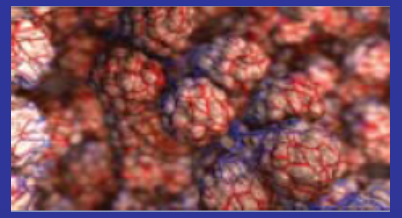


RCT Ltd
Respiratory Clinical Trials

Dr Brian Leaker
Dr B O'Connor

Prof PJ Barnes

RC T
Respiratory
Clinical Trials

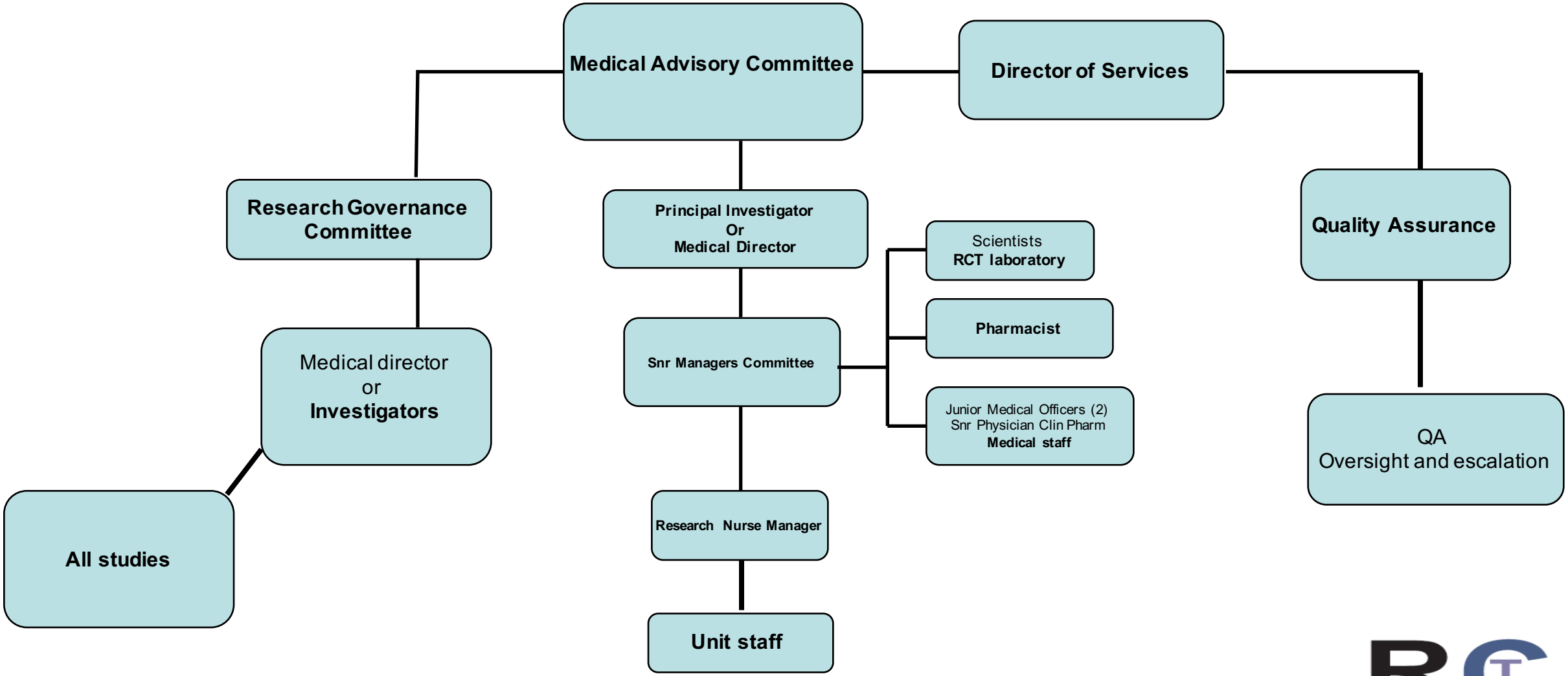
RCT @ QASMC

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.

