First-in-human data for the inhaled IL-4Rα antagonist AZD1402/PRS-060 reveals a promising clinical profile for the treatment of asthma

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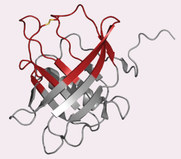
Introduction

- Disease control is not achieved in approximately 5–10% of patients with asthma, despite the availability of standard-of-care therapies (inhaled corticosteroids in combination with long-acting β_2 agonists).[1]
  - This inability to achieve asthma control reduces patients' quality of life and increases healthcare costs.
- Type 2 cytokines, interleukin (IL)-4, IL-5 and IL-13, play crucial roles in asthma pathogenesis.[2,3]
- AZD1402/PRS-060 is an anti-IL-4 receptor α (IL-4Rα) tear lipocalin-derived Anticalin protein being developed for moderate-to-severe asthma (**Figure 1**).
  - AZD1402/PRS-060 has a high potency (KD 0.023 nM) and selectivity for human IL4-Rα and is being developed to target asthma locally via inhalation.
- Dupilumab is a fully human IL-4Rα monoclonal antibody given by subcutaneous injection, which inhibits IL-4 and IL-13 signaling.[4]
  - It has been shown to reduce exacerbations and improve lung function in patients with moderate-to-severe asthma.
- Pitrakinra is an inhaled IL-4 mutein that antagonizes IL-4Rα and has been shown to have beneficial effects in a subset of patients with asthma.[5]
- Here, we describe the results of a phase 1, first-in-human study of AZD1402/PRS-060.

Figure 1. PRS-060 protein structure.



Objectives

- Primary objective: safety and tolerability of single inhaled doses and single intravenous doses of AZD1402/PRS-060 in healthy volunteers.
  - Secondary objective: to evaluate serum and urine pharmacokinetics (PK) after single inhaled and single intravenous doses of AZD1402/PRS-060 in healthy volunteers.
  - Exploratory objective: to evaluate taste characteristics.
  - Exploratory objective: to assess the biomarker impact of single inhaled doses of AZD1402/PRS-060 (including inhibition of *ex vivo* whole blood activation downstream of IL-4Rα signaling).

Methods

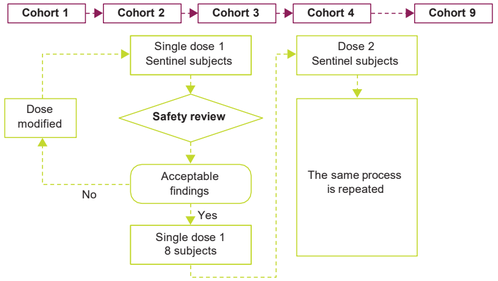
Study design

- This was a single-blind, randomized, phase 1, dose-escalating study. The overall study design is shown in **Figure 2**.
  - Subjects received AZD1402/PRS-060 or matching placebo administered using an InnoSpire Go nebulizer (Philips Healthcare, Amsterdam, Netherlands) or intravenously.
  - Subjects were healthy men or women of non-childbearing potential between 18 and 55 years of age.
  - Subjects were assigned to one of seven cohorts according to a randomization code produced by the phase 1 clinical research organization.
  - Each cohort included eight individuals: six received AZD1402/PRS-060 and two received placebo.
  - Subjects started at a dose of 0.25 mg (delivered dose 0.1 mg) and received up to 400 mg (delivered dose 160 mg) (**Table 1**).
- After safety evaluation of all cohorts and all subjects who received oral inhalation doses, an additional two cohorts were admitted for intravenous dosing.
  - Drug or placebo was infused in a 10 mL volume over a 60-minute period.
  - The intravenous dose cohorts 8 and 9 received 1 mg and 2 mg, respectively.

Ethics approval

- The protocol, the subject information and consent form, and other relevant study documentation were approved by the ethics committee (Alfred Health, Melbourne, Australia) before initiation of the study. Protocol amendments were approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) before being implemented/submitted to the IEC/IRB for information, as required.
- ClinicalTrials.gov identifier: NCT03384290.

Figure 2. Overall study design.



A pharmacokinetic and safety review occurred between cohorts.

Criteria for evaluation

Safety

- Changes from baseline or incidence in the safety variables.
- Safety variables included adverse events, laboratory data (hematology, serum chemistry and urinalysis), vital signs, spirometry assessment, 12-lead electrocardiogram parameters and assessment of taste characteristics.

