AstraZeneca

Clinical Study Report Addendum (Final Analysis) Synopsis

Drug Substance	ZD4054
Study Code	D4320C00006
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A Phase II, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, Multi-Centre Study to Assess the Efficacy and Safety of Once-Daily Orally Administered ZD4054 15 mg and 10 mg Doses in Pain-Free or Mildly Symptomatic Patients with Prostate Cancer and Bone Metastases, who have Rising Serum Prostate Specific Antigen (PSA) Levels Despite Medical or Surgical Castration (Data Cut-Off 18 December 2008)

Study dates:	First patient enrolled: 14 July 2004 Last patient enrolled: 10 January 2006
Phase of development:	Therapeutic exploratory (II)

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

Summary of relevant information

This is the final addendum to the Clinical Study Report (CSR) synopsis for study D4320C00006, and presents the results of the *final analysis* (data cut-off 18 December 2008).

The *initial* (formal) statistical analysis was performed when 165 progression events had been observed – the results of this analysis (data cut-off 10 April 2006) are reported in the CSR dated 8 February 2008. The analysis of the time to death data was performed at the same time as the analysis of the time to progression data.

As a result of the survival benefit observed at the *initial* analysis, the protocol was amended to collect more mature survival data (see Protocol Amendment 2, dated 8 November 2006). An additional *update* analysis was therefore planned upon reaching a minimum of 110 patient death events – the results of the *update* analysis (data cut-off 28 February 2007) are reported in the CSR addendum dated 18 February 2008.

A further subsequent *final* analysis (Overall Survival, Progression Free Survival (PFS), Safety and Tolerability) was planned when a minimum of 200 patient deaths had occurred - the results of the *final analysis* (data cut-off 18 December 2008) are reported herein.

Study centre(s)

This study was conducted in 60 study centres in the United Kingdom, USA, Netherlands, Belgium, France, Sweden, Poland, Denmark, Norway, Finland, Canada, Australia, Switzerland and Indonesia (as per Protocol Amendment 1, dated 21 March 2005).

Publications

James ND, Caty A, Borre M, Zonnenberg BA, Beuzeboc P, Morris T, et al. Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: A double-blind, placebo-controlled, randomised, phase 2 trial. Eur Urol 2009;55:1112-1123.

Objectives and variables

The main objective of this *final analysis* (data cut-off 18 December 2008) was to explore the overall survival benefit of ZD4054 observed in the *initial* (data cut-off 10 April 2006) and *update* (data cut-off 28 February 2007) *analyses* of the data. In addition, to investigate the effect of ZD4054 on PFS, now that the data has further matured, and to monitor patient safety and tolerability. All other endpoints were considered to be reasonably mature, and therefore unlikely to change from the results obtained at the *initial* and *update* analyses.

No formal statistical analysis was performed on the following variables at this *final* analysis: change in PSA over time, and objective tumour response rate (RECIST). Pharmacokinetic parameters and sub-protocol variables are not reported at this *final* analysis as there were no new data to report. Please refer to the CSR and CSR addendum for presentation of the results for these variables, as reported at the *initial* and update analyses, respectively.

Table S1 summarises the scope of the *final* analysis with regards to the objectives and variables reported in this *final* CSR addendum.

