AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD1446 |
| Study Code | D1950C00013 |
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# A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Modified-Release Formulations of AZD1446 in Young and Elderly Healthy Japanese volunteers after oral Single and Repeated Doses

**Study dates:** First subject enrolled: 18 September 2010
Last subject last visit: 12 December 2010

**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 one centre in Japan.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

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

| Objective | | | Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Safety | To investigate safety and tolerability of Modified-Release (MR) capsules of AZD1446 during single and repeated administrations to young and elderly healthy Japanese volunteers. | Adverse events (AEs)<br>Laboratory variables<br>Vital signs: Blood pressure, Pulse rate, Body temperature<br>Electrocardiograms (ECG)<br>Physical examination<br>Columbia-Suicide Severity Rating Scale (C-SSRS) |
| Secondary | PK | To characterize the pharmacokinetics (PK) of MR capsules of AZD1446 during single and repeated administrations to young and elderly healthy Japanese volunteers. | Day 1 and Day 7:<br>– $C_{max}$, $t_{max}$, $t_{½\lambda z}$, $AUC_{0-t}$, AUC, $AUC_{0-\tau}$, CL/F, $V_z$/F<br>Day 7 following the repeated dose in addition to the above:<br>– $C_{min}$, $t_{min}$, $C_{avg}$, fluctuation ratio, $RC_{max}$, $RAUC_{0-\tau}$ |

$C_{max}$: Maximum plasma concentration, $t_{max}$: Time to maximum plasma concentration, $t_{½\lambda z}$: Terminal half-life, $AUC_{0-t}$: Area under plasma concentration-time curve from zero to last sampling time, AUC: Area under the plasma concentration-time curve from zero to infinity, $AUC_{0-\tau}$: Area under the plasma concentration-time curve over the dosing interval, CL/F: Apparent oral plasma clearance, $V_z$/F: Apparent volume of distribution during terminal phase, $C_{min}$: Minimum plasma concentration, $t_{min}$: Time of minimum plasma concentration, $C_{avg}$: Average plasma concentration during a dosing interval, $RC_{max}$: Accumulation ratio for $C_{max}$, $RAUC_{0-\tau}$: Accumulation ratio for $AUC_{0-\tau}$

## Study design

This was a Phase I randomised double-blind placebo-controlled single centre study to assess the safety, tolerability and PK of AZD1446 MR capsules following single and repeated doses administration to healthy Japanese young and elderly volunteers. One dose level was planned for the young volunteers and maximum two dose levels for the elderly volunteers.

## Target subject population and sample size

Eight healthy Japanese young male volunteers aged 20 to 50 years and 16 elderly male and postmenopausal female volunteers aged 65 to 80 years in 1 panel and 2 panels respectively.

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

**Table S2 Details of investigational product and other study treatments**

| Investigational product | Dosage form, strength, and route of administration | Manufacturer | Formulation number | Batch number |
|---|---|---|---|---|
| AZD1446 MR | Capsule 30 mg, Oral administration | AstraZeneca R&D Sweden | D1000192 | 10-003179AZ |
| AZD1446 MR | Capsule 60 mg, Oral administration | AstraZeneca R&D Sweden | D1000214 | 10-003338AZ |
| Placebo | Capsule, Oral administration | AstraZeneca R&D Sweden | D1000240 | 10-003717AZ |

**Duration of treatment**

Each volunteers received a single dose of AZD1446 MR capsule/placebo on Day 1. Repeated dosing commenced on Day 3 with AZD1446 MR capsule/placebo once daily during 5 days.

**Statistical methods**

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability and PK were summarised descriptively including tables, listings and graphs, as appropriate.

**Subject population**

In total 8 young (20 to 45 years) and 16 elderly healthy volunteers (65 to 78 years) were randomised to AZD1446 (n=18) or placebo (n=6) at 1 study site. All healthy volunteers received 6 administrations of study drug and completed the study.

There were no protocol deviations in this study. All volunteers were included in the safety and PK analysis sets.

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

**Summary of pharmacokinetic results**

Following single oral dose administration of 180 mg AZD1446 given as a MR formulation in young and elderly healthy volunteers, median $t_{max}$ was 3 h in young and elderly healthy volunteers. Geometric mean $C_{max}$ values were 2180 nmol/L and 3080 nmol/L, and geometric mean AUC values were 15200 h*nmol/L and 20900 h*nmol/L in young and elderly healthy volunteers. The corresponding geometric mean $t_{½\lambda z}$ values were 7.7 h and 9.1 h, and geometric mean CL/F values were 49 L/h and 36 L/h, respectively.

Following multiple oral dose administration of 180 mg for 5 days, median $t_{max}$ was 2 h and 2.5 h in young and elderly healthy volunteers. Geometric mean $C_{max,ss}$ values were 2220 nmol/L and 3250 nmol/L, and geometric mean $AUC_{\tau,ss}$ values were 14100 h*nmol/L and 20600 h*nmol/L in young and elderly healthy volunteers. The corresponding geometric mean $t_{½\lambda z}$ values were 7.6 h and 8.9 h, and geometric mean $CL_{ss}/F$ values were 53 L/h and 36 L/h, respectively. The $t_{max}$, CL/F and $t_{½\lambda z}$ were comparable following single and multiple dose administration and $AUC_{\tau}$ (Day 7)/AUC (Day 1) was close to 1 and thus there was no indication of time dependent PK. The mean accumulation ratios ($R_{ac}$) (Day 7/Day 1) were 1.0 to 1.1 based on $C_{max}$ and 1.0 to 1.2 based on $AUC_{\tau}$, suggesting negligible accumulation of AZD1446 in plasma after once daily multiple dosing.

The steady state exposure to AZD1446 ($AUC_{\tau,ss}$ and $C_{max,ss}$) at 180 mg was approximately 50% higher in elderly healthy volunteers than in young healthy volunteers.

In two elderly dosing panels (90 and 180 mg), there were no remarkable differences in geometric mean $CL_{ss}/F$, $t_{½\lambda z}$ and $V_{z,ss}/F$.

**Summary of safety results**

There were no deaths, other serious adverse events, AEs leading to discontinuation of investigational product, or any other significant adverse events in the study.

In total, 2 AEs (diarrhoea and contusion) were reported in 2 elderly volunteers and both AEs were mild intensity. No AEs provoked by study specific procedure, ie, orthostatic challenge, were reported in the study.

There were no clinically significant changes or findings in any laboratory safety variables, vital signs, ECG recordings, physical examination assessment and C-SSRS in healthy volunteers exposed to AZD1446 during the study.