AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6280
Study Code	D0850C00002
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A Phase I, Single-Center, Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AZD6280 When Given in Multiple Ascending Oral Doses in Healthy Male and Healthy Female Subjects of Non-Child-Bearing Potential

Study dates: First healthy volunteer enrolled: 10 March 2008
Last healthy volunteer completed: 21 July 2008

Phase of development: Clinical pharmacology (I)

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

Study center(s)

Forty-eight healthy volunteers were randomized at a single study center (
). The first healthy
volunteer was enrolled on 10 March 2008.

Publications

None at the time of writing this report.

Objectives

Primary Objective

The primary objective of the study was to assess the safety and tolerability of multiple ascending oral doses of AZD6280 compared to placebo by assessment of adverse events (AEs), vital signs, physical examinations, laboratory parameters, and electrocardiograms (ECGs).

Secondary Objectives

The secondary objectives of the study were

1. To evaluate and characterize the pharmacokinetics (PK) of AZD6280 when given orally in multiple ascending doses by assessment of drug concentration in plasma and urine

2. To evaluate the pharmacodynamic (PD) effects of AZD6280 on selected psychometric (cognitive and psychomotor) assessments and subjective effect measures using Visual Analogue Scale (VAS), Modified Wilson Sedations Scale, and CogState battery

3. To evaluate time dependencies in the PK of AZD6280 after repeated dosing with regard to auto induction and indirect assessment of cytochrome P450 (CYP) 3A4 activity

4. To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety, and tolerability of AZD6280

Study design

This was a single-center, double-blind, placebo-controlled, multiple ascending dose study. In this study, each healthy volunteer participated in 1 of the 4 dose panels. Each dose panel included 12 volunteers randomized 3 to 1 (AZD6280 to placebo). Panel A consisted of administration of AZD6280 10 mg or matching placebo once a day (qd) on Day 1 and on Days 3 through 9. Panel B consisted of administration of AZD6280 20 mg or matching placebo qd on Day 1 and on Days 3 through 9. Panel C consisted of administration of AZD6280 5 mg or matching placebo qd on Day 1, twice a day (bid) on Days 3 through 8, and

qd on Day 9. Panel D consisted of administration of AZD6280 30 mg or matching placebo qd on Day 1 and on Days 3 through 9.

Target healthy volunteer population and sample size

Men and women between the ages of 18 and 55 years (inclusive) were eligible for the study. Women with child-bearing potential were not eligible. Approximately 48 healthy volunteers were planned to provide 12 volunteers in each of the 4 dose panels.

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

AZD6280 was provided as 5- and 20-mg oral capsules (batch numbers 2000115157 and 2000115155, respectively). Matching placebo capsules were also provided (batch numbers 2000115476 and 2000115152, respectively). AZD6280 was administered as a 5-mg dose administered qd on Days 1 and 9 and bid on Days 3 through 8 or as 10-, 20-, or 30-mg doses qd on Day 1 and on Days 3 through 9.

Duration of treatment

The duration of each healthy volunteer's participation was approximately 51 days, including a visit during the 30-day screening period, a 13 day/12-night confinement period (which included 8 days of study drug administration), and a follow-up visit 7 to 10 days after discharge from the study center.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

Blood samples were analyzed to determine plasma concentrations of AZD6280. PK parameters were separately generated for samples obtained following a single dose and following multiple doses. PK parameters included the following: time to reach maximum plasma concentration following drug administration (t_{max}), elimination half-life in plasma ($t_{1/2\lambda z}$), maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), apparent oral clearance (CL/F), apparent fraction of AZ6280 dose excreted unchanged in urine up to 48 hours post-dose (F_e), renal clearance (CL_R), accumulation ratio of AUC ($R_{[AUC]}$), and temporal change parameter (TCP).

Time dependencies in the PK of AZD6280 after repeated dosing with regard to auto induction and indirect assessment of CYP3A4 activity were to be examined with the minimum plasma trough drug concentration after repetitive dosing before steady state is reached (C_{min}), AUC on Day 1 compared to that of Day 9, and the 6-beta-OH-cortisol/cortisol ratio in urine.

