AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8931
Study Code	D0102C00004
Edition Number	1
Date	
EudraCT Number	2009-012934-63

A Phase II, Randomised, Double-blind, Placebo-controlled, Multi-centre Study to Assess the Efficacy and Safety of AZD8931 In Combination with Anastrozole, Compared to Anastrozole alone, in Post-menopausal Women With Hormone Receptor-positive, Endocrine Therapy-naïve, Locally-advanced or Metastatic Breast cancer (MINT)

Study dates: First subject enrolled: 4 June 2010
Date of early study termination due to futility: 14 November 2012
Data cut-off date: 31 August 2012
Last subject last visit: 31 January 2013

Phase of development: Therapeutic exploratory (II)

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.

Based on an interim analysis for this study (D0102C00004; MINT), and consequent recommendation by the Independent Data Monitoring Committee, AstraZeneca made the decision to stop the study, due to futility. This meant that this study was stopped and all patients withdrawn from treatment. No further data were required and, therefore, the data cut-off for the interim analysis was used to report the results for this study (31 August 2012). As a result, the bulk of the planned secondary and exploratory analyses were not performed.

This clinical study report has, therefore, been prepared in a synopsis format in accordance with the Food and Drug Administration Guidance for Industry 1999.

Publications

Johnston SRD, Basik M, Hegg R, Lausoontornsiri W, Grzeda L, Clemons M, et al. Phase II randomized study of the EGFR, HER2, HER3 signaling inhibitor AZD8931 in combination with anastrozole (A) in women with endocrine therapy (ET) naive advanced breast cancer (MINT) [abstract]. J Clin Oncol 31, 201 (Suppl; Abstr 531).

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives		Outcome Variables
Priority	**Description**	**Description**
Primary	To compare PFS in patients treated with AZD8931 given in combination with anastrozole versus anastrozole alone	PFS as evaluated by RECIST 1.1
Secondary	To investigate the safety and tolerability of AZD8931 given in combination with anastrozole	AEs, laboratory findings, physical examination, vital signs, cardiac monitoring (including 12-lead ECGs and echocardiography/MUGA)
Secondary	To compare the ORR and CBR in patients treated with AZD8931 given in combination with anastrozole, versus anastrozole alone	ORR and CBR as evaluated by RECIST 1.1
Secondary	To compare the OS in patients treated with AZD8931 in combination with anastrozole versus anastrozole alone	OS
Secondary	To investigate the population PK of AZD8931 and O-desmethyl AZD8931 in combination with anastrozole	AZD8931, O-desmethyl AZD8931 and anastrozole population PK parameters derived from plasma concentrations
Secondary	To compare the effect of AZD8931 in combination with anastrozole on HRQoL versus anastrozole alone	Time to deterioration of FACT-B TOI and FACT-ES total score as evaluated by FACT-B and FACT-ES

Objectives		Outcome Variables
Priority	**Description**	**Description**
Secondary	To explore the association between quantitative ER expression (using standardised central testing) and patient clinical outcomes by PFS	ER and PgR status analysed by immunohistochemistry
Exploratory	To collect and store plasma, serum and tumour samples for potential future exploratory research into factors that may influence development of AZD8931 and/or response to AZD8931 (where response is defined broadly to included efficacy, tolerability or safety)	Biomarkers in plasma, serum and tumour samples
Exploratory	To explore the relationship between AZD8931 plasma concentrations/exposure and efficacy/safety	Plasma concentration data, AEs
Exploratory	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD8931 treatment	To obtain optional blood samples for DNA extraction for future host pharmacogenetic biomarker research
Exploratory	To investigate the effect of AZD8931 in combination with anastrozole versus anastrozole alone on patients' utility scores by assessment of EQ-5D data	To investigate the effect of AZD8931 in combination with anastrozole versus anastrozole alone on patients' utility scores by assessment of EQ-5D data
Exploratory	To compare the percentage change in tumour size relative to baseline, in patients treated with AZD8931 in combination with anastrozole versus anastrozole alone	Percentage change in tumour size

