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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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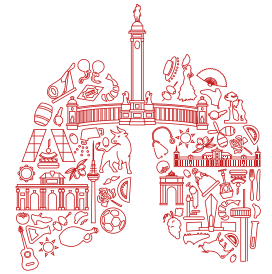
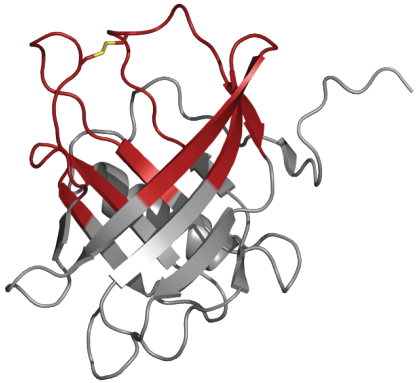
Conflict of interest disclosures



- This study was sponsored by Pieris Pharmaceuticals and funded by AstraZeneca
- IB Bruns is an employee and shareholder of Pieris Pharmaceuticals.
- MF Fitzgerald is a consultant and shareholder of Pieris Pharmaceuticals.
- G Mensing is an employee of Pieris Pharmaceuticals.
- M Tsung is an employee of Pieris Pharmaceuticals.
- K Pardali, P Gardiner, DJ Keeling, LT Axelsson, M Olsson, C Ghobadi and DR Close are employees of AstraZeneca and may own stock or stock options.
- O Walsh is an employee of Nucleus Network Limited, Melbourne, Australia.
- K McLendon is an employee of Q-Pharm Pty Ltd, Herston, Australia.
- N Farinola is an employee of CMAS Clinical Research Pty Ltd, Adelaide, Australia.
- L Hatchuel is an employee of Linear Clinical Research Ltd, Nedlands, Australia.

Rationale

- Asthma is a chronic, complex and heterogeneous respiratory disease[1]
- Interleukin (IL)-4 and IL-13, which both signal through the IL-4 receptor alpha subunit (IL-4Rα), have been identified as two key cytokines contributing to the pathogenesis of asthma[2]
- As demonstrated in clinical trials, agents that either antagonize IL-4Rα directly or its agonists reduce fractional exhaled nitric oxide (FeNO) levels[3–5]
- AZD1402/PRS-060 is a novel inhaled Anticalin® molecule that selectively antagonizes IL-4Rα and therefore inhibits the pro-inflammatory actions of IL-4 and IL-13



AZD1402/PRS-060 protein structure

Here, we describe the interim analysis of a phase 1 dose-escalation study that assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple inhaled doses of AZD1402/PRS-060 in patients with mild asthma

FeNO, fractional exhaled nitric oxide; IL, interleukin; IL-4Rα, IL-4 receptor alpha subunit

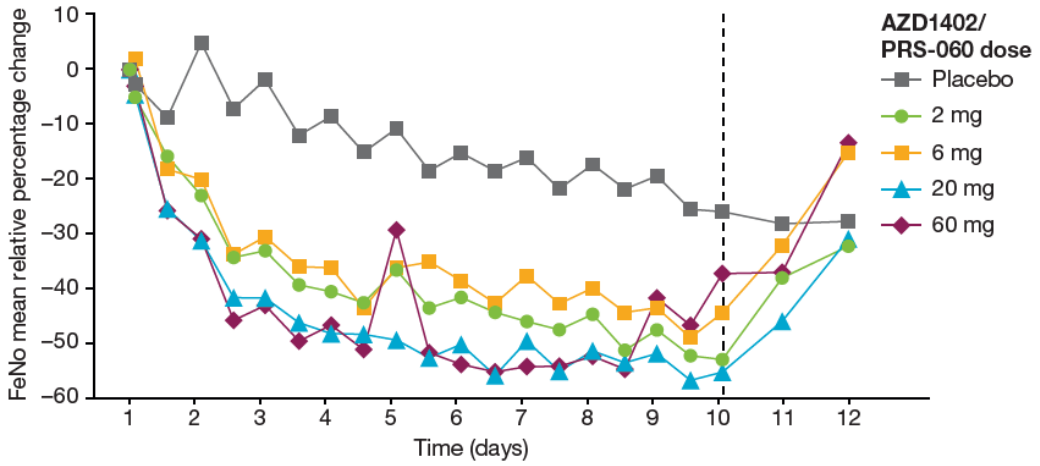
1. Reddel *et al. Eur Respir J* 2015;46:622–39; 2. Vatrella *et al. J Asthma Allergy* 2014;7:123–30; 3. Wenzel et al *New Eng J Med* 2013;368:2455–66; 4. Otulana *et al. AJRCCM* 2011;183:A6179; 5. Cai *et al. AJRCCM* 2016; 193:A1405