Table S1 *Final* analysis: Objectives and variables

Primary objectives:	**Primary outcome variables:**
To assess the effect of ZD4054 on time to progression in metastatic hormone refractory prostate cancer, which will recommend a dose of ZD4054 for use in future studies.	Time to progression, progression defined as any one of the following: - Clinical progression, defined as intervention with chemotherapy, radiotherapy or surgery (excluding TUR with negative histology), or a new dose of a hormone based therapy. - Requirement for any opiate analgesia listed in Appendix E of the study protocol (CSP), for the management of disease-related symptoms. - Objective progression of malignant soft tissue disease assessed according to the response evaluation criteria in solid tumours (RECIST) criteria. - Death from any cause prior to progression.
Secondary objectives:	**Secondary outcome variables:**
Effect of ZD4054 on the time to death.	Time to death from any cause.
[a]Effect of ZD4054 on PSA	Change in PSA over time
Tolerability and safety profile of ZD4054 at the studied doses.	Safety and tolerability: incidence and severity of AEs, vital signs, laboratory and ECG findings.
[a]Effect of ZD4054 on objective response rate.	Objective response rate in patients with measurable malignant soft tissue disease at baseline, assessed according to the RECIST criteria.
Rate of development of new bone lesions.	Change in the number of bone metastases.
Tertiary (exploratory) objectives:	**Tertiary (exploratory) outcome variables:**
Effect of ZD4054 dose on serum biomarkers of bone metastasis.	Change in serum biomarkers of metastatic bone disease (bone ALP, PINP, CTX-1 and CTX-MMP) from baseline to 4 and 12 weeks on study treatment.
Effect of ZD4054 on PSA response.	The effect of ZD4054 on PSA response: - Incidence of PSA response, defined as ≥50% decrease in serum PSA from randomisation, documented on at least 2 separate occasions, at least 4 weeks apart. - The time to a doubling of PSA. - PSA concentration (total and ratio of free:total) at 4 and 12 weeks. - Change and percentage change from baseline in PSA (total and ratio of free:total) calculated for each time point.
Effect of ZD4054 on time to PSA progression.	Time to PSA progression, defined as the time to the first of 2 serum PSA values showing a ≥50% increase in the serum PSA from randomisation, documented on at least 2 separate occasions, at least 2 weeks apart. This should be a minimum increase, in absolute terms, of 5 ng/mL.
QoL tools that are planned to be used in Phase III development of ZD4054.	Patient-reported QoL, as recorded by the EORTC QLQ-C30 plus PR25 (see CSP Appendix I), and the FACT-P (see CSP Appendix J) questionnaires.
Effect of ZD4054 on pain reduction in symptomatic patients and delaying the onset of pain in asymptomatic patients, using the McGill pain scale.	Change in pain level over time, assessed using the McGill pain scale (see CSP Appendix K).
Effects of ZD4054 on ET-1.	Serum ET-1 (endothelin-1) measurements.

[a] No formal statistical analysis performed at the *final* analysis - only summaries and listings provided.

Pharmacokinetic and sub-protocol parameters – no new data to report at *final* analysis – please refer to CSR & CSR addendum for results of *initial* and *update* analyses, respectively.

Bone alkaline phosphatase (bone ALP), Procollagen type I N propeptide (PINP), C-terminal crosslinking telopeptide of type I collagen (CTX-1), C-terminal crosslinking telopeptide of type I collagen generated by matrix metalloproteinases (CTX-MMP); Quality of life (QoL); European Organisation for Research and Treatment of Cancer (EORTC); Functional Assessment of Cancer Therapy for Prostate Cancer (FACT-P).

Study design

This was a randomised, double-blind, parallel-group, multi-centre, Phase II study comparing the efficacy and safety of once daily, orally administered ZD4054 (15 mg and 10 mg) with placebo, each combined with best supportive care, in patients with metastatic hormone resistant prostate cancer (HRPC).

Target patient population and sample size

Patients with prostate cancer who had bone metastases with no pain or mild symptoms of pain (ie, symptoms of pain controlled without the use of any of the opiates listed in Appendix E of the study protocol) and a rising serum PSA, despite a serum testosterone of ≤2.4 nmol/L (70 ng/dL) (as per Protocol Amendment 1, dated 21 March 2005). Approximately 260 patients were to be recruited in the main study.

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

Patients were to be randomised 1:1:1 to receive ZD4054 15 mg or ZD4054 10 mg or placebo, given orally once daily in tablet form (batch numbers 50910B07, 51051J07 and 43614B06, respectively).

