Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00019
Edition Number	1
Date	

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase I Study to Assess the Biological Activity of AZD8931 in Patients with Early Breast Cancer Who Are Ineligible for Treatment with Trastuzumab as Defined by IHC Status

Study dates: First patient enrolled: 10 August 2012
Last patient last visit: 7 December 2012

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Publications

None at the time of writing this report.

Closure of AZD8931

The report of this study is in the synopsis format as AstraZeneca development of AZD8931 has been permanently stopped. Due to the premature termination of the study, the data collated in this study are not validated and partially complete.

Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables of the study.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To compare the effects of AZD8931 versus placebo in tumor tissue on cytoplasmic p-MAPK after ≥7 days of treatment	Cytoplasmic p-MAPK
Secondary	Efficacy	To compare the effects of AZD8931 versus placebo on p-EGFR, p-erbB2, p-erbB3, nuclear p-MAPK, p-AKT, and Ki67 after ≥7 days of treatment	p-EGFR, p-erbB2, p-erbB3, nuclear p-MAPK, p-AKT, and Ki67
	Safety	To assess safety and tolerability of AZD8931	AEs (nature, incidence, severity); Laboratory findings (clinical chemistry, hematology, urinalysis); Vital signs; Physical examination; Cardiac measurements (ECG assessments, MUGA scans/echocardiograms); Skin reactions; Ophthalmic assessments
	PK	To assess the plasma PK of AZD8931	Plasma and tumor concentration of AZD8931 Population PK parameters: CL/F and V_{ss}/F and individual listings of AUC_{ss} and C_{minss}

AE Adverse event; AUC_{ss} Area under the curve at steady state; CL/F Apparent clearance of the analyte; C_{minss} Minimum plasma concentration at steady state; ECG Electrocardiogram; Ki67 A nuclear protein that is associated with and may be necessary for cellular proliferation; MUGA Multiple uptake gated acquisition; p-AKT phosphorylated A serine/theronine protein kinase; p-EGFR phosphorylated Epidermal growth factor receptor; p-ER phosphor-Estrogen receptor; p-erbB2 Epithelial growth factor receptor type 2; p-erbB3 Epithelial growth factor receptor type 3; p-MAPK phosphorylated Mitogen activated protein kinase; PK Pharmacokinetics; SAE Serious adverse event; V_{ss}/F Apparent volume of distribution at steady state.

Study design

This was a Phase I, randomized, double-blind, placebo-controlled, multicenter study in women with histologically confirmed early breast cancer and who were not suitable for treatment with trastuzumab. Local clinical testing practice was to be followed to confirm this and was to include immunohistochemistry (IHC) analysis to determine human epidermal growth factor receptor-2 status and/or amplification status by fluorescent *in situ* hybridization/chromogenic *in situ* hybridization as per local practice.

Target subject population and sample size

The target population included female patients aged ≥18 years with histologically confirmed early breast cancer who were scheduled for surgery and who were ineligible for treatment with trastuzumab, as defined by IHC status and World Health Organization performance status 0-1.

Approximately 60 patients were planned to be enrolled in the study.

Investigational product: Dosage, mode of administration, and batch numbers

Plain, beige, film-coated, biconvex, round tablets of AZD8931 40 mg or matching placebo tablets were administered twice daily, orally.

The batch numbers for AZD8931 40 mg and the matching placebo 40 mg were P/5406/24 and P/5406/21, respectively.

Duration of treatment

Patients were to receive twice daily dosing of AZD8931 40 mg/placebo for ≥7 days between randomization and definitive surgery. The final dose of the investigational product (IP) was to be taken on the day of definitive surgery. If the surgery was delayed, patients were to continue on the IP for up to a maximum of 14 days.

Statistical methods

The primary outcome variable, percentage change in cytoplasmic phosphorylated mitogen activated protein kinase (p-MAPK) levels, was planned to be analyzed using an analysis of covariance (ANCOVA) model, with treatment as a factor and baseline p-MAPK level as a covariate. The percentage change from baseline value was to be included in the ANCOVA model as the response variable. The treatment effect was to be estimated on the difference in least square means for AZD8931 vs placebo, with corresponding 2-sided 80% and 95% confidence intervals and 2-sided p-values. The secondary biomarker variables (as mentioned below) were planned to be analyzed using the same approach as the primary outcome variable:

- phosphorylated epidermal growth factor receptor (p-EGFR)
- epithelial growth factor receptor type 2 (p-erbB2)

- epithelial growth factor receptor type 3 (p-erbB3)
- nuclear p-MAPK
- phosphorylated serine/theronine protein kinase (p-AKT)
- Ki67 (nuclear protein that is associated with and may be necessary for cellular proliferation) after ≥7 days of treatment.

