The safety, tolerability and pharmacokinetics of AZD5069, a novel CXCR2 antagonist, in healthy Japanese volunteers

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Background

- AZD5069 is a reversible antagonist at the human CXC chemokine receptor-2 (CXCR2), with potential as an oral treatment for inflammatory conditions such as chronic obstructive pulmonary disease (COPD) and severe asthma.
- Neutrophils appear to be the dominant inflammatory cells in COPD and in some patients with severe asthma.[1,2] The CXCR2 receptor plays a key role in the recruitment of neutrophils to the lung.[1,3]
- CXCR2 antagonists are thought to reduce neutrophilic inflammation in the lung. As a result, mucus production and neutrophil proteinase-mediated tissue destruction may also be reduced.[3–5]

Primary objective

- To assess the safety, tolerability and pharmacokinetics of single and multiple daily dosing of AZD5069 in healthy Japanese subjects.

Methods

Study design

- A phase I, randomised, double-blind, placebo-controlled, single-centre, six cohort study (ClinicalTrials.gov identifier: NCT01100047; study code: D3550C00005).
- Subjects received a single dose of AZD5069 (10–120 mg) or placebo on day 1.
- From days 4–10, subjects received twice-daily doses of AZD5069 (10–80 mg) and a single dose on day 11, or placebo. There was no multiple-dose phase after the 120 mg dose.

Subjects

- Healthy Japanese males aged ≥20 and ≤65 years.

Assessments

- Safety and tolerability
  - Adverse events (AEs), laboratory variables, vital signs and electrocardiograms (ECGs) were assessed.
- Pharmacokinetics
  - AZD5069 pharmacokinetics were assessed by non-compartmental analysis.
  - Variables included area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), terminal half-life ($t_{1/2}$) and plasma clearance (CL/F).

Results

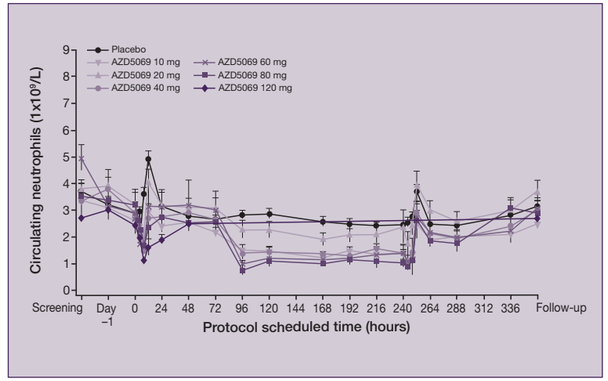
Subject demographics

- All subjects were healthy Japanese males (n=63).
- Subjects were aged 22–39 years, with a body mass index (BMI) of 18.3–26.8 kg/m^2.
- In each cohort, subjects were balanced in terms of age, height, weight and BMI.

Safety and tolerability

- AZD5069 (≤120 mg as single doses, ≤80 mg twice daily) was well-tolerated with an acceptable safety profile.
  - There were no deaths or any other significant drug-related AEs.
  - 28 subjects reported 46 AEs.
  - AEs were not dose-dependent.
  - All AEs were of mild intensity.
- A number of subjects were withdrawn due to expected persistently low blood neutrophil counts, particularly at high doses.
- Two subjects were withdrawn because of raised high sensitivity C-reactive protein; both had concurrent infections.
- Redistribution of neutrophils was more marked as plasma AZD5069 concentrations increased.
- Mean blood neutrophil counts were generally recovering at 12 hours post-dose (Figure 1).

Figure 1. Mean blood neutrophil counts after AZD5069 dosing (safety analysis set)

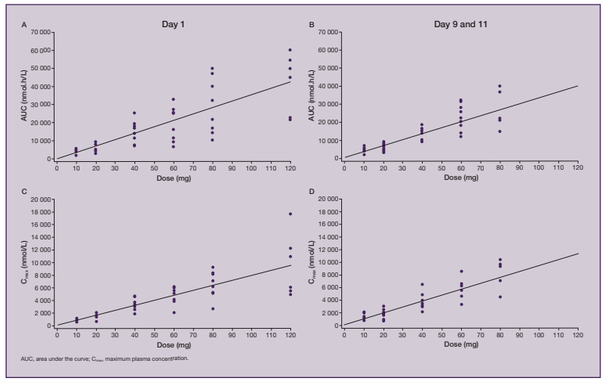


- There were no clinically relevant AZD5069-related changes in blood pressure or heart rate during the study.
- All ECG data were within the physiological range for the studied population.

Pharmacokinetic results

- Steady-state was reached within 2–3 days following twice-daily dosing, with no, or minor drug accumulation.
- The pharmacokinetics of AZD5069 appeared independent of dose and day.
  - Absorption was rapid with median t_{max} of 1–3 hours.
  - Geometric mean $t_{1/2}$ was 8.1–23.3 hours.
  - Geometric mean CL/F was 4.7–8.3 L/hour.
- AUC and C_{max} increased approximately dose-proportionally with single and multiple doses over the dose-range studied (Figure 2).

Figure 2. AUC (A, B) and C_{max} (C, D) values for AZD5069 dosing



Conclusions

- AZD5069 was well-tolerated in this study population of healthy Japanese subjects, with an acceptable profile in terms of AEs, ECGs and vital signs.
- An expected redistribution of neutrophils was observed, consistent with that seen in Caucasians; this was more marked at higher concentrations of AZD5069.
- AZD5069 was rapidly absorbed, with dose-proportional systemic exposure.
- No safety concerns were identified to preclude further evaluation of AZD5069 in future studies.

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