RCT Respiratory Clinical Trials

Clinical trials Unit



Respiratory Clinical Trials

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

Risk	IMP	Methods	Intended population
1	Product with known good safety profile based on exposure in population of thousands of patients.	Non-invasive except for venepuncture and low risk e.g. spirometry, psychometrics, most tests of CVS, imaging with low radiation exposure	Healthy young volunteers
2	Drug in development with good safety record based on exposure at relevant doses and route of administration in ≥200 subjects.	Non-invasive procedures of low risk but with potential for undesired effects e.g. tilt table, exercise testing, methacholine and other bronchial challenges.	Healthy elderly, and patients with mild, non-life threatening conditions, requiring intermittent medication e.g. hayfever mild asthma, osteoarthritis.
3	Novel NME in early development with no or very limited previous exposure in humans e.g. <200 healthy volunteers/patients, including those at doses lower than considered of therapeutic interest. No preclinical or clinical evidence of high risk.	Invasive procedures generally of low risk if performed by a skilled operator e.g. arterial puncture, bronchoscopy, gastroscopy and / or non-invasive procedures which carry significant risk e.g. allergen bronchial challenge, influenza challenge, anticoagulation administration.	Patients with disease of moderate severity, typically requiring regular medication, e.g. moderate asthma, COPD, renal impairment, hepatitis, inflammatory bowel disease or significant past medical history e.g. MI, head injury > 1 year previously.
4	Novel NME with very limited or no previous exposure in humans and / or uncertain mechanism of action and / or known high risk features such as possible involvement of cascades, agonist activity, effects on the immune system	Invasive procedures with known incidence of complications even when performed by skilled operators e.g. liver biopsy, lumbar puncture, bronchial biopsy, urinary bladder catheterisation.	Patients with advanced disease e.g. severe COPD, interstitial pulmonary fibrosis, asthma, unstable CAD, hypertension, rheumatoid arthritiis

Add risks to max 12; Low risk = ≤ 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

Risk Score and Interpretation

Low risk = ≤ 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 2nd study in development program

Case studies

Respiratory Clinical Trials

- 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)

