AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Faslodex and exemestane
Study Code	NIS-ODE-FAS-2009/1
Edition Number	
Date	20.11.2014
NCT-Number	NCT01171417

ACT-FASTER: **A**n epidemiological prospective **C**ohort study to describe **T**reatment patterns of **F**ulvestrant **A**nd Exeme**ST**ane in postmenopausal patients with advanced HR+ breast cancer under real-life conditions in G**ER**many

Study dates: First subject enrolled: 12.08.2010
Last subject last visit: 30.11.2013

Phase of development: Post-authorization

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

Altogether 115 centres in Germany, specialised clinics and office-based gynaecologists or oncologists, participated in the NIS.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
primary	*Effectiveness*	Time to progression (TTP) for patients treated with Faslodex 500 mg	Period from patients inclusion date (date of informed consent) to the date of progression as judged by the investigator
primary	*Exploration of real-life data*	Epidemiology and management of PMP patients with HR+ ABC treated with Faslodex 500 mg or exemestane	Medical history, Health related QoL (EQ5D), Health economic parameters
secondary	*Effectiveness*	Overall survival (OS),	Period from inclusion to death of any cause
secondary	*Effectiveness*	Progression-free survival (PFS)	Period from inclusion to the date of progression or death (of any cause) whichever occurred before >
secondary	*Effectiveness*	Time to progression (TTP) for patients treated with exemestane	Period from inclusion to the date of progression
secondary	*Effectiveness*	Objective response rate (ORR)	Proportion of patients with a best overall tumour assessment of complete response or partial response (used method at the discretion of the investigator)
secondary	*Effectiveness*	Clinical benefit rate (CBR)	Proportion of patients who experienced an objective response (OR) or stable disease (SD) for ≥ 24 weeks
secondary	*Exploration of real-life data*	Real-life pharmacoeconomic data	Outpatient therapy, Primary care visits, Hospital stays, Emergency visits, Home care, Other resource use
secondary	*Exploration of real-life data*	Health-related quality of life	Standard QoL questionnaire (EQ5D)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
secondary	*Safety*	Adverse events / serious adverse events	Type of adverse event , intensity, causal relationship to Faslodex or exemestane, outcome , seriousness

Study design

This study was a so-called 'Nicht-interventionelle Studie' (non-interventional study; NIS) according to the German Drug Law (AMG, §67(6)) and was performed in Germany under sponsorship of AstraZeneca GmbH.

Under daily routine conditions and without any intervention by the sponsor regarding the selection of subjects, diagnostic procedures, routine assessments or therapeutic decisions (medicinal and non-medicinal therapy, duration of treatment, dose reductions etc.), postmenopausal patients with hormone-receptor positive advanced breast cancer who were eligible for Faslodex 500 mg or exemestane treatment as 1st, 2nd or 3rd line treatment according to the respective product specifications and for whom the decision to start this endocrine treatment had been documented could be included in this NIS within the first 28 days of treatment.

Target subject population and sample size

The patient population consisted of postmenopausal patients with hormone-receptor positive advanced breast cancer who were eligible for Faslodex 500 mg or exemestane treatment as 1st, 2nd or 3rd line treatment.

Patients were eligible for inclusion in this NIS if they had had a prior treatment with tamoxifen and were suitable to undergo endocrine treatment for ER+ ABC with SERD / steroidal AI.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Treatment with Faslodex or exemestane according to SmPC. There was no comparator drug.

Faslodex: Monthly injection of Faslodex 500mg, applied as two consecutive intramuscular 5 ml injections, each in one half of the buttocks.

Exemestane: One tablet (corresponding to 25 mg exemestane) to be taken daily after a meal.

Duration of treatment

As this was a NIS, there was no treatment period defined by protocol.

Statistical methods

Binary, categorical and ordinal parameters were summarized by means of absolute and percentage numbers within the various categories (including 'missing data' as valid category at Visit 1 (baseline)). Numerical data were summarized by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile). Wherever useful, the summary statistics are presented by visit. All statistical tests were performed two-sided at a 5% level of significance. However, the p-values of all statistical tests are interpreted only in a descriptive-exploratory way. Two-sided confidence intervals (CI) are presented for important parameters, if considered relevant, but should be interpreted in a descriptive way. In addition, appropriate figures (e.g. bar charts, Box-Whisker-Plots) are presented to summarize the results for some parameters also in a graphical way.

Subject population

In 115 study centers 537 patients were recruited. Finally 498 patients were evaluable for statistical analysis.

