AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | Saracatinib |
| Study Code | D8180C00023 |
| Edition Number | 1 |
| Date | 14 June 2010 |

# A Phase I, Open-label Study To Assess the Safety and Tolerability of Saracatinib (AZD0530) in Combination With Carboplatin and/or Paclitaxel Chemotherapy in Patients with Solid Tumours

**Study dates:** First subject enrolled: 15 March 2007
Last subject enrolled: 12 August 2009
Data cut-off: 14 January 2010

**Phase of development:** Clinical pharmacology (I)

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.

As Study D8180C00023 will not represent a key clinical pharmacology study in any future marketing application, it is being reported as a synopsis-format clinical study report (CSR) rather than a full CSR. Full safety tables and listings are provided with the report. This is in accordance with the available regulatory guidance in the 'FDA Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (1999)'.

## Study centre(s)

The study was conducted at 7 sites in 4 countries (France, Netherlands, Norway and United Kingdom).

## Publications

Han LY, Aamdal S, Bowen E, et al. Treatment profile of saracatinib (AZD0530) in combination with chemotherapy in patients with advanced ovarian carcinoma (OC). Gynecologic Oncology 2010;116 (3 suppl 1): Abstract 151.

## Objectives and criteria for evaluation

**Table S1 Primary, secondary and exploratory objectives and outcome variables**

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | **Primary** | |
| To evaluate the safety and tolerability of saracatinib in combination with carboplatin and/or paclitaxel regimens in patients with solid tumours by assessment of adverse events, physical examination, blood pressure, pulse, electrocardiogram, laboratory findings, pulmonary function test and thoracic computed tomography scan | Adverse events, physical examination abnormalities, blood pressure (systolic, diastolic, mean arterial), pulse, electrocardiograms, laboratory safety measurements (clinical chemistry, haematology and urinalysis), pulmonary function tests ($FEV_1$, FVC, DLCO and % predicted DLCO), high resolution thoracic computed tomography scans, World Health Organization performance status | Safety |
| **Secondary** | **Secondary** | |
| To determine the maximum tolerated dose of saracatinib when administered in combination with carboplatin and/or paclitaxel by assessment of safety and tolerability data generated for each treatment arm | Dose limiting toxicities | Safety |
| To make a preliminary evaluation of clinical response by assessment of response evaluation criteria in solid tumours (RECIST) evaluation, time to progression and serum tumour markers | Objective tumour response (RECIST)<br>Progression-free survival<br>Serum tumour markers [a] | Efficacy |
| To investigate the pharmacokinetics of saracatinib, paclitaxel and carboplatin when co-administered to patients with solid tumours, by assessment of appropriate pharmacokinetic parameters | Saracatinib: $Css_{max}$, $Css_{min}$, $t_{max}$, $AUCss_{0-24}$, CL/F<br>Carboplatin: $C_{max}$, AUC, $AUC_{0-t}$, $t_{½}$, CL, Vss<br>Paclitaxel: Cmax, AUC, $AUC_{0-t}$, $t_{½}$, CL, Vss | PK |

**Table S1 Primary, secondary and exploratory objectives and outcome variables**

| Objectives | Outcome variables | Type |
|---|---|---|
| **Exploratory** | **Exploratory** | |
| To obtain blood samples for DNA extraction for future pharmacogenetic analysis and other potential correlative markers of saractainib activity | Blood samples for DNA extraction for analysis of genetic factors [a] | PGx |
| To obtain serum, urine, tumour cells from proximal fluids and historical tumour samples for investigation of exploratory biomarkers | Serum, urine, tumour cells from proximal fluids and historical tumour samples for investigation of exploratory biomarkers [a] | PD |
| To explore the pharmacokinetics of the N-desmethyl metabolite of saracatinib (M594347) | $Css_{max}$, $Css_{min}$, $t_{max}$, $AUCss_{0-24}$, drug to metabolite ratio | PK |
| To compare predictions of carboplatin AUC calculated from the glomerular filtration rate and 24-hour plasma platinum concentrations | Carboplatin AUC predicted from 24-hour plasma platinum concentration [b]<br>Glomerular filtration rate measured using $^{51}Cr$ edetic acid methodology [b] | Safety |
| To compare the dose of carboplatin derived from measured glomerular filtration rate and using calculated methods | Doses of carboplatin derived using calculated and measured glomerular filtration rate [b] | Safety |

