Clinical Study Report Synopsis

Drug Substance	Vandetanib
Study Code	D4200L00009
Edition Number	N 1
Date	25 July 2014
EudraCT Number	2008-000579-12

A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, MULTICENTRE, PHASE II STUDY TO EVALUATE THE SAFETY AND PHARMACOLOGICAL ACTIVITY OF THE COMBINATION VANDETANIB (100 OR 300 MG/DAILY OR PLACEBO) WITH FULVESTRANT (LOADING DOSE), IN POSTMENOPAUSAL ADVANCED BREAST CANCER PATIENTS

First subject enrolled	First subject enrolled: 22 December 2008
Last subject completed	Last subject last visit: 28 september 2013

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the event-free survival (EFS), defined as the time from randomisation to progression, death without progression, loss to follow up, whichever occurred first.	Event-free survival (EFS)
Secondary	Efficacy	To evaluate success rate at 6 months	Success rate (patients without progression and still on treatment at 24 weeks
Secondary	Efficacy	To evaluate objective tumor response rates (complete response, CR and partial response, PR) according to RECIST criteria.	Objective tumour assessments (RECIST criteria)
Secondary	Efficacy	To evaluate time to progression	Time to progression
Secondary	Efficacy	To evaluate progression-free survival (PFS)	Progression-free survival (PFS)
Secondary	Safety	To evaluate the tolerability and safety of vandetanib/placebo in combination with fulvestrand	Adverse events (AEs), clinically significant laboratory or vital signs abnormalities, and electrocardiogram (ECG) changes

Study design

This was a phase II, parallel group, randomised, double-blind, double-dummy, comparator, multi-centre clinical study design to assess in terms of clinical activity two doses of vandetanib (100 mg/daily and 300 mg/daily) in combination with fulvestrant Loading Dose (LD) (500 mg intramuscular, im, at day 1 and 250 mg at day 14, 28 and thereafter every 28th day ± 3) .

Eligible patients were randomised in a 1:1:1 to receive either:

- **Arm A:** vandetanib at the dose of 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im at day 1 and 250 mg at day 14, 28 and thereafter every 28th day ± 3) .
- **Arm B**: vandetanib at the dose of 300 mg orally once-daily plus placebo to match vandetanib 100 mg orally once-daily plus fulvestrant LD (500 mg im at day 1 and 250 mg at day 14, 28 and thereafter every 28th day ± 3).
- **Arm C**: placebo to match vandetanib 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im at day 1 and 250 mg at day 14, 28 and thereafter every 28th day ± 3).

Target subject population and sample size

The study population included postmenopausal women with estrogen receptor (ER) + and/or progesterone receptor (PR) + advanced breast cancer. Patients had to have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) < 2 and a life expectancy of at least 12 weeks.

Assuming a median EFS in the control arm equal to 6 months and a median EFS in the experimental arm equal to 9 months (corresponding to a relative increase of 50% and an Hazard ratio of 0.67) 69 events were needed for each comparison. With a possible accrual rate of 6 patients/month (4 for each comparison), 135 patients (90 for each comparison) could have been enrolled in about 22 months and primary analysis could be planned after 29 months. Calculation of sample size was based on the assumptions of uniform accrual over time, no loss to follow-up, and exponentially distributed death times.

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

Vandetanib (100 mg or 300 mg in tablet form) or matching placebo were dosed orally, once daily, preferably at the same time each morning.

In addition to vandetanib or matching placebo, patients received fulvestrant 500 mg (2 x 5 mL) im injections as a Loading Dose (LD) on Day 1, followed by 250 mg (1 x 5 mL) on Day 14, Day 28 and every 28 ± 3 days thereafter.

Batch numbers are not available.

Duration of treatment

Fulvestrant was administered until proven progression or undue toxicity and vandetanib/placebo was administered once daily. The combination treatment started from Day 1. Patients received fulvestrant and vandetanib/placebo until progression unless any of the criteria for treatment discontinuation were met.
Following discontinuation of study treatment (vandetanib/placebo and or fulvestrant), patients were to be followed up for survival, unless they withdrew consent.

Statistical methods

Due to the premature interruption of the study with 39 enrolled patients, out of the 135 scheduled by protocol, no statistical analysis of data was performed. Only listings of serious adverse events (SAEs) were produced.

Subject population and study closure

The study was prematurely interrupted after the enrolment of the first 39 patients, out of the 135 patients scheduled by protocol. The decision on premature interruption of the study was taken according with the opinion of the Principal Investigator of the study, Dr. Francesco Perrone (Istituto dei Tumori Fondazione Pascale di Napoli, Naples, Italy). The Ethic Committees were notified on the study interruption.

The decision on study interruption was taken after the evaluation of the data of the studies ZD6474 (vandetanib, Zactima, Zictifa), which showed a poor activity as monotherapy or

combined with chemotherapy in the treatment of breast cancer in phase II studies, and as second or third line in the treatment of advanced NSCLC (monotherapy or combined with chemotherapy) in 4 registrative phase III studies, which did not support the registration of the drug in NSCLC.

Furthermore, the posology of one of the drugs under study, i.e. fulvestrand, has been changed in common clinical practice. This drug was approved by EMA in March 2010 at a dose of 500 mg, and therefore the previously approved dose of 250 mg, which is the dose scheduled by the study protocol, is no more actual. The above reasons have determined a slowing of the recruitment process that, at the actual rate, would not have allowed that the scheduled target of 135 patients would have been reached in a reasonable time. Then, the decision to close the study to potential newly recruited patients has been taken.

The treatment and the follow-up of patients enrolled in the study were continued, and the collection of data scheduled in the protocol was continued as well.

After the closure of the study, AstraZeneca (as scheduled by protocol) has continued to provide ZD6474 to patients that, according to the Investigator's judgment, benefited from the therapy, up to disease progression, consent withdrawal or unacceptable toxicity, and, for safety reasons, AstraZeneca requested the Investigators to provide information on possible adverse events. Finally, AstraZeneca has confirmed its commitment in making public the results of the study, despite its premature interruption with a sample of patients lower than that scheduled.

Summary of safety results

Serious adverse events:

A total of 8 serious adverse events were reported in 5 patients overall. Two patients had two SAEs.

The following SAEs were reported:

- Patient No. 020: grade 2 anaemia:
- Patient No. 001: diabetes complication;
- Patient No. 023: grade 3 erythema and grade 3 diarrhoea;
- Patient No. 061: grade 3 erythema;
- Patient No. 036: right iliac fracture:
- Patient No. 070: severe arthralgia and gastroenteritis.

Four SAEs in 3 patients (grade 2 anaemia in patient No. 20, grade 3 erythema and grade 3 diarrhoea in patient No. 023, and grade 3 erythema in patient No. 061) were considered as

related with treatment with vandetanib 100/300/placebo. None of the SAEs was considered as related with treatment with fulvestrand. One patient (patient No. 001) died due to the SAE (diabetes complication), whilst all the other SAEs were resolved at follow-up.