AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | Saracatinib |
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# A Phase I, Randomised, Open-label, Cross-over, Single-centre Study in Healthy Volunteers to Determine the Relative Bioavailability of the Phase III Tablet Formulation Compared to the Phase II Tablet Formulation of Saracatinib (AZD0530)

**Study dates:** First healthy volunteer enrolled: 6 November 2008
Last healthy volunteer completed: 18 March 2009

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

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

## Study centre

Single-centre study in the UK.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

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

| Objectives | Outcome variables |
|---|---|
| **Primary** | **Primary** |
| To determine the relative bioavailability of saracatinib Phase III formulation in relation to the saracatinib Phase II formulation. | Relative bioavailability based on AUC and $C_{max}$ of plasma saracatinib.<br>(PK profiles also include: $t_{max}$, $AUC_{(0-t)}$, CL/F, $V_{ss}$/F, $t_{1/2}$, $t_{last}$ and $\lambda z$.) |
| **Secondary** | **Secondary** |
| To further investigate the safety and tolerability of saracatinib. | AEs, physical examination (including BP and pulse), evaluation of laboratory parameters (clinical chemistry, haematology and urinalysis) and 12-Lead ECG. |
| **Exploratory**[a] | **Exploratory**[a] |
| To characterise the PK profile of an oral solution of saracatinib and the 4 additional tablet variants of the Phase III formulation of saracatinib. | AUC, $C_{max}$, $t_{max}$, $AUC_{(0-t)}$, CL/F, $V_{ss}$/F, $t_{1/2}$, $t_{last}$ and $\lambda z$. |

a Reported separately.

AE Adverse event; AUC Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to time t; BP Blood pressure; CL/F Total apparent clearance; $C_{max}$ Maximum plasma concentration after single dose administration; CSP Clinical study protocol; ECG Electrocardiogram; PK Pharmacokinetic; SAP Statistical analysis plan; $t_{last}$ Time of the last measurable plasma concentration; $t_{max}$ Time to reach maximum plasma concentration; $t_{1/2}$ Terminal half-life; $V_{ss}$/F Apparent volume of distribution at steady-state after oral dose; $\lambda z$ The rate constant of the slowest disposition rate constant.

## Study design

This was a 2-part, randomised, open-label, crossover, single-centre study in healthy volunteers. In Part I, healthy volunteers received single doses of both the Phase II and Phase III formulations (A and B, respectively) of the saracatinib tablet, and in Part II, the same healthy volunteers received a single dose of saracatinib oral solution, then 2 out of the 4 tablet variants (C, D, E and F) of the Phase III formulation of the saracatinib tablet.

**Target subject population and sample size**

A total of 18 healthy male or female volunteers were to be enrolled, to ensure that at least 12 healthy volunteers completed both dose periods (received both the Phase II and Phase III formulation).

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

Saracatinib (AZD0530) was supplied as an oral tablet (125 mg) or as a powder (125 mg) for reconstitution. The formulations tested in the study included an oral solution (as a reference formulation [batch number ST76122-001-FA01]), the wet granulation tablet formulation (Phase II formulation, Formulation A [P/5022/33]) and the roller compaction formulation (Phase III formulation, Formulation B [batch number ST76109-002-FA01]). In addition, 4 formulations (tablet variants C, D, E and F [batch numbers ST76109-003-FA01, ST76109-004-FA01, ST76109-005-FA01, and ST76109-006-FA01, respectively) of the roller compaction process were also dosed.

**Duration of treatment**

Single dose cross-over, with 5 study drug periods, separated by at least 14 days.

**Statistical methods**

The primary PK outcome variables of area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration after single dose administration ($C_{max}$) of saracatinib were formally statistically analysed using the PK analysis set. The PK analysis set included all healthy volunteers who received both Phase II formulation (A) and Phase III formulation (B) and who had reportable PK parameters for both formulations. It was to exclude healthy volunteers who had important deviations that could impact the PK data for either formulation.

An analysis of variance model was fitted to the logarithmically transformed AUC and $C_{max}$ endpoints using the SAS™ software PROC MIXED procedure. The model included terms for sequence, period and treatment as fixed effect factors and subject as a random effect. The results of this analysis for each of AUC and $C_{max}$ were presented in terms of adjusted geometric least square means (glsmeans), for both formulations, the relative bioavailability (ie, the ratio of the Phase III and Phase II treatment formulation glsmeans) and its 95% confidence interval. Assumptions of normality and constancy of variance was explored in all analyses and, if necessary, an appropriate transformation (eg, rank) or non-parametric technique (eg, Mann-Whitney test) was used to validate the results of the main analysis.

## Subject population

The disposition of the healthy volunteers in this study is summarised in Table S2.

**Table S2 Healthy volunteer disposition**

| Disposition | Number (%) of Healthy volunteers[a] |
|---|---|
| Healthy volunteers enrolled[b] | 18 |
| Healthy volunteers randomised | 18 (100) |
| Healthy volunteers who received saracatinib | 18 (100) |
| Healthy volunteers who completed study | 13 (72) |
| Healthy volunteers who discontinued from the study | 5 (28) |
| Incorrect enrolment | 1 (6) |
| Adverse event | 1 (6) |
| Voluntary discontinuation by healthy volunteer | 3 (17) |

[a] Percentages calculated out of healthy volunteers randomised.
[b] Informed consent received.

The demographic data were consistent with that expected for a healthy volunteer population. The majority of the subjects were male and White. The median age was 41 years and median BMI was 27 $kg/m^2$.

