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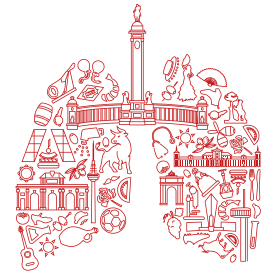
Phase 1 evaluation of the inhaled IL-4Rα antagonist, AZD1402/PRS-060, a potent and selective blocker of IL-4Rα
Abstract: OA5336

Bruns IB,[1] Fitzgerald MF,[1] Pardali K,[2] Gardiner P,[3] Keeling DJ,[2] Axelsson LT,[2] Jiang F,[2] Lickliter J,[4] Close DR[5]

[1]Pieris Pharmaceuticals, Boston, MA, USA; [2]Early Research and Development, Respiratory, Inflammation and Autoimmune, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [3]Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [4]Nucleus Network, Melbourne, Australia; [5]Early Research and Development, Respiratory, Inflammation and Autoimmune, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

Conflict of interest disclosure



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Affiliation / Financial interest	**Commercial Company**
Grants/research support:	• This study was sponsored by Pieris Pharmaceuticals and funded by AstraZeneca • Lickliter J is an employee of Nucleus Network; AstraZeneca provided funding to Nucleus Network for conducting this study
Honoraria or consultation fees:	• Fitzgerald MF is a consultant of Pieris Pharmaceuticals
Participation in a company sponsored bureau:	
Stock shareholder:	• Bruns IB is a paid employee and shareholder of Pieris Pharmaceuticals • Fitzgerald MF is a shareholder of Pieris Pharmaceuticals • Pardali K, Gardiner P, Keeling DJ, Axelsson LT, Jiang F and Close DR are employees of AstraZeneca, and may own stock or stock options
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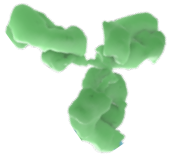
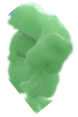
Anticalin® proteins – a new class of biopharmaceuticals

