STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: FASLODEX Intramuscular injection 250mg
ACTIVE INGREDIENT: Fulvestrant 250mg

Study No: D6997C00008
NCT01501266

Developmental Phase: post-marketing
Study Completion Date: January/2015
Date of Report: July/2015

OBJECTIVES:

The FASLODEX Specific Clinical Experience Investigation (S-CEI) was conducted with the following objectives: to confirm characteristics of ADRs in usual clinical settings, e.g. ADRs not expected from the Precautions for Use of the FASLODEX JPI and safety of FASLODEX in the long-term use, and to confirm factors which may affect safety and efficacy of FASLODEX.

METHODS:

Observational Study

RESULTS:

1. Treatment period of FASLODEX in the S-CEI

(1) In the safety analysis set of 566 patients, the treatment with FASLODEX was continued for at least 4 weeks in 96.1% (544 patients), at least 12 weeks in 81.4% (461 patients), at least 24 weeks in 57.8% (327 patients) and at least 1 year (52 weeks) in 28.1% (159 patients).

(2) The treatment with FASLODEX was discontinued within the observation period of the S-CEI in 374 patients (66.1%). The most common reason of the discontinuation was disease progression (including breast cancer deaths) in 319 patients. Other common reasons included “Others” (the patients' request) in 26 patients, “stopped visiting the physicians” in 22 patients, and “adverse events” in 7 patients.

2. Safety

(1) Adverse Drug Reactions (ADRs)

In the safety analysis set of 566 patients, 125 events of ADRs were reported in 74 patients (13.1%). The ADR incidence was remarkably decreased from that in the clinical studies before approval which was 67.9% in Japanese patients.
The ADRs reported from at least 3 patients were "Injection site pain" in 29 patients (5.1%), "Injection site induration" in 23 patients (4.1%), "Hepatic function abnormal" in 8 patients (1.4%), "Injection site erythema" in 6 patients (1.1%), "Aspartate aminotransferase increased" in 5 patients (0.9%), "Headache" and "Injection site pruritus" each in 4 patients (0.7%), and "Nausea", "Rash" and "Malaise" each in 3 patients (0.5%). The most common ADRs were those related to injection site reactions, and the incidences of these events were comparable with those in the clinical studies before approval.
Serious ADRs were "Injection site erythema/Injection site ulcer" in one patient, "Gastric ulcer haemorrhage" in one patient and "Arrhythmia/Cardio-respiratory arrest" in one patient. There were other possible factors than FASLODEX in the events.
The ADRs not expected from the FASLODEX JPI were "Malaise" in 3 patients (0.5%), "Muscle spasms" in 2 patients (0.4%), and "Neutropenia", "Dysgeusia", "Arrhythmia", "Cardio-respiratory arrest", "Lymphoedema", "Gastric ulcer haemorrhage" and "Pain" each in one patient (0.2%). The number of patients of each event was small, the events other than "arrhythmia", "cardio-respiratory arrest" and "gastric ulcer haemorrhage" were non-serious, and causal relationship between each event and FASLODEX was not definitely apparent. Accordingly, there was no new safety finding in the data. In addition, there was no new safety issue in the characteristics of ADR development in the long-term use of FASLODEX.

(2) Serious Adverse Events (SAEs)

Of the safety analysis set of 566 patients, 31 events of SAEs were reported in 24 patients (4.2%). The serious adverse events reported in the S-CEI included "Pneumonia", "Anaemia", "Dyspnoea" and "Interstitial lung disease" each in 2 patients (0.4%), "Abdominal abscess", "Endometrial cancer", "Disseminated intravascular coagulation", "Thrombocytopenia", "Hypocalcaemia", "VIIth cranial nerve paralysis", "Arrhythmia", "Cardio-respiratory arrest", "Ventricular fibrillation", "Abdominal pain", "Gastric ulcer", "Gastric ulcer haemorrhage", "Hepatic failure", "Hepatic function abnormal", "Hyperbilirubinaemia", "Stevens-Johnson syndrome", "Osteitis", "Osteonecrosis of jaw", "Injection site erythema", "Injection site ulcer", "Sudden death", and "Aspartate aminotransferase increased" each in 1 patient (0.2%). There was no new safety issue in the SAE data.

(3) ADR/infection incidence classified by patient demography factors

Significant differences of ADR/infection incidence were observed in the following factors: TNM classification [T classification] (p=0.0198), the site of the cancer lesion at baseline [Other sites] (p=0.0012), WHO Performance Status classification (p=0.0134), and concomitant allergy (p=0.0418). There was no safety issue which may require a new safety measure. There was no significant difference of the ADR incidences in the treatment factors.

(4) Key investigation items

ADRs related to 1) injection site reactions, 2) thromboembolism, and 3) hepatic function disorder were investigated as the key investigation items in the S-CEI, and the results are shown below. There was no safety finding in the data.

1) Injection site reactions
   ADRs which were considered to be related to the injection site reactions were 71 events in 52 patients (9.2%). The ADRs were "Injection site pain" in 29 patients (5.1%), "Injection site induration" in 23 patients (4.1%), "Injection site erythema" in 6 patients (1.1%), "Injection site pruritus" in 4 patients (0.7%), and "Application site pruritus", "Injection site bruising", "Injection site rash", "Injection site reaction", "Injection site ulcer" and "Injection site dysaesthesia" each in one patient (0.2%).
   In the 71 events, most of them were lower than Grade 3 except only one event of "Injection site ulcer" which was Grade 3 or higher.

2) Thromboembolism
   There was no report of ADR related to thromboembolism.

3) Hepatic function disorder
   The incidence of ADRs related to hepatic function disorder was 2.5% (14/566 patients). The hepatic function disorder-type events included "Hepatic function abnormal" in 8 patients (1.4%), "Aspartate aminotransferase increased" in 5 patients (0.9%), "Gamma-glutamyltransferase increased" in 2 patients (0.4%), and "Alanine aminotransferase increased" in one patient (0.2%). All events were lower than Grade 3.

3. Efficacy

Efficacy of FASLODEX was investigated for (1) Proportion Progression Free, and (2) Time to Treatment Failure of FASLODEX.

(1) Proportion Progression Free

1) In the efficacy analysis set of 531 patients, the patients without progression of the lesion was 38.8% (206/531 patients, 95% CI 34.6-43.1%) at Treatment Month 6, and 23.2% (123/531 patients, 95% CI 19.6-27.0%) at Treatment Year 1.

2) In the analysis of Proportion Progression Free survival classified by the patient demographic factors at Treatment Month 6, significant differences were observed in the age (p=0.0328), the disease period (p=0.0081), the site of the lesion at the baseline in the liver (p=0.0007) and in the brain (p=0.0032) and WHO Performance Status (p=0.0002).
   In the analysis of progression free survival classified by patient demographic factors at Treatment Year 1, significant differences were observed in the factors of the age (p=0.0304), the disease period (p=0.0445), the site of the lesion at the baseline in the liver (p=0.0013) and WHO Performance Status (p=0.0049).

(2) Time to Treatment Failure

1) In the efficacy analysis set of 531 patients, FASLODEX was discontinued during the S-CEI period in 349 patients (65.7%), and the median Time to Treatment Failure was 6.7 months (95% CI 5.9-7.9).

2) In the analysis of the Time to Treatment Failure classified by patient demographic factors, significant differences of efficacy were observed in the factors of the site of the lesion at the baseline in the liver ($p<0.0001$) and in the brain ($p=0.0059$), and previous chemotherapy (for advanced/recurrent breast cancer) ($p=0.0239$).