AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00025
Edition Number	1
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An Open-label Comparative Study of the Pharmacokinetics, Safety and Tolerability of ZD4054 following a 10 mg Single Oral Dose of ZD4054 to Healthy Subjects and to Subjects with Mild, Moderate and Severe Hepatic Impairment

Study dates: First subject enrolled: 17 April 2008
Last subject completed: 06 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(s)

This was a 2-centre study.

Publications

None at the time of writing this report.

Objectives

The primary objective was to characterise the pharmacokinetic profile of ZD4054 following a single 10 mg oral dose in subjects with normal hepatic function and in subjects with varying degrees of hepatic impairment.

The secondary objective of the study was to assess the safety of ZD4054 following a single 10 mg oral dose in subjects with normal hepatic function and in subjects with varying degrees of hepatic impairment.

The exploratory objective of the study was to explore changes in protein binding of ZD4054 and the subsequent effects on its pharmacokinetics in subjects with normal hepatic function and in subjects with varying degrees of hepatic impairment.

Study design

This study was an open-label, 2-centre, single-dose, parallel group study in a single country investigating the pharmacokinetic and safety profile of ZD4054 in hepatically impaired subjects and in subjects with normal hepatic function.

Target subject population and sample size

Thirty-two subjects were to be enrolled into the following groups:

- Eight evaluable subjects with normal hepatic function, matched to the hepatic impaired groups with respect to age, gender and weight (control group)
- Eight evaluable subjects with mild hepatic impairment (Child Pugh A)
- Eight evaluable subjects with moderate hepatic impairment (Child Pugh B)
- Eight evaluable subjects with severe hepatic impairment (Child Pugh C)

There were to be a minimum of 2 subjects of each sex in each group.

For inclusion in the study **hepatically impaired subjects** had to fulfil the criteria of having stable liver cirrhosis and hepatic impairment for at least 3 months prior to the start of the study.

The primary outcome variable for this study upon which sample size calculation was based is the AUC (area under the plasma concentration-time curve from time zero to infinity) of

ZD4054. Study D4320C00005 has been used to provide an estimate of the between-subject variability of AUC after an oral dose (SD of 0.35 on the log scale). Assuming that this estimate of variability was typical of the variability to be found in this study, calculations showed that in a study including 6 subjects per arm, there would be at least 80% chance that a 1-sided 95% confidence interval would exclude the possibility of a doubling in AUC. However, as the SD is based on a small number of subjects, 8 evaluable subjects per group were recruited. Regulatory guidelines suggest a minimum of 6 evaluable subjects per group. Evaluable subjects were those with pharmacokinetic data available with no violations or deviations that would have a significant impact on the pharmacokinetic parameters.

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

Single oral dose of 10 mg ZD4054. Two batches of ZD4054 were used in this study (P/4097/29 and P/5225/012 of formulation F013466).

Duration of treatment

Single dose.

Criteria for evaluation - pharmacokinetics (main variables)

Primary variable: Plasma concentrations of ZD4054 were used to determine the following pharmacokinetic parameters: maximum plasma concentration ($C_{max)}$, area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve from zero to the time of the last quantifiable sample (AUC_{0-t}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal elimination rate constant (λz), apparent clearance (CL/F), apparent volume of distribution at steady state (Vss/F) and mean residence time (MRT).

Exploratory variable: Plasma concentrations of ZD4054 were used to determine the following pharmacokinetic parameters: free C_{max}, free AUC and unbound CL/F.

Criteria for evaluation - safety (main variables)

Secondary variable: Safety and tolerability was assessed by measuring vital signs (heart rate and blood pressure), electrocardiogram (ECG), clinical chemistry, haematology and adverse events.

Statistical methods

Two analysis sets were considered in this study; the safety analysis set comprising all subjects that received a dose of study medication; and the pharmacokinetic analysis set comprising all evaluable subjects with pharmacokinetic data available with no violations or deviations that would have had a significant impact on the pharmacokinetic parameters. All evaluable data was included in the pharmacokinetic analyses.

AUC, $AUC_{(0-t)}$ and C_{max} were logarithmically transformed using natural logarithms (back-transformed results were reported). These parameters were analysed using an analysis of variance model (ANOVA) with a factor fitted for hepatic impairment status (mild/moderate/severe or normal).