PK

- Serial blood samples were drawn for analysis of AZD1402/PRS-060 levels (up to 48 hours after administration of each dose).
- The following PK parameters were derived after administration of AZD1402/PRS-060: maximum (peak) observed serum concentration (C_{max}), time to maximum serum concentration (T_{max}), apparent terminal elimination half-life ($t_{1/2}$), area under the serum concentration time curve from time 0 to infinity (AUC_{inf}), mean residence time (MRT), volume of distribution at terminal phase (V_z), apparent volume of distribution at steady state (V_{ss}), systemic clearance (CL) and absolute systemic bioavailability (BA) after inhalation.
- Serum AZD1402/PRS-060 PK profiles were determined in cohorts who met the limit of quantitation (1.56 ng/mL).

Pharmacodynamic (PD) analysis to establish target engagement

- Blood was drawn from subjects at 0, 1, 4, 8 and 24 hours after dosing with inhaled AZD1402/PRS-060 or placebo, and was stimulated with 10 ng/mL IL-4 for 15 minutes.
- Phosphorylated signal transducer and activator of transcription 6 (pSTAT6) was assessed by FACS in the CD3 T-cell subpopulation.

Results

Subject disposition and baseline characteristics

- A total of 72 healthy volunteers were enrolled in this study.
  - Fifty-four subjects were randomized to receive AZD1402/PRS-060; 18 were randomized to receive placebo.
  - Eight subjects were allocated to each cohort.
  - All 72 enrolled subjects completed this study.
- The mean age was 26.4 years and all subjects were men.
  - The majority of the subjects (66.7%) were white.
  - The mean body mass index was 24.5 kg/m^2.

Safety

- Single inhaled doses and single intravenous doses of AZD1402/PRS-060 were well tolerated.
- Twenty-five subjects (35%) experienced 28 treatment-emergent adverse events (TEAEs) (**Table 2**).
  - Twenty subjects (80%) reported mild TEAEs.
  - Five subjects (20%) reported moderate TEAEs.
  - No subjects reported severe TEAEs.
- The most frequent TEAE was headache, reported for six subjects (8%; 6 events), followed by upper respiratory tract infection (URTI) for five subjects (7%; 5 events) (**Table 2**).

Table 1. Doses of AZD1402/PRS-060 and matching placebo.

Cohort	Oral inhalation device doses (delivered doses), mg
1	0.25 (0.1)
2	1.25 (0.5)
3	5.00 (2.0)
4	20.0 (8.0)
5	60 (24.0)
6	180 (72.0)
7	400 (160.0)
	Intravenous doses, mg
8	1.0
9	2.0

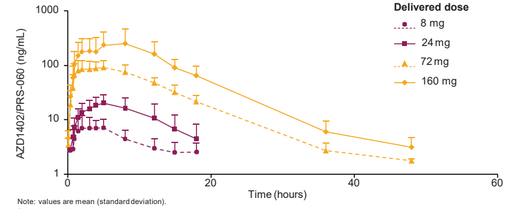
Table 2. Incidence of TEAEs for all subjects (safety population).

System organ class Preferred term	Placebo (n = 18) n (%) m	AZD1402/ PRS-060 (n = 54) n (%) m	Overall (N = 72) n (%) m
Subjects with TEAEs	6 (33) 8	19 (35) 20	25 (35) 28
Nervous system disorders	1 (6) 1	5 (9) 6	6 (8) 7
Headache	1 (6) 1	5 (9) 5	6 (8) 6
Somnolence	0	1 (2) 1	1 (1) 1
Infections and infestations	2 (11) 2	5 (9) 5	7 (10) 7
URTI	2 (11) 2	3 (6) 3	5 (7) 5
Respiratory tract infection	0	1 (2) 1	1 (1) 1
Tonsillitis	0	1 (2) 1	1 (1) 1
Respiratory, thoracic and mediastinal disorders	2 (11) 2	3 (6) 3	5 (7) 5
Dry throat	0	2 (4) 2	2 (3) 2
Pleuritic pain	0	1 (2) 1	1 (1) 1
Throat irritation	2 (11) 2	0	2 (3) 2
General disorders and administration site conditions	1 (6) 1	2 (4) 2	3 (4) 3
Fatigue	0	1 (2) 1	1 (1) 1
Influenza-like illness	0	1 (2) 1	1 (1) 1
Application site dermatitis	1 (6) 1	0	1 (1) 1
Musculoskeletal and connective tissue disorders	1 (6) 1	2 (4) 2	3 (4) 3
Back pain	0	1 (2) 1	1 (1) 1
Musculoskeletal chest pain	1 (6) 1	1 (2) 1	2 (3) 2
Gastrointestinal disorders	0	1 (2) 1	1 (1) 1
Nausea	0	1 (2) 1	1 (1) 1
Investigations	0	1 (2) 1	1 (1) 1
Blood pressure increased	0	1 (2) 1	1 (1) 1
Injury, poisoning and procedural complications	1 (6) 1	0	1 (1) 1
Muscle injury	1 (6) 1	0	1 (1) 1

