Multiple ascending dose study of the inhaled IL-4Rα antagonist, AZD1402/PRS-060, in mild asthmatics demonstrates robust FeNO reduction and a promising clinical profile for the treatment of asthma

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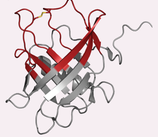
Introduction

- Asthma is a chronic, complex and heterogeneous respiratory disease characterized by a range of pathogenic features, including pulmonary inflammation, mucus hypersecretion, variable airway obstruction and airway remodelling.[1]
- Interleukin (IL)-4 and IL-13, which both signal through the IL-4 receptor alpha subunit (IL-4Rα), have been identified as two of the key cytokines contributing to the pathogenesis of asthma.[2]
- Fractional nitric oxide concentration in exhaled breath (FeNO) is a marker of eosinophilic airway inflammation.[3] As demonstrated in clinical trials, agents that either antagonize IL-4Rα directly or its agonists reduce FeNO levels.[4-6]
  - Dupilumab, a fully humanized anti-IL-4Rα monoclonal antibody, has been shown to significantly reduce FeNO levels after 4 weeks in patients with moderate to severe asthma.[4]
  - Pitrakinra is a recombinant IL-4 mutein that competitively antagonizes IL-4Rα, and inhaled pitrakinra has been shown to reduce FeNO in specific subgroups of patients with uncontrolled asthma, which correlated with improvements in forced expiratory volume in the first second (FEV_1).[5]
- AZD1402/PRS-060 is a novel inhaled Anticalin® molecule which selectively antagonizes IL-4Rα and therefore inhibits the pro-inflammatory actions of IL-4 and IL-13 (**Figure 1**).
- Here, we describe the interim analysis of a phase 1 dose-escalating study that assessed the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of multiple inhaled doses of AZD1402/PRS-060 in patients with mild asthma.

Figure 1. AZD1402/PRS-060 protein structure.



Objectives

- Primary objective
  - To evaluate the safety and tolerability of multiple inhaled doses of AZD1402/PRS-060 in men and non-pregnant, non-breastfeeding women with mild asthma.
- Secondary objectives
  - To evaluate plasma and urine PK.
  - To evaluate the potential development of anti-drug antibodies* against AZD1402/PRS-060.
  - To evaluate the change from baseline in FeNO.

*Data to be presented in the future.

Methods

Study design

- This was a phase 1, single-blind, randomized, dose-escalating study of multiple doses of AZD1402/PRS-060 administered by inhalation in men and women with mild asthma (FeNO ≥ 35 parts per billion [ppb]) (**Figure 2**).
- FeNO levels were assessed for eligibility during screening and run-in (day -1) visits, and measured as part of the study assessments on multiple occasions during the study dosing period and at follow-up visits.

Ethics approval

- The protocol, protocol amendments, patient information, consent form and other relevant study documentation were approved by the Independent Ethics Committee/Institutional Review Board for each study centre before study initiation (ClinicalTrials identifier: NCT03574805).

Criteria for evaluation

- Safety
  - Participants were monitored for adverse events (AEs) during the study period (at the time the study drug was first administered) until 30 days after the last dose of study drug.
  - Safety variables included AEs, demographic/medical history/prior treatments, laboratory data (haematology, serum chemistry and urinalysis), vital signs, weight and height, electrocardiogram parameters and pregnancy screen.
- Efficacy
  - Change in FeNO levels from baseline compared with placebo were assessed as an index of pharmacological activity.
  - Systemic target engagement was determined *ex vivo* by inhibition of IL-4-stimulated phosphorylation of signal transducer and activator of transcription 6 (STAT6) in whole blood.
- PK
  - The following PK parameters were derived after administration of AZD1402/PRS-060: maximum observed serum concentration (C_{max}), average concentration, time to C_{max} (T_{max}), area under the concentration–time curve (AUC) from 0 to 24 hours (AUC_{0-24}), AUC up to the last measurable concentration (AUC_{0-last}), AUC from 0 to infinity (AUC_{inf}), accumulation ratio (R_{ac})(AUC_{0-t}), R_{ac}(C_{max}), temporal change parameter, dose-normalized exposure parameters (AUC_{0-24}/dose, AUC_{0-last}/dose, AUC_{inf}/dose), terminal half-life ($t_{½}$), apparent total body clearance, apparent volume of distribution, cumulative amount of unchanged drug excreted into urine, fraction excreted into the urine and renal clearance from plasma.
- Exploratory analysis
  - Plasma and serum were used to assess potential soluble biomarkers associated with the IL-4Rα pathway.
- The end-of-trial date for the last patient in cohort 4 was 16 August 2019 and data lock for cohorts 1–4 for the interim analysis was completed on 30 August 2019.

