# 1.0 Abstract

**Title**

Prospective, Multi-Center, Observational Program to Assess Routine Use of Intermittent Adjuvant Deprivation Therapy with Lucrin Depot® in Patients with Advanced Prostate Cancer in the Russian Federation.

**Keywords**

Advanced Prostate Cancer (PCa), Intermittent Androgen Deprivation (IAD), Gonadotropin releasing hormone (GnRH) agonists.

**Rationale and Background**

Hormonal therapy is the standard of care for advanced PCa. The optimal hormone treatment strategy in PCa is uncertain. IAD is currently widely offered to patients with PCa in various clinical settings, but seems to be often underused in the Russian Federation.

This was a non-interventional, observational program in which Lucrin Depot®, a GnRH agonist, was prescribed in the usual manner in accordance with the terms of the local marketing authorisation with regards to dose, population and indication. There were no data to characterize patient population and Lucrin Depot® administration in the Russian Federation. Further, it was important to characterize the rates of hormone refractory in patients with prostate cancer receiving intermittent hormone monotherapy with GnRH agonists in Russian Federation.

**Research Question and Objectives**

**Primary Objectives**

To describe treatment patterns in use of Lucrin Depot® in intermittent adjuvant regimen in the Russian Federation during 2 years.

**Secondary Objectives**

1. To describe the rates of hormone refractory stage in patients with advanced prostate cancer receiving intermittent hormone monotherapy with GnRH agonists in Russian Federation during 2 years.
2. To describe the patient population.
3. To evaluate median percentage of time off-treatment during 2 years.

**Study Design**

This program was conducted in prospective, open label, non-comparative, observational format. Lucrin Depot® was used according to labelled recommendations and was administered in accordance with the approved local leaflet.

After Enrollment into the program, subjects returned to the site for visit assessments at a next visit scheduled by the doctor. The visits were defined as follows: "Visit 1 (Enrollment)," "Visit 2 (after 1 year)," "Visit 3 (after 2 years)," "Visit 4 (Follow-Up/Program Completion)."

Duration of observation of treatment period was 24 months and follow-up period. Follow-up period continued until 30 days after 2 years of observation period of the program drug for each patient.

**Setting**

The study took place in 23 clinical sites specialized in oncology and urology and located in different regions of Russia. Five sites were situated in Moscow, four sites in St-Petersburg, two sites in Saratov, two sites in Tyumen, one site in each of cities Penza, Voronezh, Rostov-on-Don, Samara, Ufa, Chelyabinsk, Izhevsk, Ekaterinburg, Krasnoyarsk and Stavropol. Data received from the site [redacted] were excluded from statistical analysis because of impossibility to contact the investigator for data clarification.

**Subjects and Study Size, Including Dropouts**

A total of 300 patients were enrolled into the study. Data of 17 patients from the site No. 22 were excluded from analysis, so 283 patients were included in statistical analysis. Patients had to meet all of the following criteria:

**Inclusion Criteria**

1. Male, 18 – 75 years of age
2. Histologically confirmed advanced prostate cancer meeting the following criteria:
   - Any T, N1, M0
   - Any T, N0, M1 (according to TNM classification 2009)
3. Patients planned for administration of Lucrin Depot®
4. WHO status 0 – 1
5. Life expectancy at least 2 years

**Exclusion Criteria**

1. Contraindications to administration of Lucrin Depot® (Leuprorelin):
   - Hypersensitivity to Leuprorelin similar products of protein origin or any of the excipients in drug product composition;
   - Surgical castration.
2. Hormone-refractory PCa.
3. Presence of another malignant tumour (except skin cancer).
4. Previous administration of hormone therapy with GnRH agonists or antiandrogens.
5. Previous administration of radiotherapy or chemotherapy course within 1 month.
6. Testosterone level ≤ 50 ng/dL (≤ 1.7 mmol/L) at time of inclusion.

7. Extremely high level of PSA (≥ 1000 ng/ml).
8. Other severe diseases in stage of decompensation.
9. Other contraindications, that make the patient's participation impossible (by investigator judgment).
10. Previous enrollment in the present program.

**Variables and Data Sources**

All diagnostic procedures in the program were performed in the frames of routine clinical practice. The data obtained from the assessments were recorded in the patients' source documentation and CRF. The efficacy and safety assessment used in the study were standard for this indication and patient population.

**Results**

**Primary Endpoint:**

Lucrin Depot® regimen used for IAD treatment was evaluated in this study. The mean total duration of study drug exposure was 19.74 (SD 6.39) months, varying from 1 to 33.3 months. Median number of cycles administered to the patients enrolled in this study was 2. In patients without disease progression, a maximum of 5 cycles were performed and the mean total duration of Lucrin Depot® exposure was 21.25 (SD 5.31) months. In patients with progression of disease, a maximum of 3 cycles were performed and the mean total duration of Lucrin Depot® exposure was 13.62 (SD 6.79) months.

