Clinical Study Report Synopsis

Drug Substance	Fulvestrant 250mg
Study Code	NIS-OAR-FAS-2008/1
Edition Number	1
Date	26th September 2008

Non interventional report on the parameters of acceptability, fulfillment and efficacy of fulvestrant on posmenopausic patients with hormone-sensitive advanced breast cancer progressed to an antiestrogen therapy.

Study dates:

First subject enrolled: 15-April-2009
Last subject last visit: 15-December-2010

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

A total of 49 sites have participated and included patients in the study.

Publications

No publications at moment.

Objectives and criteria for evaluation

The primary study objective is:

To assess efficacy, acceptability and fulfillment of a FASLODEX® (Fulvestrant) treatment scheme in posmenopausic women with advanced breast cancer with positive hormone receptors, who are already receiving this agent from before having entered the current study.

The efficacy of the treatment has been determined by objective criteria of response and tabulated in complete response, partial response, stable disease or progression, according to RECIST criteria.

The acceptability of the treatment has been assessed according to the degree of acceptance (both at baseline as well as in the follow-up) of the patient to the proposed treatment by the physician, discriminating the objections, observations and preferences expressed by the patient.

The fulfillment of the treatment (adherence) has been based on the percentage of deviation established between the foreseen dates of injection (every 28 [+/- 3] days) and the ones actually performed.

Study design

Post-marketing, open, prospective and multicenter study in order to collect data of the acceptability, efficacy and fulfillment of a treatment with fulvestrant in posmenopausic women with advanced breast cancer with positive hormone receptors in the regular care practice.

The current study was planned to have 24-month duration, and had been planned to be possible cancelled by AstraZeneca in case of a specific reason.

The patient participation in the current study was extended until the prescription of Faslodex was discontinued, the current study was terminated, patient withdrawal the consent to participate, due to the treating physician's decision or due to AstraZeneca's decision, whichever happened first.

All patients have only received Fulvestrant at the discretion of the treating physician.

The current study was planned with the objective of not performing any influence on the physician's decision nor in the treatment drug neither in the duration of the treatment.

Inclusion criteria

- 18 years or older
- Posmenopausic women with advanced breast cancer with positive hormone receptors in the regular care practice, already receiving Faslodex for the treatment of their disease.
- Patients must sign an inform consent before entering into the study

Target subject population and sample size

Up to 500 post-menopausic women who have started treatment with fulvestrant due to a hormone-sensitive locally advanced or metastatic breast cancer will be incorporated.

When inviting each patient to participate in this study the doctor provided her an explanation of the study and made them sign the informed consent.

Patients could have received any prior oncologic treatment, such as chemotherapy, hormone therapy or radiotherapy, since the sole requisite is that the medical practitioner based on his/her best knowledge and understanding of the assistance practice, had a prescribed treatment with fulvestrant.

Statistical methods

The sample calculation was obtained taking into consideration the quantity of patients constituting the population.

In the sample practice, since the variability of the variable considered as more relevant -that is measured by the standard deviation- is not known, therefore it is usually resorted to the search of higher values. These are obtained assuming that the variable is dichotomically distributed and that the binomial law is valid assuming the fulfillment of its assumptions, and the **p**=0.5 is chosen, which leads to the maximal σ2 variance.

Therefore, the following formula was applicable for the sample calculation, randomly considering the simple sample:

$$\mathbf{n} = N.\mathbf{p}.(1-\mathbf{p})/[(\varepsilon 2/4)*(N-1)+\mathbf{p}.(1-\mathbf{p})]$$

Where:

N is the size of the population

n is the size of the sample

p is the parameter of the binomial distribution.

ε is the maximum value of mistake, here the value of 5% was used

A confidence level of 95% was fixed, which would lead to take **Z** values from the table of normal distribution of Laplace-Gauss equal to 1.96 (near to 2), what appears as in the prior expression.