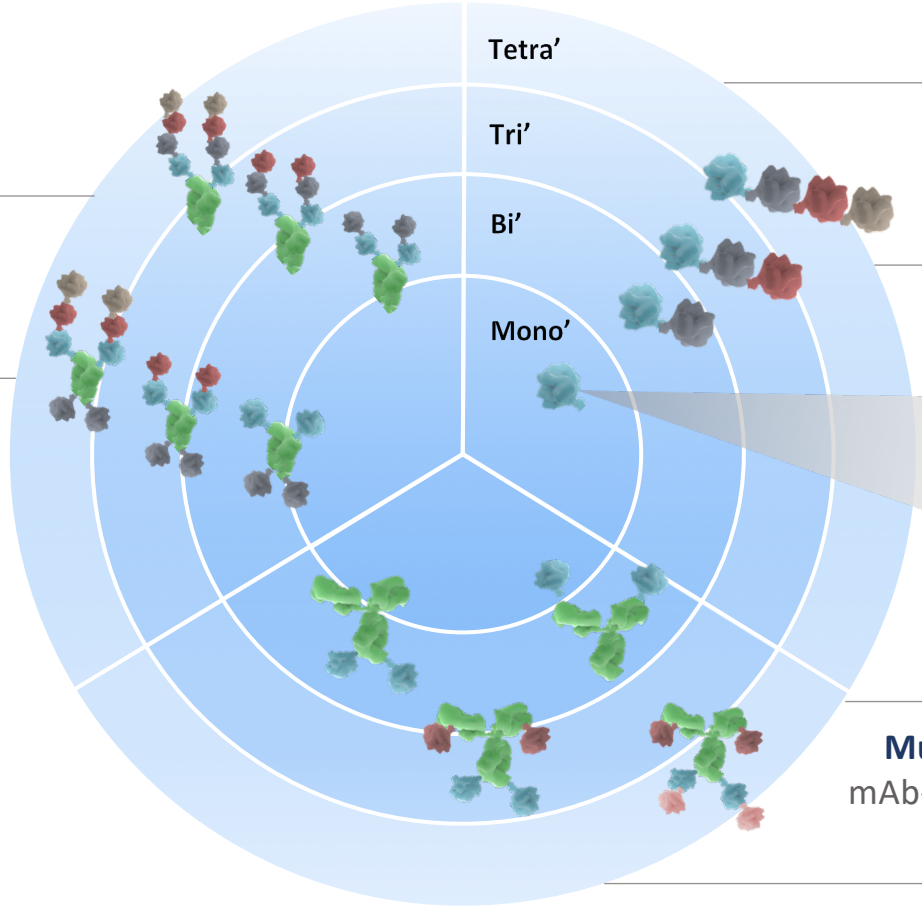
Building blocks


Anticalin® Protein


Antibody


Fc

Multispecific
Fc-Anticalin® proteins



Mono-/multispecific
Pure Anticalin® proteins

AZD1402/ PRS-060

