AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0530
Study Code	D8180C00034
Edition Number	1
Date	3 December 2010

A Phase II, Randomised, Open-label, Pilot Study to Evaluate the Safety and the Effects on Bone Resorption of AZD0530 in Patients with Prostate Cancer or Breast Cancer with Metastatic Bone Disease

Drug substance:	AZD0530
Study code:	D8180C00034
Study dates:	First subject enrolled: 13 February 2008 Last subject last visit: 20 January 2010 (Subjects who did not enter the extension phase. Data from this phase, including follow-up data, will be reported separately in an addendum and are not reported in this CSR)
Phase of development:	Therapeutic exploratory (II)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

A total of 33 sites in the United States, Canada, and Europe enrolled patients.

Publications

Aklilu M. et al. Proc 10th Int Conf Cancer Ind Bone Dis, Sheffield, UK, 25-25 Sept2010.

Finkelman R.D. et al. Proc IX Int Meet Cancer Ind Bone Dis, Arlington, VA, USA, 28-31 Oct 2009.

Finkelman R.D. et al. J Bone Miner Res 22 (Supp1): S409 (#W189), 2007.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To estimate the effect of saracatinib plus standard of care (SoC) compared with zoledronic acid plus SoC on bone resorption by assessment of serum Beta C-terminal cross-linking telopeptide of Type I collagen (βCTX).	The absolute and percentage change from baseline in serum βCTX calculated at the end of the 4-week study treatment period.
Secondary	**Secondary**
1. To investigate the safety and tolerability of saracatinib in patients with either breast cancer or prostate cancer who have metastatic bone disease by assessment of adverse events (AE), physical examination, blood pressure (BP), pulse, electrocardiogram (ECG), and laboratory findings.	Safety and tolerability by assessment of AEs, physical examination, vital signs including BP, pulse, ECG, and laboratory findings including clinical chemistry, haematology, and urinalysis.
2. To estimate the effect of saracatinib plus SoC on bone turnover (bone resorption and bone formation) by assessment of serum markers bone-specific alkaline phosphatase (bALP), N-terminal propeptide of Type I procollagen (PINP), cross-linked C-terminal telopeptide of Type I collagen (ICTP), and tartrate-resistant acid phosphatase 5b (TRAP5b) and urine markers N-terminal cross-linking telopeptide of Type I collagen normalised to creatinine (NTX/Cr) and alpha-alpha C-terminal cross-linking telopeptide of Type I collagen normalised to creatinine (ααCTX/Cr).	The absolute and percentage change from baseline in serum bALP, PINP, ICTP, and TRAP5b and urine NTX/Cr and ααCTX/Cr calculated at the end of the 4 weeks study treatment period.
3. To investigate the steady state pharmacokinetic (PK) of saracatinib in this patient population by assessment of appropriate PK parameters.	For saracatinib: minimum plasma concentration at steady-state (Cssmin), maximum plasma concentration at steady-state (Cssmax), time to Cssmax (tmax), area under the curve at steady state (AUCss), and plasma clearance at steady state (CLss/F). For the N-desmethyl metabolite of saracatinib (M594347): Cssmin, Cssmax, tmax, AUCss, and AUCss metabolite to parent ratio.

Exploratory objectives are listed in the CSR. The analysis of some exploratory endpoints was no longer considered critical, therefore no results are presented in the CSR for PK-PD or PRO-PD relationships. Results for other exploratory objectives, where available, are presented in the CSR.

Study design

This was a Phase II, randomised, controlled, open-label, parallel-group, multi-centre study to estimate the effects on bone turnover and safety of saracatinib plus SoC, compared with zoledronic acid plus SoC.

Target subject population and sample size

Approximately 122 patients were planned for enrolment in the study. A total of 139 patients with prostate or breast cancer with bone metastases were randomised 1:1 to receive saracatinib 175 mg (69 patients) or zoledronic acid 4 mg (70 patients), plus SoC. Patients were bisphosphonate naïve, had at least 1 confirmed metastatic bone lesion, and had no change of cancer therapy for at least 8 weeks prior to randomisation.