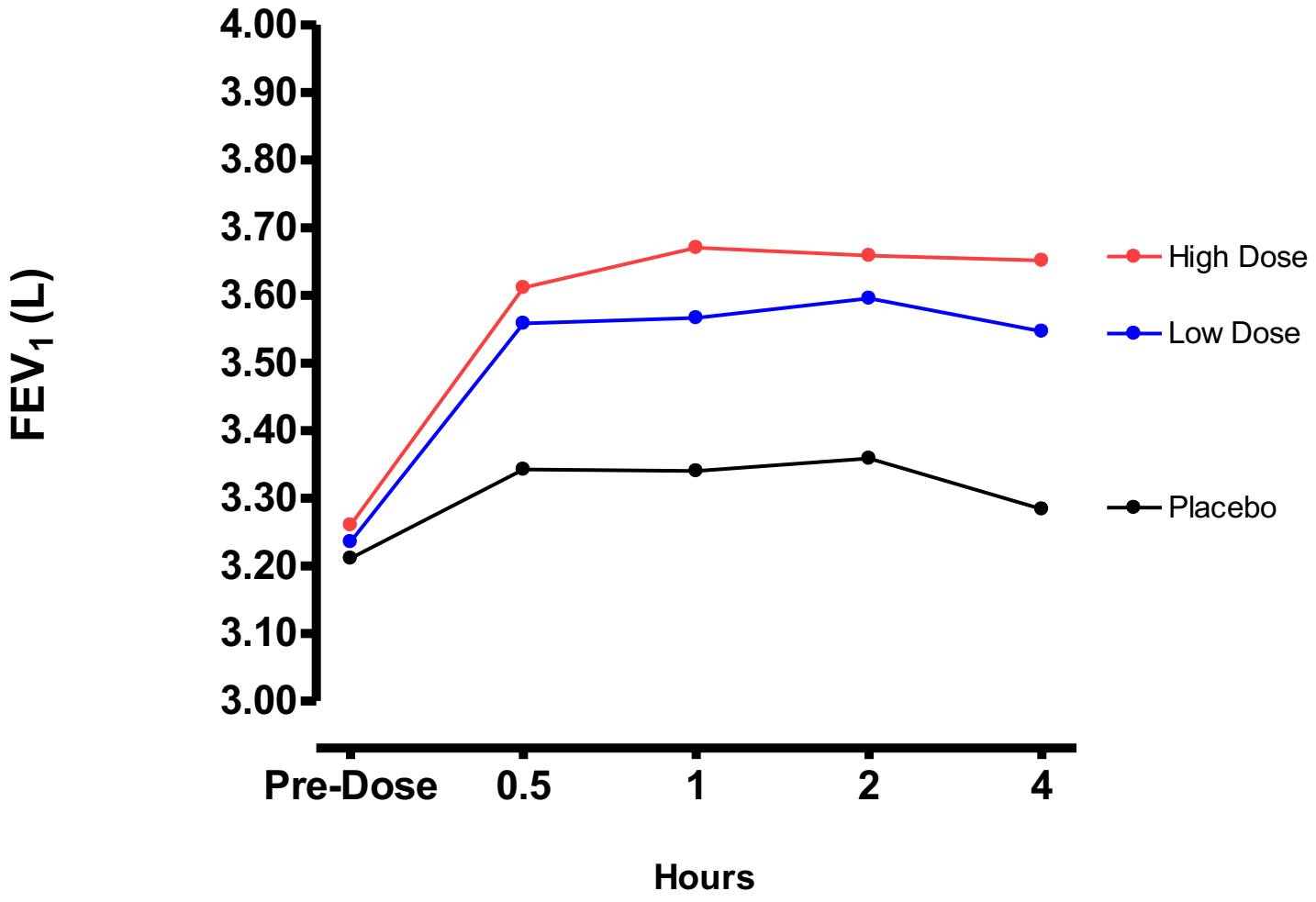
* joint primary end points

Risk Rating for Clinical Studies in Drug Development

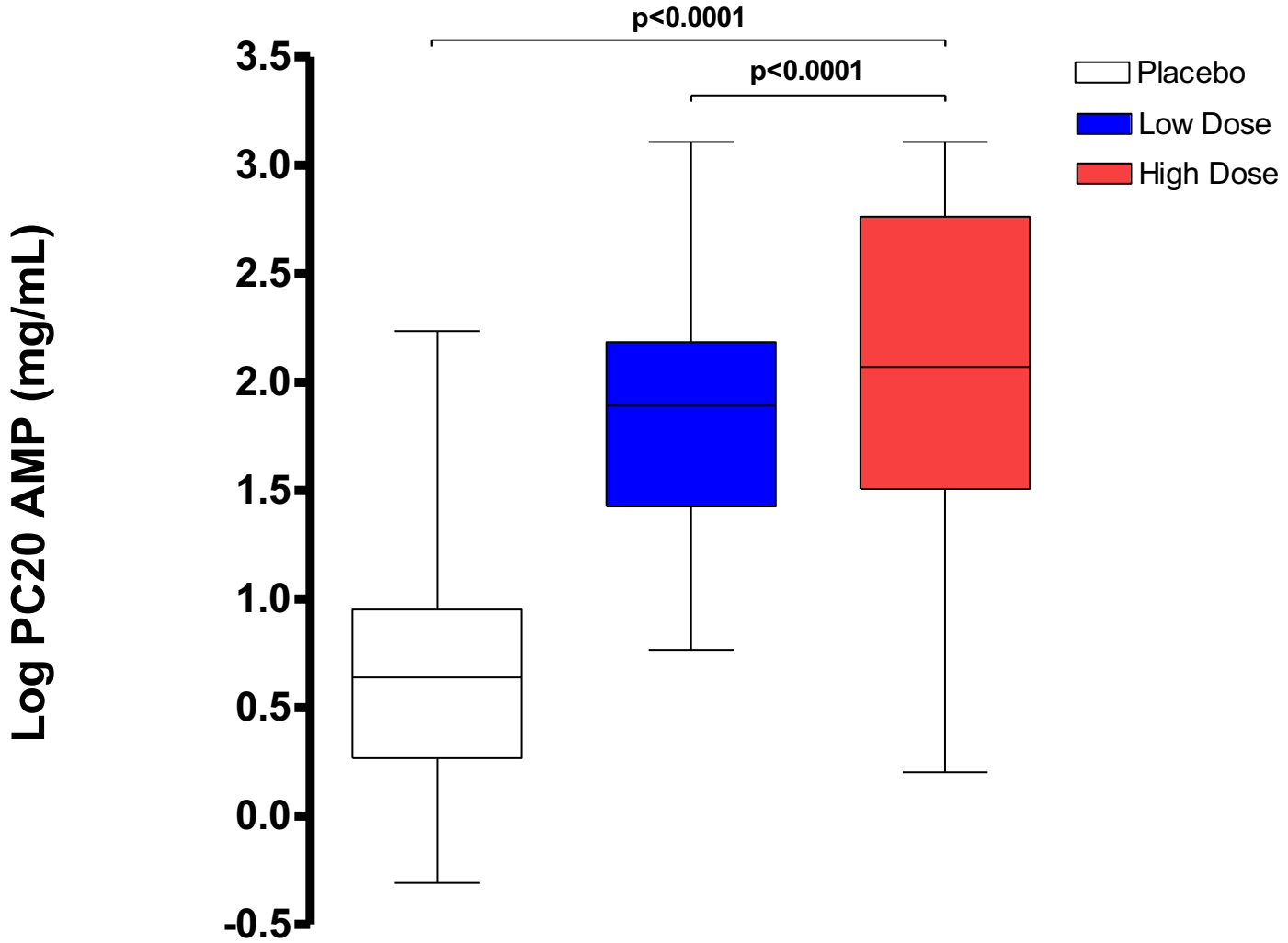
Risk	IMP	Methods	Intended population
1	Product with known good safety profile based on exposure in population of thousands of patients.	Non-invasive except for venepuncture and low risk e.g. spirometry, psychometrics, most tests of CVS, imaging with low radiation exposure	Healthy young volunteers
2	Drug in development with good safety record based on exposure at relevant doses and route of administration in ≥200 subjects.	Non-invasive procedures of low risk but with potential for undesired effects e.g. tilt table, exercise testing, methacholine and other bronchial challenges.	Healthy elderly, and patients with mild, non-life threatening conditions, requiring intermittent medication e.g. hayfever mild asthma, osteoarthritis.
3	Novel NME in early development with no or very limited previous exposure in humans e.g. <200 healthy volunteers/patients, including those at doses lower than considered of therapeutic interest. No preclinical or clinical evidence of high risk.	Invasive procedures generally of low risk if performed by a skilled operator e.g. arterial puncture, bronchoscopy, gastroscopy and / or non-invasive procedures which carry significant risk e.g. allergen bronchial challenge, influenza challenge, anticoagulation administration.	Patients with disease of moderate severity, typically requiring regular medication, e.g. moderate asthma, COPD, renal impairment, hepatitis, inflammatory bowel disease or significant past medical history e.g. MI, head injury > 1 year previously.
4	Novel NME with very limited or no previous exposure in humans and / or uncertain mechanism of action and / or known high risk features such as possible involvement of cascades, agonist activity, effects on the immune system	Invasive procedures with known incidence of complications even when performed by skilled operators e.g. liver biopsy, lumbar puncture, bronchial biopsy, urinary bladder catheterisation.	Patients with advanced disease e.g. severe COPD, interstitial pulmonary fibrosis, asthma, unstable CAD, hypertension, rheumatoid arthritiis

