AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Arimidex ODF
Study Code	D539EC00001
Edition Number	Ver.1.0
Date	18 October 2012

A Randomised, Open label, Single centre, 2 way Crossover Bioequivalence Study Comparing Arimidex® Tablet 1 mg and Anastrozole Orally Rapid Disintegration Film Formula 1 mg After Single Oral Administration in Japanese Healthy Male Subjects

Study dates: First subject enrolled: 11 April 2012
Last subject last visit: 22 June 2012

Phase of development: Clinical Pharmacology

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

Study centre(s)

This study was conducted at a single centre in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and outcome variables are shown in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetics	To investigate whether Anastrozole Orally Rapid Disintegration Film Formula (ODF) 1 mg is bioequivalent with Arimidex® tablet 1 mg, by assessment of AUC_t and C_{max} of anastrozole after a single oral administration of each anastrozole formulation.	AUC_t, C_{max}
Secondary	Pharmacokinetics	To evaluate the pharmacokinetic (PK) properties of Arimidex® tablet 1 mg and Anastrozole ODF 1 mg following a single oral dose, by assessment of AUC, MRT, t_{max}, k_{el} and $t_{½}$ of anastrozole.	AUC, MRT, t_{max}, k_{el} and $t_{½}$
	Safety	To evaluate the safety and tolerability of Anastrozole ODF 1 mg by assessment of adverse events, clinical laboratory tests, 12-lead ECG, blood pressure, pulse rate, body temperature, and physical examination.	Adverse events, clinical laboratory tests (haematology, clinical chemistry, and urinalysis), 12-lead ECG, blood pressure, pulse rate, body temperature, and physical examination.

Study design

This study was an open, randomised, two-way cross-over study. Two dosing conditions for Anastrozole ODF dose, with or without water, were assessed. Two single-dose periods were separated by a wash-out of at least 21 days. Allocation of treatments and the number of subjects in each dosing condition are shown in Table S2.

Table S2 Allocation of treatments and number of subjects

Dosing condition	Group	Number of subjects	Period 1	Wash-out	Period 2
1	A	10	Anastrozole ODF 1 mg with water	≥ 21 days	Arimidex® tablet 1 mg with water
	B	10	Arimidex® tablet 1 mg with water		Anastrozole ODF 1 mg with water
2	C	10	Anastrozole ODF 1 mg without water	≥ 21 days	Arimidex® tablet 1 mg with water
	D	10	Arimidex® tablet 1 mg with water		Anastrozole ODF 1 mg without water

Target subject population and sample size

The target population included healthy Japanese male subjects aged 20 - 45 years with a body mass index of 18 - 27 kg/m^2 and a body weight of 50 to < 85 kg.

Total of 40 (10 per group) was determined as a sufficient number of subjects to confirm the bioequivalence for both conditions, taking into account for some withdrawals. The drug concentration data from a healthy male subject study of single dose of anastrozole and the Japanese guidelines for bioequivalence studies were referred in the determination of the number of subjects. Bioequivalence of the two formulations was concluded if the 90% confidence intervals of the ratios for the both AUC_t and C_{max} fell within the range of 0.80 to 1.25.

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

A single dose of Anastrozole ODF 1 mg (batch number: 2C01ADX, Kyukyu Pharmaceutical Co., LTD., Japan) was administered with water to subjects in dosing condition 1 and without water to subjects in dosing condition 2, respectively. A single dose of Arimidex® tablet 1 mg (batch number: 14211, AstraZeneca K.K., Japan) was administered with water to subjects in both dosing conditions. All subjects were requested to fast (except for water) for more than 10 hours before the administration of investigational products and for 4 hours post-dose. Water was not allowed for 1 hour post-dose.

Duration of treatment

Each subject took part in two treatment periods, and received a single dose of Anastrozole ODF 1 mg or Arimidex® tablet 1 mg in each treatment periods.

Statistical methods

Data on safety, tolerability and pharmacokinetics were presented using descriptive statistics. Tables and figures were presented appropriately.

T_{max} was analyzed based on untransformed data, and the other pharmacokinetic parameters were analyzed based on log-transformed data.

Ratios of the test formulation to the standard formulation for C_{max} and AUC_t, were presented.

For the primary endpoints, bioequivalence was evaluated by a comparison between the formulations for each condition. For each dosing condition, 90% confidence interval of the ratio of the test formulation to the standard formulation for C_{max} and AUC_t was calculated from the 90% confidence interval of the difference between the means on the log scale. Bioequivalence of the two formulations was concluded if the 90% confidence intervals of the ratios for the both parameters fall within the range of 0.80 to 1.25. Secondary endpoints for PK, except for t_{max}, were analyzed similarly but the results were not used formal bioequivalence test and were treated as supportive. As a secondary analysis of primary endpoints, C_{max} and AUC_t were also analyzed using combined data from the both dosing conditions. The evaluation method followed the Japanese guidelines for bioequivalence studies ("Guideline for Bioequivalence Studies of Genetic Products" and "Guideline for Bioequivalence Studies for the Addition of Different Dosage Forms"). Details of statistical analysis are presented in the statistical analysis plan.

