Characterisation of pharmacokinetics, safety and tolerability in a first-in-human study for AZD8154, a novel inhaled selective PI3Kγδ dual inhibitor targeting airway inflammatory disease

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Aims: This 3-part, randomised, phase 1 first-in-human study (NCT03436316) investigated the safety, tolerability and pharmacokinetics (PK) of AZD8154, a dual phosphoinositide 3-kinase (PI3K) γδ inhibitor developed as a novel inhaled anti-inflammatory treatment for respiratory disease.

Methods: Healthy men, and women of nonchildbearing potential, were enrolled to receive single and multiple ascending inhaled doses of AZD8154 in parts 1 and 3 of the study, respectively, while part 2 characterised the systemic PK after a single intravenous (IV) dose. In part 1, participants received 0.1–7.7 mg AZD8154 in 6 cohorts. In part 2, participants were given 0.15 mg AZD8154 as an IV infusion. In part 3, AZD8154 was given in 3 cohorts of 0.6, 1.8 and 3.1 mg, with a single dose on Day 1 followed by repeated once-daily doses on Days 4–12.

Results: In total, 78 volunteers were randomised. All single inhaled, single IV and multiple inhaled doses were shown to be well tolerated without any safety concerns. A population PK model, using nonlinear mixed-effect modelling, was developed to describe the PK of AZD8154. The terminal mean half-life of AZD8154 was 18.0–32.0 hours. The geometric mean of the absolute pulmonary bioavailability of AZD8154 via the inhaled route was 94.1%.

Conclusion: AZD8154 demonstrated an acceptable safety profile, with no reports of serious adverse events and no clinically significant drug-associated safety concerns reported in healthy volunteers. AZD8154 demonstrated prolonged lung retention and a half-life supporting once-daily dosing.

KEYWORDS
asthma, pharmacokinetics, phosphoinositide 3-kinase, PI3Kγδ, respiratory, safety

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The authors confirm that the PI for this paper is Dr Rainard Fuhr and that he had direct clinical responsibility for patients.

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1 | INTRODUCTION

Asthma is a chronic inflammatory disease affecting approximately 358 million people worldwide. Asthma is increasingly being recognised as a heterogeneous disorder that results from a complex interplay between environmental and genetic factors.

Historically, asthma was characterised by a robust T helper type 2 (Th2) cytokine response. It is now understood that T helper type 1 (Th1), T helper type 17 (Th17) and other immune cells also contribute to the pathogenesis of asthma. Therefore, therapies aimed at specific pathways may be effective in some but not others. To produce significant therapeutic benefits in a broad patient population, it might be necessary to block the bioactivity of multiple pathways.

Respiratory diseases are frequently managed using inhaled therapies. Administering a drug directly to the lungs facilitates high pulmonary drug concentrations and lower systemic drug concentrations, reducing systemic adverse events (AEs). To achieve optimal drug deposition in the airways, multiple factors must be considered, including physiochemical properties of the drug, particle size distribution, device used and physiological factors. Inhaled corticosteroids (ICS) are the most widely used anti-inflammatory asthma treatment, but many patients with moderate-to-severe asthma still experience persistent asthmatic symptoms, despite receiving ICS.

There remains, therefore, a need for novel anti-inflammatory therapies that reduce asthma symptoms. The phosphoinositide 3-kinase (PI3K) pathway, a key signalling pathway involved in asthma pathophysiology, has the potential to provide a therapeutic option for restoration of corticosteroid sensitivity in severe asthmatics with a reduced response to mainstay corticosteroid treatment. AZD8154, a novel dual inhaled PI3Kδ inhibitor developed for the treatment of respiratory disease, was designed to selectively target the δ isoforms of PI3K, with the aim of reducing the downstream effects caused by cytokine release and mixed cellular infiltration of the airways. This first-in-human phase 1 study (NCT03436316) investigated the safety, tolerability and pharmacokinetics (PK) of AZD8154 in healthy volunteers. Postinhalation cough monitoring using objective measurement was included as an exploratory endpoint because cough was observed as an AE with the inhaled PI3Kδ inhibitor nemiralisib in chronic obstructive pulmonary disease and asthma, with a greater incidence observed in the nemiralisib treatment groups compared with placebo.

2 | METHODS

2.1 Study design

This 3-part phase 1 study in volunteers was performed at a single centre (Parexel Early Phase Clinical Unit, Berlin, Germany) between 26 July 2018 and 29 July 2019 (Figure 1). The sample size chosen allowed reasonable evidence of safety and tolerability without exposing undue numbers of volunteers to the compound.

