Drug Substance	AZD0530 (saracatinib)	**Synopsis**	(For national authority use only)
Study Code	D8180C00021		
Date	29 August 2011		

A Phase I, Open-label, Dose-escalation Study to Assess the Safety and Tolerability of AZD0530 in Patients with Advanced Solid Malignancies

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

Study dates

First subject enrolled: 6 June 2008

Last subject last visit: 6 May 2011

Phase of development

Clinical pharmacology (I)

Study centre(s)

The study was conducted at two centres in Japan. The first patient was enrolled on 6 June 2008, and the last patient completed the study on 6 May 2011.

Publications

The 2011 European Multidisciplinary Cancer Congress, Stockholm, Sweden, 26 September 2011 (in press).
The 49th Japan Society of Clinical Oncology, Nagoya, Japan, 29 October 2011 (in press).

Objectives

The primary objective of this study was to evaluate the safety and tolerability of AZD0530 (hereinafter referred to as saracatinib) in Japanese patients with advanced solid malignancies.

The secondary objectives of this study were:

1. To determine the single and multiple dose PK of saracatinib when administered orally to patients with advanced solid malignancies

2. To seek preliminary evidence of the anti-tumour activity of saracatinib in patients with advanced solid malignancies as measured by tumour response

The exploratory objectives of this study were:

1. To determine the maximum tolerated dose (MTD) according to the reported dose limiting toxicity (DLT), if MTD exists in the range of the doses which is investigated in the ascending dose phase.

2. To assess the biologic activity of saracatinib in patients with advanced solid malignancies by measuring surrogates such as markers of bone turnover*

3. To explore the PK of the N-desmethyl metabolite of saracatinib (M594347) in patients with advanced solid malignancies

4. To obtain blood samples for DNA extraction for future pharmacogenetic analysis.**

* This objective was not addressed.
** The results corresponding to this objective are not included in this study report.

Study design

This was a Phase I, open-label, dose-escalation study. The study assessed safety, tolerability, PK and biological activity. The study consisted of a multiple, ascending oral dose design. Patients received single daily oral doses of saracatinib. The starting dose level was to be 50 mg and the maximum dose level was to be 175 mg.

A single dose followed by a multiple dose design was adopted in order to obtain both single and multiple dose PK profiles in patients with advanced solid malignancies. There was a minimum of 3 and a maximum of 6 evaluable patients per cohort at each dose level.

An evaluable patient was defined as a patient who

1. Completed 75% of planned daily doses in the single and 21 days of multiple dosing period and has enough information to assess the dose escalation. If a patient had less than 75% compliance, since a patient was discontinued due to the adverse event(s), the patient was to be considered evaluable

   or

2. Experienced a DLT, which was considered by the investigator to be possibly related to saracatinib in the single and 21 days of multiple dosing period.

Target subject population and sample size

The target population was Japanese patients who have advanced solid malignancy, refractory to or unsuitable for standard therapy, or for whom no standard therapy exists.

Sample size was a minimum of 3 and a maximum of 6 evaluable patients per cohort.

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

Dose-escalation occurred based on the toxicity information from a minimum of 3 evaluable patients obtained during the 28 days of single and multiple dosing of the previous cohort. Saracatinib 50 mg, 125 mg, and 175 mg once daily were chosen for the dose-escalation. No intra-patient dose-escalation was permitted in this study.

Duration of treatment

Patients received a single dose of saracatinib on Day 1 followed by a washout period of 7 days. Single daily doses were then administered from Day 8 until Day 29 or, if earlier, the patient's withdrawal from the study. Patients only continued to be treated if in the opinion of the investigator they were gaining some clinical benefit until clear disease progression or they met a withdrawal criterion.