Multispecific
mAb-Anticalin® proteins

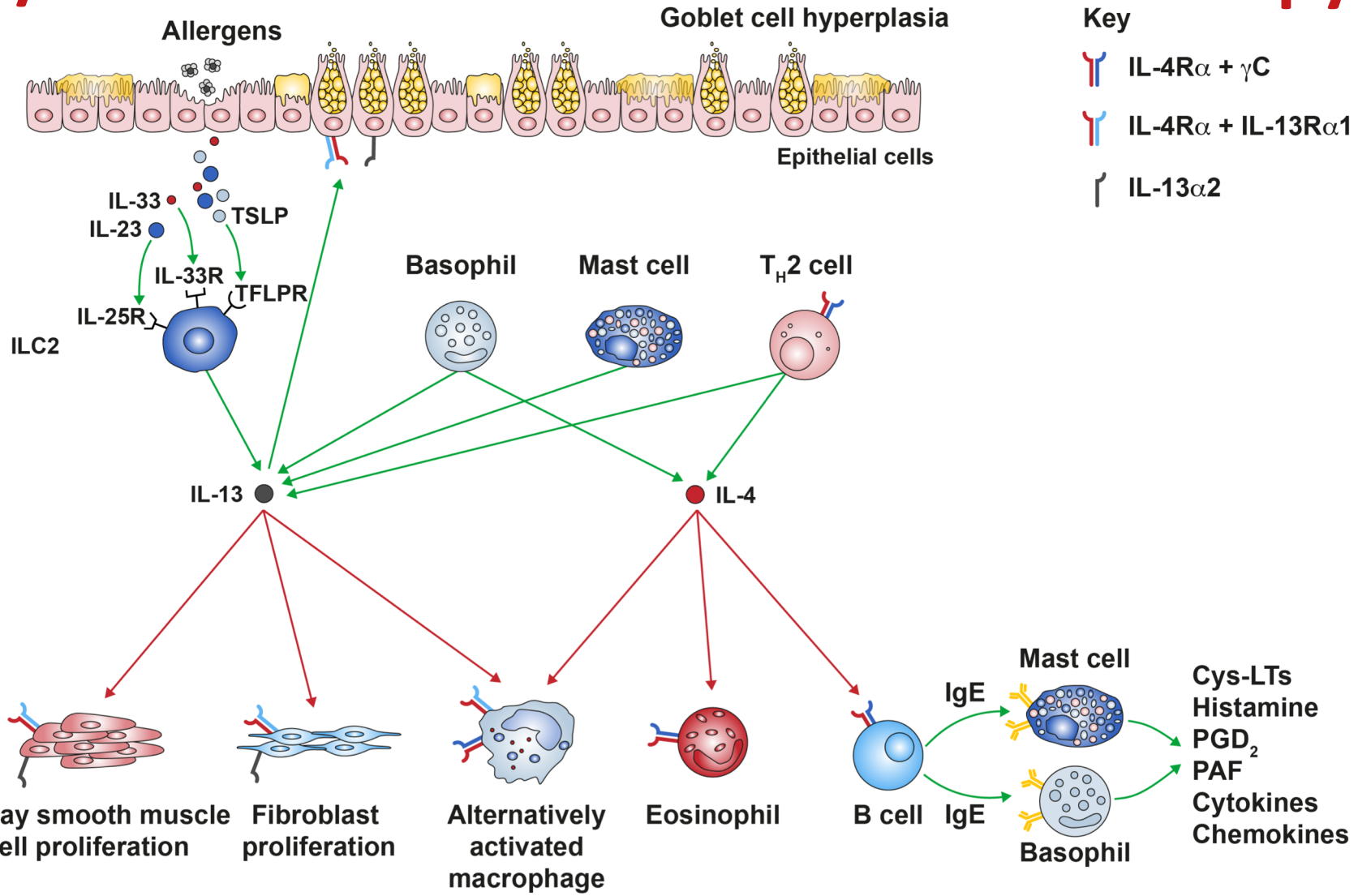
Potent multi-target engagement • Novel inhaled and multispecific MoA • Favorable drug-like properties