What is already known about this subject

- Asthma is a heterogeneous disorder with many patients experiencing persistent symptoms, despite standard of care.
- Novel targeted therapies aimed at the key pathophysiological drivers may be effective in those patients who still have uncontrolled disease.
- Phosphoinositide 3-kinases play an important role in pulmonary inflammation and the development of airway obstruction.

What this study adds

- In this first-in-human study, AZD8154, a novel dual phosphoinositide 3-kinase δ inhibitor, demonstrated a good safety profile, with no clinically significant drug-associated safety concerns reported in healthy volunteers.
- AZD8154 also demonstrated prolonged lung retention and a half-life supporting once-daily dosing, making it a promising therapy for further clinical development.

2.2 Study population

Healthy men, and women of nonchildbearing potential, aged 18–45 years were eligible for the study. Volunteers were required to have a forced expiratory volume in 1 second of ≥80% of the predicted value at the screening visit (Supplementary material A). Participants were confined to the study centre for the duration of the study.

2.3 AZD8154 treatment regimens

Single ascending delivered doses (SAD) administered by nebulised inhalation for part 1 were 0.1, 0.3, 0.9, 2.7, 5.4 and 7.7 mg of AZD8154. In part 2, participants received AZD8154 0.15 mg by intravenous (IV) infusion, followed by a single delivered dose of AZD8154 2.7 mg by inhalation after a washout period of 7–14 days. In part 3, the multiple ascending delivered doses (MAD) were 0.6, 1.8 and 3.1 mg, administered by nebulised inhalation. In each ascending dose cohort, sentinel dosing was initiated in 2 participants; 1 participant was randomised to receive placebo and 1 received AZD8154. In part 2, 1 participant received an IV dose as a sentinel cohort. In all parts, safety data from the sentinel cohort were reviewed by the Principal Investigator before the remaining participant in the cohorts were dosed, at least 48 hours after the sentinel cohort.

Dose rationale is reported in Supplementary material B.
2.3.1 | Part 1

Part 1 had a randomised, single-blind, placebo-controlled, sequential group design, to assess the safety, tolerability and PK following inhaled administration of a SAD of AZD8154 (0.1, 0.3, 0.9, 2.7, 5.4 or 7.7 mg). Six cohorts each comprising 8 participants were included: within each cohort, 6 participants received a single inhaled dose of AZD8154 and 2 received inhaled placebo. Participants in the 2.7 mg cohort, following a 7–14-day washout period, received an additional dose of 2.7 mg AZD8154 of the same formulation but with a relatively larger particle size (particle size cohort). The particle size cohort was included to explore the sensitivity of PK to a small change in particle size; these data will be presented in a future publication.

2.3.2 | Part 2

Part 2 was initiated after completion of part 1 and comprised a single-cohort, open-label, 2-period design comparing the safety, tolerability and PK of a single inhaled dose of AZD8154 nebuliser suspension with a single IV dose of AZD8154. Six participants were enrolled and received an IV infusion of AZD8154 0.15 mg and, after a 7–14-day washout period, an inhaled dose of AZD8154 2.7 mg.

2.3.3 | Part 3

Part 3 had a randomised, single-blind, placebo-controlled, MAD sequential group design to assess the safety, tolerability and PK of AZD8154 following the inhaled administration of MADs to steady state. Six participants within each cohort received multiple inhaled doses of AZD8154 (0.6, 1.8 or 3.1 mg) and 2 received placebo, with a single dose on Day 1 followed by repeated once-daily doses on Days 4–12.

2.4 | Study objectives

The primary objective was to assess the safety and tolerability of AZD8154: following inhaled administration of single doses (part 1); following inhaled and IV administration of single doses (part 2); and following inhaled administration of multiple doses to steady state (part 3). Secondary objectives included characterisation of the PK of AZD8154 following single doses (part 1) or following inhaled and IV doses (part 2); characterisation of the multiple-dose PK of AZD8154 and the time required to reach steady state, degree of accumulation of AZD8154 and time dependency of the PK (part 3); and assessment of the induction potential of AZD8154 on cytochrome P450 (CYP)3A by measurement of 4-β-hydroxy-cholesterol at baseline and at steady state (part 3). Objective cough monitoring was an exploratory endpoint (part 3).

