AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7624
Study Code	D2550C00002
Edition Number	1
Date	27 May 2015
EudraCT Number	2013-000067-83

A Phase I, Randomised, Double-blind, Placebo-controlled Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Inhaled Doses of AZD7624 in Healthy Subjects and Patients with Chronic Obstructive Pulmonary Disease

Study dates:	First subject enrolled: 09 September 2013 Last subject last visit: 24 October 2014
Phase of development:	Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD7624 in healthy volunteers and patients with COPD following administration of multiple ascending inhaled doses.	AEs, physical examinations, vital signs, ECG, clinical laboratory variables, telemetry, and spirometry
Secondary	PK	To characterise the multiple dose PK of AZD7624 and assess the time required to reach steady state, dose proportionality, degree of accumulation, and the time dependency of the PK in healthy volunteers and patients with COPD.	**Cohort 1 (bd in healthy volunteers):** C_{max}, t_{max}, $AUC_{(0\text{-}tau)}$ and $AUC_{(0\text{-}last)}$, dose normalised exposure parameters, C_{max}/dose, $AUC_{(0\text{-}tau)}$/dose, $AUC_{(0\text{-}last)}$/dose and accumulation ratios for C_{max}, and $AUC_{(0\text{-}tau)}$, where tau = 12 hours for the SPIRA nebuliser on Days 1 and 8. **Cohort 2 and 3 (bd in healthy volunteers):** C_{max}, t_{max}, $AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}\text{-}tau)}$/dose, C_{max}/dose, $t_{1/2}$, AUC, CL/F, and V_z/F for SPIRA device on Day 1 C_{max}, t_{max} , C_{min}, CL/F, $AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}tau)}$/dose, accumulation ratios for C_{max}, and $AUC_{(0\text{-}tau)}$, and time dependency after morning and evening doses via SPIRA device on Day 9, and after morning dose via new (test) device on Day 10. In addition, $C_{max,PM}/C_{max,AM}$ and $AUC_{(0\text{-}tau),PM}/AUC_{(0\text{-}tau),AM}$ were to be reported only at steady state on Day 9. **Cohort 4 (od in COPD patients):** C_{max}, t_{max}, $AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}last)}$, C_{max}/dose, $AUC_{(0\text{-}tau)}$/dose, $AUC_{(0\text{-}last)}$/dose and accumulation ratios for C_{max}, and

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
			$AUC_{(0\text{-}tau)}$,where tau = 24 hours for the new (test) device on Days 1 and 7, and for SPIRA on Day 8. **Cohort 5 (od in healthy volunteers):** C_{max}, C_{min}, t_{max}, $AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}last)}$, C_{max}/dose, $AUC_{(0\text{-}tau)}$/dose, $AUC_{(0\text{-}last)}$/dose, accumulation ratios for C_{max}, and $AUC_{(0\text{-}tau)}$, where tau = 24 hours for the SPIRA nebuliser on Days 1 and 8. **Cohort 6 (od in COPD patients):** wherever possible, the below PK parameters were to be calculated: C_{max}, t_{max}, $AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}last)}$, C_{max}/dose, $AUC_{(0\text{-}tau)}$/dose, $AUC_{(0\text{-}last)}$/dose and accumulation ratios for C_{max}, and $AUC_{(0\text{-}tau)}$, where tau = 24 hours for the new (test) device on Days 1 and 7.
Exploratory	PK	To collect and store plasma and urine samples for possible exploratory analysis of metabolites of AZD7624.	Not applicable
	Safety	To explore the safety and performance of the ADI test inhalation device.	Not applicable
	PK	To explore and evaluate AZD7624 plasma exposure assessed by AUC and C_{max} when the dose is inhaled via the SPIRA Electro 2 dosimeter (SPIRA nebuliser) and the test inhalation device.	Evaluation/exploration of AZD7624 plasma exposure [C_{max} and $AUC_{(0\text{-}tau)}$] when: - the dose is inhaled via a SPIRA nebuliser (Day 9 in Cohorts 2 and 3; and Day 8 in Cohort 4) - the dose is inhaled via the test inhalation device on Day 10 in Cohorts 2 and 3; and on Day 7 in Cohort 4

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	PGx	To identify and explore PD, biomarker, or genetic variations that may affect the PK, PD, safety, and tolerability profile related to AZD7624 treatment.	Identification/exploration of PD biomarker, or genetic variations that may affect the PK, PD, safety, and tolerability profile related to AZD7624 treatment