Criteria for evaluation

Efficacy variables: best overall response according to the RECIST criteria (Ver. 1.0), the percentage change from baseline in sum of the diameters of target lesions

PK variables:

Saracatinib; C_{max}, C_{ssmax}, t_{max}, C_{min}, C_{ssmin}, AUC_{0-24}, AUC_{0-t}, AUC, AUC_{ss0-24}, CL/F, $t_{1/2}$ and R

N-desmethyl metabolite of saracatinib; C_{max}, C_{ssmax}, AUC_{0-24}, AUC_{0-t}, AUC and AUC_{ss0-24}

Safety variables: adverse events (AE), vital signs, electrocardiogram (ECG), laboratory findings, and thoracic imaging (HRCT)

A DLT was defined as the following toxicities which, in the opinion of the investigator, was related to the study drug:

Haematological:

- Febrile neutropenia (CTCAE Grade 3 with temperature ≥38.5°C or CTCAE Grade 4 with temperature ≥38°C)
- Any other CTCAE Grade 4 haematological toxicity (Except for lymphopenia)

Non-haematological:

- Any other CTCAE Grade 3 or above toxicity which, in the opinion of the investigator, is related to the study drug, with the exception of sub optimally treated nausea, vomiting or diarrhoea and transient electrolyte abnormality

Statistical methods

All safety data were listed for each patient. Changes from baseline were included for the listings of haematology, clinical chemistry, quantitative urinalysis results, pulse rate and blood pressure data. All summaries of safety data were by dose initially received. Unless otherwise stated, the baseline value was defined as the closest observation prior to the administration of investigational product.

PK data (plasma concentrations and PK parameters for both saracatinib and the N-desmethyl metabolite of saracatinib) were listed, summarised and plotted by dose level received and for the single and multiple dose period separately.

All tumour response data were listed for all patients. Best overall response was summarised by dose level and overall. Tumour response rate was defined as the proportion of patients analysed whose best response was either complete response or partial response.

Subject population

A total of 18 patients were enrolled in this study. Six patients failed screen and the remaining 12 patients took the study medication (3 patients in 50 mg cohort, 6 patients in 125 mg cohort and 3 patients in 175 mg cohort) (see Table S1 and S2).

The median age of patients was 57 years (range: 38-78 years). Seven patients (58.3%) were male and five patients (41.7%) were PS 0. All patients received previous chemotherapy. Primary tumour was colorectal in 4 patients, lung in 4 patients, and breast, oesophagus, stomach and ovary in one patient each. Overall demographic and baseline characteristics were representative of the intended population.

Ten patients discontinued the study treatment due to disease progression and 2 patients were withdrawn from the study due to AE. There were no major protocol deviations in the study. Efficacy, PK and safety evaluations were completed in all 12 patients.

Table S1 Subject population and disposition

Disposition	Number (%) of patients			
	50 mg	125 mg	175 mg	Total
Patients enrolled*	-	-	-	18
Patients allocated to treatment	3 (100.0)	6 (100.0)	3 (100.0)	12 (100.0)
Patients who were not allocated to treatment	-	-	-	6
Incorrect Enrolment	-	-	-	6
Patients who received treatment	3 (100.0)	6 (100.0)	3 (100.0)	12 (100.0)
Patients who discontinued study	3 (100.0)	6 (100.0)	3 (100.0)	12 (100.0)
Adverse Event	0	0	2 (66.7)	2 (16.7)
Condition Under Investigation Worsened	3 (100.0)	6 (100.0)	1 (33.3)	10 (83.3)

* Informed consent received

Table S2 Demographic characteristics

Demographic characteristics	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)	Total (n=12)
Age (years)				
n	3	6	3	12
Mean	67	50	65	58
SD	11	7	3	11
Median	67	51	65	57
Min	57	38	63	38
Max	78	57	68	78
Sex n (%)				
n	3	6	3	12
Male	2 (66.7)	5 (83.3)	0	7 (58.3)

Demographic characteristics	50 mg (n=3)		125 mg (n=6)		175 mg (n=3)		Total (n=12)	
Female	1	(33.3)	1	(16.7)	3	(100.0)	5	(41.7)
Race n (%)								
n	3		6		3		12	
Asian - Japanese	3	(100.0)	6	(100.0)	3	(100.0)	12	(100.0)

Summary of efficacy results

Neither a complete response nor a partial response were reported. The best response was stable disease (SD), reported for three patients (50 mg cohort: 2 patients: colorectal and stomach cancer, 125 mg cohort: 1 patient: oesophageal cancer); the treatment period were 149, 65, and 49 days, respectively.