2.5 | Safety evaluations

Safety and tolerability evaluations included reports of AEs, vital signs, 12-lead digital electrocardiogram telemetry, physical examination, laboratory assessments, spirometry and diffusing capacity of the lungs for carbon monoxide measurement (DLCO; Supplementary material C). DLCO was measured for detection of any potential adverse pulmonary effects, because approximately 5% of patients treated with oral PI3Kδ or PI3Kγδ inhibitors develop pneumonitis.18,19 Treatment-emergent AEs (TEAEs) were defined as AEs with onset after the first dose of AZD8154.

2.6 | PK assessments

PK parameters were derived using noncompartmental methods (Supplementary material D). The timing of PK blood sampling is described in Table S1. Plasma concentrations of AZD8154 were determined using a validated bioanalytical method with a lower limit of quantification of 10 pmol/L. The PK parameters were estimated using a population modelling approach using the first-order conditional estimation method with interaction in NONMEM (version 7.320 (Supplementary material D).

2.7 | 4-β-hydroxy-cholesterol measurement

Blood was collected on Day –1, Day 12 (pre dose) and at the follow-up visit from volunteers in part 3 for the determination of 4-β-hydroxy-cholesterol concentrations. The induction potential of
AZD8154 on CYP3A was assessed by measuring 4-β-hydroxy-cholesterol at baseline and at steady state.

2.8 | Cough monitoring

In part 3, cough monitoring was performed using an ambulatory cough monitor, VitaloJAK (VitaloGraph, Buckingham, UK). To assess baseline, cough monitoring commenced shortly before assessments began and continued up to 12 hours on Day –1. On the day of dosing (Day 1), cough monitoring was commenced shortly before dosing and continued up to 12 hours postdose.

2.9 | Statistical analysis

All original and derived parameters, as well as demographic and disposition data, were listed and described using summary statistics. Descriptive statistics were calculated for each quantitative variable unless otherwise stated. All statistical analyses were performed using SAS (version 9.4 or higher) (SAS Institute Inc., Cary, NC, USA). Additional software used during the model development included PsN (version 4.4.8) and R (version 3.5.1).

Frequency of cough per hour was calculated per participant and summarised as means and standard deviations (Supplementary material E).

2.10 | Ethical conduct of the study

The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with the International Council for Harmonisation, good clinical practice, and the AstraZeneca policy on bioethics and human biological samples. Ethical approval from the State Office of Health and Social Affairs in Berlin was obtained before enrolling participants. All volunteers provided written informed consent before any study-specific procedures.

2.11 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

3.1 | Demographics and baseline characteristics

In total, 78 volunteers were randomised (part 1, n = 48 [AZD8154, n = 36; placebo, n = 12]; part 2, n = 6 [all AZD8154]; part 3, n = 24...
AZD8154, \( n = 18 \); placebo, \( n = 6 \)); all participants completed the study. Most patients were male (99%). Baseline characteristics were well balanced between treatment groups within each cohort of each study part and across the study (Tables 1A–C).

### 3.2 AZD8154 safety results

No clinically significant safety signals, no deaths, and no serious AEs (SAEs) or AEs leading to discontinuation were observed in this study. AZD8154 was found to be well tolerated in each study part. Of 78 volunteers, 30 reported at least 1 AE (AZD8154, \( n = 22/60 \) [37%]; placebo, \( n = 8/18 \) [44%]). Of a total of 57 AEs reported, 54 were classified as mild and 3 as moderate. All mild AEs were short in duration and resolved spontaneously. TEAEs are presented in Table 2 and Tables S2A–C. There was 1 AE (rhinitis of mild intensity) that occurred before treatment in a participant who received placebo, which was not classified as a TEAE and therefore not included in Table 2 or Table S2C.

No clinically significant findings were observed in any pulmonary function test. A decline in DLCO was noted for all participants in cohorts 1 and 2 of part 1, regardless of treatment, with a mean change of \(-11.0\%\) and \(-8.6\%\) in cohorts 1 and 2, respectively (Table S3). However, the decline in DLCO was asymptomatic for all individuals,
and was not observed in subsequent cohorts following standardisation of the time of DLCO measurement (Tables S3 and S4).\textsuperscript{25,26}

Three out of 60 participants receiving AZD8154 had an AE of cough. All events were mild, transient and occurred postinhalation. No cough AEs were reported with the highest dose (3.1 mg) in part 3. Similarly, no clinically significant changes or trends were observed in electrocardiograms, vital signs, safety laboratory values or oral body temperature.

