Faslodex® Intramuscular injection 250mg
Specific Clinical Experience Investigation Protocol

1. Purpose of the investigation

This investigation is to figure out the following items on fulvestrant used under actual (real-world) conditions after marketing.

(1) Adverse drug reactions (ADRs) unexpected from "Precautions for Use" of Faslodex JPI
(2) Status of occurrence of ADRs (including capturing of long-term safety information)
(3) Factors possibly affect safety, and efficacy

2. Target number of patients and its rationale

Target number of patients: 500 (planned no. of pts. for registration: 550)

[Rationale]
By including 500 patients in this investigation, the probability that one or more AEs with true incidence of 0.6% or higher are reported is about 95%. This sample size, therefore, is judged enough to know the common AEs in fulvestrant treatment.

To define the planned number of patients for registration, the clinical experience investigation of Arimidex tablet (observation period : 6 months, investigation period: 3 years) which is an endocrine therapy drug indicated for postmenopausal breast cancer was referred, where more than 95% of the overall registered patients were included in the analysis set.

For the thromboembolic events and hepatic impairment defined as important investigation items, thromboembolic events at an incidence of 0.9% (5/560 patients) and hepatic impairment of 1.4% (8/560 patients) were reported as adverse events in the clinical studies (overseas combined data). Assuming that the incidences in the actual use are similar, the probabilities of one or more reports of thromboembolic events and of hepatic impairment are both about 99% when 500 patients are enrolled. In conclusion, the above number of patients was judged enough.

3. Subject of the investigation

Patients with postmenopausal breast cancer, ie, the indication of fulvestrant, who receive fulvestrant for the first time. However, fulvestrant should be used for patients whose hormone receptor status is other than negative and who had been treated with endocrine therapy, for the following reasons: fulvestrant should not be administered to hormone receptor negative patients and; the efficacy and safety of fulvestrant in patients not previously treated with endocrine therapy as well as the efficacy and safety of fulvestrant used as supplementary to surgery have not been established (see "Precautions related to indications" in the draft prescribing information).

Dosage and administration: Usually for adults, Fulvestrant 500 mg will be given as two intramuscular injections (2 fulvestrant injections), one in each buttock, on days 0, 2 week and 4 weeks later, and every 4 weeks thereafter.

4. Number of investigation sites where the investigation is conducted

Approximately 300 institutions mainly consisted of surgery departments including surgery, mammary gland surgery, endocrine surgery, and internal medicine departments treating cancer

[Rationale]
Since fulvestrant is an endocrine therapy drug for “postmenopausal advanced or recurrent breast cancer”, medical institutions meeting all the following three requirements will be selected.

(1) There are physicians with sufficient knowledge and experience in drug therapy for cancer.
(2) It is possible that the head (or equivalent) of the institution concludes the contract of this surveillance.
(3) Regular visit by AZ Medical Representatives (hereinafter referred to as MRs) to promote the appropriate use of fulvestrant is accepted, and cooperation for information collection and this surveillance is extended.

About 300 sites are considered possible to participate in this surveillance among the institutions that meet the above requirements, and that aromatase inhibitors (ie, an endocrine therapy drug for postmenopausal advanced or recurrent breast cancer) are delivered and fulvestrant treatment is expected in at least one patient a year.

5. Investigation methods

(1) Target investigation medical institutions are hospitals where this drug has been delivered and started to be used. MRs will explain the objectives, target and method of the investigation to physicians of the hospitals who will conduct the investigation, and will request the investigation to the head of the hospital. Written contract must be obtained before the investigation is started. The investigation method should be central registration method. The method of collecting the data should be EDC (Electronic Data Capture) via Internet in principle. As to EDC system, Rave of Medidata Solutions Japan KK should be used. For the institutions where EDC is not available, paper CRF should be prepared, and after the conclusion of contract, MR in charge should distribute Case Registration Form and CRF to the investigator.

(2) The investigator should enter the required information on the registration screen of Rave to register the patient within 14 days after the drug is started in the patient defined as ‘3. Subject of the investigation’ as the above (the start date should be Day 1). In case of institutions where paper CRF should be used, the investigator should fill in the Case Registration Form and send it to the registration centre by fax. If the Case Registration Form is sent to the registration centre on and after 14 days after the drug was started or the next day of the end of registration period and after, it is not acceptable.

(3) After the case is registered, MR communicates completion of registration to the investigator in writing.

(4) The observation period is 1 year.