These were planned statistical methods. However, due to early termination of the study, no formal analyses were carried out.

Subject population

The first and last patients were enrolled on 10 August 2012 and 29 October 2012, respectively, and the last patient's last study visit was on 7 December 2012. A total of 3 patients were enrolled at 2 centers: 2 patients from Korea and 1 patient from Germany.

Summary of efficacy, pharmacokinetic, and biomarker results

Due to the premature termination of the study and the small number of enrolled patients (n=3), a decision was made not to analyze the pharmacokinetic sample data and tumor biomarker data. No formal analysis was conducted; hence, there are no results to report.

Summary of safety results

Patient E6001001

This 53-year-old Asian patient with breast cancer entered the study and was randomized to the AZD8931 40 mg arm, receiving the first dose on 4 September 2012. No relevant medical history was reported; the patient's baseline tumor was a well-differentiated ductal carcinoma *in situ* with primary tumor stage T2N0M0. Concomitant medications included Ambroxol® (ambroxol) 15 mg 4 times daily, atropine sulfate 1 mg once daily (qd), Avelox® (moxifloxacin) 400 mg qd, Esmeron® (rocuronium br) 50 mg qd, neostigmine 1.5 mg qd, and Pentothal® (thiopental) 250 mg qd for operation; Keromin® (ketorolac) 15 mg and Macperan® (metoclopramide) 10 mg were used, as needed, for pain and nausea, respectively.

On 29 August 2012, prior to taking any IP, the patient was diagnosed with a non-specific intra-ventricular conduction delay with a QT interval of 452 ms and a PR interval of 148 ms. This was not considered an AE and no treatment was given for the event. As per the ECG performed at randomization, the QT interval was 412 ms and the PR interval was 150 ms. From 4 September 2012 to 12 September 2012, the patient received AZD8931 40 mg twice daily, orally, and on 13 September 2012, the patient received only 1 dose in the morning. On 13 September 2012, the patient underwent resection of the breast quadrant and the IP was discontinued as per the protocol defined criteria.

No adverse events (AEs) were reported for this patient. Vital signs were unremarkable, while laboratory data were unavailable to draw any conclusions.

Patient E6002001

This 61-year-old Asian patient with breast cancer entered the study and was randomized to the AZD8931 40 mg arm, receiving the first dose on 4 October 2012. The patient received AZD8931 40 mg twice daily, orally, till 10 October 2012 and a single dose in the morning of 11 October 2012. Her medical history included hypertension managed with Rozetinplus® (hydrochlorothiazide and losartan potassium). The patient was also a hepatitis B carrier, and this was managed with Baraclude® (entecavir) 0.5 mg and Welltamine® (vitamins and minerals). The patient's baseline invasive ductal tumor was moderately differentiated with distant metastases (M0).

The patient experienced epistaxis on Day 3 (6 October 2012), followed by acneiform rash on Day 5 and hematuria on Day 8. All these events were of CTCAE grade 1. No action was taken with the IP and no treatment was given for the events. Epistaxis was resolved on Day 7, while rash and hematuria were still ongoing at the time of the last available report. On Day 8 (11 October 2012), the patient underwent total mastectomy with right and axillary lymph node dissection. Vital signs were unremarkable, while laboratory data were unavailable to draw any conclusions.

Patient E2603001

This 62-year-old patient with breast cancer entered the study and was randomized to the placebo arm, receiving the first dose on 30 October 2012. The patient received placebo, twice daily, orally, till 7 November 2012. Her medical history included hypothyroidism managed with L-Thyroxin 50 mg, dizziness managed with Arlevert® (cinnarizine dimenhydrinate) 40 mg thrice daily, and hypertension managed with valsartan 80 mg qd. The patient's baseline invasive ductal tumor was a poorly-differentiated, stage T2N1M0.

No AEs were reported for this patient. The patient underwent tumor resection with sentinel node biopsy on 8 November 2012. Vital signs were unremarkable, while laboratory data were unavailable to draw any conclusions.