Statistical methods

- A sigmoid maximum effect (E_{max}) function was fitted by means of a non-linear mixed-effect model, simultaneously to placebo and all active groups, utilizing baseline (pre-dose day 1 measurement) and all 2-hour post-dose measurements from day 1 to day 10. The model included baseline as a covariate and dose group as a factor. The model was fitted to logged data and results were then translated to linear scale and percentage reduction. The estimates shown in the tables should thus be interpreted as relative percentage reduction estimates (relative to baseline, and relative to placebo).

Results

Baseline characteristics and safety

- In total, 42 patients were enrolled; 30 patients were randomized to receive AZD1402/PRS-060 and 12 were randomized to receive placebo (**Table 1**).
  - In the overall cohort, mean age was 28.4 years and most patients were white.
  - The mean body mass index was 25.7 kg/m^2.
- All doses of AZD1402/PRS-060 tested in the study were well tolerated; no treatment related serious AEs were observed (**Table 2**).

PK exposure data

- Limited systemic exposure was observed in the 2 mg cohort (cohort 1).
- Dose-related increases in systemic exposure were observed.
- Day 10 systemic exposure was higher than on day 1, consistent with twice-daily dosing and PK $t_{½}$ (**Figure 3** and **Table 3**).

FeNO reduction

- Pulmonary target engagement was determined by reduction in FeNO levels.
- Significant and pronounced lung target engagement, as measured by reduction of FeNO levels (≥ 24%), was observed at all doses, including the 2 mg delivered dose, with which no systemic target engagement and minimal systemic exposure was observed (**Figure 4** and **Table 4**).

Table 1. Baseline characteristics.

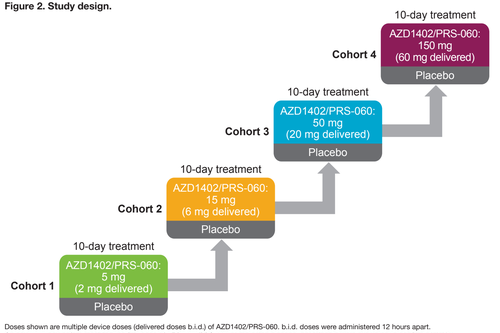
Parameter	Placebo (N = 12)	AZD1402/PRS-060 (N = 30)	Overall (N = 42)
Age, years, mean (range)	28.8 (19–52)	28.4 (19–51)	28.4 (19–52)
Sex, male, n	11	26	37
Race, n			
White	8	25	33
Asian/Pacific Islander	2	3	5
Other	2	2	4
BMI, kg/m^2, mean (range)	27.7 (22.5–34.8)	25.0 (20.5–33.4)	25.7 (20.5–34.8)
FeNO, ppb at pre-dose day 1, mean (range)	61.2 (28–122)	81.7 (32–178)	75.9 (28–178)
FEV_1, mL at pre-dose day 1, mean (range)	3730.8 (2560–4770)	3901.7 (2580–5070)	3852.9 (2560–5070)
FEV_1/FVC ratio, % at pre-dose day 1, mean (range)	74.1 (63–85)	74.9 (62–87)	74.7 (62–87)

Patients from cohorts 1–4.
BMI, body mass index; FeNO, fractional nitric oxide concentration in exhaled breath; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; ppb, parts per billion.

