RCT Ltd
Respiratory Clinical Trials

Dr Brian Leaker
Dr B O’Connor

Prof PJ Barnes
RCT is located within Queen Anne St Medical Centre, an independent private hospital with excellent medical facilities;

- imaging including Doppler USS & 64 slice PET / CT;
- theatre
- full endoscopy services including bronchoscopy;
- cardiac and pulmonary function lab
- biomarker laboratory;
- clinical trials unit with overnight stay facilities.
Risk management

- **Research Governance Committee**
  - Reviews new trial protocols & related information (IB; toxicology, safety)
  - Determines level of risk for each study prior to Ethics submission
  - Reviews additional safety & updates from sponsor for ongoing studies
  - Required majority vote of approval

- **External Chair plus two external experts**
  - Clinical pharmacologist (Chair)
  - QP
  - Toxicologist
  - Non-Voting medical director and physicians
Risk management

- Research Governance Committee (quarterly)
  - Reports level of risk to MAC for proposed study
  - Safety review

- Medical Advisory Committee (quarterly)
  - Oversight of all hospital & clinical trial activities
  - Independent Chairman

- Senior management Committee (every fortnight)
  - Reports to MAC
  - Day to day management of clinical trials
  - Holds risk register for ongoing study activities
  - QA review

- Governance Committee
  - Oversight of control measures in place
### Risk Rating of Human Pharmacology Studies in Drug Development

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Risk Score and Interpretation

Low risk = \leq 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

**BUT a rating of 4 in any category implies that the study is of high risk.**

**Potential ‘Low risk’ studies**

Medical Director & Chairman discuss

RGC Chairman will normally approve these without requiring assessment of the full RGC.

**Other studies**

All studies of greater than ‘low risk’ will be assessed by the full RGC.
Case studies

- Marketed product
  - Intended patient population
  - Inhaled Challenge

- Generic drug
  - Novel formulation and delivery
  - First study in intended patient population (elderly COPD)
  - Only 2\textsuperscript{nd} study in development program
Case studies

- Novel Inhaled Immuno-modulator (NCE)
  - First patient study (asthma)
  - Second study in man hence design
  - Allergen challenge and invasive procedures
  - Long term safety issues

- Novel oral anti-inflammatory (NCE)
  - Second study in man (healthy volunteers)
  - LPS challenge
  - Safety issues
Study 1

• Combination inhaler
  – Effects on bronchodilation and inflammation
Bronchoprotective and anti-inflammatory effect of Beclomethasone Dipropionate plus Formoterol HFA fixed combination in asthmatic patients (Fostair)

- Randomised double dummy dbl blind placebo controlled three way cross-over
- 3 days treatment with 10 days wash-out
  - Low dose BDP 200 Fom12;
  - High dose BDP 800 Fom 48
- 10 days washout between treatments
- N= 18 mild asthmatics FEV1>70% pred
- Evaluation of dose response by;
  - Lung Function (AUC 0-4 FEV1)*
  - AMP challenge (PC20) 4hrs post dose)*
  - FeNO* (2 & 4hrs post dose)
* joint primary end points
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Dose Response Effect of Fixed Combination Beclometasone/Formoterol on AUC(0-4 hours) of FEV$_1$ (L)

FEV$_1$ (L)

- High Dose
- Low Dose
- Placebo

Hours

Pre-Dose 0.5 1 2 4
Dose Response Effect of Fixed Combination Beclometasone/Formoterol on Adenosine Monophosphate Bronchial Challenge

Log PC20 AMP (mg/mL)

- Placebo
- Low Dose
- High Dose

p<0.0001
Summary

• There was a significant early bronchodilator effect following combination BDP/F treatment

• Dose response to PC20 AMP & FeNO
  – Demonstrate anti-inflammatory effects

• Safe and well tolerated

O’Connor, Leaker BMC Pulm Med 2011
Efficacy and Safety of nebulised Glycopyrrolate in COPD using high efficiency nebuliser in pts with COPD

- To determine effects of EP 101 on bronchodilation up to 30 hrs post dose
  - Overnight stay in Unit
- 6 way cross over design (one week WO)
- Single Dose X 5 doses (12.5 – 200ug)
  - Placebo
- Patients
  - 40 COPD pts Gold stage 2 & 3
  - FEV1 30-75% post bronchodilator
  - Reversibility >12% (150mls) post ipratropium
- End points
  - FEV1 up to 30 hours
  - ECG & QTc
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Figure 1. Mean change in FEV₁

