2 ABSTRACT

2.1 Title

A Prospective, Single Arm, Non-Interventional Study to Evaluate the Extent to Which Handling Errors Lead to Lack of Efficacy in Patients Treated with ELIGARD™ in France.

2.2 Keywords

Prostate cancer, leuprorelin acetate, handling error, lack of efficacy.

2.3 Rationale and Background

On 09 February 2016, the National Agency for the Safety of Medicines and Health Products (Agence nationale de sécurité du médicament et des produits de santé or ANSM), in application of the provisions of Article R. 5121-79 of the French Public Health Code, informed Astellas to modify sections in Annexes I, II, and IIA of the Marketing Authorizations for ELIGARD™, to address concerns around potential lack of efficacy due to handling errors associated with the improper storage, preparation, reconstitution and/or administration with ELIGARD™. In addition, in agreement with the ANSM, Astellas conducted a study in France to obtain objective data to increase knowledge about any potential lack of efficacy (LOE) associated with handling errors (HEs). Two main points for consideration in the design of the study were that it needed to be conducted in a “real life” setting and serum levels of testosterone were to be measured.

The new Conditions for the Prescription and Supply (conditions de prescription et de délivrance or CPD) of ELIGARD™ are:

"List I. Medicinal product requiring particular surveillance during treatment:

- The pursuit of treatment requires the conduct of a serum testosterone assay every 3 months; it is necessary for prescribing physicians to ensure, at least every 3 months, that serum testosterone levels have reached or are remaining at castrate levels (serum testosterone ≤ 50 ng/dl). If not, a modification of the therapeutic management should be considered according to the guidelines issued by the European Association of Urology in 2016.
- The prescribing physician must mention on the prescription for renewal that this assay has been performed."

While high efficacy of ELIGARD™ has been demonstrated in clinical trials in prostate cancer (PCa) patients, little published data exists on LOE of ELIGARD™ in clinical practice.

2.4 Research Question and Objectives

The primary objective of the study was to assess the LOE following a HE, as measured by serum testosterone, in a selected sample of French patients with PCa who were treated with ELIGARD™ following the HE or where the HE occurred during the administration of ELIGARD™

2.5 Study Design

This was a non-interventional, prospective study set in routine clinical practice in France. The Drug Safety Officer (DSO) in France was to receive safety information, from a spontaneous report sent from the site, regarding the occurrence of a HE associated with the administration of ELIGARD™, and a Pharmacovigilance (PV) case was to be created for processing in the safety database according to Astellas internal procedures.

2.6 Selection Criteria

Inclusion criteria:

- All male patients ≥ 18 years old on ELIGARD™ treatment (3-month formulation [22.5 mg] or 6-month formulation [45 mg]), with a reported HE associated with the administration of ELIGARD™.
- Patients who were informed of the study and the investigator did not receive any objection by the patient to collect their data.

Exclusion criteria:

- Any patient/s correctly re-injected with a new dose of ELIGARD™ shortly after the HE and before a blood sample for serum testosterone was taken.

2.7 Setting

Local DSO was to (1) call the reporter of the case to complete the ELIGARD™ "Target Data Questionnaire for lack of efficacy and/or problems/errors in preparation, reconstitution and/or administration", including asking for the name of the physician and asking for agreement to use the collected data for a study; (2) contact the physician to follow-up on the PV case; (3) ask the physician if he/she agreed that the collected data would be used for a study and if the clinical operations representative/contract research organization (CRO) could contact him/her to ascertain whether he/she would be willing to participate in the study.

The clinical operations representative/CRO was to:

- Call the physician, confirm his/her participation in the study and explain the financial agreement
- Explain that the physician should inform the patient that the data would be collected and ensure that the patient had no objection to their data being used, per the regulations in France concerning data privacy for non-interventional studies which only derive information from the patients' medical files but did not involve the patient. This non-objection was to be recorded in the patient's medical notes.

- Remind the physician to call the patient to ensure they monitor testosterone, per the summary of product characteristics (SmPC), after the mishandled ELIGARD™ injection.
- After the CRO received the signed financial contract, a site initiation was to be done by telephone with the physician. Data collection could begin after site initiation.
- After the site initiation call, the CRO was to send the physician the patient information leaflet and the financial agreement.
- The physician was to send the patient information leaflet to the patient.

When the physician received the serum testosterone level post injection, he/she was to decide what action to take next in terms of the clinical management of the patient. The decision taken was to be recorded on the case report form (CRF) as well as in the patient's medical record.