[a] Not reported in this clinical study report.
[b] Not reported in synopsis. Results can be found in the clinical study report.
AUC = area under the plasma concentration-time curve from zero to infinity, $AUCss_{0-24}$ = area under the curve at steady-state from time zero to 24 hours, CL = total clearance, CL/F = plasma clearance, $Css_{max}$ = maximum plasma concentration at steady-state, $Css_{min}$ = minimum plasma concentration at steady-state, DLCO = diffusing capacity of the lung for carbon monoxide, DNA acid = deoxyribonucleic, $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, PD = pharmacodynamic, PGx = pharmacogenetic, PK = pharmacokinetics, RECIST = response evaluation criteria in solid tumours, $t_{½}$ = terminal half-life, $t_{max}$ = time to maximum plasma concentration, Vss = volume of distribution at steady state.

## Study design

This was a Phase I, 2-part, multi-centre, open, dose escalation (Part A) and dose expansion (Part B) study to establish the safety, tolerability and pharmacokinetics of once daily oral dosing with saracatinib when administered in combination with one of the following 4 cytotoxic chemotherapy treatment regimens:

- Carboplatin and paclitaxel q3-weekly.
- Carboplatin q3-weekly.
- Paclitaxel q3-weekly.
- Paclitaxel q1-weekly.

**Target subject population and sample size**

The maximum number of evaluable patients required was 234. Male or female patients aged 18 years or older with locally advanced or metastatic cancer suitable for treatment with either carboplatin and/or paclitaxel were eligible for the study. Patients were to have a World Health Organization performance status of 0 to 2 and life expectancy >12 weeks.

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

Saracatinib was manufactured and supplied by AstraZeneca as 50 mg tablets (batch numbers: P/5022/25, P/5022/31 and ST76108-001-FA02) and 125 mg tablets (batch numbers: P/5022/26, P/5022/32, P/5022/33 and ST76109-001-FA02) for oral administration. The starting dose of saracatinib in each treatment arm was 125 mg. The dose was escalated or de-escalated based on toxicity information from the first cycle of the previous dose level for each treatment arm.

Carboplatin (AUC 5.0 mg/mL.min) from commercially available supplies was administered as an intravenous (iv) infusion over approximately 1 hour at q3-weekly cycles. Paclitaxel from commercially available supplies was administered either q3-weekly (175 mg/m$^2$ iv infusion over 3 hours) or q1-weekly (80 mg/m$^2$ iv infusion over 1 hour) on Day 1, Day 8 and Day 15 to complete a study cycle. The number of cycles of chemotherapy varied per patient. Beyond cycle 2, doses of cytotoxic chemotherapy could be reduced successively by one dose level, if toxicities were observed.

**Duration of treatment**

During Part A, saracatinib was to be taken once daily for 7 to 10 days (Cycle 0) prior to the first 21-day cycle of cytotoxic chemotherapy (Cycle 1) and continued until study withdrawal. During Part B, saracatinib was to be taken once daily from Day 3 of Cycle 1 until study withdrawal.

Each cycle of carboplatin and/or paclitaxel was to last 21 days, with treatment administered over one 21-day period (q3-weekly) or during 3 consecutive 7-day periods (q1-weekly).

**Statistical methods**

There was no formal statistical analysis. Data are summarised and listed as appropriate.