- Placebo
- 12.5 µg
- 50 µg
- 100 µg
- 200 µg
- 400 µg

FEV₁ (L) vs. Time post-dose (hours)
Clinically relevant improvement in FEV1 at doses >50ug
Summary EP-101

• Clinically relevant bronchodilation at doses > 50ug maintained for up to 30 hrs

• Safe and well tolerated
  – No effect heart rate; ECG inc QTc
  – No other safety issues

Leaker et al Br J Clin Pharm 2015
The effects of the novel Toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma

Brian Leaker,\textsuperscript{1} Dave Singh,\textsuperscript{2} Sam Lindgren,\textsuperscript{3} Gun Almqvist,\textsuperscript{3} Barbara Young,\textsuperscript{4} Brian O’Connor\textsuperscript{1}

\textsuperscript{1}Respiratory Clinical Trials, London, United Kingdom;
\textsuperscript{2}Medicines Evaluation Unit Ltd, University of Manchester, Manchester, United Kingdom;
\textsuperscript{3}AstraZeneca R&D, Mölndal, Sweden;
\textsuperscript{4}AstraZeneca R&D Charnwood, Loughborough, United Kingdom

ClinicalTrials.gov identifier: NCT00999466
AstraZeneca study code:D0540C00004
Inhaled Allergen Challenge

FEV₁

Very mild asthma

Inhaled AG

Early AR 0-2 h mast cell

Late Asthmatic Reaction 4-10 h multiple cells?

24h Sputum AHR

Proof of Concept for anti-inflammatory therapies in asthma

Allergen response to inhaled allergen challenge after 9 days of treatment with Inhaled PDE4 (CHF6001) 400µg, 1200µg or placebo
Background

- AZD8848 is a TLR7 agonist being evaluated for the treatment of asthma and allergic rhinitis

- Activation of TLR7 by agonists such as AZD8848\(^3\)
  
  - Stimulates the innate immune response
  
  - Down-regulates the Th2 adaptive response, inhibiting the inflammatory cytokine cascade

Pharmacokinetics of AZD8848

• A metabolically labile ester rapidly converted to weakly active form in plasma
  – Minimises systemic exposure
  – Limits Th1 immune activation and flu-like adverse effects

• No local inflammation with nasal administration
  – Localised to where it is dosed: nose and/or lungs
Proposed mechanism of action of AZD8848 in asthma

Hypothesis: AZD8848 rebalances the adaptive immune response leading to sustained asthma control

In asthmatic individuals, allergens presented to T cells result in an overproduction of Th2 cytokines\(^1\). AZD8848 (TLR7 agonist) activates TLR7, which releases IFN\(\alpha\). IFN\(\alpha\) suppresses Th2 cytokine production, reverting cells to naïve phenotype\(^2,3\).

Targets for TH2 mediated inflammation
**Study objectives**

**Primary objective:**
- To evaluate the efficacy of AZD8848 on the Late Asthmatic Response (LAR) compared with placebo after 8 doses of once weekly intranasal administration in mild to moderate allergic asthma patients challenged with inhaled allergen.

**Secondary objectives:**
- To evaluate the efficacy of AZD8848 as measured by the Early Asthmatic Response (EAR)
- Bronchial reactivity (methacholine PC20)
- Sputum biomarkers.
- To investigate tolerability and safety of AZD8848
- To investigate plasma concentrations of the acid metabolite around C_max after the first and last dose of AZD8848 (concentrations represent the sum of AZD8848 and acid metabolite).
Patient inclusion/exclusion criteria

**Inclusions**
- GINA-defined mild-to-moderate asthma\(^1\) for ≥6 months
- Positive SPT to grass/house dust mite/cat dander in previous 24 months
- FEV\(_1\) >70% of predicted normal
- EAR with ≥20% FEV\(_1\) decrease within 2 h of allergen challenge
- LAR with ≥15% FEV\(_1\) decrease at 4–10 h of allergen challenge
- Methacholine PC\(_{20}\) <16 mg/mL

**Exclusions**
- Symptomatic allergic rhinitis
- Treatment with ICS ± LABA 4 weeks before first study visit
- Use of antihistamines within 1 week or systemic corticosteroids within 6 weeks
- Respiratory tract infection within 2 weeks
- Asthma exacerbation within 4 weeks

