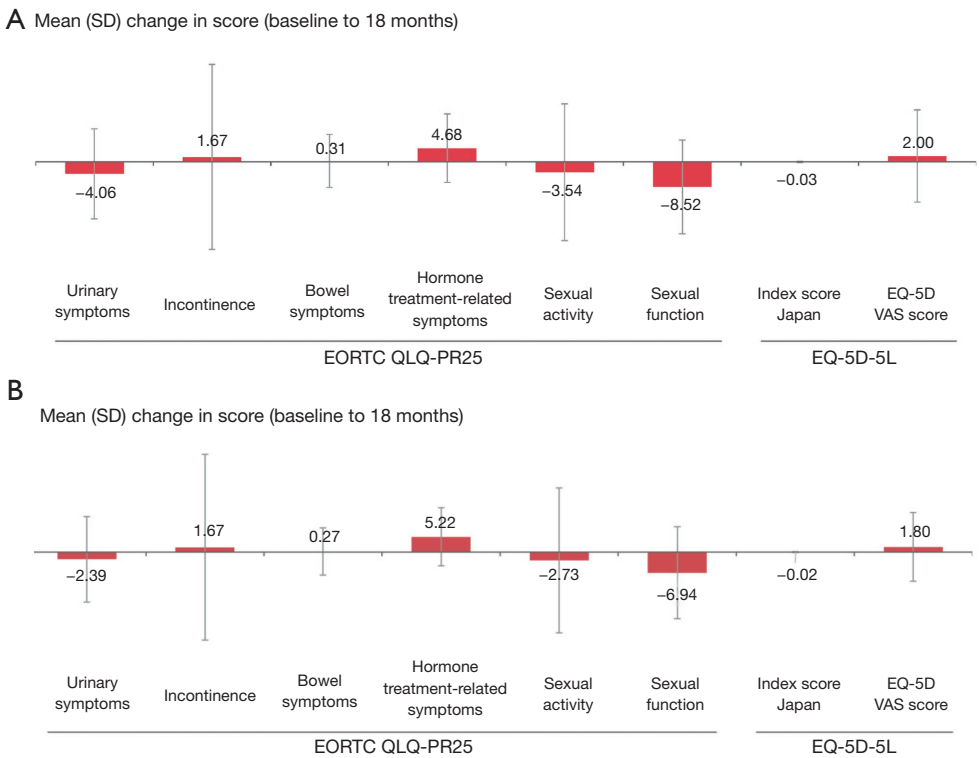

Figure 3 HRQoL EORTC QLQ-252 and EQ-5D-5L scores. Mean changes in EORTC QLQ-252 and EQ-5D-5L scores from baseline suggested that stable HRQoL was maintained with 18 months of active treatment. (A) FAS (n=105). Mean (SD) improvements from baseline were observed in EORTC QLQ-252 scores across all patients for urinary symptoms after 18 months. Mean (SD) increases from baseline EORTC QLQ-252 scores were observed for incontinence, bowel symptoms, and hormone-treatment related symptoms. Mean (SD) decreases from baseline EORTC QLQ-252 scores were observed for sexual activity and sexual function. There were minimal changes in EQ-5D-5L scores from baseline at 18 months. (B) PPS (n=65). Similarly, improvements in urinary symptoms from baseline were observed after 18 months, and mean (SD) increases from baseline were observed for incontinence, bowel symptoms, and hormone treatment-related symptoms. As in the FAS mean scores for sexual activity and sexual function decreased after 18 months. Again, there were minimal changes in EQ-5D-5L scores from baseline at 18 months. HRQoL, health-related quality of life; EORTC QLQ-252, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer module; EQ-5D-5L, European Quality of Life 5-Dimension, 5-Level questionnaire; VAS, visual analog scale; SD, standard deviation; FAS, full analysis set; PPS. per-protocol set.

are similar to those reported with LHRH agonists triptorelin and goserelin, in which 0–1.2% and 3.8% of participants, respectively, demonstrated a testosterone level of >50 ng/dL (31,32).

