AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Saracatinib
Study Code	D8180C00013
Edition Number	1
Date	21 September 2009

An Open-label, Phase I Study to Assess the Absorption, Metabolism and Excretion of a Single Oral Dose of [^{14}C]-Saracatinib (AZD0530) in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 16 March 2009
Last healthy volunteer last visit: 21 April 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(s)

This study was conducted at 1 centre in the UK (AstraZeneca Clinical Pharmacology Unit (CPU), Mereside, Alderley Park, Macclesfield, Cheshire).

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	Type
Primary	**Primary**	
To characterise the absorption, metabolism and excretion of a single oral dose of 400 mg [^{14}C]-saracatinib in healthy volunteers	Pharmacokinetics of saracatinib, M594347 (the N-desmethyl metabolite of saracatinib) and radioactivity in plasma and whole blood: • Concentrations of saracatinib and M594347 in plasma. • Concentrations of radioactivity in plasma and blood. • Ratio of plasma to whole blood radioactivity. • Ratio of plasma saracatinib concentration to plasma radioactivity. • Derived PK parameters for saracatinib (C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, λ_z, $t_{½}$, CL/F and V_{ss}/F). • Derived PK parameters for M594347 (C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, λ_z, $t_{½}$ and metabolite:parent ratio). • Derived PK parameters for plasma radioactivity (C_{max}, t_{max}). Recovery of total radioactivity: • Radioactivity in urine, faeces, other samples, and overall (expressed as % of dose administered). Metabolite profiling and identification: • Chromatographic profiles of radioactivity and investigation of metabolites in plasma, urine and faeces [a].	Pharmacokinetic

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Secondary	**Secondary**	
To evaluate the safety profile of a single oral dose of 400 mg [^{14}C]-saracatinib in healthy volunteers	AEs, physical examination, laboratory parameters (clinical chemistry, haematology and urinalysis), vital signs (blood pressure, pulse), 12-lead ECG.	Safety

[a] Reported separately from the clinical study report.

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; CL/F: oral clearance; C_{max}: maximum plasma concentration; CSP: clinical study protocol; ECG: electrocardiogram; λ_z: terminal rate constant; $t_{½}$: terminal half-life; t_{max}: time to maximum plasma concentration; V_{ss}/F: apparent volume of distribution at steady state.

Study design

This was an open-label, Phase I, single-centre study. Healthy volunteers remained resident at the Clinical Pharmacology Unit for 10 days following dosing, during which time continuous urine and faeces collection was made. Blood samples for pharmacokinetic and radiochemical analysis were also collected during the 10 days following dosing.

Target subject population and sample size

It was planned that 6 healthy male volunteers aged ≥50 years would complete the study.

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

[^{14}C]-labelled saracatinib 400 mg (400 μCi/14.8 MBq) was administered as an oral solution (2.5 mg/mL). Formulation number: F13700; Batch numbers: AZ10353926-014 and EN02654-03-1.

Duration of treatment

Single dose.

Statistical methods

No formal statistical analysis was performed on the safety or pharmacokinetic data from this study. The plasma concentration-time data were analysed using standard non-compartmental methods using WinNonLin version 4.1 (Pharsight Corporation). All data were listed and derived pharmacokinetic variables were summarised using standard descriptive statistics.

Subject population

Six healthy male volunteers were enrolled from a single centre in the United Kingdom; all 6 received investigational product and completed the study as planned.

All 6 healthy volunteers were included in the full analysis set and the safety analysis set. Since there were no major protocol deviations leading to exclusion of healthy volunteers from the pharmacokinetic analysis set, the pharmacokinetic analysis set and the safety analysis set were identical. Thus, the pharmacokinetic analysis was performed on the safety analysis set.

The 6 healthy volunteers were all males with age range 51 to 62 years; 5 (83%) were of white race and 1 (17%) was of mixed race. Weight ranged from 73 to 91 kg, height ranged from 168 to 179 cm and body mass index ranged from 23.6 to 29.8 kg/m^2.

Overall, the healthy volunteers were appropriate for this Phase I study investigating the absorption, metabolism and excretion of [^{14}C]-saracatinib.

Summary of pharmacokinetic results

Following single oral doses of 400 mg [^{14}C]-saracatinib in healthy male volunteers, saracatinib was relatively slowly absorbed (median t_{max} 6 hours), extensively distributed outside the central compartment (mean V_{ss}/F 2993 L) and cleared moderately slowly (mean CL/F 51.5 L/h). From C_{max} the disposition was biphasic, with the terminal phase having a mean $t_{½}$ of 58.4 hours.

The plasma concentration-time profiles for M594347 (the N-desmethyl metabolite) were generally of similar shape to those of saracatinib, although the terminal half-life was longer, with a mean of 75.7 hours. The extent of exposure (AUC) of M594347 ranged between 9.93% and 25.5% of the corresponding values for saracatinib exposure.

The mean C_{max} concentration of total radioactivity in plasma was attained at either 3 or 6 hours post-dose and declined in a biphasic manner to 240 hours. The concentrations of radioactivity in plasma and blood were similar at all time points examined.

The concentrations of radioactivity in plasma were higher at all time points than measured concentrations of saracatinib plus M594347. Saracatinib represented approximately 45% of the circulating radioactivity between 6 and 72 hours. Levels declined thereafter to 27% at 240 hours. The difference between levels of saracatinib and radioactivity in plasma indicates the presence of one or more metabolites (other than M594347) in the circulation.

Although there was some variation, at the majority of time points examined the ratio of plasma to whole blood radioactivity was approximately 1.0. This indicates that the drug related radioactivity was distributed equally between the plasma fraction and the cellular components of the blood.

The mean total recovery ± SD to 240 hours for all volunteers was 85.8% ± 3.93 (ranging from 80.1 to 90.0%), with 71.7% ± 5.30 (ranging from 64.5 to 78.0%) of this recovered in faeces and 14.1% ± 2.50 (ranging from 9.3 to 16.1%) recovered in urine. The recovery of radioactivity in faeces was slow with the majority (>70%) eliminated by 144 hours. There was large variability in the speed of faecal recovery up to 168 hours post-dose due to irregular sample production at early time points. The excretion of radioactivity in urine was almost

complete by 96 hours post-dose with a mean of 11.5%. In the final collection period (216-240 hours) the mean recovery for urine and faeces combined had decreased to 1.7%.

Summary of safety results

AEs were reported for 5 of 6 (83%) healthy volunteers participating in this study. In total, 15 AEs were reported; 11 of the AEs were considered by the investigator to be causally related to investigational product. No deaths were reported, no AE was serious, none led to discontinuation of investigational product, and none was considered to be significant by the sponsor.

The most commonly reported AE was contusion (described as bruising in the right or left antecubital fossa or bruising to right or left forearm, at the site of venepuncture), which was reported for 4 of 6 (67%) healthy volunteers. Vessel puncture site haematoma and vessel puncture site pain were also reported in one of the healthy volunteers with contusion.

All AEs were considered to be of National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE v3.0) grade 1, except for vessel puncture site haematoma which was considered to be of CTCAE grade 2. AEs considered by the investigator to be causally related to investigational product were contusion (6 events in 4 volunteers), nausea (3 events in 2 volunteers), abdominal pain (1 event) and diarrhoea (1 event). All AEs were self-limiting and did not require any medication, except 1 event of headache that was managed with paracetamol.

There were no haematology, clinical chemistry, urinalysis, vital signs or ECG findings of clinical concern.