Results: FeNO reduction and pSTAT6

- Pulmonary target engagement was determined by reduction in FeNO levels
  - **Significant and pronounced inhibition of FeNO levels was observed at all dose levels evaluated**
- Systemic target engagement was determined ex vivo by inhibition of IL-4-stimulated phosphorylation of signal transducer and activator of transcription 6 (pSTAT6) in whole blood
  - **Inhibition of pSTAT6 ranged from minimal to near complete as a function of dose level**

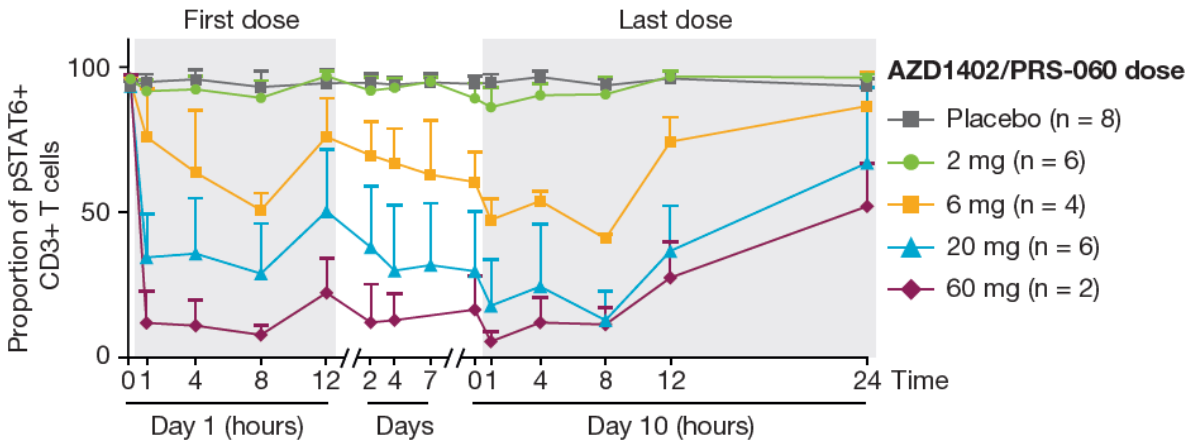
Local

Relative percentage change in FeNO[a]



Systemic

pSTAT6 levels following inhalation of AZD1402/PRS-060

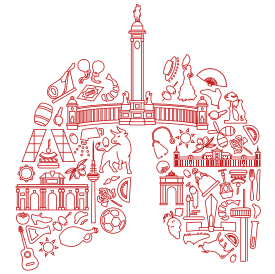


[a]Relative reduction at time t is derived as 1 minus the ratio of the geometric mean at time t to the geometric mean of baseline, i.e $1-\left\{\frac{\prod FeNO}{\prod FeNO_{BL}}\right\}^{1/n}$

FeNO, fractional exhaled nitric oxide; pSTAT6, phosphorylated signal transducer and activator of transcription 6

FeNO (percentage change) and % pSTAT6+ in CD3 T-cell subpopulation: group means

Results: incidence of AEs occurring in ≥ 5% of overall patients [a]



- All doses of AZD1402/PRS-060 tested in the study were well tolerated; no treatment related serious AEs were observed

System organ class AE Preferred Terms[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

MedDRA v21.0 coding applied

[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, which occurred 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

AE, adverse event; m, number of events; n, number of patients reported with specific AEs; N, total number of patients in each treatment group

Conclusions

- The FeNO-reduction potential of AZD1402/PRS-060 is unparalleled with other inhaled therapies
- Pharmacological versatility, given low-dose FeNO reduction with no observed systemic activity (pSTAT6) versus high-dose FeNO reduction with systemic activity
- AZD1402/PRS-060 was very well tolerated and safe; there were no related SAEs, and AEs were evenly distributed between treatment and placebo groups
- The overall profile of AZD1402/PRS-060 demonstrates its suitability for continued development as an inhaled therapy for asthma

Please see poster **PA3709** for more details: 08:30–10.30, 1 October 2019 in RETIRO

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AE, adverse event; FeNO, fractional exhaled nitric oxide; signal transducer and activator of transcription 6

