AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9831C00008
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A Phase I, open, randomized non-comparative parallel group study of potential cytochrome P450 3A induction after repeat twice daily oral dosing with 100 and 500 mg AZD1981 tablets for 14 days to healthy male volunteers with single oral doses of midazolam 7.5 mg

Study dates: First healthy volunteer enrolled: 9 March 2009
Last healthy volunteer completed: 9 April 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

The first healthy volunteer (hereafter referred to as subject) was enrolled on 9 March 2009 and the last subject completed the study on 9 April 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate if the exposure of midazolam was clinically significantly changed by 14 days of exposure to AZD1981 by assessment of area under the plasma concentration-time curve from 0 to infinity (AUC) and maximum plasma concentration (C_{max}) of midazolam.

The secondary objectives of the study were

1. To explore if the concentration of endogenously formed 4β-hydroxycholesterol was significantly increased by AZD1981 by assessment of the plasma concentration of 4β-hydroxycholesterol after an overnight fast

2. To estimate additional basic systemic pharmacokinetic (PK) variables of midazolam before and after 14 days of exposure to AZD1981

3. To estimate basic systemic PK variables of AZD1981 after repeated administration during 14 days

4. To evaluate tolerability and safety of AZD1981 when dosed with midazolam by assessment of reported adverse events (AEs) and clinical laboratory tests

In addition, exploratory objectives of the study were

1. To assess the effect of acidification and refrigerated centrifugation on the stability of selected plasma samples

2. To collect and store DNA for future exploratory research into genes that may influence response ie, distribution, safety, tolerability and efficacy of AZD1981 treatment

The results from the stability evaluation and the future exploratory genetic research are not reported in the clinical study report.

Study design

This was a Phase I, open-label, randomized parallel group study comprising 2 doses of AZD1981, which is developed as an anti-inflammatory drug for treatment of patients with respiratory diseases such as asthma and chronic obstructive pulmonary disease. A single 7.5 mg oral dose of midazolam (used as a probe to assess possible clinically relevant effects of AZD1981 on the induction of cytochrome P450 3A [CYP3A]) was administered on Day 1 before administration of 100 mg or 500 mg oral AZD1981 tablets. The AZD1981 tablets were administered in the morning and evening over 14 consecutive days (Days 2 to 15), and a further single 7.5 mg oral dose of midazolam was given alone on the final treatment day, Day 16.

Target subject population and sample size

The target population was healthy white male volunteers aged 18 to 55 years with a body mass index between 19 and 30 kg/m^2 and a weight of at least 50 kg and no more than 100 kg. The subjects were to be non-smokers or ex-smokers who had stopped smoking for >6 months prior to Visit 1 (pre-entry).

A total of 28 subjects were planned to be randomized in order to ensure that at least 12 subjects participated in each dose group.

Investigational product and any other study treatments: dosage, mode of administration and batch numbers

Investigational products	Dosage and mode of administration	Batch number
AZD1981	50 mg oral tablet (100 mg twice daily [bid])	H2066-01-02-01 /09-000713AZ
AZD1981	250 mg oral tablet (500 mg bid)	H2032-01-03-01 /09-000716AZ
Midazolam	1 mg/mL oral solution (1 single dose of 7.5 mg on 2 separate occasions)	2378020 and 2429861

Duration of treatment

A single 7.5 mg oral dose of midazolam was administered on Day 1 before administration of 100 mg or 500 mg AZD1981 in the morning and evening over 14 consecutive days (Days 2 to 15). A further single 7.5 mg oral dose of midazolam was given on the final treatment day, Day 16.

Criteria for evaluation - pharmacokinetics (main variables)

The primary PK parameters were AUC and C_{max} of midazolam on Day 1 and 16.

