AZD5069 is 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 The CXCR2 receptor plays a key role in the recruitment of neutrophils to the lung.1,2

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.3,4

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 1, randomised, double-blind, placebo-controlled, single-centre, six cohort study (ClinicalTrials.gov identifier: NCT01000047; study code: D3550CD00005).

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.

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/m².

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– A number of subjects were withdrawn due to expected persistently low blood neutrophil counts, particularly at high doses.

– Two subjects were withdrawn because of raised high sensitivity C-reactive protein; both had concurrent infections.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).

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).

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.

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).

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

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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References