One patient with non-evaluable disease (lung cancer) in the 125 mg cohort was treated for more than 22 months (675 days).

Summary of pharmacokinetic results

After single and multiple doses of saracatinib, the median time to maximum plasma concentration (t_{max}) of unchanged compound was between 2 to 4 hours post-dose. Following maximum plasma concentrations (C_{max}), the distribution was biphasic with a mean terminal elimination half-life (t½) of approximately 45 hours. The dose increase from 50 to 125 mg (2.5-fold) and 50 to 175 mg (3.5-fold) resulted in 4.1 to 4.6-fold and 4.7 to 6.1-fold increase in the exposures (C_{max} and AUC after single dosing), respectively, suggesting a trend of slightly more than proportional increase in exposures to saracatinib over the dose range studied (see Figure S1, Table S3 and S4). The geometric-mean oral clearance (CL/F) of saracatinib was slightly higher in 50 mg cohort (54.0 L/h) than those in 125 and 150 mg cohorts (32.8 and 40.3 L/h, respectively).

The single dose pharmacokinetics were not predictive of those after once daily multiple dosing. The 4- to 8-fold accumulation was greater than predicted. In addition, the AUC_{0-24} after multiple dosing was higher than the AUC after single dosing (1.5 to 3.5-fold). Steady state exposure was achieved by approximately Day 10.

After a single dose of saracatinib the N-desmethyl metabolite was detected in plasma in all patients, and the shape of the plasma concentration-time profile was similar to that of saracatinib. The steady state exposure to the N-desmethyl metabolite was 15% to 20% of the steady state exposure determined for saracatinib.

In comparison of pharmacokinetic data with the Western Study (D8180C00004), exposures to saracatinib in Japanese patients were 0.8 to 2.1-fold of those in Western patients.

Figure S1 Geometric mean AZD0530 plasma concentration (ng/mL) versus time following single dosing [PK set]

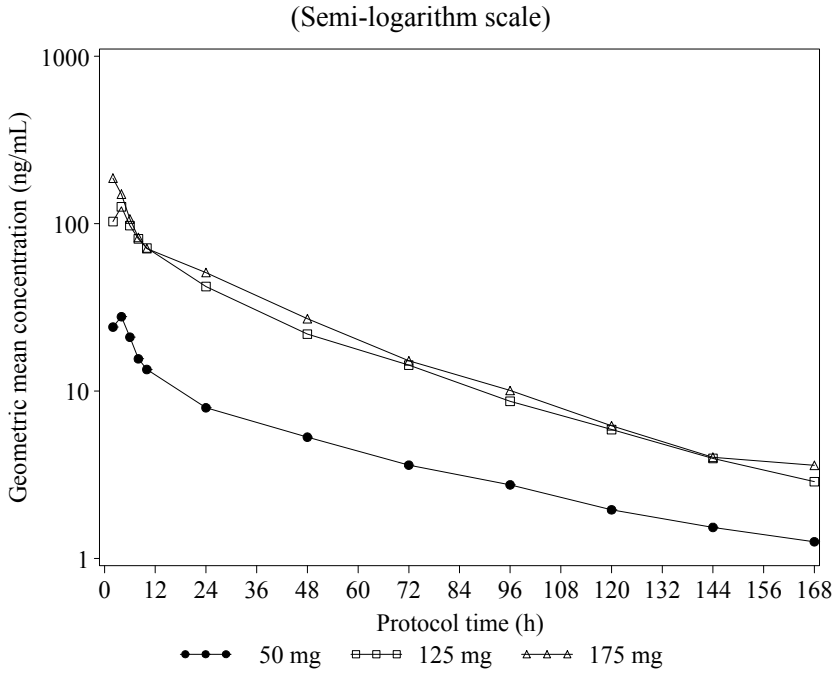

Table S3 Pharmacokinetic parameters of AZD0530 after single dosing [PK set]