Adapted from Rothe C, Skerra A[1]

Fc, fragment crystallizable; mAb, monoclonal antibody; MoA, mechanism of action

1. Rothe C, Skerra A. *BioDrugs* 2018;32:233–43

AZD1402/PRS-060 – a first-in-class asthma therapy

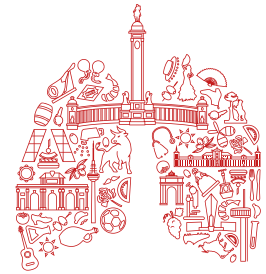


Adapted from Bagnasco D *et al*. 2016[1]

IL, interleukin; IL-4Rα, IL-4 receptor α

1. Bagnasco D *et al. Intl Arch Allerg Immunol* 2016;170:122–31

AZD1402/PRS-060 – a first-in-class asthma therapy

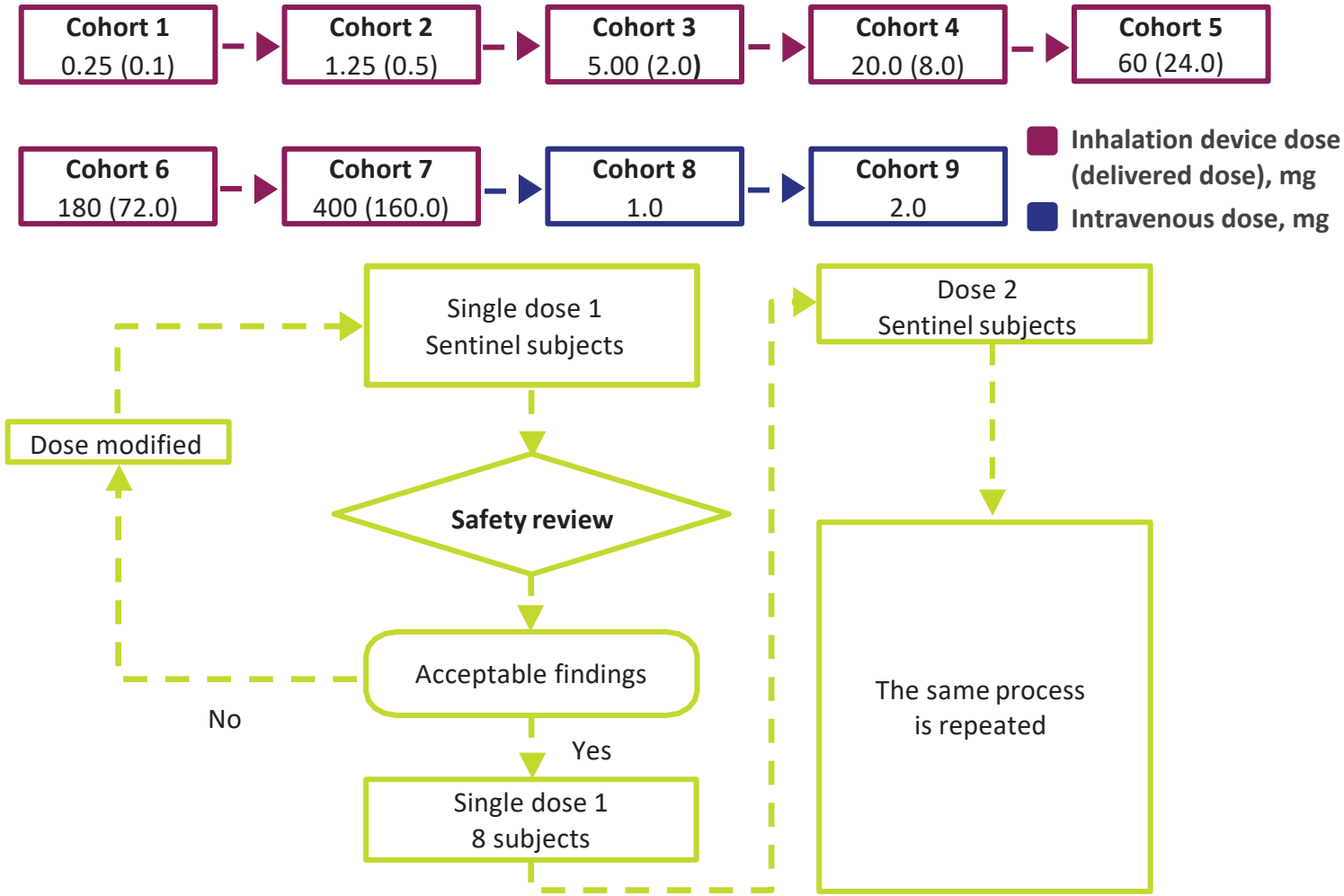


- Despite the availability of standard-of-care therapies, disease control is not achieved in 5–10% of patients with asthma[1]
- Type 2 cytokines **IL-4** and **IL-13** signal through **IL-4Rα**, and play crucial roles in asthma pathogenesis[2–4]
- **AZD1402/PRS-060** is a tear lipocalin-derived Anticalin protein antagonist of **IL-4Rα** that is being developed as an inhaled treatment for **moderate-to-severe asthma**
- This presentation details the results of **a phase 1, single-blind, randomized, first-in-human dose-escalation study of AZD1402/PRS-060** in healthy volunteers (NCT03384290)