[Rationale]
Given that the median TTP (time to progression) was 6.5 months in the overseas Phase III study D6997C00002 and 6.0 months in the Japanese Phase II study D6997C00004 as well as overseas Phase II study D6997C00006, it is expected that after the market launch, about half the patients in the real world will continue the treatment for at least 6 months. For the 4 pivotal Japanese and overseas clinical studies, adverse events judged causally related to fulvestrant (hereinafter adverse reactions) were combined, sorted by time of onset (<24 weeks and ≥24 weeks, and <52 weeks and ≥52 weeks) and summarized. As a result, of the 173 types of adverse reactions, there are 21 types (12.1%) reported only after 24 weeks and 4 types (2.3%) only after 52 weeks. Therefore, the one-year observation period is considered enough to collect the adverse reactions of fulvestrant overall.

(5) The investigator should enter the required information on the case report form of Rave for each patient, and e-sign it. In case of institutions where paper CRF should be used, the investigator should fill in the CRF within 6 weeks after the end of observation period, and pass it to MR.

6. Investigation period

Registration period: Jan 2012 - Jun 2013 (1.5 years)
Investigation period: Jan 2012 -Jun 2014 (2.5 years)

7. Data to be collected

(1) Patient identification
Identification number

(2) Patient demography data (the condition at the start of the drug)
Age, with/without pregnancy, with/without lactation, height, weight, inpatient/outpatient, indication of the drug, time of definite diagnosis of breast cancer, receptor status (ER, PgR, HER2), TNM classification, date of treatment start, the site of lesion at the time of treatment start, WHO Performance Status (PS), with/without allergy, past medical history, complication, previous treatment for breast cancer (with/without endocrine therapy, chemotherapy, radiation, or anti HER2 therapy)

(3) Faslodex administration
Date of administration, continue or discontinue administration of the drug, and reason for withdrawal

(4) Concomitant medications
With/without concomitant drug(s) during treatment with the drug, (if any concomitant drug was used, the drug name, administration route, and indication, and in case with AE, daily dosage and treatment duration.)

(5) Concomitant therapy (other than drugs)
With/without concomitant therapy during treatment with the drug (if any concomitant therapy was performed, the therapy name and the purpose of the therapy, and in case with AE, treatment duration.)

(6) Response evaluation
With/without aggravation of the lesion after six months from the start of treatment and at the end of observation period, response evaluation date, WHO PS at response evaluation

(7) Adverse event
The adverse events during the observation period [regardless the causality with administration of the drug, presence or absence of all undesirable or unintended signs (including abnormal clinical laboratory tests)], symptoms, and disease (if any of them exists, the items below should be confirmed.)
AE term, onset date, outcome, outcome date, seriousness*, severity (CTCAE Grade: <3 or >=3**), causality with the drug, alternative contributing factor, clinical laboratory tests related to the AE (test item, test date, test data including reference values at the institution), withdrawal of the drug due to the AE.
Regarding serious event, comment on the progress of the AE and the causality should be described.
If the outcome of the adverse event was ‘death’, the date of death, the cause of death (AE, breast cancer), existence of the causality between the death and the drug, and with/without autopsy (if autopsy was conducted, the findings should be described.)
In this investigation, aggravation of the breast cancer lesion and breast cancer death should not be handled as AE.

(8) Rationale and practical investigation method for key items to be investigated

As the adverse events following fulvestrant administration, details of the development of injection site reaction, thromboembolic events and hepatic impairment will be investigated.

[Rationale]

Injection site reaction can be seen with a high frequency for this drug. Therefore, it is important to investigate the actual condition in clinical practice by confirming development of the event and administration status of the drug and to utilize the data for appropriate drug use.

Thromboembolism and hepatic function disorder have been reported rarely in the clinical studies in Japanese patients. However, as they are important identified risk, it is important to investigate the development in Japanese and to provide the information. For the reason, they were set as key investigation item.

[Practical investigation method]

1) 'Injection site reaction'

Confirm development of injection site reaction, and investigate the developmental condition and administration of the drug after the onset.

- Developmental condition of the injection site: frequency, duration of the symptoms (onset date, outcome, and outcome date), area of the symptoms (localized to the injection site or broad area)
- Administration of the drug after the onset: suspension, change or not change of the injection site, the new injection site if changed.

2) 'Thromboembolism'

Confirm development of thromboembolism, and investigate the frequency, the onset period, and severity (CTCAE Grade <3 or >=3**).