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
AUC (ng*h/mL)	n	3	6	3
	Geometric mean	925	3814	4345
	CV (%)	57.8	36.2	23.8
	Arithmetic mean	1025	4024	4428
	SD	595	1512	1098
	Median	734	3821	3849
	Min	631	2661	3741
	Max	1710	6725	5695

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
AUC 0-24 (ng*h/mL)	n	3	6	3
	Geometric mean	344	1734	1981
	CV (%)	47.8	22.2	19.8
	Arithmetic mean	369	1770	2007
	SD	177	398	406
	Median	299	1720	1867
	Min	238	1365	1690
	Max	571	2410	2465
AUC 0-t (ng*h/mL)	n	3	6	3
	Geometric mean	820	3630	4150
	CV (%)	54.3	35.1	24.3
	Arithmetic mean	898	3819	4233
	SD	492	1409	1069
	Median	664	3599	3705
	Min	567	2568	3530
	Max	1464	6370	5463
Cmax (ng/mL)	n	3	6	3
	Geometric mean	30.6	140	187
	CV (%)	35.3	19.4	14.3
	Arithmetic mean	31.9	143	188
	SD	11.7	27.8	27.6

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
	Median	25.4	140	176
	Min	24.8	104	169
	Max	45.4	191	220
Cmin (ng/mL)	n	3	6	3
	Geometric mean	7.95	42.1	51.0
	CV (%)	50.8	36.6	23.4
	Arithmetic mean	8.62	44.6	52.0
	SD	4.43	18.4	12.2
	Median	6.61	38.7	49.5
	Min	5.55	29.5	41.2
	Max	13.7	79.9	65.2
CL/F (L/h)	n	3	6	3
	Geometric mean	54.0	32.8	40.3
	CV (%)	57.9	36.1	23.9
	Arithmetic mean	58.8	34.4	41.0
	SD	26.3	11.1	8.9
	Median	68.1	33.0	45.5
	Min	29.2	18.6	30.7
	Max	79.2	47.0	46.8
t1/2 (h)	n	3	6	3
	Geometric mean	57.0	40.3	36.9
	CV (%)	13.0	12.2	7.8

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
	Arithmetic mean	57.3	40.6	36.9
	SD	7.7	4.8	2.9
	Median	54.3	40.4	36.3
	Min	51.6	33.2	34.4
	Max	66.0	47.0	40.1
tmax (h)	n	3	6	3
	Median	3.9	4.0	2.0
	Min	2.0	2.0	1.9
	Max	4.0	4.0	2.0

Table S4 Pharmacokinetic parameters of AZD0530 after multiple dosing [PK set]

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
AUCss 0-24 (ng*h/mL)	n	3	5	1
	Geometric mean	1356	7812	15221
	CV (%)	59.8	35.9	
	Arithmetic mean	1500	8200	15221
	SD	820	2847	
	Median	1305	7114	15221
	Min	796	5292	15221
	Max	2400	11332	15221
Cssmax (ng/mL)	n	3	5	1
	Geometric mean	76.9	431	922

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
	CV (%)	61.2	34.0	
	Arithmetic mean	85.4	449	922
	SD	47.2	137	
	Median	74.9	418	922
	Min	44.4	262	922
	Max	137	604	922
Cssmin (ng/mL)	n	3	5	1
	Geometric mean	44.5	231	451
	CV (%)	66.8	36.2	
	Arithmetic mean	50.4	243	451
	SD	31.0	85.2	
	Median	40.3	214	451
	Min	25.6	161	451
	Max	85.2	344	451
tmax (h)	n	3	5	1
	Median	4.0	4.0	2.0
	Min	2.0	2.0	2.0
	Max	4.0	6.0	2.0
R	n	3	5	1
	Geometric mean	3.95	4.43	8.15
	CV (%)	14.4	21.7	
	Arithmetic mean	3.97	4.51	8.15
	SD	0.55	0.94	