IL, interleukin; IL-4Rα, IL-4 receptor α

1. Murphy AC *et al*. *Thorax* 2012;67:751–53; 2. Voehringer D *et al. J Exp Med* 2006;203:1435–46; 3. Locksley RM. *Cell* 2010;140:777–83; 4. Wenzel S *et al. Lancet* 2016;388:31–44

NCT03384290 – study design and subject disposition



Study endpoints

Safety

PK

- Serial blood samples were drawn (up to 48 hours after administration of each dose)
- Standard PK parameters were derived for evaluation

PD to establish systemic target engagement

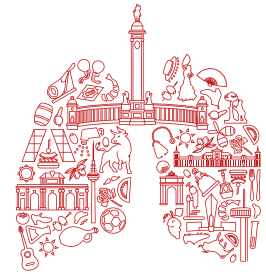
- Blood was drawn from subjects after dosing with inhaled AZD1402/PRS-060 or placebo, and was stimulated with IL-4 10 ng/mL for 15 minutes
- pSTAT6 was assessed by FACS in the CD3+ T-cell subpopulation

Study population

- 72 healthy volunteers were enrolled
- 54 received AZD1402/PRS-060
- 18 received placebo
- Sex: 100% male
- Mean age: 26.4 years
- Mean BMI: 24.5 kg/m^2

BMI, body mass index; FACS, fluorescence-activated cell sorting; IL, interleukin; PD, pharmacodynamic; PK, pharmacokinetic; pSTAT6, phosphorylated signal transducer and activator of transcription 6