Note: m, number of events, n, number of subjects in the specified category; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

- Other than headache and URTI, no other events experienced by subjects were common to those receiving AZD1402/PRS-060 and placebo.
  - Moderate TEAEs reported by subjects receiving placebo included 1 event of muscle injury and 2 events of URTI.
  - Moderate TEAEs reported by subjects receiving AZD1402/PRS-060 included 1 event each of headache, URTI and tonsillitis.
- No clinically significant abnormalities or change from baseline in hematology, clinical chemistry laboratory results, urinalysis results, vital signs or 12-lead electrocardiogram values were noted in any subjects.
- No notable changes in any of the pulmonary mechanic measurements or the forced expiratory volume in 1 second/forced expiratory volume ratio were noted in any subjects.
- Taste characteristics were evaluated as an exploratory endpoint.
  - The assessment did not identify any significant taste or smell associated with the study drug or placebo.

Figure 3. Serum PK profile of AZD1402/PRS-060 after oral inhalation.



Note: values are mean (standard deviation).
PK, pharmacokinetics.

Table 3. Serum PK parameters after AZD1402/PRS-060 oral inhalation at the delivered dose for cohorts 4–7 (PK population).

Parameter	Cohort 4 8 mg (n = 6)	Cohort 5 24 mg (n = 6)	Cohort 6 72 mg (n = 6)	Cohort 7 160 mg (n = 6)
AUC_{inf}, h.ng/mL	87.2 (27.8)[a]	261.5 (125.6)[b]	1252.1 (398.9)	3446.0 (2314.9)
C_{max}, ng/mL	8.3 (4.8)	21.2 (9.8)	93.0 (33.8)	266.8 (232.5)
MRT_{inf}, h	7.8 (2.9)[a]	8.9 (2.1)[b]	10.9 (1.6)	11.5 (1.3)
T_{max}, h	4.6 (2.1, 5.1)	4.7 (4.1, 8.2)	4.6 (1.7, 8.1)	8.2 (1.7, 8.3)
$t_{1/2}$, h	4.2 (1.7)[a]	4.1 (0.9)[b]	6.2 (0.7)	6.0 (0.7)
BA, %	7.0	7.0	11.2	13.8

Table 4. Serum PK parameters after intravenous administration for cohorts 8 and 9 (PK population).

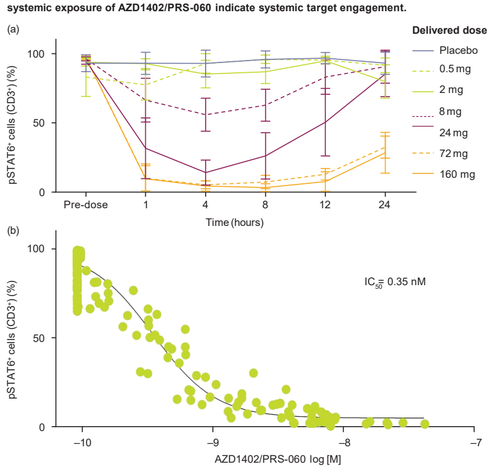
Parameter	Cohort 8 1 mg (n = 6)	Cohort 9 2 mg (n = 5)
AUC_{inf}, h.ng/mL	187.3 (32.5)	311.6 (23.0)
C_{max}, ng/mL	123.3 (13.1)	201.5 (9.0)
MRT_{inf}, h	1.4 (0.2)	1.5 (0.1)
T_{max}, h (min, max)	1.0 (0.97, 1.1)	1.0 (0.97, 1.0)
$t_{1/2}$, h	2.2 (0.75)	2.3 (0.1)
CL, L/h	5.5 (0.96)	6.4 (0.5)
V_{ss}, L	7.6 (0.69)	9.7 (0.7)
V_z, L	17.0 (4.0)	21.5 (2.4)

