Clinical Study Report Synopsis

Drug Substance	AZD9819
Study Code	D3020C00001
Edition Number	1
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A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group, 2-part Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Inhaled Doses of AZD9819 in Healthy Subjects

Study dates: First subject enrolled: 16 August 2010
Last subject last visit: 23 February 2011

Phase of development: Clinical Pharmacology (1)

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

Study centre

The study was conducted at a single study centre in the United Kingdom (Quintiles Drug Research Unit at Guy's Hospital, London).

Publications

None at the time of writing this Clinical Study Report (CSR).

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To assess the safety and tolerability of AZD9819 following inhaled administration of single and multiple ascending doses and to estimate the maximum tolerated dose (MTD; if within predefined exposure limits)	Adverse events (AEs), supine electrocardiograms (ECGs), supine blood pressure and pulse rate, physical examination, body temperature, laboratory safety assessments (haematology, clinical chemistry, urinalysis), and lung function (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC])	Safety
Secondary		
To evaluate the pharmacokinetics (PK) of AZD9819 in plasma after single and repeated inhaled doses. To evaluate exposure of subjects to the metabolite AZD6553 in plasma	Where possible, the following PK parameters were determined for AZD9819 and AZD6553: C_{max}, t_{max}, $AUC_{(0-t)}$ (calculated for all profiles) $t_{½\lambda z}$ (not calculated on Day 1 multiple dosing) AUC, AUCextrap, MRT (single dose only) $AUC_{(0-24)}$ (single dose and Day 1 multiple dose only) AUC_{τ}, C_{av} (multiple dose only [Day 10]) CL/F, V_z/F (only AZD9819 single dose) After multiple doses – linearity index (ratio AUC_{τ} last dose/AUC single dose) and accumulation (ratio AUC_{τ} last dose/AUC_{0-24} single dose) were calculated	PK
Exploratory		
To collect plasma and urine samples for possible exploratory analysis of further metabolites of AZD9819	Not applicable	PK
To collect and store deoxyribonucleic acid (DNA) for possible future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, and tolerability) to AZD9819	Not applicable	Pharmacogenetics

AUC Area under plasma concentration time curve from zero to infinity
$AUC_{(0-t)}$ Area under plasma concentration time curve from zero to last quantifiable concentration
$AUC_{(0-24)}$ Area under the plasma concentration-time curve from zero to 24 hours
AUC_{τ} Area under the plasma concentration-time curve during a dosing interval
AUCextrap Percentage of AUC extrapolated
C_{av} Average plasma concentration during a dosing interval following last dose
CL/F Apparent clearance of drug from plasma
C_{max} Maximum plasma concentration

MRT Mean residence time
t_{max} Time to C_{max}
$t_{½\lambda z}$ Terminal half-life
V_z/F Apparent volume of distribution during terminal phase
Note: Results from the exploratory analyses will not form part of this CSR

Study design

This was a Phase I, randomised, double-blind, placebo-controlled study with single (Part A) and multiple (Part B) ascending dose levels (referred to as cohorts) of inhaled AZD9819 in healthy male subjects. In both Part A and Part B, dosing of subsequent cohorts as well as the dose to be used were determined by the Safety Review Committee (SRC) following their review of available safety and PK data from the previous cohort(s). Data from the last dose of Part A was evaluated prior to dosing in Part B. The study design allowed a gradual escalation of dose with intensive safety monitoring.

Part A (single ascending dose [SAD]): The screening visit (Visit 1) was to be conducted over 1 or more days during a 30-day screening period. Following screening there was 1 residential period (Visit 2) in the study centre from the day before administration of the investigational products (AZD9819 or placebo; Day -1) until discharge from the study centre (48 hours post dose Day 3). Subjects in cohorts 4 to 6 were to return to the study centre at 72 and 96 hours after the administration of the investigational products for a PK blood sample. A follow-up visit (Visit 3) took place 5 to 10 days after administration of the investigational products.