AZD1402/PRS-060 was well tolerated after intravenous and inhaled administration



- Single inhaled doses and single intravenous doses of AZD1402/PRS-060 were well tolerated
  - Twenty-five subjects (35%) experienced 28 TEAEs
  - Most TEAEs (80%) were mild and no subjects reported severe TEAEs
- No clinically significant abnormalities or change from baseline in hematology,[a] clinical chemistry laboratory results, urinalysis results, vital signs or 12-lead electrocardiogram values were noted in any subjects
- No notable changes in pulmonary function parameters were observed in any of the subjects

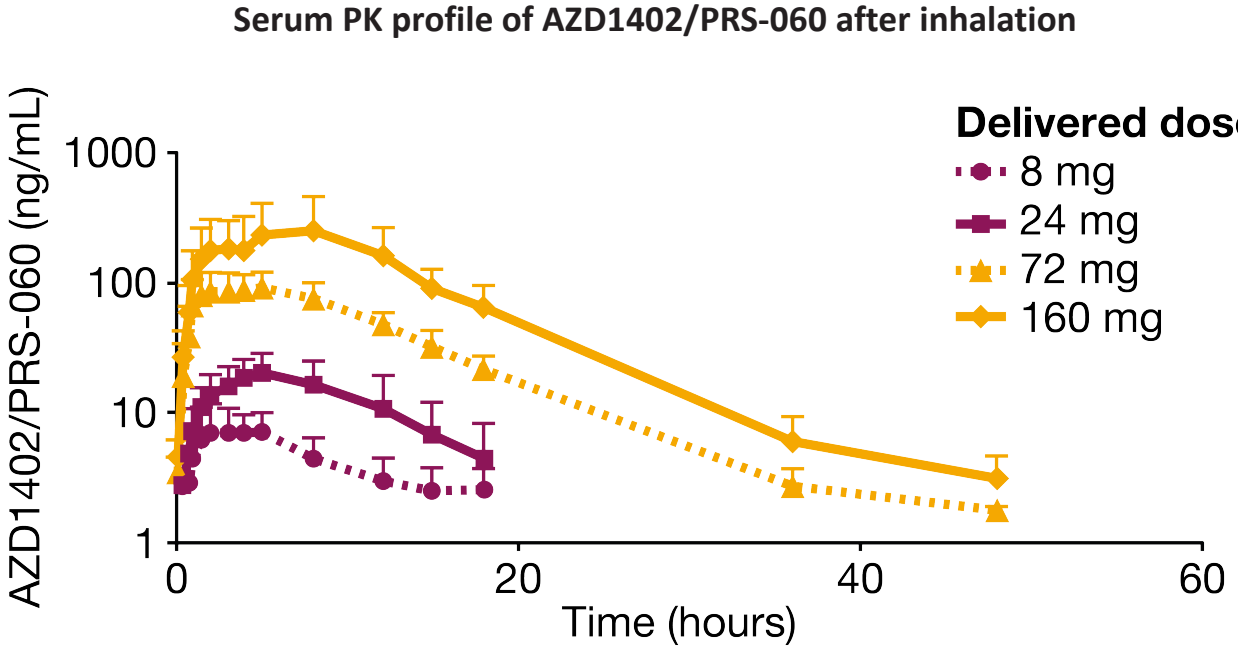
Exploratory analysis

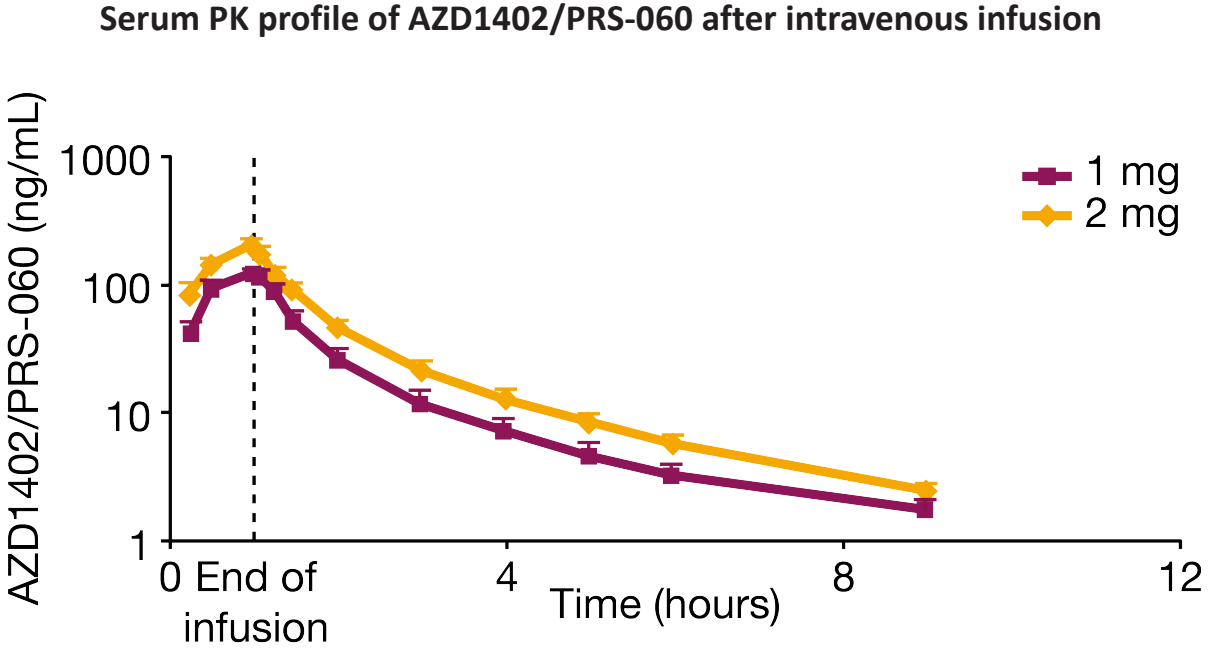
- There was no significant taste or smell associated with the study drug or placebo

System organ class Preferred term[b]	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	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
Gastrointestinal disorders	0	1 (2) 1	1 (1) 1
Nausea	0	1 (2) 1	1 (1) 1

[a]The laboratory tests analyzed hemoglobin, hematocrit, red blood cells, platelets, white blood cells, neutrophils, lymphocytes, eosinophils, basophils and monocytes
[b]MedDRA 20.1
m, number of events, n, number of subjects in the specified category; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

AZD1402/PRS-060 was absorbed after inhalation resulting in dose-dependent increases in C_{max} and AUC_{inf}