AE Adverse event; CBR Clinical benefit rate; CSR Clinical study report; ECG Electrocardiograms; ER Oestrogen receptor; EQ-5D Euro-quality of life – 5 dimensional; FACT-B Functional assessment of cancer therapy-breast; FACT-ES Functional assessment of cancer therapy-endocrine symptoms; HRQoL Health related quality of life; MUGA Multiple uptake gated acquisition scan; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PGx Pharmacogenetic biomarker research; PK Pharmacokinetics; PgR Progesterone receptor; RECIST Response evaluation criteria in solid tumours; TOI Trial outcomes index.
Note: Due to early termination of the study for futility, data on vital signs, CBR, PK, HRQoL and ER expression/patient clinical outcomes by PFS are not reported. In addition, no data are reported for the exploratory objectives.

Study design

This was a Phase II, randomised, double-blind, placebo-controlled, multicentre study that compared the progression-free survival (PFS) obtained with AZD8931 in combination with anastrozole versus that obtained with anastrozole alone, in patients with hormone receptor-positive, locally advanced, unresectable or metastatic breast cancer. Two doses of AZD8931 were investigated to determine an optimal dose in terms of the efficacy and tolerability profile. Patients were recruited globally and randomised 1:1:1 to receive AZD8931 20 mg, 40 mg or matched placebo, twice daily, each in combination with anastrozole 1 mg, once daily.

Target subject population and sample size

Patients were post-menopausal women with hormone receptor-positive, locally-advanced, unresectable or metastatic breast cancer who were endocrine therapy naïve. Patients were not to be eligible for treatment with trastuzumab or lapatanib.

The sample size was based on the primary objective of PFS. A total of 345 patients were planned to be randomised into the study. This was based upon a hazard ratio (HR) of 0.6 (critical HR=0.73), 90% power, 2-sided, 5% significance level and an assumed median PFS of 9 months for the anastrozole alone arm.

In order to control the overall type I error at 5%, the significance level was split between the two different dose comparisons such that 3% was assigned to the higher dose comparison and 2.39% was assigned to the lower dose comparison, accounting for correlation.

In July 2012, pre-defined futility boundaries were agreed for the interim analysis, based upon a conditional power of less than 10% to demonstrate a statistically significant ($p<0.05$; 2-sided) benefit of AZD8931 at the final analysis; these were exceeded for both the AZD8931 40 mg and 20 mg doses.

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

AZD8931 was available in 2 strengths as plain, round, biconvex, beige or white film-coated tablets containing either 40 mg or 20 mg of AZD8931. The beige or white tablets corresponded to 2 formulation types during the transition to the later phase roller compaction formulation (beige tablets).

Table S2 Details of investigational products

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD8931 20 mg	20 mg plain, round, biconvex, white film-coated tablet, twice daily orally	AstraZeneca	F13785	10-001310AZ 10-002938AZ 11-000577AZ 11-003290AZ
AZD8931 40 mg	40 mg plain, round, biconvex, white film-coated tablet, twice daily orally	AstraZeneca	F13394	09-000196AZ 09-005850AZ
Matched placebo to AZD8931 20 mg	plain, round, biconvex, white film-coated tablet, twice daily orally	AstraZeneca	F13788	10-001478AZ 10-002039AZ
Matched placebo to AZD8931 40 mg	plain, round, biconvex, white film-coated tablet, twice daily orally	AstraZeneca	F13437	08-001926AZ
AZD8931 20 mg	20 mg plain, round, biconvex, beige film-coated tablet, twice daily orally	AstraZeneca	F13840	10-005226AZ 11-001837AZ 11-003300AZ 12-000963AZ 12-002368AZ
AZD8931 40 mg	40 mg plain, round, biconvex, beige film-coated tablet, twice daily orally	AstraZeneca	F13831	10-005229AZ 11-000378AZ 11-001854AZ 11-003302AZ 12-000916AZ 12-002369AZ
Matched placebo to AZD8931 20 mg	plain, round, biconvex, beige film-coated tablet, twice daily orally	AstraZeneca	F13842	10-005282AZ 11-001050AZ 12-002265AZ
Matched placebo to AZD8931 40 mg	plain, round, biconvex, beige film-coated tablet, twice daily orally	AstraZeneca	F13844	10-005589AZ 11-001053AZ 12-001019AZ 12-001020AZ

Anastrozole (1 mg) was taken once daily orally and was supplied centrally.