Duration of treatment

Patients were to continue on randomised study treatment until disease progression was determined; another discontinuation criterion was met; or the Investigator no longer considered that the patient was deriving clinical benefit. Patients were to be followed up every 4 weeks for progression for the first 2 years after first dose of study treatment. After 2 years from first dose, patients were to be followed up on a 3-monthly basis until progression was determined. Patients who had withdrawn from study treatment before their 2-year anniversary were to be followed up every 4 weeks for progression. Once they reached their 2-year anniversary, they were to be followed up on a 3-monthly basis until disease progression or another discontinuation criterion was met. After progression, all patients were to be assessed for survival every 6 months until either death or the end of the study, defined as a minimum of 200 patient deaths (as amended by Protocol Amendment 2, dated 8 November 2006). Please refer to the main CSR for a detailed description of study design features.

Statistical methods

All definitions and analyses outlined in the original statistical analysis plan (SAP) dated 12 July 2006 are applicable to the data at the *final* analysis. In addition, any supplementary

definitions and changes from the planned analyses in the original SAP described in the *update* SAP (dated 5 April 2007) are also relevant to the *final* analysis. The *final* SAP outlines the endpoints analysed and/or summarised and listed at the *final* analysis, data cut-off 18 December 2008, highlighting any differences from the previous SAPs.

Demography and baseline data have been summarised by treatment group. Time to progression, time to death, time to a doubling of PSA, and time to PSA progression have been analysed using the Cox regression model. The objective response rate in patients who had measurable malignant soft tissue disease at baseline, as assessed by the RECIST criteria, has been summarised by treatment group. The number of metastatic bone lesions at discontinuation of study treatment (last available post-baseline scan prior to discontinuation) has been statistically analysed using robust MM-estimation (Maronna RA, Martin RD, Yohai VJ, Robust Statistics: Theory and Methods, Wiley, 2006). Tertiary (exploratory) endpoints have been presented and analysed to investigate trends in the data.

For the assessment of tolerability and safety, incidence and severity of adverse events (AEs) (based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 [NCI CTCAE] grading), laboratory values, vital signs and ECGs have been summarised by treatment group.

Subject population

In total, 447 patients were enrolled into this 60-centre study, of whom 312 patients were randomised and received study treatment (98, 107 and 107 patients in the ZD4054 15 mg, ZD4054 10 mg and placebo groups, respectively; Table S2). The first patient entered the study on 14 July 2004; the study is currently ongoing. At the time of the *final* analysis (data cut-off 18 December 2008), 3 patients were still receiving treatment; and 309 patients had discontinued study treatment (of whom 70 patients discontinued study treatment prematurely). At data cut-off, 43 patients were continuing in the study but off-treatment; and 266 patients had terminated the study prematurely, most commonly due to development of study-specific discontinuation criteria (ie, death). All 312 patients were analysed for safety and were included in the Full analysis set (ITT); 249 patients were included in the bone subprotocol set; 135 patients in the objective response set; and 286 patients in the quality of life set (Table S2). The patient population participating in this study comprised male patients with metastatic HRPC with no pain or mild symptoms of pain and rising PSA levels despite medical or surgical castration, and was therefore considered to be adequately representative of the target population for ZD4054. The majority of patients participating in this study were of Caucasian race (98%); mean age was 70 years (range 49 – 91 years) (Table S2). Overall the treatment groups were comparable with regards to demographic and key baseline characteristics.

