Drug Substance(s)	ZD9238 (Fulvestrant)	**SYNOPSIS**	(For national authority use only)
Study Code	D6997C00007		
Date	19 November 2007		

A Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics of Single, Ascending Intramuscular Doses of a High Strength Formulation (HS) of Fulvestrant in Healthy Postmenopausal Female Subjects

Study centre(s)

The study was conducted at a single centre in Germany.

Study dates		**Phase of development**
First subject enrolled	10 July 2006	Clinical pharmacology (I)
Last subject completed	3 July 2007	

Objectives

The primary objective of the study was to assess the safety and tolerability of fulvestrant 150mg, fulvestrant 300 mg, fulvestrant 600 mg and fulvestrant 750 mg treatment given as a high strength formulation (HSF) at a concentration of 150 mg/mL.

The primary objective was assessed using variables: adverse events (AEs), vital signs, electrocardiogram (ECG) parameters, clinical chemistry and haematology.

The secondary objective of the study was to assess the pharmacokinetics (PK) of fulvestrant in subjects treated with fulvestrant 150mg, fulvestrant 300 mg, fulvestrant 600 mg and fulvestrant 750 mg treatment given as a HSF.

This secondary objective was assessed using variables: area under the plasma concentration time curve from zero to infinity (AUC), area under the plasma concentration time curve from zero to the last measurable timepoint ($AUC_{(0-t)}$), maximum plasma drug concentration after single dose administration (C_{max}), time to reach C_{max} (t_{max}), terminal half-life ($t_{½}$) and total apparent body clearance of the study drug from plasma (CL/F).

Study design

This study was designed as a randomised, double-blind, placebo-controlled, single ascending dose design with 4 cohorts of 10 healthy postmenopausal female subjects with each cohort dosed consecutively based on the emerging safety, tolerability and observed PK profiles. Dose escalation was to be carried out in the next cohort following delineation of acceptable safety and tolerability at the previous dose level.

Target subject population and sample size

Forty healthy postmenopausal female subjects.

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

At each dose level, 10 eligible subjects were to be randomised at a ratio of 4 fulvestrant to 1 placebo within the following treatment groups:

- COHORT A - Fulvestrant HSF 150 mg (1 mL) or matching placebo
- COHORT B - Fulvestrant HSF 300 mg (2 mL) or matching placebo
- COHORT C - Fulvestrant HSF 600 mg (4 mL) or matching placebo
- COHORT D - Fulvestrant HSF 750 mg (5 mL) or matching placebo

Fulvestrant HSF (ADM number 41304B06) was provided as 750 mg in 5 mL, in a vial. The matched placebo vials also contained 5 mL into which the appropriate amount of matched placebo fluid (ADM number 41505J06) for each cohort was injected ie, 1 mL placebo for Cohort A, 2 mL for Cohort B, etc. All subjects in each cohort received a single injection in the buttock on Day 1, of either fulvestrant HSF or placebo.

Duration of treatment

Single dose.

Variables

- **Pharmacokinetic**

  AUC, $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, $t_{½}$ and CL/F.

- **Safety**

  Assessment of AEs and their severity, vital signs, ECG parameters, clinical chemistry (including liver function tests and serum lipid profile), haematology and urinalysis.

Statistical methods

The number of subjects was based on the desire to gain adequate information of the safety, tolerability and PK to support further work, whilst exposing as few subjects as possible to study medication and procedures.

The safety population comprised all subjects who received the dose of study drug. Subjects were analysed according to the treatment they actually received. This population was used for all listings and summaries of non-PK data.

The PK analysis set was a subset of the safety population but excluded data points affected by any major detected protocol deviation.

The derived PK endpoints were listed for individual subjects and summarised by treatment and dose. Plasma concentration were summarised by planned timepoint.

AUC, $AUC_{(0-t)}$, CL/F, C_{max} and $t_{½}$ were summarised using the geometric mean (gmean, calculated as exp [μ], where μ was the mean of the data on a log scale), coefficient of variation (CV, calculated as 100 x sqrt[exp(s^2)-1], where s was the standard deviation [SD] of the data on a log scale), arithmetic mean (calculated using untransformed data), median, SD (calculated using untransformed data), minimum, maximum and number of observations.

t_{max} was summarised using: median, minimum, maximum and number of observations.

The summary statistics gmean, CV, arithmetic mean and SD were only produced when n>3. Otherwise these summary statistics were displayed as non-calculable.

Plasma concentration data were summarised by planned timepoint using: gmean, CV, gmean ± SD, arithmetic mean (untransformed data), SD (untransformed data), minimum, maximum and number of observations.

Subject population

Incorrect labelling of the study drug supplies for Cohort A resulted in 8 subjects receiving placebo and only 2 subjects receiving fulvestrant HSF. This was discussed by the Safety Monitoring Committee who concluded that there was not enough data from Cohort A alone to make a decision to proceed to the next dose. As a result the 150 mg dose was repeated in Cohort B with 8 subjects receiving fulvestrant HSF and 2 subjects receiving placebo. Subjects in Cohort C were to receive a fulvestrant HSF dose of 300 mg.

Following dosing of subjects in Cohort C, the Safety Monitoring Committee concluded that from the viewpoint of safety the study could proceed to the next dose level. However, because of the low bioavailability of this fulvestrant HSF I formulation and information from preclinical and formulation work suggesting that bioavailability might be improved with a second HSF formulation (HSF II), the Safety Monitoring Committee, the trial sponsor and the principle investigator agreed that this second formulation should be investigated. The HSF II formulation had the same composition as the HSF I formulation except that it contained

100 mg/mL fulvestrant. The addition of the new formulation resulted in a protocol amendment that modified both the primary and secondary objectives of the study. The amended objectives were as follows:

- The primary objective of the study was to assess the safety and tolerability of single ascending doses of fulvestrant high strength formulation I (HSF I; 150 mg and 300 mg) and fulvestrant high strength formulation II (HSF II; 300 mg and 500 mg) treatment.

