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

Abstract: OA5336

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<table>
<thead>
<tr>
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<th>Commercial Company</th>
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</table>
| Grants/research support:        | • This study was sponsored by Pieris Pharmaceuticals and funded by AstraZeneca  
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Anticalin® proteins – a new class of biopharmaceuticals

Building blocks

- Anticalin® Protein
- Antibody
- Fc

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

Adapted from Rothe C, Skerra A1

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

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


Adapted from Bagnasco D et al. 2016
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

- Type 2 cytokines IL-4 and IL-13 signal through IL-4Rα, and play crucial roles in asthma pathogenesis

- 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
NCT03384290 – study design and subject disposition

**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/m²**

**Inhalation device dose (delivered dose), mg**
- **Cohort 1**: 0.25 (0.1)
- **Cohort 2**: 1.25 (0.5)
- **Cohort 3**: 5.00 (2.0)
- **Cohort 4**: 20.0 (8.0)
- **Cohort 5**: 60 (24.0)

**Intravenous dose, mg**
- **Cohort 6**: 180 (72.0)
- **Cohort 7**: 400 (160.0)
- **Cohort 8**: 1.0
- **Cohort 9**: 2.0

**Study endpoints**

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

**PK**
- 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

**PD to establish systemic target engagement**
- Inhalation device dose (delivered dose), mg
- Intravenous dose, mg

**Single dose 1**
- Sentinel subjects

**Dose 2**
- Sentinel subjects

**Safety review**
- Acceptable findings

**The same process is repeated**

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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

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Placebo (n = 18)</th>
<th>AZD1402/PRS-060 (n = 54)</th>
<th>Overall (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with TEAEs</td>
<td>6 (33) 8</td>
<td>19 (35) 20</td>
<td>25 (35) 28</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6) 1</td>
<td>5 (9) 6</td>
<td>6 (8) 7</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (6) 1</td>
<td>5 (9) 5</td>
<td>6 (8) 6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>2 (11) 2</td>
<td>5 (9) 5</td>
<td>7 (10) 7</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>2 (11) 2</td>
<td>3 (6) 3</td>
<td>5 (7) 5</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>0</td>
<td>1 (2) 1</td>
<td>1 (1) 1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry throat</td>
<td>2 (11) 2</td>
<td>3 (6) 3</td>
<td>5 (7) 5</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>0</td>
<td>2 (4) 2</td>
<td>2 (3) 2</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0</td>
<td>1 (2) 1</td>
<td>1 (1) 1</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (6) 1</td>
<td>2 (4) 2</td>
<td>3 (4) 3</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>0</td>
<td>1 (2) 1</td>
<td>1 (1) 1</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>0</td>
<td>1 (2) 1</td>
<td>1 (1) 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (2) 1</td>
<td>1 (1) 1</td>
</tr>
</tbody>
</table>

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 $C_{\text{max}}$ and $AUC_{\text{inf}}$

- After intravenous infusion, AZD1402/PRS-060 had a terminal $t_{1/2}$ 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 $t_{1/2}$ 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$_{\text{inf}}$, area under the serum concentration time curve from time 0 to infinity; $C_{\text{max}}$, maximum observed serum concentration; PK, pharmacokinetics; $t_{1/2}$, 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
Acknowledgments

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Back-up slides