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

Investigational product: Oral doses of saracatinib 175 mg. Individual batch numbers and further information are included in the CSR Appendix 12.1.6.

Comparator product: Zoledronic acid 4 mg was administered by a single intravenous infusion. Zoledronic acid was manufactured by Novartis AG and was obtained locally by the study sites.

Duration of treatment

The duration of the treatment period for each patient was approximately 4 weeks. Zoledronic acid was administered by a single iv infusion on Day 1. Saracatinib was taken once daily for 4 weeks. After 4 weeks, eligible saracatinib-treated patients had the opportunity to enter an extension phase and to continue to receive saracatinib treatment if there was evidence for a meaningful clinical benefit and there were no drug-related toxicities of CTCAE grade 3 or higher as assessed by the investigator.

Statistical methods

The primary analysis was the comparison of the percentage change from baseline in βCTX between saracatinib plus SoC and zoledronic acid plus SoC on bone resorption at the 4-week timepoint. The data were logarithmically transformed prior to the analyses. Change from baseline was expressed as baseline scaled ratio (BSR), the ratio of post-baseline value to baseline. An analysis of variance model (ANOVA) was used to analyse the log(BSR) using the week 4 data with fixed effects for treatment (saracatinib plus SoC or zoledronic acid plus SoC), and population stratum (hormone-refractory prostate cancer, hormone-sensitive prostate cancer, or breast cancer). The geometric least squares means from this model provided an estimate of BSR. This estimate was then converted to percentage change from baseline as 100(BSR-1). Similar analyses of secondary bone turnover and calcium homeostasis markers were performed. PK analyses were summarised and plotted.

Subject population

A total of 241 patients were enrolled and 139 randomised in this study. All patients were diagnosed with prostate or breast cancer with bone metastases and were recruited from 33 centres in the United States, Canada, and Europe.

The number of randomised patients was 69 in the saracatinib treatment arm and 70 in the zoledronic acid arm. The majority of randomised patients (98.6%) received study treatment and were therefore included in the safety analysis set. More patients who were treated with saracatinib (59.4% versus 73.9%) were excluded from the biomarker analysis sets compared with patients who received zoledronic acid (70.0% versus 94.3%).

Fourteen patients continued into the extension phase of the study; at the time of reporting, 2 patients remain in the extension phase and continue to receive treatment.

The treatment groups were generally well balanced with regard to demographic and baseline characteristics.

Summary of efficacy results

Reduction in βCTX (resorption marker) from baseline to Week 4 was statistically significant ($p<0.001$) in both the saracatinib treatment arm (-71.1%; 80% CI = -74.4, -67.5 and 95% CI = -75.9, -65.4) and zoledronic acid treatment arm (-68.4%; 80% CI = -71.5, -65.1 and 95% CI = -73.0, -63.2), indicating a decrease in bone resorption. However, no statistically significant difference between the treatment groups was achieved, suggesting similar efficacy in reducing βCTX.

Secondary bone marker analyses supported the primary variable and demonstrated statistically significant decreases from baseline to Week 4 in both treatment groups for resorption markers TRAP5b, NTX/Cr, and ααCTX/Cr and the formation marker PINP ($p<0.001$), indicating reductions in bone resorption and formation. A significant change from baseline to Week 4 was observed for ICTP (resorption marker) and bALP (formation marker) in the saracatinib group only ($p<0.001$). Statistically significant differences between the 2 treatment arms were observed in the change from baseline to Week 4 data for cross-linked C-terminal telopeptide of Type I collagen ICTP ($p<0.001$), urine NTX/Cr ($p=0.008$) and urine ααCTX/Cr ($p=0.002$).

Across the primary and secondary variables, saracatinib significantly reduced markers of bone turnover, affecting both resorption markers (serum βCTX, ICTP, TRAP5b, and urine NTX/Cr and ααCTX/Cr) and formation markers (serum bALP and PINP); the reduction in resorption markers was much greater than the reduction in formation markers.