### TABLE 2

Number of volunteers who had at least 1 treatment-emergent adverse event\textsuperscript{a}

| System organ class/preferred term | Part 1 Placebo (N = 12) | Total AZD8154 (N = 36) | Part 2 Total AZD8154 (N = 6) | Part 3 Total AZD8154 (N = 18) |
|----------------------------------|------------------------|------------------------|-------------------------------|-------------------------------|
| Volunteers with at least 1 TEAE | 5 (42)                 | 10 (28)                | 2 (33)                        | 3 (50)                        |
| Nervous system disorders        | 1 (8)                  | 6 (17)                 | 1 (17)                        | 1 (17)                        |
| Headache                        | 1 (8)                  | 4 (11)                 | 1 (17)                        | 1 (17)                        |
| Dizziness postural              | 0 (0)                  | 1 (3)                  | 0 (0)                         | 1 (6)                         |
| Hypoaesthesia                   | 0 (0)                  | 1 (3)                  | 0 (0)                         | 1 (6)                         |
| Syncpe                          | -                      | -                      | -                             | -                             |
| Respiratory thoracic and mediastinal disorders | 3 (25) | 4 (11) | 1 (17) | 1 (17) |
| Throat irritation                | 1 (8)                  | 2 (6)                  | 0 (0)                         | -                             |
| Cough                            | 0 (0)                  | 1 (3)                  | 0 (0)                         | 2 (11)                        |
| Dry throat                       | 1 (8)                  | 1 (3)                  | 0 (0)                         | 1 (6)                         |
| Rhinorrhoea                     | 1 (8)                  | 0 (0)                  | 1 (17)                        | 0 (0)                         |
| Epistaxis                        | -                      | -                      | 1 (17)                        | -                             |
| General disorders and administration site conditions | 1 (8) | 2 (6) | - | 1 (17) |
| Chest pain/discomfort           | 1 (8)                  | 2 (6)                  | 0 (0)                         | 2 (11)                        |
| Medical device site reaction    | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Asthenia                         | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Vessel puncture site inflammation | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Skin and subcutaneous tissue disorders | - | - | 1 (17) | 0 (0) |
| Hyperhidrosis                    | -                      | -                      | 1 (17)                        | 1 (6)                         |
| Dermatitis contact              | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Erythema                         | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Musculoskeletal and connective tissue disorders | - | - | - | 1 (17) |
| Muscle tightness                 | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Musculoskeletal pain             | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Back pain                        | -                      | -                      | 1 (17)                        | 0 (0)                         |
| Gastrointestinal disorders       | -                      | -                      | 1 (17)                        | 1 (6)                         |
| Flatulence                       | -                      | -                      | 0 (0)                         | 1 (6)                         |
| Diarrhoea                        | -                      | -                      | 1 (17)                        | 0 (0)                         |
| Cardiac disorders                | -                      | -                      | 1 (17)                        | 0 (0)                         |
| Ventricular tachycardia          | -                      | -                      | 1 (17)                        | 0 (0)                         |
| Metabolism and nutrition disorders | -                  | -                      | 1 (17)                        | 0 (0)                         |
| Decreased appetite               | -                      | -                      | 1 (17)                        | 0 (0)                         |

\textsuperscript{a}TEAEs were recorded using terminology specified in the MedDRA version 21.1.
3.3 | **AZD8154 PK results**

3.3.1 | **Mean plasma concentration–time profiles of AZD8154**

Systemic exposure of AZD8154 in part 1 increased in a dose-proportional manner (Figure 2). The PK of AZD8154 was characterised by an early rapid absorption phase, with the time to reach peak or maximum observed concentration following drug administration occurring at 0.17–0.75 hours postdose (Table S5A). Plasma concentrations of AZD8154 subsequently declined in a monophasic manner, with a mean terminal half-life of 18.0–32.0 hours.

Over the dose range, area under the curve increased in an approximately dose-proportional manner (Figure 2B; Table S5B). The geometric mean of the absolute pulmonary bioavailability of AZD8154 via the inhaled route was 94.1% (with a geometric mean coefficient of variation of 23.6%). In part 2, the plasma concentration–time profiles after inhaled and IV administration of AZD8154 confirmed absorption-dependent PK after inhaled administration (Figure 3).

3.3.2 | **Multiple dosing of AZD8154**

After repeated once-daily administration, AZD8154 plasma concentrations were generally at steady state after 7 days of dosing. Multiple dosing resulted in a 2–3-fold accumulation in the area under the concentration–time curve in the dose interval and maximum observed plasma concentration (Table S5B). A trend towards higher accumulation than anticipated with systemic half-life was observed in the 3.1 mg dose cohort (Figure 4).