PD effects of AZD6280 on selected psychometric assessments were evaluated, including the Bond-Lader VAS, Modified Wilson Sedation Scale, and CogState Battery.

Criteria for evaluation - safety (main variables)

Safety and tolerability were assessed by the nature and incidence of AEs, abnormalities in vital signs assessments (including supine and standing blood pressure and pulse rate, oral

body temperature, and respiratory rate), physical examination, ECGs, clinical laboratory parameters (hematology, clinical chemistry, and urinalysis), and ataxia assessments.

Criteria for evaluation - genetics (main variables)

A blood sample was collected only from volunteers who gave written informed consent for collection and analysis of genetic samples. Genetic testing results were not part of this study.

Statistical methods

No formal hypothesis testing was performed. The data were summarized using descriptive statistics with volunteers assigned to 5 groups based on regimen (ie, 1 placebo group [pooled qd and bid] and 4 AZD6280 groups: 5 mg bid, 10 mg qd, 20 mg qd, and 30 mg qd). Summary statistics for continuous data might include the mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum. Summary statistics for categorical data included the frequency and proportion.

Subject population

In total, 48 healthy volunteers, all male, were randomized into the study at the single study center. (The inclusion criteria allowed female healthy volunteers of non-child-bearing potential; however, no females were enrolled.) Overall, the regimen groups were comparable with regard to demographic characteristics. The ages and body mass indices for all groups were similar (means between 32.11 and 38.58 years and between 25.50 and 27.61 kg/m^2, respectively). Notably, all groups included between 44.4% and 100% Black volunteers.

Forty-seven volunteers completed the regimen. No protocol deviations were reported. One healthy volunteer receiving AZD6280 20 mg qd did not complete the regimen due to a serious adverse event (SAE) that was not related to AZD6280, and 2 other volunteers discontinued the study after completing the regimen (lost to follow-up).

The PK of AZD6280 was well characterized following single-dose administration and at steady state for all dose groups in this study.

(a) Single-dose pharmacokinetic parameters

Following single-dose oral administration, AZD6280 was rapidly absorbed for the 5-mg bid, 10-mg qd, 20-mg qd, and 30-mg qd dose with median t_{max} values of 1 hour for each dose group on Day 1. The geometric mean $t_{1/2\lambda z}$ values ranged from 11.7 (30 mg qd) to 18.1 hours (10 mg qd). The geometric mean C_{max} ranged from 59.4 (5 mg bid) to 351 ng/mL (30 mg qd). The geometric mean AUC ranged from 291 (5 mg bid) to 1614 h·ng/mL (30 mg qd). The CL/F was between 15.3 (20 mg qd) and 18.6 L/h (30 mg qd).

The geometric mean F_e was always below 0.25% of the dose. CL_R of AZD6280, ≤0.096 L/hr, was considered to be low. Therefore, the renal elimination of AZD6280 was considered to be insignificant.

In general, considerable inter-subject variability was observed in PK parameters, and this variability appeared to be independent of dose.

(b) Multiple-dose pharmacokinetic parameters

Following multiple oral dose administrations, AZD6280 was rapidly absorbed after the 5-mg bid, 10-mg qd, 20-mg qd, and 30-mg qd doses with median t_{max} values of 1 hour for all dose groups on Day 9. The geometric mean $t_{1/2\lambda z}$ ranged from 13.8 (30 mg qd) to 18.5 hours (20 mg bid), similar to Day 1 results. The geometric mean C_{max} ranged from 96.4 (5 mg bid) to 348 ng/mL (30 mg qd). Generally, the C_{max} values for Day 9 were slightly higher than those for Day 1, except for the 5-mg bid group (significantly higher) and the 30-mg qd group (essentially no change). The geometric mean AUC ranged from 793 (5 mg bid) to 2250 hr·ng/mL (20 mg qd). The AUC values on Day 9 were higher than those for Day 1. The CL/F values on Day 9 were between 12.7 (5 mg bid) to 18.2 L/h (30 mg qd), similar to Day 1 results.