Duration of treatment

AZD8931 40 mg, 20 mg or matched placebo were taken twice daily orally and anastrozole was taken once daily orally. The morning dose of anastrozole and either AZD8931 or

matched placebo were to be taken about the same time, and the second dose of AZD8931 or matched placebo was to be taken alone, approximately 12 hours later.

It was planned that each patient would continue to take study treatment until documented disease progression, until they wished to withdraw or until the investigator/delegate determined that discontinuation was in the patient's best interest. However, the study was terminated early due to futility, which led to all patients being withdrawn from study treatment.

Statistical methods

The primary statistical analysis was performed based on the intention-to-treat population, which included all randomised patients.

The following statistical comparisons were made:

- AZD8931 40 mg twice daily plus anastrozole 1 mg once daily versus AZD8931 matched placebo plus anastrozole 1 mg once daily

- AZD8931 20 mg twice daily plus anastrozole 1 mg once daily versus AZD8931 matched placebo plus anastrozole 1 mg once daily

The PFS analysis was performed using a stratified log-rank test based on the stratification factor at randomisation (locally advanced/metastatic). The results were presented in terms of the HR, associated 2-sided confidence interval and p-value. A Kaplan-Meier plot of PFS was also presented. This analysis was planned to be performed when approximately 233 progression events had been observed. At the time of data cut-off, a total of 141 progression events had occurred (61% of the 233 PFS events planned); these data were considered to be of an appropriate maturity for the interim analysis.

Overall survival was planned to be analysed at the time of the PFS analysis. At the time of data cut-off, a summary of survival status was produced, to present the number of patients who had died, were still in survival follow-up, were lost to follow-up or withdrew consent. A Kaplan-Meier plot of overall survival was also presented.

Objective response rate was planned to be analysed by fitting a logistic regression model adjusted for treatment and the stratification factor. At the time of data cut-off, tumour response was assessed according to the RECIST 1.1 criteria and a summary of best objective response was presented.

Safety data were listed and summarised using the safety analysis set, which included all patients who received at least 1 dose of randomised AZD8931 or matched placebo. No formal statistical testing was performed on the safety data.

The remaining objectives were not analysed due to early study termination due to futility.

Subject population

In total, 482 patients were enrolled at 78 centres in 18 countries. Of these, 359 patients were randomised (120 patients to AZD8931 40 mg, 118 patients to AZD8931 20 mg and 121 patients to matched placebo, all in combination with anastrozole); all randomised patients received treatment with AZD8931 (40 mg or 20 mg) or matched placebo and anastrozole.

At the data cut-off (31 August 2012), 105 (44%) patients had discontinued AZD8931 (54 [45%] and 51 [43%] patients in the AZD8931 40 mg and AZD8931 20 mg groups, respectively), 47 (39%) patients had discontinued placebo and 147 (41%) patients had discontinued anastrozole (52 [43%], 48 [41%] and 47 (39%) patients in the AZD8931 40 mg, AZD8931 20 mg and placebo groups, respectively). Although the study was ongoing at the time of data cut-off, all patients were subsequently withdrawn by 31 January 2013, due to early study termination.

Data continued to be collected after the data cut-off date for the interim analysis, until the date of the last subject visit. These additional data were consistent with the conclusions presented in this synopsis-format clinical study report (data on file).

The treatment groups were balanced in terms of demographic and baseline characteristics.

Summary of efficacy results

The primary objective of this study compared PFS between patients given AZD8931 in combination with anastrozole and those given anastrozole alone. At the time of data cut-off, a total of 141 progression events had occurred (61% out of the 233 PFS events planned for the final analysis). Two progression events were excluded from the primary analysis of PFS (1 event in the AZD8931 40 mg plus anastrazole group and 1 event in the anastrazole alone group); in both cases, this was due to progression or death occurring more than 26 weeks after the last evaluable assessment.