Resorption markers have been associated with specific enzymes that mediate bone matrix resorption. βCTX, NTX, and ααCTX are largely associated with cathepsin K-mediated resorption. ICTP is largely associated with MMP-mediated resorption. The reduction of ICTP due to saracatinib treatment indicated that saracatinib reduced MMP-mediated resorption as well resorption associated with cathepsin K.

The timecourse of the changes in bone turnover due to saracatinib therapy was generally delayed relative to those observed with zoledronic acid. Generally, there was also a time lag between the reduction in resorption markers and the reduction in formation markers.

Summary of pharmacokinetic results

The steady state PK parameters for saracatinib and its N-desmethyl metabolite in this study were consistent with those observed previously in the clinical research program.

Summary of safety results

The safety summary tables in this section include events with onset on or after the first day of study drug administration up until 30 days after completion of study drug treatment for all patients except for the 14 patients in the saracatinib treatment arm who continued into the extension phase of the study. For the extension patients, only the events with onset between the first day of study administration and the date of Visit 6 are included. Events that occurred for these patients in the extension period and all other events not captured as above will be reported in an addendum. For patients randomised to the zoledronic acid treatment arm, the last day of treatment was considered the same as study Day 1, the day of dosing. The summary of exposure to saracatinib includes doses administered between Visits 2 and 6, inclusive, for all patients randomised to the saracatinib treatment arm. Doses of saracatinib administered in the extension phase will be captured in the addendum.

A total of 68 patients had a median exposure of 29 days to saracatinib treatment, with 69 patients receiving the zoledronic acid injection. The incidence of AEs reported was similar in patients treated with saracatinib (52 [76.5%]) compared with patients treated with zoledronic acid (54 [78.3%]), and more saracatinib patients (31 [45.6%]) than zoledronic acid patients (22 [31.9%]) had AEs considered by the investigator to be related to the investigational product.

More patients in the saracatinib arm than in the zoledronic acid arm reported AEs in the following system organ classes: Gastrointestinal Disorders (32 [47.1%] versus 20 [29.0%] patients, respectively), Investigations (9 [13.2%] versus 3 [4.3%] patients, respectively), and Respiratory, Thoracic and Mediastinal Disorders (15 [22.1%] versus 5 [7.2%]). In the saracatinib group, the most commonly reported AEs were nausea (16 [23.5%]), diarrhoea (13 [19.1%]), and constipation (10 [14.7%]). Influenza (11 [15.9%]), musculoskeletal pain (9 [13.0%]), and influenza-like illness (8 [11.6%]) were the most commonly reported AEs in the zoledronic acid group; the events of influenza and influenza-like illness appeared largely to represent post-infusion reactions.

AEs of Common Terminology Criteria grade 3 or above were reported in 12 (18%) saracatinib patients and 9 (13%) zoledronic acid patients.

More patients in the saracatinib group (11 [16.2%]) compared with the zoledronic acid group (4 [5.8%]) experienced a serious adverse event (SAE). Three of the reported SAEs led to interruption or discontinuation of the investigational product and were considered by the investigator to be related to saracatinib: pyrexia and pulmonary oedema in 1 patient and

vomiting in 1 patient. One death, due to ischaemic heart disease and hypertension, was reported in 1 patient receiving saracatinib and was not considered by the investigator to be related to the investigational product. Ten (14.7%) patients discontinued from the study due to AEs in the saracatinib group; there were no discontinuations due to AEs in the zoledronic acid treatment arm. Since zoledronic acid was administered only once, patients could not discontinue from study treatment due to subsequent AEs.

Laboratory changes as a result of saracatinib treatment were generally consistent with the known emerging safety profile of saracatinib. Saracatinib treatment resulted in a reduction in mean serum calcium and phosphate; the changes were similar to reductions seen in the zoledronic acid group. The clinical relevance of the observations is unknown.