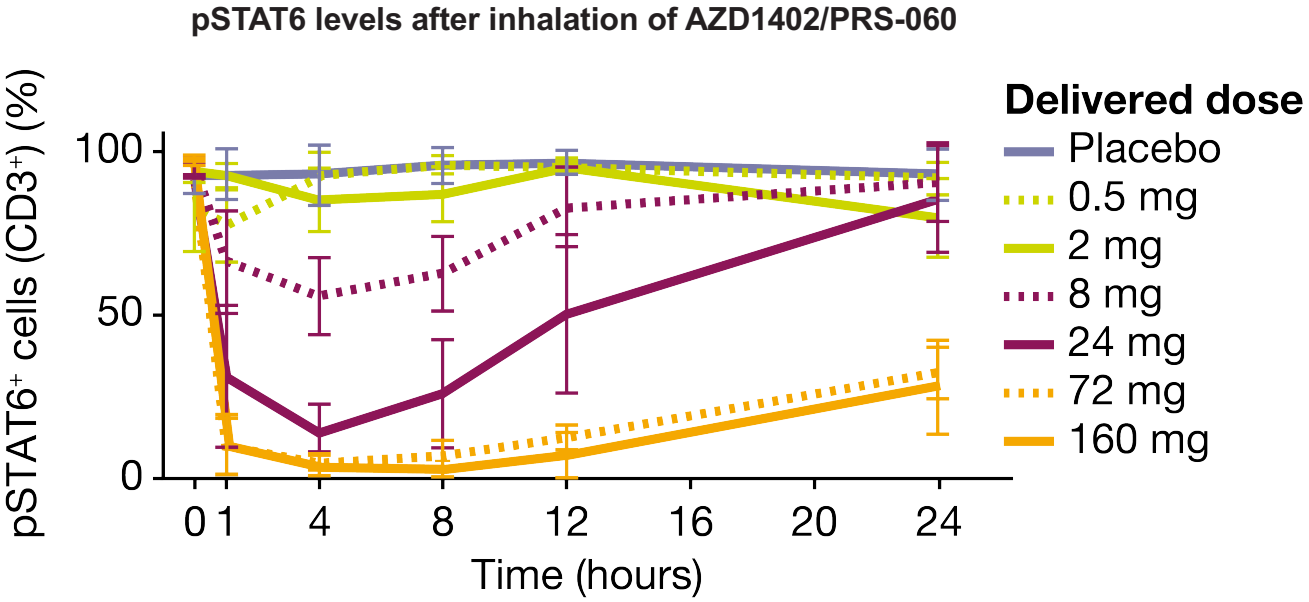


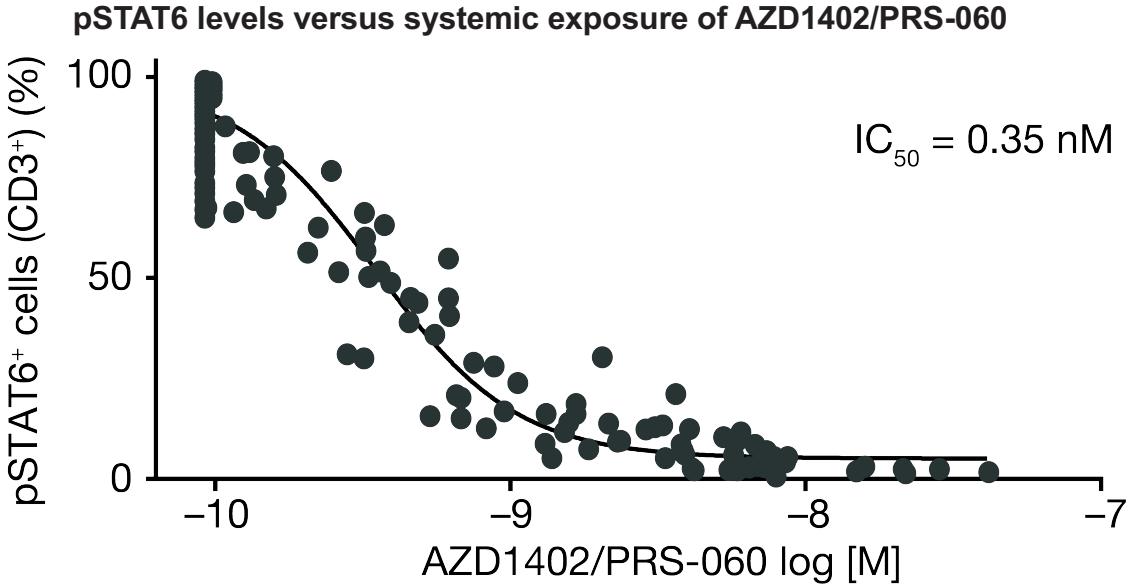


- After intravenous infusion, AZD1402/PRS-060 had a terminal $t_{½}$ of 2 hours, clearance of 6 L/hour and volume of distribution of 9 L, consistent with limited tissue distribution and clearance via renal filtration
- A longer t½ observed after inhalation (4.1–6.2 hours) than after intravenous infusion (2.2–2.3 hours) indicated involvement of an absorption lag time
- There were no confirmed positive anti-AZD1402/PRS-060 antibodies in any of the dose groups