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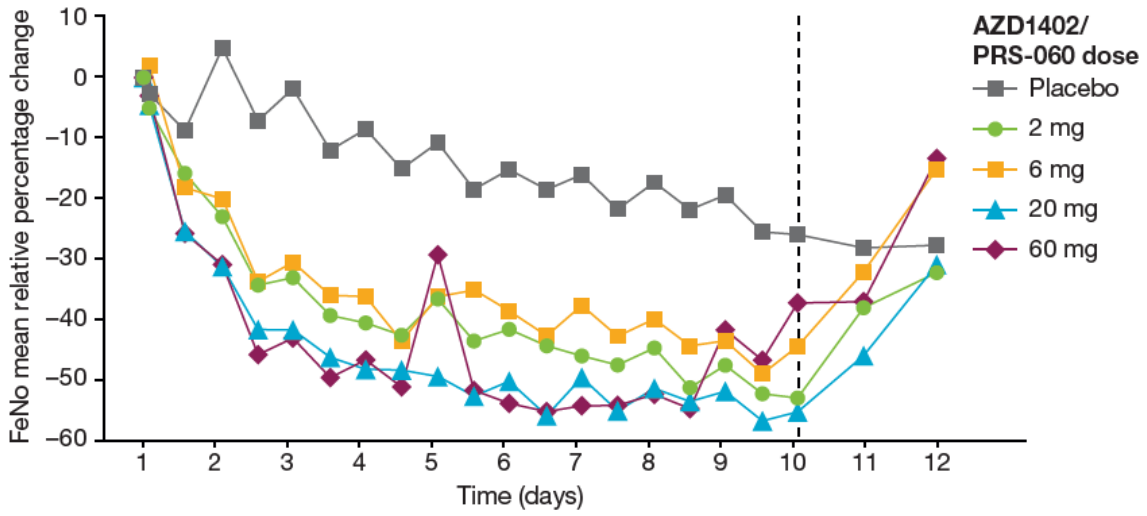
Phase 1b Interim Results: Robust FeNO Reduction

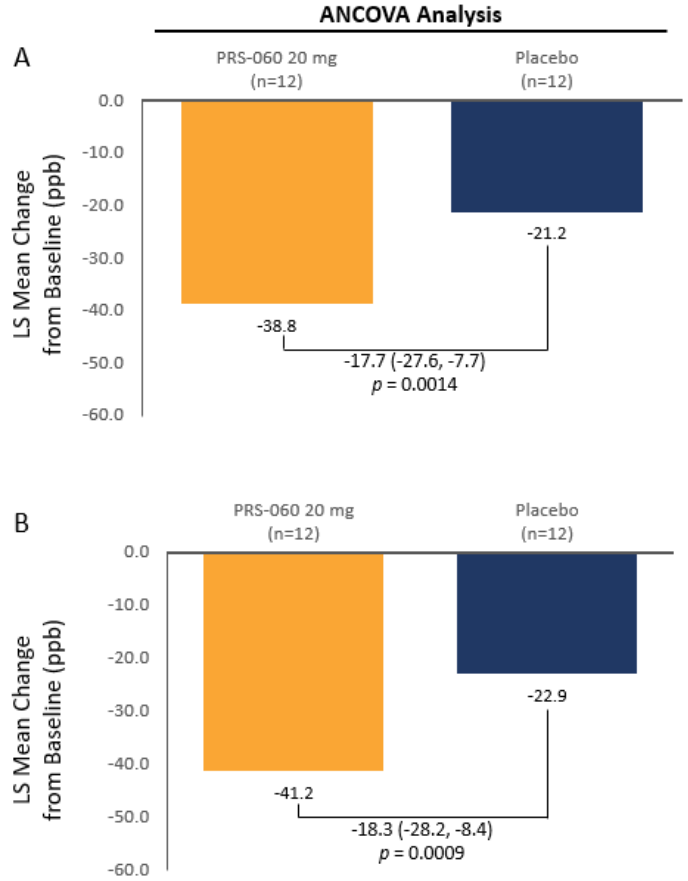
PRS-060 Relative FeNO Reduction (Emax Analysis)



PRS-060, mg (delivered)	n	Reduction vs. placebo, % (95% CI)	p-value
2	6	24.0 (1.8–41)	0.04
6	6	24.3 (2.7–41)	0.03
20	12	36.4 (22–48)	<0.0001
60	6	30.5 (10–46)	0.005
Placebo	12		

PRS-060 Relative FeNO Reduction (ANCOVA Analysis)

Mean change from baseline in FeNO levels at 0.5h (A) and 2h (B) post-dose on Day 10 in participants with mild asthma



80% relative FeNO reduction in powered cohort (20mg)

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