AE: Adverse events; AUC: Area under plasma concentration time curve; $AUC_{(0\text{-}last)}$: Area under the plasma concentration-time curve from time zero to time of last quantifiable analyte concentration divided by the delivered dose; $AUC_{(0\text{-}tau)}$: Area under the plasma concentration-time curve from zero to the end of the dose administration interval; $AUC_{(0\text{-}tau),\ PM}/AUC_{(0\text{-}tau),\ AM}$: Ratio of $AUC_{(0\text{-}tau)}$ after evening dose over $AUC_{(0\text{-}tau)}$ after morning dose (only in Cohorts 2 and 3); CL/F: Apparent clearance for parent drug; C_{max}: Maximum plasma concentration; $C_{max,\ PM}/\ C_{max,\ AM}$: Ratio of C_{max} after evening dose over C_{max} after morning dose (only in Cohort 2 and 3); C_{min}: Minimum plasma concentration; COPD: Chronic obstructive pulmonary disease; ECG: Electrocardiogram; PD: Pharmacodynamics; PGx: Pharmacogenetics; PK: Pharmacokinetics; t_{max}: Time to reach C_{max}; $t_{1/2}$: Half-life; V_z/F: Oral (apparent) volume of distribution;

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, multi-centre study, conducted in male and female (non-childbearing potential) healthy volunteers aged 18 to 55 years (inclusive) and male and female (non-childbearing potential) patients with chronic obstructive pulmonary disease (COPD) aged 18 and greater to assess the safety, tolerability, and pharmacokinetics (PK) of AZD7624 following administration of multiple ascending inhaled doses.

A total of up to 52 subjects were planned to be enrolled in the study. Cohorts 1 to 3 and Cohort 5 were conducted in healthy male and female volunteers to avoid interference from disease processes or concomitant medications. Up to 32 healthy volunteers were to be enrolled in cohorts 1, 2, 3, and 5, with up to 8 healthy volunteers in each cohort randomised to receive AZD7624:placebo in a 6:2 ratio. A total of 8 healthy volunteers each were enrolled in Cohorts 1, 2, and 5, randomised in a 6:2 ratio (AZD7624:placebo) and 7 healthy volunteers were enrolled in Cohort 3, resulting in a 5:2 randomisation ratio (AZD7624:placebo). Up to 20 COPD patients were to participate in Cohorts 4 and 6 (10 patients in each). A total of 6 COPD patients were enrolled in Cohort 4, after which, this cohort was terminated prematurely due to predetermined stopping criteria being met, resulting in a 5:1 randomisation ratio (AZD7624:placebo) and 10 COPD patients were enrolled in Cohort 6 and randomised in a 6:4 ratio (AZD7624:placebo)

Table S2 Planned dose and actual dose administered

Cohorts (in the order of execution)	Planned dose	Actual dose administered
Cohort 1 (Healthy volunteers)	300 µg delivered dose (150 µg lung deposited dose) of AZD7624 or placebo administered bd	261 µg delivered dose (151 µg lung deposited dose) of AZD7624 or placebo administered bd
Cohort 2 (Healthy volunteers)	600 µg delivered dose (300 µg lung deposited dose) of AZD7624 or placebo administered bd	522 µg delivered dose (303 µg lung deposited dose) of AZD7624 or placebo administered bd
Cohort 3 (Healthy volunteers)	1200 µg delivered dose (600 µg lung deposited dose) of AZD7624 or placebo administered bd	1027 µg delivered dose (595 µg lung deposited dose) of AZD7624 or placebo administered bd
Cohort 5 (Healthy volunteers)	Od dose based on the safety, tolerability, and PK data of Cohorts 1, 2, and 3	2053 µg delivered dose (1191 µg lung deposited dose) of AZD7624 or placebo administered od
Cohort 4 (COPD patients)	Od dose found safe and tolerable in healthy volunteers	1932 µg delivered dose (1160 µg lung deposited dose) of AZD7624 or placebo administered od

Cohorts (in the order of execution)	Planned dose	Actual dose administered
Cohort 6 (COPD patients)	Added cohort with an od 1160 µg delivered dose (580 µg lung deposited dose); lower than the dose used in Cohort 4	966 µg delivered dose (580 µg lung deposited dose) of AZD7624 or placebo administered od

bd: Twice daily; od: Once daily

Visit 1: The screening period for all the subjects was from Day -42 to Day -2.

Visit 2: All the subjects across all cohorts were admitted to the CPU on Day -1.