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EAR = early asthmatic response; FEV\(_1\) = forced expiratory volume in 1 s; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting β\(_2\)-agonist; PC\(_{20}\) = provocation concentration causing a 20% fall in FEV\(_1\); SPT, skin-prick test
Double-blind, parallel, randomised, placebo-controlled, phase II study

- Part 1: SRC acceptance of dosing
- Part 2: 8 once-weekly intranasal doses of AZD8848 (60 µg)
  - Assessments at 1 and 4 weeks after last drug dose

Use of short-acting β₂-agonists was permitted throughout the study.
SRC = Safety Review Committee
The POLAR study design

Screening → AZD8848 or placebo treatment → Treatment follow-up → Long-term safety follow-up

**Day** - 56

**Week** - 8

**Visit**

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19/20

**Blood**

- Pre allergen challenge
- Allergen challenge
- Post allergen challenge
- methacholine PC 20
- Sputum induction

**Tests**

- **a** – Tests carried out 48 to 72 hours post allergen challenge
- **b** – Tests carried out 18 to 30 hours post allergen challenge
- ***a** – Information Visit
- **b** – AZD8848 or placebo dosing
- **** – safety review visit

---

34 AZD8848 POLAR high-level results
Outcome variables

• Primary
  – LAR measured by AUC-based mean fall in FEV$_1$ at 4–10 hours post-allergen challenge

• Secondary
  – EAR
  – Methacholine PC$_{20}$
  – Sputum cells and cytokines
  – Safety and tolerability

AUC = area under the drug concentration-time curve
## Risk Rating for Clinical Studies in Drug Development

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Mean FEV$_1$ after allergen challenge
1 week after end of treatment
Safety and tolerability

- AZD8848 was generally well tolerated
- A total of 178 AEs reported
- Serious AE in placebo group was severe bacterial tonsillitis
- No clinically relevant changes in ECG or vital signs

AEs = adverse events; ECG, electrocardiography
Treatment-related adverse events

- Most AEs attributable to AZD8848 were mild in severity

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<th>Condition</th>
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<th>Placebo (n = 25)</th>
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<td>Any TRAEs</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Nasal dryness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0</td>
<td>2</td>
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<td>Arthralgia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
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TRAEs reported in ≥2 patients are shown. TRAEs = treatment-related AEs
Conclusions

At 1 week after 8 weekly doses, intranasal AZD8848
- attenuated allergen-induced LAR
- prevented allergen-induced increases in airway hyperresponsiveness

- LAR response not maintained to 4 weeks after last dose
- Trend to reduction in sputum eosinophils and Th2 cytokines (IL-5, IL-13) before allergen challenge 1 week after last dose
- AZD8848 was generally well tolerated in this dosing schedule
- A TLR7 agonist such as AZD8848 can ameliorate allergen-induced responses in the lower airways
Inhibition of LPS-induced neutrophilic inflammation in healthy volunteers

BR Leaker, PJ Barnes, B O’Connor
Resp Research 2013
Aims

• AZD8309 is an orally available, mixed chemokine antagonist (CXCR2 / CCR2b)
  – It inhibits:
    • Human neutrophil chemotaxis *in vitro*
    • LPS-induced airway neutrophilia in animal models *in vivo*
  
• hypothesis AZD8309 attenuates PMN migration into the lungs

• Inhaled LPS a model of acute airway neutrophilia in man to test the efficacy of oral treatment with AZD8309
Effect of LPS challenge in the airways

- LPS gives a dose-dependent, transient increase in neutrophil numbers and inflammatory mediators in sputum

Systemic effects

- Inhalation of LPS induces a dose dependent increase in body temperature
- The effects on body temperature limit the LPS challenge dose

Utility of the LPS challenge model

- The acute LPS model shows some similarities with the inflammatory profile observed in lung diseases such as COPD
  - Raised neutrophil numbers in sputum
  - Increased IL-8, HNE, LTB4 in sputum

- It provides a model of airway neutrophilic inflammation for evaluating new compounds

- The relevance of the LPS model for predicting efficacy in COPD is yet to be established
Targets for PMN mediated inflammation

- **Epithelial cells**
- **Macrophages/DC**
- **Neutrophils**

**Pathways:**
- **Inflam inhib**
- **MMP8, MMP9**
- **ROS**

**Targets:**
- **IKK2 inhibitor**
- **p38 MAPK inhibitor**
- **PDE4 inhibitor**

**Regulatory Cytokines:**
- **IL-1β**
- **IL-17**
- **IL-23**

**Receptors and Pathways:**
- **NF-κB, p38**
- **CXCR2, CXCL1, CXCL8**
- **Anti-TNF, Anti-IL-17, Anti-IL-23**

**Cell Types and Functions:**
- **Goblet cells**
- **Mucus hypersecretion**
- **Neutrophil elastase**
This was randomised, double-blind, placebo-controlled, two-way crossover study in healthy volunteers.