- The secondary objective of the study was to assess the PK of fulvestrant of single ascending doses of fulvestrant HSF I and fulvestrant HSF II treatment.

These changes resulted in the addition of an extra cohort of subjects to the study. At each dose level, 10 eligible subjects were to be randomised in the ratio of 4 fulvestrant to 1 placebo within the following treatment groups.

- COHORT A – Fulvestrant HSF I 150 mg (1 mL) or matching placebo[a]

- COHORT B – Fulvestrant HSF I 150 mg (1 mL) or matching placebo

- COHORT C – Fulvestrant HSF I 300 mg (2 mL) or matching placebo

- COHORT S1 – Fulvestrant HSF II 300 mg (3 mL) or matching placebo

- COHORT S2 – Fulvestrant HSF II 500 mg (5 mL) or matching placebo

[a] As described above, subjects in Cohort A were incorrectly dosed in a ratio of 1 fulvestrant to 4 placebo.

The results from the subjects included in Cohort A are not presented within the text of this report; listings of results for these subject can be found in Appendix 12.2.11. These subjects were all considered to be protocol violators.

After a review of the PK results from subjects in Cohort S1, it was decided by the Safety Monitoring Committee, in accordance with the protocol, not to proceed with dosing of the S2 Cohort. Therefore the main body of this report presents the results for the 30 patients that were randomised and received treatment in Cohorts B, C and S1. None of these subjects had protocol violations or discontinued from the study and all of these subjects were included in the safety and PK analysis sets. The demographic and key baseline characteristics, and the disposition of study subjects for these 30 patients are summarised in Table S1. All subjects were female and Caucasian, and the mean age of subjects in the safety analysis set who received active treatment was 61.4 years.

Table S1 Demographic and baseline characteristics of the safety set

Demographic or baseline characteristic		Treatment group				
		Cohort B (HSF I 150 mg) (N=8)	Cohort C (HSF I 300 mg) (N=8)	Cohort S1 (HSF II 300 mg) (N=8)	Pooled Placebo (N=6)	Total Active Treatment (N=24)
Demographic characteristics						
Sex, n (%)	Female	8 (100)	8 (100)	8 (100)	6 (100)	24 (100)
Age (years)	Mean (SD)	62.0 (5.40)	62.0 (6.74)	60.1 (5.49)	59.2 (6.91)	61.4 (5.72)
	Range	51 to 69	51 to 69	55 to 67	46 to 66	51 to 69
Race, n (%)	Caucasian	8 (100)	8 (100)	8 (100)	6 (100)	24 (100)
Baseline characteristics						
Height (cm)	Mean (SD)	164.6 (5.2)	162.0 (5.5)	161.5 (4.1)	161.8 (5.5)	162.7 (4.9)
	Range	156 to 171	154 to 171	156 to 168	156 to 170	154 to 171
Weight (kg)	Mean (SD)	69.3 (11.2)	68.6 (6.5)	69.6 (10.1)	69.7 (4.6)	69.2 (9.0)
	Range	51 to 85	55 to 74	56 to 86	64 to 76	51 to 86
BMI (kg/m^2)	Mean (SD)	25.56 (4.17)	26.21 (2.81)	26.69 (3.53)	26.58 (0.66)	26.15 (3.42)
	Range	20.4 to 32.1	20.4 to 29.3	20.6 to 30.9	25.8 to 27.5	20.4 to 32.1

BMI – Body Mass Index; HSF: High Strength Formulation; SD Standard Deviation.

Summary of pharmacokinetic results

Following single intramuscular doses of fulvestrant in high strength formulations (HSF I at 150 mg and 300 mg doses and HSF II at a 300 mg dose), quantifiable plasma concentrations of drug were measured in all subjects. The median t_{max} for both the 150 mg and 300 mg doses of HSF I was 3.5 hours and for the 300 mg dose of HSF II was 2.5 hours, with an individual range of 1 hour to 9 hours across treatments. The plasma concentration – time profiles were a similar shape for all three treatments and all indicated multiple peaking with a period of more rapid release followed by a period of slower release.

The 2-fold increase in the doses of HSF I given resulted in a 2.1-fold and 2.2-fold increase in gmean AUC and C_{max} respectively. For both 300 mg doses of HSF I and HSF II the systemic exposure to fulvestrant was very similar.

Similar gmean apparent plasma clearance values of 65.2, 62.9 and 60.8 L/h and gmean elimination half-life values of 28.0, 27.7 and 28.4 days were seen for 150 mg and 300 mg HSF I and 300 mg HSF II, respectively.

Summary of safety results

Both HSF I and HSF II of fulvestrant were well tolerated. Of the subjects that reported at least 1 AE, the majority (27/28; 96.4%) had at least 1 AE that was considered by the investigator to be related to treatment. The majority of these events were related to the injection of study treatment.

The most commonly reported AE was injection site reaction, which was reported by 2 subjects (25.0%) in Cohort B, 6 subjects (75.0%) in Cohort C, 7 subjects (87.5%) in Cohort S1 and 5 subjects (83.3%) who received placebo.

There were no deaths, serious adverse events (SAEs), AEs leading to treatment discontinuation or CTC AEs of Grade 3 or 4.

No clinically important changes were observed in any of the clinical laboratory safety parameters (haematology, clinical chemistry or urinalysis), vital signs, ECGs (specifically QTc data) or physical findings.