The analysis was carried out comparing the ratio of geometric means (gmeans) of Child-Pugh A classified subjects (mild hepatic impairment), Child-Pugh B classified subjects(moderate hepatic impairment), and Child-Pugh C classified subjects (severe hepatic impairment) compared to control group subjects (normal hepatic function).

The results of these analyses were presented in terms of geometric means for each hepatic group, the ratio of geometric means of each hepatically impaired group compared to the normal group (mild/moderate/severe: controls) and their respective 1-sided 95% upper confidence limit (ie, the upper limit of a 2-sided 90% confidence interval (CI)).

The possibility that hepatic impairment had a clinically relevant effect on the exposure of ZD4054 was considered if the upper 1-sided 95% confidence limit for the ratio of geometric means of each hepatically impaired group compared to the normal group did not lie below the limit of 2.

Safety data including adverse events were listed and summarised by means of descriptive statistics.

Subject population

Subject disposition, key demographic data, and number of subjects in each group analysed are summarised in Table S1 below. In total, 37 subjects were enrolled, of whom 32 subjects received treatment and completed the study (5 subjects were screen failures). All 32 subjects were of Caucasian race, and all 32 subjects met the required protocol eligibility criteria. The subject population participating in this study comprised 8 subjects with normal hepatic function; 8 subjects with mild hepatic impairment (Child Pugh A); 8 subjects with moderate hepatic impairment (Child Pugh B); and 8 subjects with severe hepatic impairment. Overall the treatment groups were well balanced with regards to demographic and other baseline characteristics. There were no important protocol deviations that led to exclusion of data from the pharmacokinetic or safety summaries. No subjects received disallowed concomitant medication during the study.

Table S1 Subject population and disposition

		Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	Total (n=32)
Demographic characteristics						
Sex (n and % of subjects	Male	5 (62.5)	6 (75.0)	5 (62.5)	5 (62.5)	21 (65.6)

Table S1 Subject population and disposition

		Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	Total (n=32)
	Female	3 (37.5)	2 (25.0)	3 (37.5)	3 (37.5)	11 (34.4)
Age (years)	Mean (SD)	58.4 (2.4)	56 (5.8)	59.3 (6.3)	52 (11.3)	56.4 (7.4)
	Range	55 - 62	45 - 63	49 - 68	37 - 67	37 - 68
Race (n and % of subjects)	Caucasian	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100.0)
Subject disposition				**Number (%) subjects**		
Subjects enrolled [a]						37
Subjects who failed screening						5
Subjects who received treatment		8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100.0)
Subjects who completed study		8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100.0)

a Informed consent received.
Hepatic impairment evaluated by Child Pugh classification system

Summary of pharmacokinetic results

Following administration of a single 10 mg dose of ZD4054 to subjects with normal hepatic function and subjects with varying degrees of hepatic impairment, analysis of C_{max} indicated that there was no clinically significant difference in this parameter with degree of hepatic impairment, indicating that hepatic impairment had not affected the absorption of ZD4054.

Exposure in terms of AUC was higher in subjects with hepatic impairment as a consequence of a slower clearance of ZD4054. For subjects with mild, moderate and severe hepatic impairment, mean CL/F was 25%, 29% and 64% lower, respectively, than that seen in subjects with normal hepatic function. The AUC was 40%, 45% and 190% higher in subjects with mild, moderate and severe hepatic impairment, respectively, compared to those with normal hepatic function. A trend towards longer half-lives was observed as the severity of hepatic impairment increased.

In general, there was little difference in plasma protein binding across the four hepatic groups. The mean fraction unbound of ZD4054 (Fu %) for the subjects with normal hepatic function was 22.53% and for the subjects with mild, moderate and severe hepatic impairment was 23.38%, 20.21% and 29.17% respectively.

Summary of safety results

ZD4054 10 mg was well tolerated in this study and no new AEs of concern were seen. Headache was the most commonly reported AE (CTC grade 1 or 2). There were no deaths, serious AEs, discontinuations due to AEs, or other significant AEs reported during this study. No clinically important changes were observed in any of the clinical laboratory safety

parameters (haematology, clinical chemistry, urinalysis), vital signs (blood pressure and heart rate) or ECGs. Small reductions in systolic and diastolic blood pressures were noted following ZD4054 administration, although these changes were not considered to be clinically important. Overall the safety findings of this study do not raise any new concerns about the safety of ZD4054 10 mg.