PK parameters	Summary statistic	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)
	Median	4.20	4.62	8.15
	Min	3.35	3.31	8.15
	Max	4.37	5.69	8.15

Summary of safety results

All 12 patients experienced one or more AEs (see Table S5).. Most common AEs were diarrhoea (8/12 patients), nausea (8/12 patients), decreased appetite (8/12 patients), lymphopenia (7/12 patients) and pyrexia (6/12 patients), most of which were mild or moderate (CTCAE grade 1 or 2). A total of 11 patients experienced one or more AEs that were considered drug-related by the investigator. The most common drug related AEs (frewuency ≥40%) per the investigator, were diarrhoea (6/12 patients), decreased appetite (6/12 patients), nausea (5/12 patients), and pyrexia (5/12 patients).

Two patients in 125 mg cohort experienced a dose interruption due to an AE. One patient restarted with same dose and another restarted with one dose reduction to 50 mg.

AEs with CTCAE grade ≥3 were seen in 8 patients: international normalised ratio increased in 50 mg cohort (E0001002), lymphopenia in 125 mg cohort (E0001006), haemoglobin decreased in 125 mg cohort (E0001008), febrile neutropenia, lymphopenia and leukopenia in 125 mg (E0002004), pyrexia, pneumonia bacterial, lymphopenia and procedural pain in 125 mg (E0002010), haemogrobin decreased and hypoxia in 175 mg cohort (E0001005), neutropenia in 175 mg cohort (E0002005), aspartate aminotransferase increased, γ-glutamyltransferase increased, leukopenia, and neutropenia in 175 mg cohort (E0002006). Neutropenia in E0002006 was grade 4 and others were grade 3.

Two patients reported at least one SAE: pyrexia and pneumonia bacterial (both were grade 3) in 125 mg cohort (E0002010), and cardiac failure (grade 2) in 175 mg cohort (E0001005). All three events were judged as related to saracatinib by the investigators.

Four DAEs in 2 patients were reported: hypoxia (grade 3) in 175 mg (E0001005), alanine aminotransferase increased (grade 2), aspartate aminotransferase increased, γ-glutamyltransferase increased (both were grade 3) in 175 mg (E0002006). No patient died due to an AE.

Four AEs, all of which were DAEs as above and were judged as DLTs according to the definition (see “Criteria for evaluation”), were reported for 2 evaluable patients in 175 mg cohort. Therefore it was considered that 175 mg is a non-tolerable dose in Japanese patients. Since there were no DLTs in 6 evaluable patients in 125 mg cohort, 125 mg is confirmed as the MTD in this study.

Table S5 Number (%) of patients who had at least 1 AE in any category [Safety set]

AE category	Number (%) of patients*			
	50 mg (n=3)	125 mg (n=6)	175 mg (n=3)	Total (n=12)
Any AE	3 (100.0)	6 (100.0)	3 (100.0)	12 (100.0)
Any AE of CTC grade 3 or higher	1 (33.3)	4 (66.7)	3 (100.0)	8 (66.7)
Any AE with outcome = death	0	0	0	0
Any SAE not leading to death	0	1 (16.7)	1 (33.3)	2 (16.7)
Any AE leading to discontinuation of treatment	0	0	2 (66.7)	2 (16.7)
Any other significant AE	0	0	0	0
Any drug related AE	3 (100.0)	5 (83.3)	3 (100.0)	11 (91.7)
Any drug related AE of CTC grade 3 or higher	1 (33.3)	2 (33.3)	3 (100.0)	6 (50.0)
Any drug related AE with outcome=death	0	0	0	0
Any drug related SAE not leading to death	0	1 (16.7)	1 (33.3)	2 (16.7)
Any drug related AE leading to discontinuation of treatment	0	0	2 (66.7)	2 (16.7)

* Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.