AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2927
Study Code	D4120C00001
Edition Number	1
Date	12 August 2011

A Phase I, Single-center, Single-blind, Randomized, Placebo-controlled, Single-dose Study to Assess the Safety, Tolerability and Pharmacokinetics after Single Ascending Intravenous Doses of AZD2927 in Healthy Male Subjects

Study dates: First subject enrolled: 25 January 2011
Last subject last visit: 17 May 2011

Phase of development: Clinical pharmacology (I)

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

Study center

The study was conducted at a single hospital-based study center: Quintiles AB, Global Phase I Services, Uppsala, Sweden.

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 assess the safety and tolerability of AZD2927 following administration of single ascending intravenous doses	Adverse events, vital signs (blood pressure and pulse rate), ECG variables (RR, PR, QRS, QT, and QTcF), laboratory variables (hematology, clinical chemistry, coagulation, and urinalysis), physical examination, ophthalmologic variables, body temperature, and body weight	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics of AZD2927 following administration of single ascending intravenous doses of AZD2927	C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2\lambda z}$, CL, V_{ss}	PK

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 the time of the last measurable concentration, CL: Total plasma clearance, C_{max}: Maximum plasma concentration, ECG: Electrocardiogram, iv: Intravenous, PK; Pharmacokinetic, $t_{1/2\lambda z}$: Terminal half-life, t_{max}: Time to maximum plasma concentration, V_{ss}: Volume of distribution at steady state.

Study design

This was a Phase I, randomized, single-blind, placebo-controlled study at a single hospital-based study center to assess the safety, tolerability, and pharmacokinetics of AZD2927 following single intravenous doses to healthy male subjects to support the design and conduct of the proof of principle study for target validation in an atrial flutter population. Up to 48 healthy male subjects were to be randomized in up to 8 cohorts with 6 subjects in each cohort who received either AZD2927 or placebo in a ratio of 4:2. The investigator, the study center staff and the subjects were blinded to treatment during the clinical phase of each cohort. After each cohort a Safety Review Committee reviewed and assessed all available safety and pharmacokinetic data to make a decision on the next dose level to be administered. Subject data were unblinded during the Safety Review which was chaired by the Principal Investigator.

Target subject population and sample size

Healthy male subjects aged 18 to 45 years inclusive with a body mass index of between 19.0 and 30.0 kg/m^2 and weighing at least 50.0 kg but no more than 100.0 kg. Six subjects per cohort were enrolled in 6 cohorts, as was planned, for a total of 36 subjects.

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

AZD2927 was administered as 1-hour intravenous infusions in escalating doses starting with 5 mg. The administered doses of AZD2927 were 5 mg, 10 mg, 15 mg, 25 mg, 45 mg and 50 mg, respectively. The comparator used during the study was a placebo to match AZD2927.

Details pertaining to the investigational products are presented in Table S2.

Table S2 Details of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number
AZD2927	Solution for infusion[a], 10 mg/mL, single 1 hour intravenous administration	AstraZeneca	10-006565AZ (Expiry date: November 2011)
Placebo	Solution for infusion[a], 10 mg/mL, single 1 hour intravenous administration	AstraZeneca	10-005557AZ (Expiry date: November 2014)

a 5 µmol/mL citric acid buffer in 5% mannitol.

Duration of treatment

Each subject received a single dose of AZD2927 or placebo administered as a 1-hour intravenous infusion.

Statistical methods

No formal statistical hypothesis testing was performed, except for lack of fit tests for the dose proportionality estimation, using F-tests. The analyses of safety, tolerability, and pharmacokinetic data were summarized descriptively including tables, listings, and graphs, as appropriate.

Change-from-baseline variables were calculated for the continuous safety variables, as the post-treatment value minus the value at baseline. The baseline values are defined as the last valid measurement before administration of the investigational product. If a healthy subject was missing the baseline collection, the baseline value was treated as missing.

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. Instead the sample size was based on experience from previous similar Phase I studies with other compounds.

Subject population

In total, 36 healthy male subjects were allocated to 6 cohorts and randomized to receive either AZD2927 or placebo. In total, 24 healthy male subjects were allocated to AZD2927and

12 healthy male subjects were allocated to placebo in this study. Each subject received a single administration of the investigational product during the residential period. All subjects were included in the safety analysis set and all subjects who received AZD2927 were included in the pharmacokinetic analysis set. All enrolled subjects completed the study.

Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

As expected, the maximum plasma concentration (C_{max}) appeared in the 1 hour sample taken at stop of infusion, except for 3 subjects where the time to reach C_{max} (t_{max}) was 0.75 to 0.78 hours post start of infusion. The decline in plasma concentration was multi-exponential with a geometric mean terminal half-life ($t_{1/2\lambda z}$) of 1.53 hours over the studied dose range 5 mg to 50 mg AZD2927. Geometric mean total plasma clearance (CL) was 27.3 L/h and volume of distribution at steady state (V_{ss}) was 54.8 L. There was no indication of dose dependency in $t_{1/2\lambda z}$, CL or V_{ss}.

One subject in the 50 mg dose group exceeded the pre-defined exposure limit of 3.0 µmol/L for C_{max} with a C_{max} of 3.28 µmol/L and 1 subject in the 45 mg dose group exceeded the area under the plasma concentration-time curve from zero to infinity (AUC) limit of 6.8 µmol*h/L with an AUC of 7.80 µmol*h/L.

AUC and C_{max} increased in proportion to the dose over the range studied, as assessed by a power model.

Summary of safety results

AZD2927 administered as 1 hour intravenous infusions of 5 mg, 10 mg, 15 mg, 25 mg, 45 mg and 50 mg was well tolerated. There were no deaths, other serious adverse events, discontinuations due to adverse events, or other significant adverse events reported during the study. The 10 mg dose group was the dose group which had the most subjects reporting at least 1 adverse event (100%). Overall, a larger proportion of subjects who received placebo reported at least 1 adverse event than subjects who received AZD2927 (10 [83.3%] subjects *versus* 15 [62.5%] subjects). Overall, adverse events considered causally related by the investigator were reported by 3 (25.0%) subjects who received placebo and 4 (16.7%) subjects who received AZD2927.

The investigator considered most of the adverse events of mild intensity and no adverse events were considered to be of severe intensity. The largest proportion of the subjects reported at least 1 adverse event categorized in the System Organ Class Nervous system disorders for the placebo group (47.1%) and Infections and infestations for the AZD2927 dose groups (29.2%). However, by Preferred Term the largest proportion of patients reported at least 1 adverse event of headache for the placebo group (33.3%) and the AZD2927 dose groups (25.0%).

No safety concerns based on the reported adverse events, laboratory assessments, vital signs, electrocardiograms, physical examinations, neurological examinations or the ophthalmological examinations were identified.