Similar to observation at Day 1, the renal elimination of AZD6280 was considered to be insignificant. F_e values were all below 0.10% of the dose. The CL_R values of AZD6280 were all below 0.03 L/h.

The geometric mean $R_{(AUC)}$ values were 2.11, 1.49, 1.40, and 1.19 for the 5-mg bid, 10-mg qd, 20-mg qd, and 30-mg qd dose groups, respectively. The 5-mg bid regimen had a higher accumulation ratio than 10-mg qd regimen. Geometric mean TCP values were 1.35, 1.1, 1.06, and 1.02 for the 5-mg bid, 10-mg qd, 20-mg qd, and 30-mg qd dose groups, respectively.

(c) Time dependencies

Following multiple administration of AZD6280, consistent with the terminal half-lives, apparent steady-state plasma levels were reached after 3 to 4 days at all doses. The TCP (which is the ratio of the AUC on Day 9 to the AUC on Day 1) values ranged from 1.02 to 1.35, close to 1 though with profound variability. These results suggest that the PK properties of AZD6280 are time-independent. $R_{(AUC)}$ values for both qd (1.19 to 1.49) and bid (2.11) regimens were as expected and consistent with the elimination half-life from both single-dose and multiple-dose kinetic data.

(d) Auto induction

Based on the comparison of Days 1 and 9 values for C_{min} and AUC, no evidence of auto induction was apparent.

Due to an error in collection and reporting for 6-beta-OH cortisol/cortisol, data were not available for interpretation in this study.

Summary of pharmacodynamic results

There was no drug-related effect on the self report of mental status on any of the Bond-Lader VAS items or the Modified Wilson Sedation assessments. Analysis of the CogState battery results suggest that AZD6280 exerts subtle effects on psychomotor and attention functions and can impair these aspects of cognition at a dose of 30 mg qd. There were small to moderate benefits in psychomotor and attention function associated with doses of 5 mg bid and 10 mg qd and no systematic effects for any of the cognitive functions at 20 mg qd.

Summary of pharmacokinetic/pharmacodynamic relationships

Exposure response around pharmacodynamic effects was not performed in this study.

Summary of pharmacogenomic results

As planned, samples were collected, and results will be reported at a later date.

Summary of safety results

Forty-eight healthy male volunteers were enrolled in the study: 36 volunteers received AZD6280 in 4 dose groups (5 mg bid, 10 mg qd, 20 mg qd, and 30 mg qd), and 12 volunteers received placebo and comprised a single group. Similar percentages of volunteers in each group experienced AEs (ranging from 66.7% to 88.9%) and treatment-related AEs (ranging from 50.0% to 77.8%). The incidence of AEs and treatment-related AEs (as determined by the investigator) did not appear to be dose related. However, both the number of AEs and the number of treatment-related AEs were highest for the highest dose group (30 mg qd). In this study, there were no deaths, 1 SAE, 1 AE leading to discontinuation (DAE), and no other significant AEs. (The SAE and DAE were both due to a single event, a volunteer receiving AZD6280 20 mg qd experienced a severe-intensity subcutaneous abscess not related to AZD6280.) All other AEs were mild in intensity (National Cancer Institute Common Toxicity Criteria AE Grade 1). All occurrences of the most common AEs (somnolence and dizziness) were assessed by the investigator as related to the study drug. The 20-mg and 30-mg groups had higher percentages for somnolence and dizziness. Based on the limited number of volunteers evaluated in this study, there was no evidence of withdrawal-related AEs or other dependency issues at any dose (up to 30 mg qd) during the study or during the post-treatment follow up period. In addition, there were no signs or reports of respiratory depression during the study. There was no drug-related effect on the ataxia assessments; ataxia scales did not reveal any severe or significant imbalance in any regimen group. There were no clinically relevant findings noted in vital sign, clinical laboratory, or ECG results. The predetermined stopping criteria for this study were not met. No significant tolerability issues were identified for AZD6280 dosing up to 30 mg once daily of for 7 days, and the maximum tolerated dose (MTD) was not achieved.

Conclusion(s)