Table S2 Patient population and disposition

	Number patients		
	ZD4054 15 mg n=98	**ZD4054 10 mg n=107**	**Placebo n=107**
Demographic characteristics			
Mean age (range) (years)	69 (54 – 84)	70 (53 – 85)	71 (49 – 91)
Sex: Males n (%)	98 (100)	107 (100)	107 (100)
Race: Caucasian	93 (94.9)	107 (100)	106 (99.1)
Disposition n (%)			
Patients randomised	98	107	107
Patients who received treatment	98 (100)	107 (100)	107 (100)
Patients receiving treatment at data cut-off	2 (2.0)	0 (0.0)	1 (0.9)
Discontinued IP n (%)	96 (98.0)	107 (100)	106 (99.1)
Discontinued IP not prematurely	67 (68.4)	84 (78.5)	88 (82.2)
Discontinued IP prematurely	29 (29.6)	23 (21.5)	18 (16.8)
--Adverse event	12 (12.2)	12 (11.2)	6 (5.6)
-- Other	11 (11.2)	3 (2.8)	4 (3.7)
-- Protocol non-compliance	0 (0.0)	2 (1.9)	4 (3.7)
-- Subject lost to follow-up	0 (0.0)	1 (0.9)	1 (0.9)
-- Subject withdrawal of consent to treatment	6 (6.1)	5 (4.7)	3 (2.8)
Continuing on study off treatment n (%)	16 (16.3)	13 (12.1)	14 (13.1)
Terminated study prematurely n (%)	80 (81.6)	94 (87.9)	92 (86.0)
-- Development of study-specific discontinuation criteria	62 (63.3)	74 (69.2)	75 (70.1)
-- Eligibility criteria not fulfilled	1 (1.0)	0 (0.0)	0 (0.0)
-- Subject lost to follow-up	1 (1.0)	2 (1.9)	1 (0.9)
-- Subject not willing to continue study	6 (6.1)	7 (6.5)	7 (6.5)
-- Other	10 (10.2)	11 (10.3)	9 (8.4)
Consent expired / Other	9 (9.2) / 1 (1.0)	10 (9.3) / 1 (0.9)	7 (6.5) / 2 (1.9)
Analysis sets			
Patients included in Safety sets	98	107	107
Patients included in Full analysis set	98	107	107
Patients included in bone sub-protocol set	77	86	86
Patients included in the objective response set	40	44	51
Patients included in the QoL set	90	97	99

IP Investigational product; Data cut-off 18 December 2008

Full analysis set = Intention to treat (ITT) population (efficacy population) – all randomised patients
Safety analysis set = all patients who received treatment
Bone sub-protocol set comprises patients who consented to the bone sub-protocol
Objective response set comprises patients with measurable malignant soft tissue at baseline
Quality of Life (QoL) – comprises patients who have valid baseline QoL data
The bone sub-protocol, objective response and QoL sets are subsets of the ITT population

Summary of efficacy results

There was no statistically significant treatment effect on Time to Progression (primary variable) for either dose of ZD4054 when compared with placebo (15 mg - HR 0.86, 80% CI: 0.72-1.04, p-value 0.309; 10 mg – HR 1.06, 80% CI: 0.89-1.27, p-value 0.673) at the 0.2 significance level set for this study. In total, 211/312 death events (68%) have occurred at the time of the *final* analysis; the median time to death was 23.9, 23.5 and 19.9 months for ZD4054 15 mg, ZD4054 10 mg and placebo, respectively. The reduction in the risk of death over a given period of time was 24% (HR 0.76, 80% CI: 0.61-0.94; p-value 0.103), and 17% (HR 0.83, 80% CI: 0.67-1.02; p-value 0.254), for ZD4054 15 mg and 10 mg, respectively, compared with placebo. Consistent with the results of the [1]*initial* and [2]*update* analyses, Hazard Ratios of less than one were observed for both doses, indicating improved survival with ZD4054 compared with placebo. Although the results no longer achieve statistical significance with ZD4054 10 mg at the *final* analysis, this should be considered in context with the longevity of the follow-up period (median duration ≈22 months) relative to only ≈4 months median duration of study treatment. There continues to be no clear dose response for ZD4054 15 mg and 10 mg. There was similar usage of post-progression anti-cancer therapies (taxanes and other therapies). There were no responders observed either on active or placebo treatment, based on RECIST response rates. There were no differences between treatment groups in the number of bone metastases over time. There were no differences between ZD4054 and placebo with regards to PSA response, time to PSA doubling, change from baseline PSA, or time to PSA progression.