Cohort 1: The healthy volunteers were administered AZD7624/placebo twice daily (bd) from Day 1 through Day 8 via SPIRA nebuliser with serial blood samples for full 24-hour PK profiles on Day 1 and Day 8 and predose (morning and evening dose) sample collections on Days 2 through 7. The healthy volunteers were discharged on Day 9.

Cohorts 2 and 3: The healthy volunteers were administered AZD7624/placebo once daily (od) on Day 1 via SPIRA nebuliser with serial blood samplings for a 72-hour PK profile. Days 4 through 9 administration of AZD7624/placebo bd was via SPIRA nebuliser and Day 10 administration of AZD7624/placebo bd was via the test inhalation device, aqueous droplet inhaler (ADI). Serial blood samples were collected for full 24-hour PK profiles on Days 9 and 10, and predose (morning and evening) samples were to be collected on Days 5 through 8). The healthy volunteers were discharged on Day 11.

Cohort 4: Day 1 to Day 7 administration of AZD7624/placebo od in COPD patients via the test inhalation device, ADI. Day 8 administration of AZD7624/placebo was via SPIRA nebuliser. Serial blood samples were collected for full 24-hour PK profiles on Days 1, 7, and 8 and only predose samples were collected on Days 2 through 6. The patients were discharged on Day 9.

Cohort 5: The healthy volunteers were administered AZD7624/placebo od from Day 1 through Day 8 via SPIRA nebuliser with 24-hour PK profiling on Day 1 and Day 8 and predose sampling on Days 2 through 7. The healthy volunteers were discharged on Day9.

Cohort 6: Day 1 to Day 7 administration of AZD7624/placebo od in COPD patients via the test inhalation device, ADI, with serial blood sampling for 24-hour PK profiles on Day 1 and Day 7 and only predose sampling from Days 2 through 6. Patients in Cohort 6 were given an option to be discharged from the CPU at 6 hours postdose and to visit the CPU every day for subsequent dose administration and pre and postdose sampling assessments.

Visit 3: Telephonic visit at 48 hours post last administration of the investigational product for all the subjects across all cohorts.

Visit 4: The healthy volunteers in Cohorts 1, 2, 3, and 5 and COPD patients in Cohort 4 were to visit the CPU at 72 hours post last administration of the investigational product for myoglobin and creatinine kinase assessments. For patients in Cohort 6 this was to be a telephonic visit as there were no myoglobin and creatinine kinase assessments planned.

Visit 5: The healthy volunteers in Cohorts 1, 2, 3, and 5 and COPD patients in Cohort 4 were to visit the CPU at 120 hours post last administration of the investigational product for myoglobin and creatinine kinase assessments. For patients in Cohort 6 this was to be a telephonic visit as there were no myoglobin and creatinine kinase assessments planned.

For Cohorts 1, 4, and 5, Visit 4 corresponded to Day 11 and Visit 5 to Day 13 and for Cohorts 2 and 3, Visit 4 was on Day 13 and Visit 5 on Day 15. For Cohort 6, Visits, 3, 4, and 5 were telephonic visits on Days 9, 10, and 12, respectively.

Visit 6: A follow-up visit for all cohorts was conducted 7 to 9 days following administration of the last dose of the investigational product.

Target subject population and sample size

The first 3 cohorts of the study and Cohort 5 were to be conducted in healthy male and female volunteers to avoid interference from disease processes or concomitant medications. The selection criteria were defined such that volunteers selected for participation in Cohorts 1 through 3 and Cohort 5 were known to be free from any significant illness. To enhance the confidence for the safety and tolerability of AZD7624 in the target population, a dose found safe and tolerable during multiple dose administration in healthy volunteers was to be administered to 2 cohorts of patients with COPD (Cohorts 4 and 6) following completion of Cohorts 1 through 3 and Cohort 5.

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

Table S3 Details of investigational product(s)

Investigational product	Dosage form and strength	Material ID number/Manufacturer	Batch number
AZD7624	Nebuliser solution with concentration interval 1.0 mg/mL-20 mg/mL	D1300014/AstraZeneca	13-000896AZ
Placebo	Nebuliser solution	D1300015/AstraZeneca	14-001224AZ

AZD7624 nebuliser solution and placebo nebuliser solution was supplied as study-specific labelled bulk by AstraZeneca R&D Mölndal, Sweden. A technical agreement between the Investigator and AstraZeneca was in place to cover all pharmacy-related activities, detailing roles, and responsibilities prior to receipt of the investigational product at the CPU.

