AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6553
Study Code	D2580C00001
Edition Number	1
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A Phase I, Randomised, Double-Blind, Placebo-Controlled, 3-Part study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Oral Doses of AZD6553 in Healthy Volunteers (Parts A and B) and Patients (Part C) with Chronic Obstructive Pulmonary Disease

Study dates: First subject enrolled: 15 January 2010
Last subject last visit: 07 May 2010

Phase of development: Clinical pharmacology (1)

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

Study centre(s)

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 investigate the safety, tolerability and pharmacokinetics of single and multiple ascending oral doses of AZD6553 in healthy volunteers (Parts A and B) and in one cohort of patients with COPD (Part C).	Adverse events, clinical chemistry, haematology, urinalysis, 12 lead ECG, dECG, supine blood pressure, supine pulse, 24 h Lead II bedside monitoring (Part A only) Part A Plasma PK parameters: C_{max}, t_{max}, λ_z, $t_{½\lambda z}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, AUC, CL/F, V_z/F and MRT. Part B Plasma PK parameters: Day 1: C_{max}, t_{max}, $AUC_{(\tau)}$. Day 6: $C_{min,ss}$, $C_{max,ss}$, t_{max}, $AUC_{(\tau)}$. Day 8: $C_{min,ss}$, C_{maxss}, $t_{max,ss}$, $AUC_{(\tau),ss}$, $AUC_{(0\text{-}t),ss}$, $AUC_{,ss}$, $\lambda_{z,ss}$, $t_{½\lambda ,ss,}$ $V_z/F_{,ss}$, $CL/F_{,ss}$, R_{ac}. .
Secondary	**Secondary**
To measure renal clearance of AZD6553 following single (Part A) and multiple oral doses (Parts B and C).	Urine PK parameters: Part A Day 1: A_e, $F_{e(0\text{-}48)}$ and CL_R. Part B Day 1: A_e, $F_{e(0\text{-}24)}$ and CL_R Day 8: $A_{e,ss}$, $F_{e,ss(0\text{-}24)}$ and $CL_{R,ss}$.
To perform a preliminary assessment of the effect of food on the pharmacokinetic parameters of AZD6553 (Part B).	Part B Plasma PK parameters: Day 6: $C_{max,ss}$, t_{max}, $AUC_{(\tau),}$ C_{24}.

The study was stopped after completion of the first group of Part B due to a late increase in plasma concentration 24 hours post dose and lower than expected absorption. The late peak in plasma concentration was seen after administration of single doses of 30 mg, 90 mg and 270 mg AZD6553 in Part A. Part C was not conducted.

Study design

This Phase I study was designed to be conducted in 3 parts: Single Ascending Dose (SAD) (Part A), Multiple Ascending Dose (MAD) and food effect (Part B) in healthy volunteers and one multiple dose regimen in COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) category II and III patients (Part C). All 3 parts were of a randomised, parallel-group double blind and placebo controlled design.

Target subject population and sample size

Males or females of non child bearing potentials aged 18 to 60 years (inclusive). They were to have a body mass index ≥18.0 and ≤30.0 kg/m^2.

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

Tabel S2 Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD6553	Oral suspension, 1 mg/g	AstraZeneca	09-007128AZ	09-008592AZ
AZD6553	Oral suspension, 20 mg/g	AstraZeneca	09-007130AZ	09-008609AZ
Placebo AZD6553	Oral suspension	AstraZeneca	09-007127AZ	09-008623AZ

In Part A (SAD), 6 subjects were randomised to AZD6553 (2, 10, 30, 90 or 270 mg) and 2 subjects to placebo. In Part B (MAD) 6 subjects were to be randomised AZD6553 (10 mg) and 3 subjects to placebo.

Blinding and procedures for unblinding the study

AZD6553 dosing suspension and placebo were matched.

The methods for ensuring blinding and the procedures for unblinding the study are described in Section 5.4 of the CSP.

The study blind was maintained during the study.

Duration of treatment

Part A subjects received a single oral dose of AZD6553/placebo.

Part B subjects received daily oral doses of AZD6553/placebo for 8 days.

Statistical methods

Descriptive statistics were used for all parameters and variables in the study.

The effect of food on the PK parameters of AZD6553 in Part B was assessed using analysis of variance, analysing the log-transformed data (where appropriate) to assess the ratio of fed/fasted states of the PK variables. The ratio and 90% confidence interval were produced. No statistical hypothesis was tested.