Part B (multiple ascending dose [MAD]): Screening visit (Visit 1) was to be conducted over 1 or more days during a 30-day screening period. Following the screening period there was 1 residential period (Visit 2) in the study centre from the day before administration of the investigational products (Day -1) until discharge from the study centre 48 hours after the final administration of the investigational products (Day 12). Subjects were to return to the study centre for the collection of PK blood samples 72 and 96 hours after the last administration of the investigational products. Repeated administration of the investigational products started on Day 1 of Visit 2 and subjects were administered the investigational products once daily for 10 days (maximum 14 days). A follow-up visit (Visit 3) took place 5 to 10 days after administration of the investigational products.

Target subject population and sample size

The target population was healthy male and female (non-childbearing potential) subjects aged 18 to 50 years with a body mass index (BMI) between 18 and 30 kg/m^2.

Part A: Six cohorts of 8 healthy male subjects each, 48 subjects in total, were randomised.

Part B: Two cohorts of 9 healthy male subjects each and a third cohort of 8 healthy subjects, 26 subjects in total, were randomised.

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

Single (Part A) and multiple (Part B) ascending inhaled doses of AZD9819 suspension were administered via the SPIRA Electro 2 dosimeter nebuliser.

Part A: The doses for Part A were 27 µg AZD9819, 130 µg AZD9819, 541 µg AZD9819, 1595 µg AZD9819, 4513 µg AZD9819, and 13400 µg AZD9819, or placebo. The doses were expressed as the amount of AZD9819 that was estimated to be deposited in the lungs.

Part B: A low, a medium and a high dose was administered. The low dose was approximately 1/10 of the high dose (dose 541 µg AZD9819), the medium dose approximately 1/3 of the high dose (dose 2106 µg AZD9819), and the high dose (dose 8087 µg AZD9819) to give an exposure equivalent to or below the exposure seen after the maximum dose administered in Part A.

Duration of treatment

Part A: Each subject received a single inhaled dose of the investigational products.

Part B: Each subject received an inhaled dose of the investigational products once daily for 10 days.

Statistical methods

In all analyses, change-from-baseline variables were calculated as the post-treatment value minus the value at baseline. Baseline is defined as the last non-missing measurement before the first administration of the investigational products. If no non-missing value existed before the first administration of the investigational products, then the baseline value was treated as missing.

Safety analysis set: All subjects who received at least one dose of the randomised investigational products, and for whom postdose safety data was available were included in the safety analysis set.

PK analysis set: The PK analysis set included all evaluable PK data appropriate for the evaluation of interest from all subjects who received AZD9819. Subjects who received placebo were not included in the PK analysis set.

The sample size was primarily based on experience from previous similar Phase I studies with other compounds, and it was not based on formal statistical considerations.

Subject population

Part A: In total, 36 healthy male subjects were allocated to 6 cohorts of AZD9819 and 12 healthy male subjects were allocated to placebo in this part of the study. Each subject inhaled a single dose of the investigational products during the residential period.

Part B: In total, 17 healthy male subjects were allocated to 3 cohorts of AZD9819 and 9 healthy male subjects were allocated to placebo in this part of the study. Each subject inhaled multiple doses of the investigational products during the residential period. All randomised subjects, except 1 subject, completed the study. Subject E0001178 received all 10 doses of 541 µg AZD9819, but discontinued from the study due to lost to follow-up.

Summary of pharmacokinetic results

Pharmacokinetics Part A: The absorption of AZD9819 after a single inhaled dose of 27 to 13400 µg AZD9819 was rapid and comparable between doses with a median t_{max} ranging from 0.52 to 1.53 hours. Peak concentration was followed by a multi-phasic decline with a geometric mean $t_{½\lambda z}$ ranging from 18.4 to 21.7 hours (in the 130 to 13400 µg AZD9819 cohorts for which the terminal phase was judged to be captured). Geometric mean CL/F ranged from 32.4 to 50.6 L/h. Dose proportionality for single dose data of 27 to 13400 µg AZD9819 was analysed using a power model in which the 90% confidence intervals (CIs) for β were not too wide and included 1 for AUC but not for C_{max}. There was no indication of dose dependent changes in $t_{½\lambda z}$, CL/F, or V_z/F over the studied dose range.