Duration of treatment

The treatment part of the study including 3 cohorts was anticipated to be minimum 3 weeks excluding the screening period.

Statistical methods

No formal statistical hypothesis testing was performed in this study. All safety, tolerability, and pharmacokinetic data recorded during the study were listed and summarised as appropriate. Continuous variables were summarised using descriptive statistics by treatment and by time points where applicable. Categorical variables were summarised in frequency tables by treatment group. Graphical presentations were used as appropriate.

When appropriate data were available dose proportionality of AZD7624 was assessed graphically and analysed using the power model. Attainment of steady state was assessed by visual inspection of geometric mean AZD7624 trough plasma concentration versus day plots for each cohort. Accumulation and time dependency data was summarised via descriptive statistics.

Subject population

Healthy volunteers

A total of 31 healthy male volunteers was enrolled into the study at 1 clinical pharmacology unit (CPU) in United Kingdom (UK). Cohorts 1, 2, and 5 had 8 healthy volunteers each, randomised in a 6:2 ratio, while Cohort 3 had 7 healthy volunteers resulting in a 5:2 randomisation ratio to receive AZD7624 or placebo, respectively. The mean age of the healthy volunteers across the AZD7624 cohorts was comparable. Most of the healthy volunteers who received AZD7624 were White and were Not Hispanic. The body mass index (BMI) of all the healthy volunteers in the study met the protocol-specified criterion.

All the healthy volunteers across the treatment cohorts randomised to receive AZD7624 completed the study, whilst 2 of the healthy volunteers randomised to receive placebo withdrew from the study

COPD patients:

A total of 16 COPD patients were enrolled into the study at 2 CPUs in UK. Six patients were enrolled in Cohort 4, after which, this cohort was terminated prematurely due to predetermined stopping criteria being met, resulting in a 5:1 randomisation ratio to receive AZD7624 or placebo, respectively. Ten patients were enrolled in Cohort 6 and randomised in a 6:4 ratio to receive AZD7624 or placebo, respectively. All but 1 patients who were enrolled in Cohorts 4 and 6 to receive AZD7624 were males. The mean age of the COPD patients across the AZD7624 cohorts was 65 years. All the patients who received AZD7624 were White and Not Hispanic. The BMI of all the patients in the study met the protocol-specified criterion.

Majority of the patients randomised to receive AZD7624 completed the study, except for 2 patients in Cohort 4 who were withdrawn from the study due to adverse events (AEs).

Summary of pharmacokinetic results

Following a single and multiple inhaled delivered doses either bd (Cohorts 1 to 3) or od dose administration (Cohorts 4 to 6) via SPIRA or the ADI test device, AZD7624 appeared rapidly in plasma (median t_{max} of 5 to 15 minutes) and concentration-time profiles were characterised by a rapid distribution phase followed by a slower terminal phase (geometric mean $t_{½\lambda z}$, 32.2 hours; evaluable only in Cohort 3). Elimination half-life for the AZD7624 has been well defined in a previously completed single ascending dose study (D2550C00001) at delivered doses of 1088 and 2030 µg dose levels with extended sampling time of 0 to 144 hours and a reported terminal half-life ($t_{½\lambda z}$) of 64 and 72 hours, respectively. Due to the limited PK sampling time in Cohort 3 (0 to 72 hours postdose), terminal phase $t_{½\lambda z}$ was not completely captured.

Primary exposure parameters ($AUC_{(0\text{-}tau)}$, $AUC_{(0\text{-}tau)AM}$ and $C_{max}/C_{max,AM}$) increased across the 261 to 1027 µg dose range (bd regimen) and across the 966 µg to 2053 µg dose range (od regimen) following single and multiple inhaled-delivered doses, with the exception of Cohort 2 (522 µg), which only showed minimal increase on Day 1 (single dose). Based on formal statistical analysis of dose-proportionality using the power model approach, total exposure within dose administration interval [$AUC_{(0\text{-}tau)}$] exhibited dose-proportionality within the 261 to 1027 µg dose range (on both Day 1 and Days 8 or 9) with slope being close to 1.0 (ranged from 0.93 to 1.02) and 95% confidence interval (CI) encompassing value of unity. Maximum exposure (C_{max}) did not meet these criteria and proved to be less than dose proportional (slopes were 0.867 and 0.696 after single and multiple dosing).