Efficacy data are summarised for the Full Analysis Set which includes all enrolled patients who were allocated to receive treatment. Safety data are summarised for the Safety Analysis Set which includes all patients who received investigational product (ie, saracatinib). Patients who did not receive saracatinib, but received chemotherapy are not included in the Safety Analysis Set.

**Subject population**

The data cut-off date for this report is 14 January 2010.

A total of 149 patients were enrolled from 7 sites in 4 countries. A total of 117 patients were allocated to receive treatment (Full Analysis Set) and 116 patients received saracatinib (Safety Analysis Set) (24 patients in the Part A carboplatin and paclitaxel q-3 weekly arm, 21 patients in the Part A carboplatin q-3 weekly arm, 27 patients in the Part A paclitaxel q-3 weekly arm, 24 patients in the Part A paclitaxel q-1 weekly arm, and 20 patients in the Part B carboplatin and paclitaxel q-3 weekly arm). Of the 116 patients who received saracatinib, 103 received chemotherapy.

The median age of patients was 60.0 years (range 26 to 77 years) and 51% were female. Baseline characteristics were representative of a population of patients with locally advanced or metastatic solid tumours.

**Summary of efficacy results**

For all doses of saracatinib combined, a confirmed objective tumour response was observed for 5 of 45 (11%) patients in the pooled Part A and Part B carboplatin and paclitaxel q-3 weekly arms, 0 of 21 (0%) patients in the carboplatin q-3 weekly arm, 0 of 27 (0%) patients in the paclitaxel q-3 weekly arm, and 5 of 24 (21%) patients in the paclitaxel q-1 weekly arm. All of the confirmed objective tumour responses were partial responses.

For all doses of saracatinib combined, median progression-free survival was 2.99 months for patients in the pooled Part A and Part B carboplatin and paclitaxel q-3 weekly arms (27 [60%] progression events), 1.84 months for patients in the carboplatin q-3 weekly arm (12 [57%] progression events), 1.58 months for patients in the paclitaxel q-3 weekly arm (14 [52%] progression events), and 3.25 months for patients in the paclitaxel q-1 weekly arm (17 [71%] progression events).

**Summary of pharmacokinetic results**

A summary of the PK parameters of saracatinib 225 mg, paclitaxel and carboplatin, for those patients who had reportable PK parameters, when dosed both in the presence and absence of the other drug, is shown in Table S2. Whilst the numbers of patients are small, there was no evidence that the exposure of carboplatin or paclitaxel in patients with solid tumours was affected by the co-administration of saracatinib. Similarly, there was no evidence that the exposure of saracatinib was affected by the co-administration of carboplatin and/or paclitaxel.

The pharmacokinetics of the N-desmethyl metabolite of saracatinib in patients with solid tumours were similar when saracatinib was dosed alone or co-administered with carboplatin and/or paclitaxel (Table S3).

**Table S2 Summary of PK parameters of saracatinib, paclitaxel and carboplatin when co-administered to patients**

| Dosing regimen | N | Summary statistic | $C_{max}$ / $C_{max, ss}$ (ng/mL) | AUC / $AUC_{ss}$ (ng.h/mL) |
|---|---|---|---|---|
| Saracatinib alone | 9 | Gmean (% CV) | 590 (38.4) | 10600 (43.8) |
| Saracatinib + carboplatin / paclitaxel | 9 | Gmean (% CV) | 545 (42.2) | 9990 (35.5) |
| Ratio of saracatinib in combination : alone | 9 | Gmean (Range) | 0.923 (0.675 – 1.25) | 0.940 (0.774 – 1.23) |
| Carboplatin without saracatinib | 4 | Gmean (% CV) | 33600 (20.4) | 3.90 (24.8) |
| Carboplatin in combination with saracatinib | 4 | Gmean (% CV) | 36500 (15.5) | 4.43 (16.0) |
| Ratio of carboplatin with saracatinib : without saracatinib | 4 | Gmean (Range) | 1.087 (0.898 – 1.53) | 1.14 (0.921 – 1.67) |
| Paclitaxel without saracatinib | 6 | Gmean (% CV) | 2970 (35.4) | 9850 (22.8) |
| Paclitaxel in combination with saracatinib | 6 | Gmean (% CV) | 2840 (22.2) | 10100 (20.9) |
| Ratio of paclitaxel with saracatinib : without saracatinib | 6 | Gmean (Range) | 0.957 (0.682 – 1.82) | 1.02 (0.871 – 1.51) |