3.3.3 | **PK modelling of AZD8154**

The IV model was a 3-compartment distribution model with a systemic clearance estimate of 44.2 L/h (Table S6A). The model describes the trends and variability in the observed data, evident from the visual predictive check (Figure 5A).
FIGURE 5  Visual predictive check of (A) the systemic PK model for AZD8154 based on the IV data and (B) the absorption model for 2 representative SAD cohorts after inhaled administration. Solid and dotted lines represent median, 5th and 95th percentiles of observations; shaded areas around these lines represent 95% confidence intervals for the median, 5th and 95th percentiles of model predictions. IV, intravenous; SAD, single ascending dose; PK, pharmacokinetic.

FIGURE 6  (A) Mean coughs per hour pre and postdose for placebo and AZD8154; (B) change from baseline in coughs per hour. The analysis was conducted both on the original scale and on log-transformed data; no difference in results was observed. Original scale data are shown. CI, confidence interval.
The final pulmonary absorption model was based on 2 first-order and 1 zero-order rates of absorption. Absolute pulmonary bioavailability (based on SAD-MAD data) was estimated to be 81%, assuming a negligible contribution from gastrointestinal tract absorption (Table S6B). A visual predictive check of how appropriately this absorption model is describing the systemic PK after inhaled administration of AZD8154 is depicted in Figure 5B.

3.3.4 | Induction potential of AZD8154 on CYP3A

The induction potential of AZD8154 on CYP3A was assessed by measuring 4-β-hydroxy-cholesterol at baseline and at steady state in part 3 (Table S7). The change from baseline (mean [standard deviation, SD]) at Day 12 predose was 1.8 (1.1), –1.1 (2.8) and –0.2 (1.7) for AZD8154 0.6, 1.8 and 3.1 mg, respectively.

3.3.5 | Postinhilation cough after AZD8154 administration

Mean cough/h was 0.76 (SD: 1.16) at baseline and 1.01 (SD: 1.09) postdose (Figure 6A). The average change from baseline was 0.25 (SD: 0.96). No significant differences were observed between AZD8154 and placebo either at baseline (P = .11) or postdose (P = .3) in cough frequency. AZD8154 was not associated with change from baseline in cough frequency (P = .43; Figure 6B) and no trends were observed with increasing doses.

4 | DISCUSSION

AZD8154 is a novel, selective, inhaled PI3K inhibitor designed to target the γ and δ isoforms of PI3K, which is involved in both the Th1/Th17 and Th2 subtypes of asthma, making it an attractive target for an effective asthma therapy to reduce pulmonary inflammation.10 The PI3K γ and δ isoforms have distinct roles in immune cell function. PI3Kγ has a role in the production of reactive oxygen species, important mediators of airway cell damage.27 PI3Kδ is important to the early phases of mast cell degranulation, T-cell differentiation, B-cell development and proliferation, and immunoglobin class switching.27 In preclinical studies, inhibition of PI3K decreased mucus production,28 prevented mast cell degranulation29 and facilitated bronchodilation. Although oral PI3K inhibitors have been utilised for the treatment of cancers, to our knowledge, AZD8154 is one of the first dual PI3Kγδ inhibitors assessed for the treatment of respiratory diseases. Dual targeting of the PI3K γ and δ isoforms provides a novel mechanism of action, targeting unmet medical need in respiratory disease, and it has been suggested that γδ dual inhibition has the potential to be more efficacious than inhibition of either single isoform alone.30,31

This first-in-human phase 1 study showed that, following single and multiple ascending inhaled administration and single IV administration in volunteers, AZD8154 was well tolerated at all doses; there were no SAEs or AEs leading to treatment discontinuation. Oral PI3K inhibitors have been associated with various systemic AEs, including hepatic dysfunction, infection, pneumonia, gastrointestinal effects and cough.18,19 In addition, postinhilation cough was observed as an AE with the inhaled PI3Kδ inhibitor nemiralisib.16,17 A low number of cough AEs were observed in this study but no event was reported in the highest dose after multiple dosing. Furthermore, we did not observe any changes in cough frequency for up to 12 hours post-inhalation in part 3 using objective cough monitoring.

Inhaled drug administration is complex, and multiple PK processes exist to achieve optimal drug delivery to the target site and high pulmonary efficacy.7 Strategies such as using basic compounds to achieve lysosomal trapping and the use of compounds with low solubility to achieve lung retention have been applied to help inhaled drugs to achieve lung targeting (i.e. selectively higher concentration in the lungs than in the systemic circulation).32 AZD8154 was designed to have low solubility and was therefore expected to have a long retention in the lung. In addition to prolonged lung retention, AZD8154 was shown to have low systemic exposure compared with anticipated local lung concentrations, suggesting that these parameters of an inhaled compound have been well optimised. Furthermore, AZD8154 demonstrated high pulmonary bioavailability, suggesting that the absorption of AZD8154 is via the target organ.