Phosphorylated STAT6

- Inhibition of systemic phosphorylated STAT6 was dose-dependent and aligned with systemic levels of AZD1402/PRS-060 (**Figure 5**).
- Near-complete and sustained inhibition was observed at the 60 mg delivered dose (**Figure 5a**).

Figure 2. Study design.



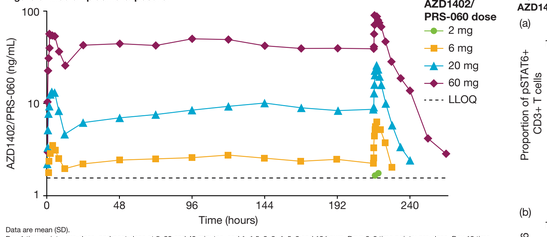
Doses shown are multiple device doses (delivered dose b.i.d.) of AZD1402/PRS-060. b.i.d. doses were administered 12 hours apart.
On day −1, 1 day before receiving the first dose of AZD1402/PRS-060 or matching placebo, participants were evaluated to confirm eligibility.
Participants checked into the hospital/study site and remained in the hospital/study site until checkout 48 hours after (day 12) the last dose of the study medication (day 10).
Study medication was administered using an InnoSpire Go nebulizer at delivered doses between 2 mg and 60 mg b.i.d. for 9 days with one dose on day 10.
The study duration from screening to post-study follow-up visit was approximately 9 weeks for each participant.
b.i.d., twice daily.

Table 2. Incidence of AEs occurring in ≥ 5% of overall patients.[a]

System Organ Class AE Preferred Term[b]	Placebo (N = 12) n (%), m	AZD1402/PRS-060[c] (N = 30) n (%), m	Overall (N = 42) n (%), m
Gastrointestinal disorders	**4 (33.3) 4**	**13 (43.4) 14**	**17 (40.5) 18**
Dry mouth	1 (8.3) 1	2 (6.7) 2	3 (7.1) 3
Nausea	1 (8.3) 1	3 (10.0) 3	4 (9.5) 4
Infections and infestations	**1 (8.3) 1**	**7 (23.3) 8**	**8 (19.0) 9**
Upper respiratory tract infection	1 (8.3) 1	3 (10.0) 4	4 (9.5) 5
Nervous system disorders	**5 (41.7) 9**	**13 (43.4) 18**	**18 (42.9) 27**
Headache	3 (25.0) 6	5 (16.7) 7	8 (19.0) 13
Presyncope	0	4 (13.3) 6	4 (9.5) 6
Respiratory, thoracic and mediastinal disorders	**6 (50.0) 6**	**14 (46.7) 15**	**20 (47.6) 21**
Cough	1 (8.3) 1	4 (13.3) 4	5 (11.9) 5
Rhinorrhoea	2 (16.7) 2	1 (3.3) 1	3 (7.1) 3
Wheezing	2 (16.7) 2	4 (13.3) 5	6 (14.3) 7

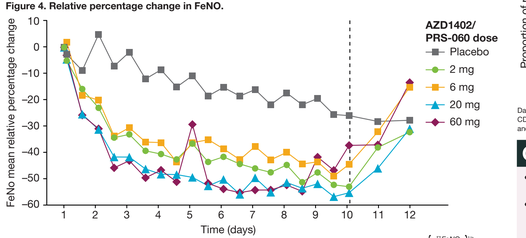
[a]Percentage is based on Preferred Term (i.e. the incidence of AEs which occurred in ≥ 5% of overall patients by Preferred Term).
[b]AEs are from cohorts 1–4, with AEs occurring in ≥ 5% of overall patients.
[c]Delivered doses of AZD1402/PRS-060 were 2 mg, 6 mg, 20 mg and 60 mg.
One pregnancy leading to a serious AE of miscarriage was observed. This was considered to be due to the patient's age, and not related to the study drug by the investigator.
Note: MedDRA v21.0 coding dictionary applied.
AE, adverse event; m, number of events; n, number of patients reported with specific AEs; N, total number of patients in each treatment group.

Figure 3. Median plasma exposure.