$AUC_{ss}$ = area under the plasma concentration-time curve during any dosing interval at steady state (for saracatinib); AUC = area under the plasma concentration-time curve (for carboplatin and paclitaxel); $C_{max, ss}$ = maximum plasma concentration at steady state (for saracatinib); $C_{max}$ = maximum plasma concentration (for carboplatin and paclitaxel); CV = coefficient of variation; Gmean = geometric mean; N = number subjects used to calculate parameters.

**Table S3 Summary of PK parameters of N-desmethyl metabolite of saracatinib with and without the presence of carboplatin /paclitaxel**

| Parameter | N | Summary statistic | N-desmethyl metabolite without carboplatin/paclitaxel | N-desmethyl metabolite with carboplatin/paclitaxel |
|---|---|---|---|---|
| $C_{max, ss}$ (ng/mL) | 9 | Gmean (% CV) | 92.6 (27.4) | 96.8 (29.4) |
| $AUC_{ss}$ (ng.h/mL) | 9 | Gmean (% CV) | 1630 (29.0) | 1860 (27.5) |
| N-desmethyl metabolite : saracatinib $AUC_{ss}$ ratio | 9 | Gmean (Range) | 0.154 (0.097 – 0.234) | 0.186 (0.135 – 0.271) |

$AUC_{ss}$ = area under the plasma concentration-time curve during any dosing interval at steady state; $C_{max, ss}$ = maximum plasma concentration at steady state; CV = coefficient of variation; Gmean = geometric mean; N = number subjects used to calculate parameters.

## Summary of safety results

Dose limiting toxicities are shown in Table S4.

**Table S4 Summary of dose escalation based on stopping criteria for Part A of the study (Dose limiting toxicity evaluable set)**

| | Number of patients with DLT/ number of patients evaluable for dose escalation decision<br>Adverse event associated with DLT (CTCAE grade and preferred term) | | | |
|---|---|---|---|---|
| **Sara-catinib dose** | **Carboplatin + Paclitaxel q3-weekly + Saracatinib**<br>**n=16** | **Carboplatin q3-weekly + Saracatinib**<br>**n=14** | **Paclitaxel q3-weekly + Saracatinib**<br>**n=19** | **Paclitaxel q1-weekly + Saracatinib**<br>**n=19** |
| 125 mg | 0/5 | 0/6 | 0/3 | 0/3 |
| 175 mg | 0/6 | 2/8 [a] (Gr 3 fatigue; Gr 3 colitis ulcerative) | 1/6 (Gr 5 neutropenic sepsis) | 2/10 [b] (Gr 3 neutropenia; Gr 3 neutropenia) |
| 225 mg | 1/5 (Gr 3 hyponatraemia) | - | 0/4 | 2/6 (Gr 3 neutropenia; Gr 4 febrile neutropenia) |
| 250 mg | - | - | 1/6 Gr 3 febrile neutropenia | - |
| 300 mg | - | - | 0/0 [c] | - |

DLT = dose limiting toxicity; Gr = grade.

a Dose cohort was expanded above the maximum of 6 evaluable patients per cohort following the recommendation of the Safety Review Committee as documented in Protocol Amendment Number 4.

b Dose cohort was repeated using criteria defined in Protocol Amendment Number 2 following the recommendation of the Safety Review Committee. Of the 10 evaluable patients in this cohort, 5 were enrolled prior to and 5 were enrolled after the protocol amendment.

c Five patients were enrolled in this cohort, but 2 discontinued prior to saracatinib dosing. The remaining 3 patients received saracatinib but were non-evaluable: 2 discontinued before exposure to the combination with paclitaxel and 1 progressed during the DLT evaluation period. As recruitment to this cohort was challenging, the Safety Review Committee decided that further exploration of this combination dose level was pragmatically inappropriate within the circumstances under consideration.