In this way, the size of the sample was greater than the one that would have resulted if the true variance had been known, but the pre-fixed level of confidence and pre-fixed maximum value for the mistake of calculation is guaranteed to be achieved.

With 1800 estimated patients for the 2007 / 2008 years, and with a sample size of 500, the maximum value of mistake is 3.8%, lower than the usual value of 5%.

Subject population

212 patients have been included in the study

204 patients have been considered as evaluable

Mean age of patients included: 64,5 years

Gender: female (100%)

Mean age of menopause: 47 years

Summary of efficacy results

The distribution of visits during the study was as follows:

Less than 5 visits performed: 14,7%

5-10 visits performed: 38,7%

More than 10 visits performed: 46,6%

Patient characteristics and clinical response have been evaluated in the last visit of each of them

164 patients (82.4%) presented data to be evaluated in reference to treatment efficacy.

Efficacy results obtained based in RECIST criteria are described in Table 1:

Table 1: Response evaluated in the last visit of each patient	
Complete response	10,4%
Partial response	16,5%
Stable disease	39%
Disease progression	34,1%

According to patient´s age, efficacy results are described in Table 2:

Table 2: Response evaluated in the last visit, according to patient´s age			
	Less than 60 years (43; 26,4%)	60-80 years (105; 63,8%)	More than 80 years (16; 9,8%)
Complete response	7%	12,5%	6,2%
Partial response	14%	13,5%	25%
Stable disease	46,5%	36,5%	50%
Disease progression	32,5%	37,5%	18,8%

Efficacy, according to the quantity of doses of fulvestrant received, is described below (Table 3):

Table 3: Efficacy according to the quantity of doses of fulvestrant received			
	Less than 6 (38; 27%)	6-10 (41; 29%)	More than 10 (62; 44%)
Complete response	7,9%	11,6%	12,9%
Partial response	13,1%	19,5%	19,3%
Stable disease	34,2%	31,7%	61,4%
Disease progression	44,8%	37,2%	6,4%

Clinical response was evaluated in the last visit, considering the time from breast cancer diagnosed, until the moment of starting with fulvestrant treatment, Results are the following (Table 4):

Table 4: Efficacy and time until fulvestrant treatment initiation

	≤ 2 years (22; 13,8%)	3-5 years (55; 33,7%)	6-10 years (47; 28,5%)	> 10 years (39; 24,6%)
Complete response	27,3%	7,5%	8,9%	7,7%
Partial response	22,7%	22,6%	6,7%	12,8%
Stable disease	36,4%	47,3%	35,5%	41%
Disease progression	13,6%	22,6%	48,9%	38,5%

Adherence to treatment

Treatment adherence is called the application of fulvestrant between 28 +/- 3 days.

Lack of adherence is the time of drug application with a period of time between doses longer than 32 days.

- 50% of patients presented lack of adherence to their treatment, in less than 50% of applications.
- 32.5% of patients presented lack of adherence to their treatment, in 50% or more of the applications.
- 17.5% of patients presented lack of adherence to their treatment, in all the applications of fulvestrant

Acceptability to treatment

Patients acceptability to a monthly injectable treatment was excellent in 96,6 % of the cases. The acceptability for the other 0.4% was good.

Summary of safety results

During the study, 19 adverse events have been reported. 8 non serious and 11 serious (1 related to the study drug). The detailed information is included in Table 5.

	Related to medication (yes/no)
Non Serious Adverse Events	
Pain at site of application	No
Pain at site of application	No
Face redness	No
Hot flush/morning sweating	No
Hot flush	No
Headache	No
Bilirrubin elevation	No
Hip pathological fracture	No
Serious Adverse Events	
Digestive hemorrhage	No
Death of unknown cause	No
Death of unknown cause	No
Second primary colorectal cancer	No
Pneumonia	No
Aspiration pneumonia	No
Death	No
Rotator cuff rupture of right shoulder	No
Death	No
Death	No
Diarrhea	Yes