The metabolite AZD6553 had a median t_{max} ranging from 4.00 to 7.61 hours after a single inhaled dose of 27 to 13400 µg AZD9819 and a geometric mean $t_{½\lambda z}$ ranging from 17.8 to 22.4 hours (in the 130 to 13400 µg AZD9819 cohorts for which the terminal phase was judged to be captured). Exposure, in terms of geometric mean AUC, was approximately 50% to 70% of parent AZD9819. Dose proportionality for AZD6553 after single doses of 27 to 13400 µg AZD9819 was analysed using a power model in which the 90% CIs for β were not too wide and included 1 for both AUC and C_{max}.

Pharmacokinetics Part B: Steady state conditions for AZD9819 could in general be assumed from Day 6 (ie, after the 5th dose) after once daily dosing of 541, 2106 and 8087 µg AZD9819. Dose proportionality for AZD9819 at steady state for 541, 2106 and 8087 µg AZD9819 was analysed using a power model in which the 90% CIs for β were not too wide and included 1 for both AUC_τ and C_{max}. Accumulation was estimated to be 64%, 88%, and 151%, respectively, in the 541, 2106 and 8087 µg AZD9819 cohorts after repeated once daily dosing. The linearity index was close to 1 in the 541 and 2106 µg AZD9819 cohorts, which indicated time independency, but the ratio was 0.55 for the 8087 µg AZD9819 cohort. The ratios should however be regarded with caution as the extrapolated part of AUC on Day 1 was large (25.8% to 96.8%). There was no overall indication of time dependent kinetics.

Steady state conditions for the metabolite AZD6553 could in general be assumed from Day 6 (ie, after the 5th AZD9819 dose) after once daily dosing of 541, 2106 and 8087 µg AZD9819. Dose proportionality for AZD6553 at steady state for 541, 2106 and 8087 µg AZD9819 was analysed using a power model in which the 90% CIs for β were not too wide and included 1 for both AUC_τ and C_{max}. Accumulation of AZD6553 was estimated to be 76%, 113%, and 221%, respectively, in the 541, 2106 and 8087 µg AZD9819 cohorts, after repeated once daily dosing of AZD9819. The geometric mean linearity index was 0.399, 0.816, and 0.987 for the 541, 2106 and 8087 µg AZD9819 cohorts. The ratios should however be regarded with

caution as the extrapolated part of AUC on Day 1 was very large (38.3% to 99.3%). There was no overall indication of time dependent kinetics.

Exposure Part A and B: Geometric mean C_{max} following the 13400 µg dose in Part A did not exceed the predefined exposure limit of 150 nmol/L, but geometric mean AUC was slightly above the 1140 nmol/L limit. Geometric mean C_{max} in the 8087 µg AZD9819 cohort in Part B was above the geometric mean C_{max} in the highest dose group in Part A, but did not exceed 150 nmol/L, and the geometric mean AUC was below the predefined exposure limit.

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuations of the investigational products due to adverse events (DAEs), or any other significant adverse events (OAEs) were reported during the study in both Part A and Part B. All of the reported AEs in both Part A and Part B were considered to be mild in intensity by the Investigator.

Part A: Five (14%) subjects reported AEs after administration of a single dose of AZD9819 (3 subjects in 1595 µg AZD9819 and 2 subjects in 4513 µg AZD9819). Two (6%) of the 5 subjects reported AEs considered causally related to AZD9819 by the Investigator, namely procedural site reaction (1595 µg AZD9819) and dry throat (4513 µg AZD9819).

Part B: Eight (47%) subjects reported AEs during administration of multiple doses of AZD9819 (3 subjects in 541 µg AZD9819, 1 subject in 2106 µg AZD9189, and 4 subjects in 8087 µg AZD9819). Six (67%) subjects reported AEs during administration of multiple doses of placebo. All the subjects who reported AEs during the administration of multiple doses of the investigational products, reported AEs considered causally related to the investigational products by the Investigator. These AEs were throat irritation, tongue ulceration, pruritus, influenza like-illness, upper respiratory tract infection, procedural site reaction, pain in extremity, dizziness, headache, and night sweats in AZD9819 and lip blister, chest pain, rhinitis, headache, hypoaesthesia, and night sweats in placebo.

All doses administered to subjects in Part A and Part B of the study were well-tolerated.