Subject population

Healthy male and non-fertile female subjects were randomised into the study at 1 site. In Part A (SAD) 40 subjects and Part B (MAD) 7 subjects were randomised. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety analysis included all randomised subjects. It is of note that the majority of subjects were white males. However, the study was not designed to investigate either sex or race differences therefore, this was considered to have no effect on the integrity of the data. Overall, the treatment groups were well balanced/comparable with regards to the other demographic characteristics.

Summary of pharmacokinetic results

Plasma concentrations >LLOQ for a majority of the subjects were measurable up to 8, 24, 48, 72 and 72 hours post dose after a single dose of 2, 10, 30, 90 and 270 mg AZD6553, respectively. The geometric mean plasma concentration vs time profiles were characterised by a rapid absorption phase and extensive distribution/elimination during the first 10 hours post dose. A second peak in plasma concentration, 24 hour post dose, followed by a slower elimination phase was apparent in the 30, 90 and 270 mg dose groups.

Geometric mean C_{max} after a single dose AZD6553, given as oral suspension, appeared approximately 1 hour after dosing (t_{max}) and there was no consistent dose dependent change. However, t_{max} appeared in the second peak for 2 subjects in the 270 mg dose group, (48 and 24 hours post dose) and median t_{max} was 2.53 hours for this dose group.

The 90% CIs for $AUC_{(0-24)}$ and C_{max} in the power model did not include 1 and the increase in exposure with increasing dose was concluded to be significantly less than dose proportional. The geometric mean C_{max} and $AUC_{(0-24)}$ attained at the highest single dose, 270 mg, was well below the pre-defined limits and the variability was in general low (CV% range was 14 to 34%).

$t_{½\,\lambda z}$ varied over the dose range as there was a faster initial distribution/elimination up to 10 hours and a terminal $t_{½\,\lambda z}$ following the second peak in concentration. The precisions of the $t_{½\,\lambda z}$ estimate was considered low for several subject, especially in the lower dose groups.

V_z/F increased with increasing dose, $F_{e(0-48)}$ decreased with increasing dose and there was no apparent dose-dependent change in CL_R. This was consistent with the lower than expected increase in exposure over the dose range.

Individual plasma trough concentrations following multiple once daily oral doses of 10 mg AZD6553 indicated that steady-state was reached by Day 4. Median t_{max} was delayed by approximately 2 hours at steady-state compared to after a single dose and the exposure to AZD6553 was higher after multiple doses once daily compared to after a single dose with an accumulation ratio (R_{ac}) of 1.51. The accumulation indicated a $t_{½\lambda z}$ of approximately 15 hours and was thus as expected based on single dose data. $t_{½}$, CL/F and CL_R were comparable to after a single dose.

The 90% CI of the ratios of fed (Day 6)/fasting (Day 8) for C_{max} and $AUC_{(\tau)}$ did not include 1 and hence a significant food effect was indicated. C_{max} and $AUC_{(\tau)}$ was estimated to be approximately 2.5 and 2 times higher, respectively, during fed conditions compared to during fasting conditions. The 90% CI for the estimate of C_{24} was contained within the traditional bioequivalence bounds of 0.80 and 1.25 and hence the parameter appeared similar under fed and fasting conditions. There was no indication of a significant food effect on t_{max}.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study. All of the AEs were of either mild ormoderate intensity.

In Part A, 11 adverse events were reported; 9 after administration of AZD6553 and 2 after administration of placebo.

Two of the adverse events were of moderate intensity; influenza like illness (10 mg AZD6553) and joint dislocation (90 mg AZD6553).

Adverse events considered by the investigator to have a reasonable possibility of a relationship to AZD6553 were lethargy (2 mg), dry mouth (10 mg), influenza like illness (10 mg) and arthralgia (270 mg).

In Part B, 2 adverse events were reported; 1 after administration of AZD6553 and 1 after administration of placebo.

Head injury (accidental) was reported by a subject receiving AZD6553 and oropharyngeal pain was reported by a subject receiving placebo.

The adverse events were mild intensity and considered by the investigator to be unrelated to treatment.

No safety concerns were identified in the clinical laboratory assessments, vital signs or ECG (including 24 h lead II) measurements during the study.