3) 'Hepatic function disorder'

Confirm development of hepatic function disorder, the frequency, and the onset period, and obtain the data of AST (GOT), ALT (GPT), ALP, gamma-GTP, and billirubin as much as possible and severity (CTCAE Grade <3 or >=3**) observed after the baseline.

*: Definitions of "serious" follows the ICH definitions:
Death, life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, other medically important, and congenital anomaly/birth defect

**:Refer to CTCAE v4.0 Japanese version, JCOG, 25 Apr 2011.

<Observation schedule>

	Start of treatment	Sixth month	End of observation period (termination of the observation period (1 year) [a] or withdrawal of the drug [b])
Patient's background factors	○		
Dosage and administration of this drug	←	—	→
Concomitant medications	←	—	→
Concomitant therapy	←	—	→
Efficacy	○	○	○
Adverse event [c]	←	—	→

a. In case the drug is continuing at termination of the observation period, the observation day should be the closest day to the planned termination date of observation period during the period of planned termination date +- 4 weeks. If the patient did not visit the site during the period of the termination date of observation period +- 4 weeks, the observation day should be the last day of administration before the planned termination day of observation period.

b. If the drug was discontinued, the tumor assessment day should be the last day of administration of the drug.

c. In case of withdrawal of the drug, follow-up investigation of AE should be conducted for eight weeks after the last dose (safety follow-up period).

8. **Items to be analyzed**

(1) Analysis set

1) Safety analysis set

2) Efficacy analysis set

(2) Analysis items

1) Items related to composition of the population

Number of registered patients, number of patients collected for data, number of patients for safety analysis, number of patients for efficacy analysis, number of patients excluded from the investigation as well as the number of patients sorted by the reason for exclusion, number of discontinued patients as well as the number of patients sorted by the reason for discontinuation

2) Distribution of demographics of patients and reference values

3) Items related to patient demography

Age (at the time of registration, <65 years, ≥65 years), inpatient or outpatient, reason for fulvestrant use (advanced, recurrent), number of years since breast cancer development, hormone receptor status, HER2 status, TNM classification, lesions by site at the time of treatment start, PS, allergy, complications (hepatic disorder, renal disorder, other complications), medical history, etc.

4) Distribution of treatment factor

Previous treatment of breast cancer (with/without adjuvant therapy or treatment of progression/recurrence; if with any of these treatments, with/without endocrine therapy, chemotherapy, radiation, or anti HER2 therapy, and type of drugs for endocrine therapy), frequency of administration of the drug, the ration of actual frequency of administration to expected frequency (<0.8, >=0.8 and <1, 1), withdrawal of the drug (the reason if the drug was withdrawn), concomitant drugs (with/without and type), concomitant therapy (with/without and type), etc.

5) Safety items

- Status of occurrence of adverse reactions/infectious diseases by type and period
- Status of occurrence of adverse reactions/infectious diseases by patient demography
- Status of occurrence of serious adverse events by type
- Status of occurrence of adverse events subject to key investigation items by type

6) Efficacy items

The number and rate of patients in each category with/without aggravation of the lesion after six months from the start of treatment and at the end of observation period.

No interim analysis will be performed.

9. Organisation to conduct the investigation

The organisation to conduct the investigation is same as that in Attachment 2 to PMS Basic Plan.

10. Organisations to which the operations are to be outsourced, and scope of the contract

Name:

Address:

Scope of the contract:

Reception of patient enrollment, and operations of data management (data entry, CRF check/data lock, and request of re-investigation, database lock, and dataset compilation)

11. Other necessary items

(1) Amendment of the protocol

During the investigational period, the number of withdrawal, development of unexpected serious ADRs, remarkable increase of incidence of specific ADRs, and validity of investigational items should be grasped continuously. If needed, the protocol should be reviewed and revised.

In case of s-NDA is approved for dosage and administration or indications during the investigation period of this drug (except the case when the re-examination period is established newly), the protocol should be reviewed and revised appropriately.

In case the organization or the consignment contract is changed, the protocol should be revised appropriately.

(2) Actions when issues/questions are recognized

Conduct of Specific Clinical Experience Investigation and Post-marketing Clinical Studies is to be examined to detect/confirm their factors and to verify discussion outcome in following conditions: when development of a significant ADR unexpected from the Precautions for use is suggested, when the frequency of an ADR is excessively increased, when an issue was recognized in safety and efficacy compared to their condition before launch, and when development of a different kind of ADR is suggested.