The secondary PK parameters were

- 4β-hydroxycholesterol plasma concentration pre-dose on Day 1 and Day 15
- Day 1 and Day 16 midazolam: area under the plasma concentration-time curve from 0 to the time of the last measurable concentration (AUC_{0-t}), time to maximum plasma concentration (t_{max}), apparent plasma clearance (CL/F), terminal half-life ($t_{½\lambda z}$), apparent volume of distribution during terminal phase (V_z/F) and mean residence time (MRT)
- Day 15 AZD1981: area under the plasma concentration-time curve during a dosing interval (τ) at steady state (AUC_{τ}), maximum plasma concentration during a dosing interval at steady state ($C_{ss,max}$), time to maximum plasma concentration at steady state ($t_{max\ ss}$) and the apparent plasma clearance at steady state (CL_{ss}/F), and the last Day 12 to Day 15 AZD1981 plasma concentration measured before the next dose in a repeated dosing study (C_{trough})
- AZD1981 plasma concentration (for assessment of the effect of acidification and refrigerated centrifugation on the stability of selected plasma samples; not reported in the clinical study report)

Criteria for evaluation - safety (main variables)

Safety and tolerability of AZD1981 when dosed with midazolam was assessed by AEs and clinical laboratory tests. In addition, vital signs assessments, physical examinations and ECG were used to monitor safety.

Statistical methods

A linear mixed effects model was used to assess the CYP3A induction potential by comparing AUC and C_{max} of midazolam pre- and post-dose AZD1981. The model included time, group (100 mg or 500 mg AZD1981) and time*group as fixed factors, and subject as a random factor. The analyses were based on log_e-transposed variables and the results were exponentially back-transformed in order to provide estimates of the true ratios post-dose/pre-dose. Least squares mean point estimates and corresponding 95% confidence intervals (CIs) were presented by dose group. If deemed relevant, $AUC_{(0-t)}$ of midazolam could be analyzed and presented in the same way as AUC and C_{max}.

Correspondingly, the exposure levels of 4β-hydroxycholesterol were assessed in a model with 4β-hydroxycholesterol plasma concentration as the response variable.

Subject population

A total of 28 subjects were planned to be randomized in this study, and 35 subjects were enrolled (consented) and 28 subjects (14 in each dose group) aged between 18 and 28 years were randomized to participate in the study. The first subject was enrolled on 9 March 2009

and the last subject completed the study on 9 April 2009. The number of subjects who completed the study was 26 (13 in the 100 mg dose group and 13 in the 500 mg dose group).

Two (2) subjects were discontinued from the study due to AEs. One (1) subject in the 100 mg AZD1981 dose group was discontinued due to vomiting, and 1 subject in the 500 mg AZD1981 dose group was discontinued due to urticaria.

All 28 randomized subjects were included in the safety population, and 26 subjects (all except the 2 subjects that were discontinued) were included in the PK population.

The number of subjects and their demography and baseline characteristics were in line with the population that was intended to be included in the study, and the dose groups were comparable in terms of demographics.

Summary of pharmacokinetic results

Oral administration of AZD1981 slightly suppressed plasma exposure of orally administered midazolam, a typical substrate for CYP3A. This induction of metabolism was small and only perceived at 500 mg AZD1981 in the AUC of midazolam. The decline in AUC after 7.5 mg of the CYP3A substrate was statistically significant ($AUC_{post\text{-}AZD1981}/AUC_{pre\text{-}AZD1981}<1$) after AZD1981 500 mg twice daily (geometric mean 0.73; 95% CI, 0.64-0.84) but not after AZD1981 100 mg twice daily (geometric mean 0.90; 95% CI, 0.79-1.04). This observed effect is considered to be of negligible clinical relevance.

Oral administration of AZD1981 increased the morning plasma concentration of 4β-hydroxycholesterol, a metabolite of cholesterol and endogenous biomarker of CYP3A activity. This effect on CYP3A was statistically significant after both AZD1981 100 mg bid (geometric mean 1.30; 95% CI, 1.19-1.42) and 500 mg bid (geometric mean 1.22; 95% CI, 1.12-1.33).

Summary of pharmacogenetic results

Any future genetic analyses will be reported separately.

Summary of safety results

No safety or tolerability concerns were identified in this study. There were no serious adverse events. Two (2) subjects, 1 in each dose group, discontinued due to AEs (vomiting and urticaria, respectively). All AEs were of mild or moderate intensity. Based on subject incidence, the most common treatment emergent AEs were somnolence (100 mg AZD1981) and somnolence and dizziness (500 mg AZD1981), and the most common treatment emergent AE that was judged by the Investigator to be related to treatment was somnolence (100 mg and 500 mg AZD1981). Somnolence and dizziness were the most common AEs reported post midazolam treatment on Day 1 or post midazolam treatment on Day 16. Therefore, it is likely that the treatment related AEs were caused by midazolam. There were no clinically relevant changes in clinical laboratory, ECG or vital signs variables.