Data are mean (SD).
Day 1 time points: pre-dose, and post-dose at 5, 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 5, 8 and 12 hours. Days 2–9 time points: pre-dose. Day 10 time points: pre-dose, and post-dose at 5, 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 5, 8, 12, 18, 24, 36 and 48 hours.
LLOQ, lower limit of quantification; SD, standard deviation.

Figure 4. Relative percentage change in FeNO.



Relative reduction at time t is derived as 1 minus the ratio of the geometric mean at time t to the geometric mean of baseline, i.e. $1-\left\{\frac{\text{TI FeNO}}{\text{TI FeNO}_{BL}}\right\}^{\text{Time}}$
FeNO, fractional nitric oxide concentration in exhaled breath.

Table 3. Mean steady-state exposures.

AZD1402/PRS-060 delivered dose b.i.d., mg	$AUC_{(0-12)}$, h*ng/mL	C_{max}, ng/mL
2	ND	ND
6	54 (14)	6.3 (1.6)
20	210 (98)	28 (13)
60	780 (340)	103 (31)

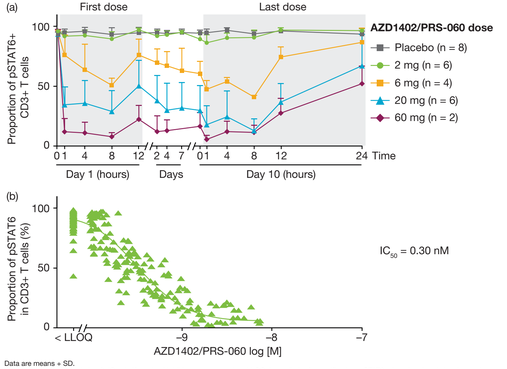
Data are mean (SD).
$AUC_{(0-12)}$, area under the concentration–time curve from 0 to 12 hours; b.i.d., twice daily; C_{max}, maximum concentration; ND, not determined; SD, standard deviation.

Table 4. Estimated relative percentage reduction in FeNO.

AZD1402/PRS-060 delivered dose b.i.d., mg	n	LS mean reduction vs baseline, % (95% CI)	Reduction vs placebo, % (95% CI)	*p* value[a]
2	6	43.9 (31–54)	24.0 (1.8–41)	0.04
6	6	44.1 (31–54)	24.3 (2.7–41)	0.03
20	12	53.1 (46–59)	36.4 (22–48)	< 0.0001
60	6	48.7 (37–58)	30.5 (10–46)	0.005
Placebo	12	26.2 (14–36)		

[a]*p* values of two-sided test of equal reduction in placebo and active group.
CI, confidence interval; FeNO, fractional nitric oxide concentration in exhaled breath; LS, least-squares.

Figure 5. (a) pSTAT6 levels over time following inhalation of AZD1402/PRS-060 and (b) pSTAT6 levels vs AZD1402/PRS-060 systemic concentration.



Data are means + SD.
CD3, cluster of differentiation 3; IC_{50}, half maximal inhibitory concentration; LLOQ, lower limit of quantification; pSTAT6, phosphorylated signal transducer and activator of transcription 6; SD, standard deviation.

Conclusions

- **All doses of AZD1402/PRS-060 were well tolerated; no serious AEs considered related to the study drug by the investigators were observed.**
- **The significant and pronounced (≥ 24%) inhibition of FeNO at a delivered dose of 2 mg, where there is minimal systemic target exposure, suggests that pulmonary target engagement by the drug is sufficient to reduce airway inflammation.**
- **The onset of FeNO reduction was rapid (after a single dose) and the maximum effect (days 4–5) versus placebo was sustained until dosing completion.**
- **Systemic target engagement (STAT6 phosphorylation) was dose-dependent and closely aligned with systemic exposure of the drug.**
- **PK exposure data demonstrated that dose-related increases in exposure were observed and day 10 exposure was consistent with twice-daily dosing and day 1 PK parameters.**
- **Pulmonary target engagement, as shown by a substantial reduction in FeNO and the overall profile of AZD1402/PRS-060, demonstrates its suitability for continued development as an inhaled therapy for asthma.**

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