## Summary of pharmacokinetic results (primary objective)

A summary of the derived PK parameters for both formulations (Phase II and Phase III) using data from the individuals in the PK analysis set are included in Table S3. These show that the Phase II and Phase III formulations were very similar in terms of their PK properties.

**Table S3 Summary of plasma pharmacokinetic parameters of saracatinib (pharmacokinetic analysis set)**

| Parameter | Summary statistic | Phase II (A) (N=16) | Phase III (B) (N=16) |
|---|---|---|---|
| AUC (ng.h/mL) | Geometric mean (CV [%]) | 1501 (33.06) | 1502 (29.93)[a] |
| CL/F (L/h) | Arithmetic mean (SD) | 87.70 (31.73) | 86.73 (26.80)[a] |
| $AUC_{(0-t)}$ (ng.h/mL) | Geometric mean (CV [%]) | 1431 (31.75) | 1405 (28.48) |
| $C_{max}$ (ng/mL) | Geometric mean (CV [%]) | 51.24 (27.78) | 48.32 (36.59) |
| $t_{1/2}$ (h) | Arithmetic mean (SD) | 39.96 (7.342) | 38.34 (7.627)[a] |
| $t_{max}$ (h) | Median (range) | 5.00 (3.0 to 10.0) | 5.00 (3.0 to 6.0) |
| $V_{ss}/F$ (L) | Arithmetic mean (SD) | 3979 (1089) | 3935 (873.6)[a] |

AUC Area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from zero to time t; CL/F Total apparent body clearance of drug from plasma after an oral dose; $C_{max}$ Maximum plasma concentration; CV Coefficient of variation; SD standard deviation; $t_{1/2}$ Terminal half-life; $t_{max}$ Time to reach maximum plasma concentration; $V_{ss}/F$ Volume of distribution (apparent) at steady-state after an oral dose.
[a] N=15.

The relative bioavailability of the Phase III saracatinib formulation to the Phase II saracatinib formulation has been determined to be 99.9% based on total exposure (AUC) and 94.0% based on maximum plasma concentration ($C_{max}$) (Table S4). There was no statistical difference between the two formulations and the 90% CIs for the glsmean ratios for both AUC and $C_{max}$ fall between 0.8 and 1.25.

**Table S4 Analysis of relative bioavailability of Phase III formulation to Phase II formulation (pharmacokinetic analysis set)**

| | Phase III Formulation | | Phase II Formulation | | Point estimate of glsmean ratio[a] | 90% confidence interval of glsmean ratio[a] |
|---|---|---|---|---|---|---|
| | n | glsmean | n | glsmean | | |
| AUC (ng.h/mL) | 16 | 1450.42 | 16 | 1452.37 | 0.9987 | 0.9258, 1.0773 |
| $C_{max}$ (mg/mL) | 16 | 47.86 | 16 | 50.91 | 0.9400 | 0.8187, 1.0794 |

[a] Phase III formulation to Phase II formulation.
AUC Area under the plasma concentration-time curve from zero to infinity; $C_{max}$ Maximum plasma concentration after single dose administration; glsmean Geometric least square mean.

Results for the exploratory PK objective will be reported separately.

**Summary of safety results (secondary objective)**

Of the 18 healthy volunteers randomised to the study, all 18 received at least 1 dose of saracatinib. In Part 1 of the study, 18 healthy volunteers were dosed with the Phase II formulation of saracatinib and 16 healthy volunteers were dosed with the Phase III formulation. In Part II of the study, 15 healthy volunteers received the oral solution, 5 received tablet variant C, 8 received tablet variant D, 8 received tablet variant E and 7 received tablet variant F.

Fourteen (78%) healthy volunteers reported at least 1 AE during the study.

The most commonly reported AE was dysgeusia (8 [44%] healthy volunteers overall). All reported AEs of dysgeusia occurred during Part II of the study when healthy volunteers received the oral solution of saracatinib (reported by 8/15 [53%] of healthy volunteers that received the oral solution of saracatinib; 3 healthy volunteers did not receive the oral solution). Volunteers reported a "bitter taste in mouth after dose" (Investigator verbatim text). The duration of the events was short (a median of 3.5 minutes) and none lasted for more than 76 minutes. These events were subsequently coded as the MedDRA Preferred Term Dysgeusia, a term that implies involvement of a neurological effect. However, the original reporting text for the AEs is considered to indicate that the healthy volunteers found the taste of the oral solution bitter, but that there was no neurological effect. No bitter taste was reported with either the Phase II or Phase III tablet formulations or variants.

The next most common AEs reported were headache and lethargy, reported by 5 (28%) and 4 (22%) healthy volunteers, respectively. The majority of AEs were CTCAE Grade 1 or 2. Grade 3 AEs of headache and nausea were reported for 1 healthy volunteer during Part II of the study after dosing with the Phase III formulation of saracatinib. All of these Grade 3 AEs resolved and were reported as unrelated to the study drug by the Investigator.

One healthy volunteer had AEs that led to permanent discontinuation of saracatinib (Phase II formulation) (sciatica, back pain, post-traumatic pain, and paraesthesia). In the Investigator's opinion there was no reasonable possibility that these AEs were related to dosing with saracatinib, and they were reported to be related to a road traffic accident.

No other significant adverse events, serious adverse events or deaths were reported during the study.

There were no clinically relevant changes in clinical laboratory values, electrocardiogram evaluations or vital signs during the study.