Subject population

A total of 58 healthy Japanese male subjects were enrolled. Of these, 40 subjects were randomised into the study and all 40 subjects completed the study per protocol with no subject who had discontinued the study treatment. The mean age of the subjects randomized was 27.9 years (range: 20 to 43 years), with the mean weight of 64.3 kg (range: 51.9 to 77.7 kg) and BMI of 21.9 kg/m^2 (range: 18.4 to 26.9 kg/m^2). The treatment groups were balanced in terms of demographic and baseline characteristics. The key baseline characteristics are summarised in Table S3.

Table S3 Baseline characteristics (All randomized subjects)

Demographic characteristics		**Group A** (N=10)	**Group B** (N=10)	**Group C** (N=10)	**Group D** (N=10)	**Total** (N=40)
Age (years)	Mean ± SD	28.5 ± 7.9	28.1 ± 6.6	26.7 ± 7.7	28.4 ± 6.4	27.9 ± 7.0
Sex (%)	Male	100.0	100.0	100.0	100.0	100.0
Ethnic group (%)	Japanese	100.0	100.0	100.0	100.0	100.0
Weight (kg)	Mean ± SD	66.04 ± 9.56	60.71 ± 5.88	66.11 ± 5.82	64.42 ± 4.45	64.32 ± 6.81
BMI (kg/m^2)	Mean ± SD	21.78 ± 3.10	21.01 ± 2.11	22.43 ± 2.34	22.21 ± 2.44	21.86 ± 2.49

Summary of pharmacokinetic results

The mean plasma concentration-time profiles of anastrozole were almost identical for the Anastrozole ODF 1 mg and the Arimidex tablet 1 mg in the both dosing conditions with water or without water. Anastrozole was absorbed rapidly from both formulations regardless of the dosing condition, with peak mean plasma concentrations occurring at 1 hour after dosing. The

median t_{max} was 1.0 hour for the both formulations in the both dosing conditions. Mean C_{max} was similar after administration of each of the formulations, as was the rate of decline of plasma concentrations after the peak. The mean $t_{½}$ was approximately 37 hours for the both formulations with water as well as without water.

Results of statistical analysis for the primary pharmacokinetic parameters are summarised in Table S4.

Table S4 Statistical analysis for the primary pharmacokinetic parameters

ODF dosing condition	Parameter	N	Anastrozole ODF 1 mg (Glsmean)	Arimidex® tablet 1 mg (Glsmean)	Ratio	90% Confidence Interval
With water	AUC_t (ng·h/mL)	20	596	603	0.99	(0.96, 1.02)
	C_{max} (ng/mL)	20	15.4	15.7	0.98	(0.93, 1.03)
Without water*	AUC_t (ng·h/mL)	20	594	572	1.04	(1.01, 1.07)
	C_{max} (ng/mL)	20	14.2	14.2	1.00	(0.95, 1.05)

*: Arimidex® tablet was given with water
Glsmean: Geometric least-square mean

The 90% confidence intervals for the ratios of AUC_t and C_{max}, the primary pharmacokinetic parameters defined by the Japanese bioequivalence guidelines, of Anastrozole ODF 1 mg to Arimidex® tablet 1 mg are wholly contained within the acceptance limits for bioequivalence (0.8, 1.25) in the both dosing conditions with water or without water.

Consequently, it is concluded that the Anastrozole ODF 1 mg is bioequivalent to the Arimidex® tablet 1 mg. In addition, comparison of the secondary pharmacokinetic parameters of AUC, MRT, t_{max}, k_{el} and $t_{½}$ also supported the conclusion of bioequivalence between Anastrozole ODF 1 mg and Arimidex® tablet 1 mg.

Summary of safety results

For the dosing condition with water, no adverse events were reported in both treatments of Anastrozole ODF 1 mg and Arimidex® tablet 1 mg.

For the dosing condition without water, two adverse events of tonsillitis were reported in 2 of twenty subjects (10.0%) who received Anastrozole ODF 1 mg. The events were mild in intensity, resolved without any treatment and the investigator considered the events were unrelated to the treatment. No adverse events were reported in the treatment of Arimidex® tablet 1 mg.

There were no deaths or serious adverse events.

For the two dosing conditions, no clinically significant findings or changes in clinical laboratory tests, 12-lead ECG, blood pressure, pulse rate and body temperature were observed in both treatments of Anastrozole ODF 1 mg and Arimidex® tablet 1 mg.