Study powered to detect a 50% reduction in sputum neutrophil numbers with a power of at least 80% when testing at the 5% level (2-sided test).

16 subjects were required to complete the study.
Inclusion Criteria

- Healthy volunteers aged 18 – 50
- Non-smokers, or ex-smokers (not smoked in the previous 12 months with a <10 pack-year history)
- FEV$_1$ ≥80% predicted normal & FEV$_1$/FVC ratio >70%
- Normal response to inhaled methacholine: PC$_{20}$ ≥16 mg/mL
- Able to produce a minimum of 200 µL sputum volume at screening
- Sputum eosinophilia <2%
- Sputum neutrophilia <80%
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Study Demographics

- 20 subjects randomised
  - 3 past smokers

- 16 subjects completed

- No subjects withdrew due to adverse effects of AZD8309 or the LPS challenge
  - 2 for entering other trials
  - 1 on placebo with migraine
  - 1 withdrew prior to dosing
Results: Sputum Cells

Total Cells

<table>
<thead>
<tr>
<th>Placebo</th>
<th>AZD8309</th>
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<tr>
<td>25 x 10^6/g</td>
<td>7 x 10^6/g</td>
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P < 0.001

Neutrophils

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<tr>
<td>6 x 10^6/g</td>
<td>0.5 x 10^6/g</td>
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P < 0.05

Macrophages

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<td>3 x 10^6/g</td>
<td>1.5 x 10^6/g</td>
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P = 0.15

-77% reduction in total cells

-79% reduction in neutrophils

-47% reduction in macrophages
Results: Inflammatory Markers

**IL-8**
- Placebo: [Graph showing IL-8 levels]
- AZD8309: [Graph showing IL-8 levels]
- **P=0.10**
- **-52%**

**Groα**
- Placebo: [Graph showing Groα levels]
- AZD8309: [Graph showing Groα levels]
- **P<0.05**
- **-25%**

**NEA**
- Placebo: [Graph showing NEA levels]
- AZD8309: [Graph showing NEA levels]
- **P<0.05**
- **-67%**

**LTB4**
- Placebo: [Graph showing LTB4 levels]
- AZD8309: [Graph showing LTB4 levels]
- **P=0.08**
- **-39%**
Results: Effect on Lung Function

- LPS-induced initial fall in FEV\(_1\) was similar for AZD8309 and placebo
- AUC of FEV\(_1\) over 6 hours was greater with AZD8309 compared with placebo (p<0.05)
## Results: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>AZD8309 (N=18)</th>
<th>Placebo (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of subjects with DAE</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>No. AEs</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>No. (%) of subjects with AEs</td>
<td>14 (61%)</td>
<td>10 (53%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AEs by preferred term</th>
<th>N=18</th>
<th>N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyrexia</td>
<td>5 (28%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>headache</td>
<td>2 (11%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>dizziness</td>
<td>0</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>nasal congestion</td>
<td>2 (11%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>3 (17%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>rhinitis</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>pharyngolaryngeal pain</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>
● Following LPS challenge in healthy subjects
  – AZD8309 reduced neutrophil numbers in sputum
  – AZD8309 reduced sputum levels of
    • IL-8, LTB4, Groα and neutrophil elastase activity
● There were no adverse events to an LPS challenge of 30 µg or treatment with AZD8309
● This model successfully demonstrated efficacy of an anti-neutrophil target in man
  – Uses small numbers of healthy subjects
  – Short, simple challenge procedure
  – Challenge agent (30 µg LPS) well tolerated
CXCR2 antagonists in COPD (Navarixin)

- Dose response study versus placebo n=616.
- Reduction in sputum neutrophils by >50% at 3/12
  - trend at 6/12.
- Increased FEV$_1$ overall 67ml versus placebo.
- Significant improvement in FEV$_1$ in smoking subgroup (n=58) 168ml.
- Significant neutropenia (<1.5 x10$^9$/L) and AEs (18% withdrawal with 50mg dose versus 1% with placebo).

- Rennard et al. AJRCCM 2015; 191:1001
Spare slides