The median PFS results were 13.8, 10.9 and 14.0 months in the AZD8931 40 mg plus anastrazole, AZD8931 20 mg plus anastrazole and anastrozole alone groups, respectively. There was no statistically significant improvement in PFS, either when comparing the AZD8931 40 mg plus anastrazole and anastrozole alone groups (HR=1.16; CI 0.77, 1.75; p=0.485) or when comparing the AZD8931 20 mg plus anastrazole and anastrozole alone groups (HR=1.37; CI 0.91, 2.06; p=0.135). Based on the interim analysis, the chances of showing a statistically significant improvement in PFS ($p<0.05$; HR=0.73), at the end of the study, were reported as 4.8% and 0.3% for the AZD8931 40 mg and AZD8931 20 mg groups, respectively;[1] this assumed the true effect of AZD8931 was a PFS HR of 0.6 for the remaining data.

[1] Lachin JM. A review of methods for futility stopping based on conditional power. Statist Med 2005;24:2747-64.

The secondary objectives compared objective response rate and overall survival between patients given AZD8931 in combination with anastrozole and those given anastrozole alone. For objective response rate, there was a small numerical increase in patients receiving AZD8931 in combination with anastrozole (36 patients [34.6%] and 29 patients [31.2%] for AZD8931 40 mg and 20 mg, plus anastrozole, respectively) compared with patients receiving anastrozole alone (30 patients [28.8%]). For overall survival, there was a numerical imbalance in the number of deaths reported between patients receiving AZD8931 in combination with anastrozole (16 [13.3%] and 20 [16.9%] patients for AZD8931 40 mg and 20 mg, plus anastrozole, respectively) compared with patients receiving anastrozole alone (12 [9.9%] patients).

Summary of pharmacokinetic results

Pharmacokinetic data will not be reported.

Summary of pharmacodynamic results

Pharmacodynamic data will not be reported.

Summary of pharmacokinetic/pharmacodynamic relationships

Pharmacokinetic/pharmacodynamic data will not be reported.

Summary of pharmacogenetic results

Pharmacogenetic data will not be reported.

Summary of safety results

The median exposure to study treatment was lower in patients receiving AZD8931 in combination with anastrozole (169.0 and 172.0 days for AZD8931 40 mg and 20 mg, plus anastrozole, respectively) compared with patients receiving anastrozole alone (207.0 days).

There was a higher incidence of adverse events (AEs) in patients receiving AZD8931 in combination with anastrozole (116 [97%] and 112 [95%] patients for AZD8931 40 mg and 20 mg, plus anastrozole, respectively, compared with 102 [84%] patients for anastrozole alone). There was also a higher incidence of severe AEs (common terminology criteria for adverse events [CTCAE] Grade 3 or higher; 44 [37%] and 22 [19%] patients compared with 18 [15%] patients, respectively); serious adverse events (SAEs) (17 [14%] and 14 [12%] patients compared with 11 [9%] patients, respectively) and AEs leading to discontinuation of AZD8931 or placebo (10 [8%] and 6 [5%] patients compared with 3 [2%] patients, respectively) in the AZD8931 plus anastrozole groups compared with the anastrozole alone group.

The most commonly reported AEs (≥10% patients) in the AZD8931 40 mg plus anastrozole group were diarrhoea (61 [51%] patients), rash (57 [48%] patients), dermatitis acneiform (33 [28%] patients), dry skin (30 [25%] patients), paronychia (22 [18%] patients), nausea (16 [13%] patients),urinary tract infection (14 [12%] patients), rash pustular (15 [13%] patients), vomiting (14 [12%] patients) and Palmar-Plantar erythrodysaesthesia

syndrome (13 [11%] patients). The most commonly reported AEs (≥10% patients) in the AZD8931 20 mg plus anastrozole group were diarrhoea (47 [40%] patients), rash (38 [32%] patients), dry skin (22 [19%] patients), dermatitis acneiform (19 [16%] patients), pruritus (15 [13%] patients), arthralgia (14 [12%] patients), back pain (14 [12%] patients), decreased appetite (14 [12%] patients), nausea (13 [11%] patients) and pain in extremity (13 [11%] patients). The most commonly reported AEs (≥10% patients) in the anastrozole alone group were arthralgia (23 [19%] patients), headache (18 [15%] patients), diarrhoea (15 [12%] patients), rash (15 [12%] patients), back pain (13 [11%] patients), and nausea (12 [10%] patients).