**Secondary Endpoints:**

Overall, 36 patients (14.1% of Full Analysis Set) had progression to HRPC during the study, 28 (11.0%) patients were on IAD treatment, and 8 (3.1%) patients didn't start IAD therapy. The median time to progression in patients on IAD therapy (19.10 months) was more than two times longer than in patients that had not received

this type of treatment (8.11 months). A Kaplan-Meier estimate of median time to progression to HRPC in patients not started on IAD was 12.8 months (95% CI 12.8, 15.4). Estimate of median time to progression to HRPC for patients that received IAD therapy was not calculated because a small number of events happened.

The mean (and median) survival time in patients on IAD therapy was almost two times longer than in patients that had not received this kind of treatment (24.44 [SD 0.46] months and 12.76 [SD 1.42] months respectively). Kaplan-Meier estimate of median survival time was not calculated because a small number of events happened.

The mean duration of treatment-off period in IAD regimen during the study was 7.12 (SD 2.61) months, varying from 0 to 14.6 months. Median percentage of time off-treatment during 2 years IAD therapy was 33.45% and varied from 0% to 67.6%.

Patients' demographic characteristics were evaluated in this study. The mean age of patients was 65.4 (SD 6.3) years varying from 50 to 76 years. The patient population belonged predominantly to white race (99.6%), only one patient (0.4%) was Asian.

**Safety Evaluation:**

Adverse events were summarized by counts and percentages using the most severe episode (severity) and also using the relationship to study drug (as indicated by the Investigator). An overall summary of adverse events was generated to show the numbers of subjects reporting adverse events, as well as an overall display of adverse events in descending order of incidence.

Overall, 73 (25.8%) patients experienced any adverse events (AEs) in this observational study. Most AEs were not related to study drug, AEs related to Lucrin Depot® were observed only in 9.2% of patients. Most frequent AEs related to study drug were hot flush – in 4.2% of patients, gynaecomastia and disease progression – in 2.1% of patients each. Adverse events reported in this study were not unexpected for

the treatment with Lucrin Depot® and for the populations of patients with advanced prostate cancer.

Thirteen (13) patients experienced SAE while participating in this study. More than half of them (8 patients) were disease progression, one case each of cardiac disorder, myocardial infarction, renal cancer, acute cholecystitis and urinary retention were registered. Most SAEs were assessed as not related to study drug. Nine (9) patients died during the study, cause of death in 8 patients was disease progression.

Discontinuation of Lucrin Depot® due to adverse events occurred in 8 (2.8%) patients, the most frequent causes were fatigue, breast enlargement and hot flush occurred in 4 (1.4%) patients each.

**Discussion**

The primary objective of this observational study was to describe treatment patterns in use of Lucrin Depot® in intermittent adjuvant regimen in the Russian Federation during 2 years. This objective was met.

The mean total duration of Lucrin Depot® exposure during 2 years of IAD treatment was 19.74 (SD 6.39) months, varying from 1 to 33.3 months. Patients receiving intermittent therapy had spent a median of 33.45% of the study period off therapy. This parameter is lower than in other studies that reported that patients on IAD treatment spent more than 50% of the study period off therapy.[1-3] This discrepancy can be explained by a shorter period of observation in this study.

The second objectives of the study were also met. The rates of progression to hormone refractory stage in patients with advanced prostate cancer during 2 years of treatment with Lucrin Depot® were evaluated. Twenty-eight (28) (11.0% of FAS) patients receiving intermittent therapy had progression to HRPC during the study. The median time to progression in patients on IAD therapy was 19.10 months, which is more than two times longer than in patients who did not receive this type of therapy (8.11 months). These results coincide with the results of some other studies.[1,2,4,5]

Kaplan-Meier estimate of median time to progression to HRPC for patients that received IAD therapy was not calculated because a small number of events happened during the relatively short period of observation in the study compared to other studies.[1,2,5]

Demographic characteristics of the patient population with advanced prostate cancer in the Russian Federation were described in this study. The mean age of patients enrolled in the study was 65.4 (SD 6.3) years; the patient population belonged predominantly to the white race.

Lucrin Depot® clinical tolerability and safety were assessed in this study. Adverse Events related to study drug were observed only in 9.2% of patients. No unexpected safety findings were found in this study. The most frequent AEs related to Lucrin Depot® in this study were hot flush (in 4.2% of patients), followed by gynaecomastia and disease progression (in 2.1% of patients each). Few patients discontinued Lucrin Depot® therapy prematurely due to adverse events (mainly due to fatigue, breast enlargement, and hot flush). In global IAD trials,the most frequently adverse events were hot flush, gynaecomastia, headache, and skin complaints/rash.[1,2,4-6] Thus, the safety profile of study drug was consistent with that previously known for Lucrin Depot® in similar populations of patients with advanced prostate cancer.[4-6]

**Marketing Authorisation Holder(s)**

Abbott Laboratories S.A, Spain

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**Names and Affiliations of Principal Investigators**

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