Note: the values indicated are mean (standard deviation) except for T_{max}, which are median (min, max). The data were analyzed using Phoenix WinNonlin (Pharsight Corporation, Mountain View, CA, USA).
[a]n = 2. [b]n = 5.
AUC_{inf}, area under the serum concentration time curve from time 0 to infinity; BA, bioavailability; CL, clearance; C_{max}, maximum observed serum concentration; h, hour; max, maximum; min, minimum; MRT, mean residence time; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; T_{max}, time to maximum serum concentration; V_{ss}, volume of distribution at steady state; V_z, volume of distribution at terminal phase.

Serum PK parameters after AZD1402/PRS-060 oral inhalation/intravenous infusion at the delivered dose for cohorts 4–9 (PK population)

- Systemic exposure was observed from 8 mg delivered dose (cohort 4) and exposure increased with dose (**Figure 3**).
- The terminal phase mean (standard deviation (SD)) $t_{1/2}$ ranged from 4.2 (1.7) hours in cohort 4 (8 mg), to 6.0 (0.7) hours in cohort 7 (160 mg) (**Table 3**).
- After intravenous infusion, the mean (SD) $t_{1/2}$ was 2.2 (0.8) hours for cohort 8 and 2.3 (0.1) hours for cohort 9 (**Table 4**).
- CL and V_z values after intravenous doses were indicative of clearance by renal filtration and a low tissue distribution.
- Longer $t_{1/2}$ after oral inhalation than after intravenous infusion indicated involvement of an absorption time (between 6.3 hours and 10.0 hours).
- The absolute percentage bioavailability of the inhaled doses was determined to be between 7.0% and 13.8%.
- Urinary excretion of unchanged AZD1402/PRS-060 was not detected after intravenous administration or oral inhalation, except in three individuals in high-dose oral inhalation cohorts.
- There were no confirmed positive anti-AZD1402/PRS-060 antibodies in any of the dose groups.

Figure 4. (a) pSTAT6 levels after inhalation of AZD1402/PRS-060 and (b) pSTAT6 levels versus systemic exposure of AZD1402/PRS-060 indicate systemic target engagement.



Note: IC_{50}, half maximal inhibitory concentration; pSTAT6, phosphorylated signal transducer and activator of transcription 6.

PD analysis to establish target engagement

- Inhibition of pSTAT6 was observed from cohort 4 onwards (delivered dose 8 mg) (**Figure 4a**).
- Inhibition of systemic pSTAT6 was dose-dependent and aligned with systemic exposure of AZD1402/PRS-060 (**Figure 4b**).
- Near complete and sustained inhibition was observed at higher inhaled doses.

Conclusions

- **The novel IL-4Rα antagonist AZD1402/PRS-060 was well tolerated when given as single inhaled or intravenous doses to healthy volunteers.**
  - **The overall profile of AZD1402/PRS-060 supports its further development as an inhaled drug for the treatment of asthma.**
- **Systemic target engagement (pSTAT6) will be compared with local lung target engagement from the ongoing multiple ascending dose study in mild asthmatics (NCT03574805).**
  - **This study will determine the local effects and dose relationship by measuring FeNO, a validated biomarker of asthma.**
  - **This will help to determine the inhaled dose levels for evaluation in future studies of this first-in-class, inhaled Anticalin molecule.**

References

1. Murphy AC *et al. J Exp Med* 2012;209:1837–52.
2. Voehringer D *et al. Thorax* 2012;67:751–53.
3. Locksley RM. *Cell* 2010;140:777–83.
4. Wenzel S *et al. Lancet* 2016;388:31–44.
5. Slager RE *et al. J Allergy Clin Immunol* 2012;130:516–22.

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Author disclosures

Bruns IB is an employee and shareholder of Pieris Pharmaceuticals. Fitzgerald MF is a consultant and shareholder of Pieris Pharmaceuticals. Pardali K, Gardiner P, Keeling DJ, Axelsson LT, Jiang F and Close DR are employees of AstraZeneca. Lickliter J is an employee of Nucleus Network. AstraZeneca provided funding to Nucleus Network for conducting this study.

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