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[1] Initial analysis (data cut-off 10 April 2006): 40 deaths (13, 9 and 18 events, respectively); and median time to death of 452, 496 and 432 days for ZD4054 15 mg, ZD4054 10 mg and placebo, respectively. Over a given period of time, the reduction in the risk of death was 39% (HR: 0.61, 80% CI: 0.38-0.99, p-value 0.190) and 62% (HR: 0.38, 80% CI: 0.22-0.64, p-value 0.019) for ZD4054 15 mg and 10 mg, respectively, compared with placebo.

[2] Update analysis (data cut-off 28 February 2007): 118 deaths (34, 33 and 51 events, respectively); and median time to death of 706, 735 and 518 days for ZD4054 15 mg, ZD4054 10 mg and placebo, respectively. Over a given period of time, the reduction in the risk of death was 35% (HR 0.65, 80% CI: 0.49-0.86; p-value 0.052) and 45% (HR 0.55, 80% CI: 0.41-0.73; p-value 0.008) for ZD4054 15 mg and 10 mg, respectively, compared with placebo.

Compliance with QoL questionnaire completion was good for both the FACT-P and the EORTC instruments. QoL scores were high at baseline and were maintained throughout the study. Scores were similar between active treatment and placebo, indicating that ZD4054 did not have a deleterious effect on health related QoL in this population. Pain did not appear to be an issue in this pre-progession population, possibly reflecting active management with non-opioid analgesics (requirement for opioid analgesia was a progression criterion, as described in the study protocol). QoL profiles were consistent between the FACT-P and the EORTC questionnaires, although the EORTC questionnaire exhibited more floor/ceiling effects. As a result, FACT-P appeared to be the more appropriate instrument for this patient population and is therefore being used in the Phase III programme.

Summary of safety results

Overall, both doses of ZD4054 were well tolerated in this patient population. The most commonly reported adverse events (AEs) were known pharmacological effects of this class of compound (ie, peripheral oedema, headache and nasal congestion), and occurred more frequently in the ZD4054 treatment groups than with placebo. Few AEs were classified as CTC grade 3 or higher; however anaemia, peripheral oedema, dyspnoea, headache, cardiac failure, nausea and pulmonary embolism of CTC grade 3 or higher occurred in at least 3 patients who received ZD4054 but in no patients who received placebo. In total, 211 deaths have occurred: 62 (63.3%), 74 (69.2%) and 75 (70.1%) patients in the ZD4054 15 mg, ZD4054 10 mg and placebo groups, respectively; the most common cause of death was prostate cancer (85% patients). Serious adverse events (SAEs) were infrequent - most commonly reported SAEs with ZD4054 treatment were anaemia (5) and cardiac failure (3), and haematuria and myocardial infarction with placebo (2 patients each). Prior or concurrent cardiac history may have led to an increased predisposition for the development of cardiac failure observed in ZD4054-treated patients. SAEs of anaemia all occurred in patients with extensive bony involvement or evidence of rapidly progressive disease. Relatively few patients discontinued study treatment due to adverse events - the most common AEs resulting in discontinuation from ZD4054 treatment were peripheral oedema (8) and dyspnoea (3). No clinically important changes were observed in any of the clinical laboratory safety parameters, vital signs or ECG, with no individual abnormalities that raise any safety concerns. Mean reductions in haemoglobin levels (~1.5 g/dL) from baseline for the ZD4054 treatment groups were unlikely to have any clinical implications, and were considered to be as a consequence of the vasodilatory effect of ZD4054. Small asymptomatic reductions in systolic and diastolic blood pressures from baseline were noted following ZD4054 treatment, but with no accompanying changes in pulse rate, and were also considered to be as a consequence of the vasodilatory effect of ZD4054. Overall, there were no new concerns about the safety of ZD4054 in this patient population.