The demographic and key baseline characteristics of study subjects revealed no significant differences between treatment groups (Faslodex 1st, 2nd, 3rd line, exemestane). The baseline characteristics of the enrolled patients are consistent with average values of the population for women with advanced / metastatic breast cancer. Thus a representative cohort of patients has been enrolled.

Regarding demographic and epidemiologic parameters there were no noticeable differences between therapy groups despite different numbers of patients in each group. The mean age of the patients was > 66 years in each treatment group. Over 80% of the patients in each treatment group had an ECOG performance status of 0-1, even in the 3rd line Faslodex treatment group. The most common comorbidities were diseases of the cardio-circulatory system followed by metabolic diseases. The majority of patients had invasive-ductal carcinoma.

Summary of effectiveness results

In Faslodex treated patients in 1st line therapy disease progression occurred significantly later than in patients in the other treatment lines. Median time to progression was 9.7 months, 6.8 months and 6.7 months within patients treated with Faslodex at 1st line, 2nd line and 3rd line, respectively.

Analysis of time to progression (TTP) comparing the Faslodex treatment lines with each other revealed a hazard ratio of 1.29 [0.97;1.70] p=0.076, 1.27 [1.08;1.49] p=0.0043 and 1.22 [0.89;1.68] p=0.2187 for 1st line vs. 2nd line, 1st line vs. 3rd line and 2nd line vs. 3rd line, respectively. Difference in TTP between 1st and 3rd line was statistically significant, but not between 1st and 2nd treatment group or 2nd and 3rd treatment group.
From the hazard ratio = 1.26 (overall analysis all Faslodex treatment lines combined) it can be assumed that the risk of progression increases by estimated 26% comparing a lower line of

therapy to the next higher line. This difference is statistically significant (p = 0.0042, Cox regression analysis). Statistically relevant prognostic factors for time to progression were 'Age class' (<65 years / ≥65 years) and 'PD after last endocrine therapy '(yes / no) (P < 0.05): For patients with age ≥65 compared to patients with age <65 years the risk decreases (Hazard ratio <1). For patients with PD after last endocrine therapy compared to patients with no such event the risk increases (Hazard ratio >1).

Patients of the exemestane group had a 3-4 times longer median PFS compared to literature data of clinical trials, irrespective of treatment.

Median time to OS could not be determined as it was not reached within the observational period.

A risk factor analysis showed no clear tendency. Most of the tested factors did not show a statistically significant influence on disease related parameters. 'Line of Faslodex-treatment' and 'age' as well as "Dose delay" and 'Dose discontinuation' modified clinical outcome parameters.. But there was no homogeneous trend. Effect size and direction were different for the different disease aspects considered.

Summary of safety results

Safety of treatment was solely assessed from the documented adverse events and serious adverse events. No additional laboratory or investigational parameters were required in the NIS.

Altogether 320 adverse events (AE) were documented, 156 of these were drug related. Most AEs were of grade 1 or 2, only 2 patients had AEs of grade 4. The majority of the AEs belong to the categories 'Gastrointestinal disorders', 'General disorders and administration site conditions' and 'Musculoskeletal and connective tissue disorders'. About 25% of patients in each group exhibited at least one adverse event.

Altogether 100 serious adverse events (SAE) have been documented, nearly all of them were non-haematological events. Most of SAEs in the Faslodex treatment groups belong to "General disorders and administration site conditions" and "Gastrointestinal disorders". In the exemestane group the great majority of SAEs concern "Gastrointestinal disorders". There were 11 drug related serious adverse events.

Patients in 1st line Faslodex treatment developed significantly more serious adverse events (SAE) than patients in 2nd line Faslodex treatment. 69 patients had at least one SAE documented: 18.2%, 10.4%, 11.8% and 13.6% of patients for Faslodex 1st line, 2nd line, 3rd line and exemestane, respectively. In the great majority of cases there was only 1 SAE per patient. The main reason for classification as SAE was "Hospitalisation or prolongation of hospitalisation" which was stated for 30.1%, 15.3%, 25.8% and 21.2% of patients in Faslodex first line, second line, third line and exemestane, respectively. SAEs due to "Death" were documented for 4.0% and 2.5% of patients in Faslodex 1st and 2nd line treatment group,

respectively. 5.75% of patients in Faslodex 1st line therapy had a hospitalisation which ended with death.

Treatment discontinuation due to AEs and SAEs occurred more often in the exemestane group than in the Faslodex treatment groups, in 15.2% versus 8.5%, 3.1% and 5.3% of patients, respectively.

The majority of SAEs had no influence on the administration of Faslodex or exemestane and recovered / resolved without sequelae. 17 patients had SAEs with fatal outcome; all patients belong to the Faslodex treatment groups.