2.8 Patient and Study Size, Including Dropouts

The study size was dependent upon the number of spontaneous reports received over a period of 2 years from centers treating PCa patients with ELIGARD™. It was estimated that about 50 patients could be enrolled based upon previous reporting to Astellas pharmacovigilance, in France.

2.9 Variables and Data Sources

Physicians/centers in France were approached to take part in the study after the local Astellas PV department in France received spontaneous information from any site that a HE associated with the administration of ELIGARD™ had occurred for one or more of their patients.

Data were to be collected from all sources where data are captured and recorded in routine clinical practice; the following documents were considered source (including but not limited to):

- Adverse drug reaction (ADR) worksheets, where applicable,
- Hospital medical records (inclusive of any reports or laboratory investigations completed as part of standard clinical practice)

The investigator or site designee was to enter data using an electronic data capture (EDC) system. The following data were to be collected from the source medical records:

- Age at baseline,
- Medical history of the prostate cancer at baseline: years post the patient's initial diagnosis of prostate cancer, whether metastases were present, prior testosterone and PSA levels if available and whether the patient was treatment naïve or not,
- Other medical history at baseline: any significant conditions or diseases other than prostate cancer,

- ELIGARD™ Use: formulation 22.5 mg or 45 mg, start date, date of mishandled injection,
- Serum testosterone: date and serum testosterone level,
- Relevant concomitant medications throughout the study. If the use of the concomitant medication was due to an adverse event (AE), the AE was to be recorded on the AE case report form,
- Adverse events and special situations, including clinically significant laboratory abnormalities,
- Discontinuation criteria: death, lost to follow-up, patient refusal of data collection, study terminated by Sponsor, site terminated by the Sponsor, other.

Primary variables:

- Number and proportion of HEs associated with confirmed LOE based on the serum testosterone level after the HE associated with the administration of ELIGARD™.

HE was defined as any unintentional error during storage, preparation, reconstitution, and/or administration of the medicinal product while in the control of the healthcare professional or consumer.

Confirmed LOE was defined as a testosterone level >50 ng/dL or 1.735 nmol/L measured after 3-4 weeks following the mishandled ELIGARD™ injection. If multiple testosterone measurements were collected 3 weeks post the mishandled ELIGARD™ injection, the first measurement was to be used to determine LOE.

Secondary variables

Safety was to be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).

TEAE was defined as an adverse event observed after patient selection and occurring within 30 days of the last ELIGARD™ injection.

2.10 Interim Analysis

The ANSM was informed in January 2020 that the interim analysis planned in the protocol would not be performed since no patients were included in the study at that time.

2.11 Results

No patients were included in the study from 19 February 2019 to 19 February 2021.

It should be noted that a limited number of HE cases associated with the administration of ELIGARD™ were reported to Astellas PV during this period and were not included in the study for the following reasons:

- Cases for which only the solvent was injected,

- Cases not confirmed by the healthcare provider (HCP),
- Cases for which a testosterone dosage-related information was not available or the testosterone dosage was not performed,
- Case confirmed but the HCP refused to participate in the study.

These HE cases were reported to the ANSM in separate quarterly reports.

2.12 Discussion and Conclusions

Overall, no patients were included in the study.

The absence of HEs associated with the administration of ELIGARD™ reported as part of the study and the limited number of HEs associated with the administration of ELIGARD™ reported to Astellas PV may be explained by the additional risk minimization measures implemented before and during the conduct of the study. These measures were detailed in the Risk Management Plan, some of them are summarized below:

- Improvement of the device (modification of the blue plunger rod in August 2015, new safety needle [Terumo] reducing the risk of overtightening and preventing needle hub cracking [January 2019]);
- Additional guidance for HCPs to prevent HEs related to improper storage, preparation, reconstitution, and/or administration of ELIGARD™ (since 2015) and to prevent the overtightening of the needle (since November 2017, information provided in the summary of product characteristics [EU-SmPC] and patient information leaflet [PIL]);
- Distribution of educational material to HCPs (instructional poster, video/DVD, smartphone application, and website) and training since September 2016;
- Instruction not to administer ELIGARD™ and to perform a testosterone dosage in case of known or suspected HEs (August 2018).

In conclusion, no patients were included in the study and no HEs associated with the administration of ELIGARD™ were documented as part of the study.

Marketing Authorization Holder

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