Although many patients had deteriorations in EORTC QLQ-PR25 and EQ-5D-5L scores, mean changes from baseline suggested that stable HRQoL was maintained with 18 months of active treatment. This observation may be due to meaningful clinical differences not being specified prior to study initiation. Since the change threshold for clinical significance using the EORTC QLQ-PR25 questionnaire typically falls between 5–10% (33), improvements in urinary, incontinence, and hormone-treatment-related symptoms, though not bowel symptoms, may have been clinically meaningful for participants. Similar observations were reported in the ICELAND study, which also noted a small improvement in urinary and hormone-related treatment symptoms using the EORTC QLQ-PR25 questionnaire (19). Interestingly, although not analyzed, improvements in HRQoL appeared to correlate with reductions in PSA level at the 12- and 18-month timepoints, supporting previous studies that noted a relationship between these two factors (34).

The ELIGANT study provides the first real-world data

in Asian men with prostate cancer using validated quality-of-life measures. To the best of the authors' knowledge, this is also the first publication to show the degree of testosterone suppression in Asian settings in a prospective longitudinal manner. In terms of limitations, the ELIGANT study had a relatively small sample size, which may have been compounded by the geographical spread of patients. Subsequently, subtle differences in tumor biology between Asian populations could potentially confound the interpretation of results. It is also important to note that while LHRH agonists, abiraterone, enzalutamide, and chemotherapy agents were prohibited during the study, bicalutamide and other antiandrogens were permitted for flare prevention only. Of the 106 patients included in the SAF, 57.5% (n=61) received concomitant bicalutamide, which could potentially confound reporting. Data analysis may also have been impacted by missing data at each timepoint, particularly with regards to PSA and testosterone assessments. Finally, interpretation of HRQoL data may be impacted by both the age and lifestyle of participants, as sexual activity declines sharply in patient aged >50 years, and hormone treatment-related symptoms may not be adequately captured in patients with an active lifestyle.

Conclusions

The ELIGANT study demonstrated a comparable safety and efficacy profile for ELIGARD® 22.5 mg in Asian men with prostate cancer relative to previous studies in Western regions. As such, there are no specific clinical concerns with regards to the use of ELIGARD® in Asian populations.

Acknowledgments

Medical writing and editing assistance were provided by Amber Tear and Lauren Smith of Complete HealthVizion, both funded by Astellas Pharma Inc.

Funding: This work was supported by Astellas Pharma Inc.

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-21-723/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-21-723/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-21-723/coif). RM was a study investigator for Astellas. RU has received a grant from Astellas during the study and personal fees for a sponsored speaker's bureau from AstraZeneca and Takeda. JT has received grants from Baxter, Bristol-Myers Squibb, Ferring, Janssen, and Merck Sharp and Dohme and received advisory board fees from Astellas, Ferring, and Janssen during the study. JK and RP were full-time employees of Astellas during the study. EC has received a research grant and manuscript writing support from Astellas during the study, received a research grant from Janssen, received speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, Beckman Coulter Singapore Pte., Ltd., Ferring, Ipsen, and Janssen, and received advisory board fees from Amgen, Astellas, AstraZeneca, Bayer, Ferring, and Janssen. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), Good Clinical Practice, International Council for Harmonisation guidelines, and applicable local laws and regulations. The study was approved by an independent ethics committee or institutional review board at each location (see Table S1 for full information for each site) and all patients were required to provide written informed consent prior to participating in the study.

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Cite this article as: Malek R, Wu ST, Serrano D, Tho T, Umbas R, Teoh J, Lojanapiwat B, Ong TA, On WK, Thai SM, Kim J, Pophale R, Chiong E. ELIGANT: a Phase 4, interventional, safety study of leuprorelin acetate (ELIGARD®) in Asian men with prostate cancer. Transl Androl Urol 2022;11(2):179-189. doi: 10.21037/tau-21-723