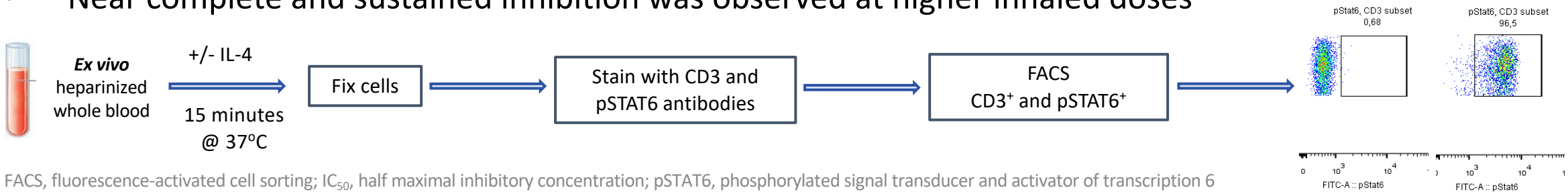
AUC_{inf}, area under the serum concentration time curve from time 0 to infinity; C_{max}, maximum observed serum concentration; PK, pharmacokinetics; $t_{½}$, terminal half-life

Inhaled AZD1402/PRS-060 shows systemic target engagement correlating with serum exposure





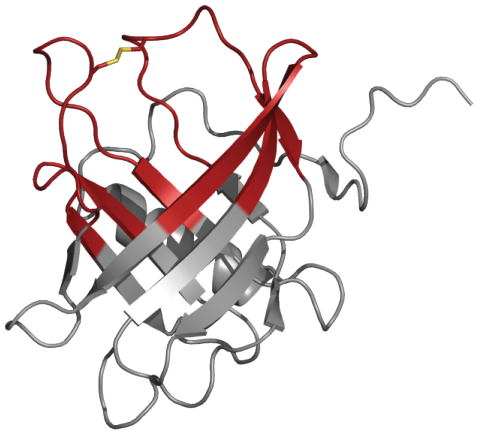
- Inhibition of pSTAT6 was observed from cohort 4 onwards (delivered dose 8 mg)
- Inhibition of systemic pSTAT6 was dose-dependent and aligned with systemic levels of AZD1402/PRS-060
- Near complete and sustained inhibition was observed at higher inhaled doses



FACS, fluorescence-activated cell sorting; IC_{50}, half maximal inhibitory concentration; pSTAT6, phosphorylated signal transducer and activator of transcription 6

Conclusions

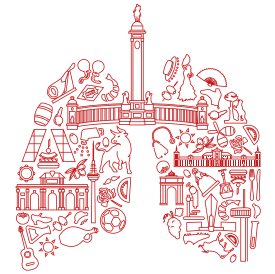
- The novel IL-4Rα antagonist AZD1402/PRS-060 was well tolerated when given as single inhaled or intravenous doses to healthy volunteers
- The overall profile of AZD1402/PRS-060 supports its further development as an inhaled drug for the treatment of asthma
- Systemic target engagement (pSTAT6) will be compared with local lung target engagement in the ongoing, multiple ascending dose study in patients with mild asthma (NCT03574805)
  - This study determined the local lung effects and dose relationship by measuring FeNO, a validated biomarker of asthma
    - Results presented on Tuesday October 1: ***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 (poster number: PA3709)***
- The outcome of this study will help to determine the inhaled dose levels for evaluation in future studies of this first-in-class, inhaled anticalin molecule



PRS-060 protein structure

FeNO, fractional concentration of exhaled nitric oxide; IL-4Rα, IL-4 receptor α; pSTAT6, phosphorylated signal transducer and activator of transcription 6

Acknowledgments



Pieris Pharmaceuticals

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360BioLabs

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- Jonathan Ferrand
- Melinda Pryor

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Back-up slides

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