AZD8154 displayed dose-proportional PK characteristics, with a half-life supporting once-daily dosing. Once-daily dosing may offer greater convenience to patients, with the potential for improved adherence and asthma control.33 The AZD8154 dose and administration route did not appear to elicit a differential safety profile: no linear relationship existed between AZD8154 dose or administration route and the number of volunteers with AEs. Although AZD8154 had high pulmonary bioavailability, its safety profile was similar to placebo, further qualifying the compound to progress through clinical development.

In part 1, the dose-linear increase in exposure indicates that after single inhaled doses of up to 7.7 mg, AZD8154 was completely absorbed from the lung. Accumulation in the first 2 cohorts with the MAD in part 3 was in line with the prediction based on the half-life observed in the SAD data. The 3.1-mg dose cohort had a 3.4-fold accumulation, which was approximately 30% higher than that predicted based on the systemic half-life observed in part 1. This indicates that doses of AZD8154 >3.1 mg might saturate some absorption mechanisms in the lung and confirms the correct dose range selection in part 3.

Many patients with moderate-to-severe asthma receiving high doses of ICS still experience asthmatic symptoms.8 Activation of PI3K is associated with corticosteroid-resistant lung inflammation34 and inhibition of PI3K provides an opportunity to modulate steroid insensitivity.35 Although untested in a clinical trial setting, PI3K inhibitors such as AZD8154 could potentially restore sensitivity to steroids, thus addressing an important unmet need in asthma.
A strength of this study was the evaluation of cough monitoring as an exploratory endpoint. The VitaloJAK15 is an objective way to measure postinhalation cough compared with more subjective patient-reported outcome measures such as the visual analogue scale or health-related quality of life questionnaires.36 Limitations include the small study size (n = 78); this was a phase 1 study in healthy volunteers. Additionally, the pharmacodynamics of AZD8154 were not assessed and the efficacy in a patient population has yet to be evaluated. Nevertheless, these data indicate that AZD8154 is suitable for further clinical development.

5 | CONCLUSION

In this phase 1 study in healthy volunteers, single inhaled, single IV and multiple inhaled doses of the novel dual PI3Kδγδ inhibitor AZD8154 were shown to be well tolerated, with no reports of SAEs and no clinically significant drug-associated safety concerns. AZD8154 displayed dose-proportional PK characteristics, with a half-life supporting once-daily dosing. These results justify further investigation of the therapeutic potential of AZD8154 in respiratory disease.

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AstraZeneca funded this study, and participated in the study design, data collection, data analysis, data interpretation and writing the study report. AstraZeneca reviewed the publication, without influencing the opinions of the authors, to ensure medical and scientific accuracy, and the protection of intellectual property. The corresponding author had access to all data in the study and had the final responsibility for the decision to submit the manuscript for publication. AstraZeneca develops and markets treatments for respiratory diseases. AZD8154 is an investigational medical product with no approved indication.

COMPETING INTEREST

M.W.S., S.A., M.G.B., W.B., R.Fr., A.H., M.H., T.J.J., J.J., C.Ke., C.Kr., J.M., S. Necander, S. Nemes and J.B. are employees of AstraZeneca. R.Fu. and T.K. are employees of Parexel, and received funding from AstraZeneca for the conduct of this study.

CONTRIBUTORS

M.W.S., S.A., M.G.B., W.B., R.Fr., A.H., M.H., T.J.J., J.J., C.Ke., C.Kr., J.M., S. Necander, S. Nemes and J.B. contributed substantially to the study design and concept; R.Fu. and T.K. were involved in data acquisition; M.W.S., S.A., M.G.B., W.B., R.Fr., A.H., M.H., T.J.J., J.J., C.Ke., C.Kr., J.M., S. Necander, S. Nemes and J.B. conducted the data analyses; and M.W.S., S.A., M.G.B., W.B., R.Fr., R.Fu., A.H., M.H., T.J.J., J.J., C.Ke., C.Kr., T.K., J.M., S. Necander, S. Nemes and J.B. assisted with interpretation of the data.

PATIENT CONSENT

All volunteers provided written informed consent before any study-specific procedures.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy, described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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