The most commonly reported AEs of Grade 3 or higher (>2 patients) in the AZD8931 40 mg plus anastrozole group were rash (9 [8%] patients), dermatitis acneiform (8 [7%] patients), anaemia (3 [3%] patients), hypertension (3 [3%] patients), increased gamma-glutamyltransferase (3 [3%] patients), mucosal inflammation (4 [3%] patients) and vomiting (3 [3%] patients). The most commonly reported AEs of Grade 3 or higher (>2 patients) in the AZD8931 20 mg plus anastrozole group were hypertension (4 [3%] patients) and diarrhoea (3 [3%] patients). The only AE of Grade 3 or higher reported in more than 2 patients in the anastrozole alone group was hyperglycaemia (3 [2%] patients).

The most commonly reported SAEs (>1 patient) in the AZD8931 40 mg plus anastrozole group were dermatitis acneiform (2 [2%] patients) and rash (2 [2%] patients). The only SAE reported by more than 1 patient in the AZD8931 20 mg plus anastrozole group was pneumonia (2 [2%] patients). The only SAE reported by more than 1 patient in the anastrozole alone group was diarrhoea (2 [2%] patients).

There was a higher incidence of AEs leading to discontinuation of anastrozole in both the AZD8931 groups (7 [6%] and 5 [4%] patients for AZD8931 40 mg and 20 mg, plus anastrozole, respectively) compared with the anastrozole alone treatment group (3 [2%] patients). The treatment duration with anastrozole was shorter for patients in the AZD8931 plus anastrozole groups (179.0 and 177.5 days for AZD8931 40 mg and 20 mg, plus anastrozole, respectively) compared with the anastrozole alone group (215.0 days).

At the time of data cut-off, 48 patients had died (16 [13.3%] and 20 [16.9%] patients in the AZD8931 40 mg and 20 mg plus anastrozole groups, respectively, compared with 12 [9.9%] patients in the anastrozole alone group). Of these, most deaths (39 patients) were reported to be due to disease progression/worsening (13 [11%] and 16 [14%] patients compared with 10 [8%] patients, respectively); the remaining deaths (9 patients) were attributed to AEs (3 [3%] and 4 [3%] patients compared with 2 [2%] patients, respectively). Of these 9 deaths, 1 AE with an outcome of death in the AZD8931 40 mg plus anastrozole group was considered by the investigator to be related to AZD8931 (gastric haemorrhage); the remaining AEs with an outcome of death were all considered unrelated to study treatment (coma, ischaemic stroke, pneumonia [AZD8931 40 mg plus anastrozole group]; acute renal failure, acute respiratory distress syndrome, aspiration pneumonia, hypercalcaemia, pneumonia, sepsis [AZD8931 20 mg plus anastrozole group] and cardiac failure, death [anastrozole alone group]).

Epidermal growth factor receptor (EGFR)-mechanism based toxicities, such as rash and diarrhoea, were reported in both AZD8931 groups and were more frequent for the 40 mg dose compared with the 20 mg dose. For rash, the AEs were of higher severity for the 40 mg dose compared with the 20 mg dose (9 [8%] versus 0 patients had AEs of Grade 3 or higher, respectively). An AE of rash was reported for 57 (48%) and 38 (32%) patients in the AZD8931 40 mg and 20 mg plus anastrozole groups, respectively, compared with 15 (12%) patients in the anastrozole alone group; an AE of diarrhoea was reported for 61 (51%) and 47 (40%) patients compared with 15 (12%) patients, respectively.

There were few shifts to Grade 3 or higher in clinical laboratory values and few clinically significant changes for electrocardiogram data were observed.