AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4818
Study Code	D3540C00004
Edition Number	1
Date	24 June 2008

A double blind, randomised, placebo-controlled, crossover (single centre) study in healthy men (aged 18-45 years) to investigate the effect of multiple dosing (7 days bid) of inhaled AZD4818 at different dose levels on white blood cells and inflammatory markers in induced sputum and blood after oral inhalation of lipopolysaccharide (LPS)

Study Dates	First healthy volunteer enrolled: 7 January 2008 Last healthy volunteer completed: 4 March 2008
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 study was performed at a single centre: Clinical Pharmacology Unit (CPU), Medical Science, AstraZeneca R&D Lund, SE-221 87 Lund, Sweden.

Publications

None at the time of this report.

Objectives

The primary objective was to investigate the effect of multiple dosing of inhaled AZD4818 at different dose levels on neutrophils and monocytes in induced sputum after oral inhalation of lipopolysaccharide (LPS).

The secondary objective of the study was to investigate the effect of inhaled AZD4818 on other white blood cells and inflammatory markers in induced sputum and blood after oral inhalation of LPS.

In this study it was optional for the healthy volunteers to permit collection of pharmacogenetic samples for possible retrospective pooled analysis to investigate any genetic influence on pharmacokinetic (PK), pharmacodynamic (PD) and safety profiles.

Study design

Double blind, randomised, placebo-controlled, crossover (single centre) study to investigate the effect of multiple dosing (twice daily for 7 days) of inhaled AZD4818 at different dose levels on white blood cells and inflammatory markers in induced sputum and blood after oral inhalation of LPS. The design was adaptive, permitting three dose levels to be tested in three different groups, starting with the highest dose (800 μg bid) to the first group of healthy volunteers. Each dose group was to be evaluated before proceeding to the next dose group. If the interim analysis indicated negative outcome with regard to inflammatory cells in induced sputum, primarily neutrophils and monocytes, study design allowed for premature termination.

In each group 24 healthy volunteers were to participate and perform a 2-period crossover study, which comprised 5 visits; Visits 1-2 (pre-entry), Visits 3-4 (study assessments) and Visit 5 (follow up).

Target healthy volunteer population and sample size

Healthy men aged 18 to 45 years. At most 72 subjects were to be randomised into the study; 24 at each dose level.

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

AZD4818 Turbuhaler, dry powder for inhalation, 400 µg/dose, 60 doses.
Batch number: 07-012069AZ

Placebo to AZD4818 Turbuhaler, dry powder for inhalation, 60 doses.
Batch number: 07-012008AZ

Duration of treatment

Each subject received AZD4818 or placebo bid for 7 days in a crossover fashion. The treatments were separated by a washout period of at least 21 days between the LPS challenges.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

- *Pharmacodynamic variables*

Primary outcome variables

- number of neutrophils and monocytes in induced sputum.

Other outcome variables

- White blood cells other than neutrophils and monocytes in induced sputum
- Inflammatory mediators LTB4, TNFα, IL-8 and MMP-9 in induced sputum
- Other inflammatory mediators (IL-6, IL-1b, MCP-1, GM-CSF, RANTES, MDC, TNFRI, TNFRII, MIP-1b, IP-10) in induced sputum
- White blood cells and differential in blood
- SAA and CRP in blood.

- *Pharmacokinetic*

individual peak plasma concentration (C_{max}) and truncated area under the curve from zero to 12 hours ($AUC_{(0-12h)}$)

Criteria for evaluation - safety (main variables)

incidence and nature of adverse events (AEs), vital signs (blood pressure, pulse and body temperature), spirometry, electrocardiogram (ECG) and safety laboratory analyses

Statistical methods

The primary outcome variables were the neutrophil and monocytes count in induced sputum. These were analysed with a multiplicative 2-period crossover multivariate ANOVA; the logarithm of the count is modelled additively with treatment, period and healthy volunteer as factors. The mean treatment difference and its confidence limits for each variable were then exponentiated to make a claim about the ratio of geometric means of the count, for AZD4818 to placebo.

The other sputum variables and the pharmacodynamic variables measured in blood were analysed similarly. Pharmacokinetics, spirometry, AEs, laboratory data, vital signs and ECG-data were analysed descriptively.

Subject population

All 24 subjects allocated to treatment were white men between the ages of 19 to 40 years (mean, 26.4 years). One subject discontinued the study before completing the first period due to an AE. All 24 subjects were analysed for safety. The PD and PK analyses are based on subjects with data from both treatment periods, ie, 21 to 23 subjects.

Summary of efficacy results

Not applicable

Summary of pharmacokinetic results

All subjects were exposed to AZD4818.

Summary of pharmacodynamic results

No differences between active treatment and placebo were shown for the primary outcome variables, number of neutrophils and monocytes in induced sputum, in the highest dose group given AZD4818 at a dose of 800 µg bid for 7 days. Similarly, there were no apparent differences between AZD4818 and placebo in the number of the other white blood cells or inflammatory markers in induced sputum and blood after LPS challenge.

In accordance with the study protocol, lower doses of AZD4818 were not administered due to the negative outcome at the highest dose level.

Summary of pharmacokinetic/pharmacodynamic relationships

Correlation was not investigated due to lack of effect on the PD variables.

Summary of safety results

Treatment with AZD4818 was safe and well tolerated. After administration of LPS, majority of subjects experienced the expected mild and transient flu-like symptoms. The incidence of AEs after administration of AZD4818 was similar to placebo. The most frequently reported adverse events were influenza like illness and headache, reported at a similar rate after both treatments. No deaths, serious adverse events, or other significant adverse events occurred in the study. One subject discontinued due to an AE.

No clinically important differences in clinical laboratory parameters were observed between AZD4818 and placebo. There were no differences between the treatment groups in vital signs, ECG or lung function as assessed by spirometry.