Saracatinib was declared tolerable at the following doses and combinations:

- Saracatinib 225 mg once daily in combination with carboplatin AUC 5.0 mg/mL.min plus paclitaxel 175 mg/m$^2$ administered every 3 weeks.
- Saracatinib 125 mg once daily in combination with carboplatin AUC 5.0 mg/mL.min administered every 3 weeks.
- Saracatinib 250 mg once daily in combination with paclitaxel 175 mg/m$^2$ administered every 3 weeks.
- Saracatinib 175 mg once daily in combination with paclitaxel 80 mg/m$^2$ administered weekly.

In the first 3 arms, dose escalation was stopped without establishing the maximum tolerated dose. In the weekly paclitaxel arm, saracatinib 175 mg was considered to be the maximum tolerated dose.

For all chemotherapy arms pooled, adverse events (AEs) with onset after the start of saracatinib dosing and within 30 days of the last dose of saracatinib, were reported as follows:

- 114 (98%) patients reported an AE. The most frequent AEs (reported by ≥30% of patients) were nausea (67 [58%]), fatigue (60 [52%]), decreased appetite (47 [41%]), diarrhoea (43 [37%]), vomiting (41 [35%]), alopecia (40 [34%]), anaemia (39 [34%]) and constipation (36 [31%]). The majority of these common AEs were Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade 1 or 2.

- Within each chemotherapy arm, there was no evidence of a dose response for AEs by preferred term, but the numbers of patients within each dose group were small.

- 89 (77%) patients had an AE of CTCAE grade 3 or higher. The most frequent AEs of CTCAE grade ≥3 (reported by ≥10% of patients) were neutropenia (22 [19%]), fatigue (16 [14%]) and anaemia (12 [10%]).

- 6 (5%) patients had an AE with outcome of death. For 3 of the 6 patients, the fatal AE (pneumonia in 2 patients, peritonitis) was considered by the investigator to be related to the patient's cancer only. A fatal AE of neutropenic sepsis was considered by the investigator to be related to paclitaxel and saracatinib, and fatal AEs of respiratory failure and pneumonitis were considered by the investigator to be related to the patient's cancer and to saracatinib.

- 66 (57%) patients had an SAE. SAEs reported for more than 1 patient were pyrexia (8 [7%]), anaemia (6 [5%]), febrile neutropenia (5 [4%]), pneumonia (5 [4%]), malaise (4 [3%]), hypokalaemia (3 [3%]), hyponatraemia (3 [3%]), catheter related infection (2 [2%]), dysphagia (2 [2%]), and hypotension (2 [2%]).

- 40 (34%) patients had an AE leading to discontinuation of saracatinib. AEs leading to the discontinuation of more than 1 patient were neutropenia (3 [3%]) and anaemia, fatigue, glomerular filtration rate decreased, hyponatraemia, melaena, mobility decreased, neuropathy peripheral, neutropenic sepsis, pneumonia and urinary tract infection (2 [2%] each).

An increased incidence of hyponatraemic episodes in patients receiving platinum-based therapy in combination with saracatinib, compared to that experienced by patients receiving non-platinum-based chemotherapy in combination with saracatinib, was observed. The incidence of these episodes did not appear to be related to the dose of saracatinib administered but did seem to be related to baseline sodium plasma concentration (higher incidences occurring in patients with baseline sodium plasma concentrations below the lower limit of normal).

There were no clinically relevant findings with regard to other laboratory parameters, vital signs, electrocardiograms or pulmonary monitoring (thoracic computerised tomography scans).