Following multiple dose administration, accumulation ratios for AZD7624 after bd dose administration via SPIRA (Cohorts 1 to 3) ranged from 2.31 to 5.24 for $AUC_{(0\text{-}tau)AM}$ and 0.706 to 2.90 for $C_{max,AM}$. Unexpected low AZD7624 exposure observed on Day 1 in Cohort 2, resulted in higher mean accumulation ratios for $AUC_{(0\text{-}tau)AM}$ (5.24) and C_{maxAM} (2.90) compared to other cohorts. For the od regimen in Cohorts 4 and 6 (via ADI in COPD patients, Day 7) and Cohort 5 (via SPIRA in healthy volunteers, Day 8) accumulation ratios were 2.29 to 3.13 and 1.05 to 1.63 for $AUC_{(0\text{-}tau)}$ and C_{max}, respectively.

Comparability of exposure parameters between the AM and PM doses (bd regimen) using the SPIRA inhaler was evaluated on Study Day 9 in Cohorts 2 and 3. Comparable results for AZD7624 PK following the morning and evening dose in Cohorts 2 and 3 as indicated by the PM/AM mean ratios of 1.04 to 1.12 for $AUC_{(0\text{-}tau)}$ and 0.918 to 1.53 for C_{max} were observed.

Performance of the ADI test device on the last day of dose administration (Day 10) versus SPIRA on Day 9 was also evaluated in Cohorts 2 and 3. Performance appeared to be comparable, as indicated by the dose-normalised exposure parameters following the AM dose administration (0.018 versus 0.017 nmol·h/L/µg for $AUC_{(0\text{-}tau)AM}$ and 0.007 versus 0.013 nmol/L/µg for $C_{max,AM}$ in Cohort 2 and 0.016 versus 0.013 nmol*h/L/µg for $AUC_{(0\text{-}tau)AM}$ and 0.006 vs. 0.005 nmol/L/µg for C_{max} in Cohort 3).

Time dependency was evaluable only in 4 healthy volunteers in Cohort 3 following bd dose administration via SPIRA on Day 9. The time-dependency was comparable for both the AM (0.876) and PM (0.942) dosing, with values close to unity indicate time-independent PK for AZD7624.

Attainment of steady state via visual inspection revealed that steady state may have been reached after 6 days of bd dose administration on Day 7 in Cohort 1, but not in Cohorts 2 and 3. In the od dose administration (Cohorts 4, 5, and 6), steady state may have been reached following 7 days of od dose administration on Day 8.

Summary of safety results

- No SAEs or deaths were reported in this study
- In both the healthy volunteers and COPD patients, the differences between the number of subjects reporting AEs were small between the AZD7624-administered group and the placebo-administered group
- Most AEs reported in the study were mild in severity, with a few moderate AEs. All but 3 AEs (thrombophlebitis, nasopharyngitis, and rash) resolved during the study
- The most frequently reported AEs in the AZD7624-administered healthy volunteers were in the SOCs gastrointestinal disorders, infections and infestations and skin and subcutaneous tissue disorders while the most frequently reported AEs in the placebo-administered healthy volunteers were in the SOCs general disorders and administration site conditions and nervous system disorders. The most frequently reported AEs in the AZD7624-administered COPD patients were in the SOCs infections and infestations and respiratory, thoracic, and mediastinal disorders while an equal proportion of placebo-administered COPD patients reported AEs in the SOCs nervous system disorders, musculoskeletal and connective tissue disorders, and respiratory, thoracic, and mediastinal disorders
- Clinically non-significant laboratory values (including myoglobin and creatinine kinase) outside the normal ranges were noted, while no trends were observed in the results within and across the cohorts
- No vital sign outliers were observed in the AZD7624-administered and placebo-administered healthy volunteers while vital sign outliers, (mainly elevated SBP and increased pulse rate) without a dose relationship, were observed in the AZD7624-administered and placebo-administered COPD patients. These values were sporadic and similarly distributed across placebo and treatment groups
- There were no differences observed in the QTcF outliers between the AZD7624-administered subjects and the placebo-administered subjects

- Clinically non-significant variations were observed in the spirometry values, but no trends were observed within and across the cohorts. In 2 of the COPD patients who received AZD7624 delivered dose of 1932 µg od, a clinically significant FEV_1 drop of 33 to 36% within 0.5 hours postdose was observed, accompanied by AEs of the SOC respiratory, thoracic, and mediastinal disorders, which led to the discontinuation of the patients from the study. This met the predetermined stopping criteria for the cohort and hence Cohort 4 was terminated early