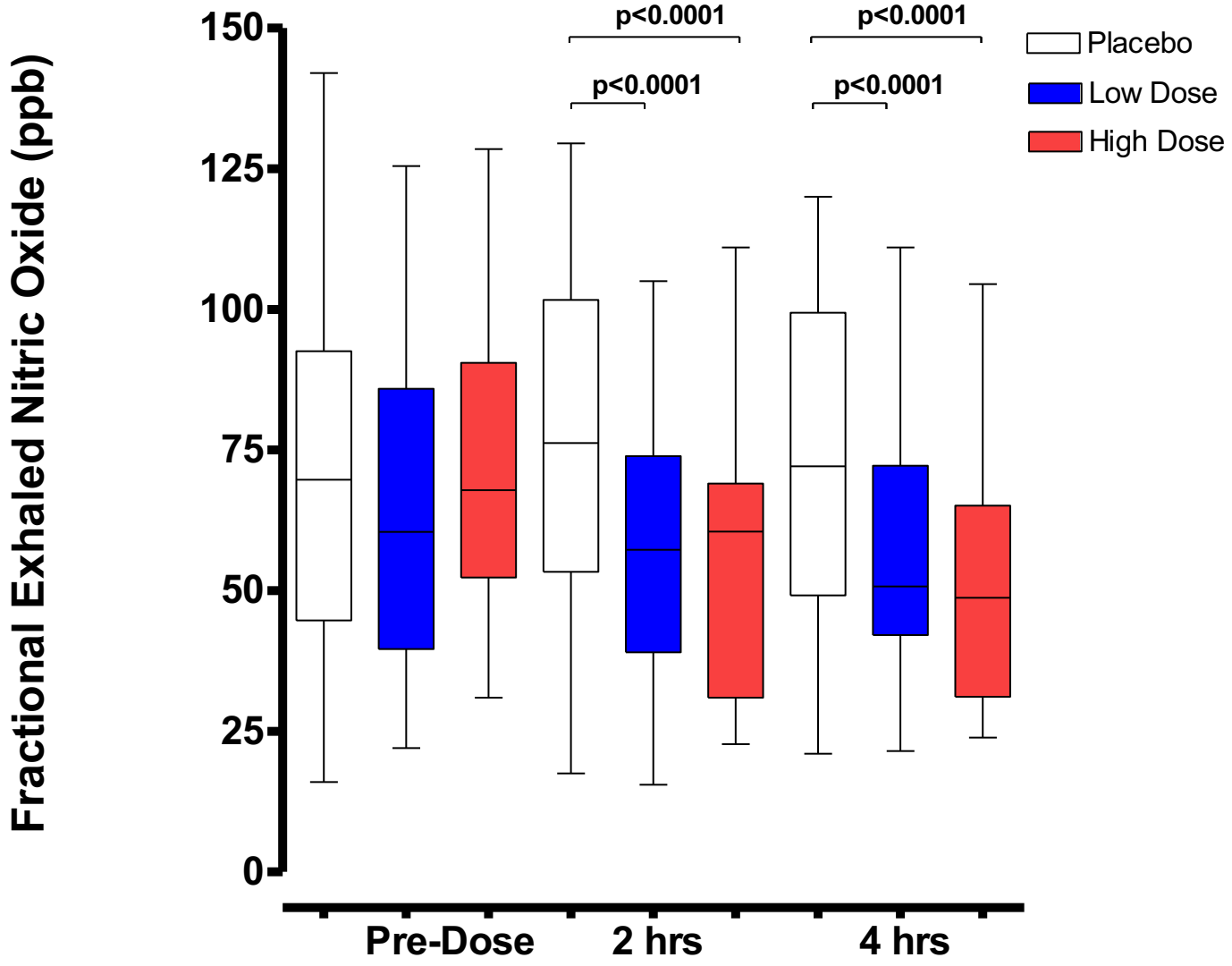
Add risks to max 12; Low risk = ≤ 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

Dose Response Effect of Fixed Combination Beclometasone/Formoterol on AUC(0-4 hours) of FEV_1 (L)



Dose Response Effect of Fixed Combination Beclometasone/Formoterol on Adenosine Monophosphate Bronchial Challenge




Fractional Exhaled Nitric Oxide (ppb)
150
125
100
75
50
25
0
p<0.0001
p<0.0001
p<0.0001
p<0.0001
Placebo
Low Dose
High Dose
Pre-Dose
2 hrs
4 hrs

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 in pts with COPD

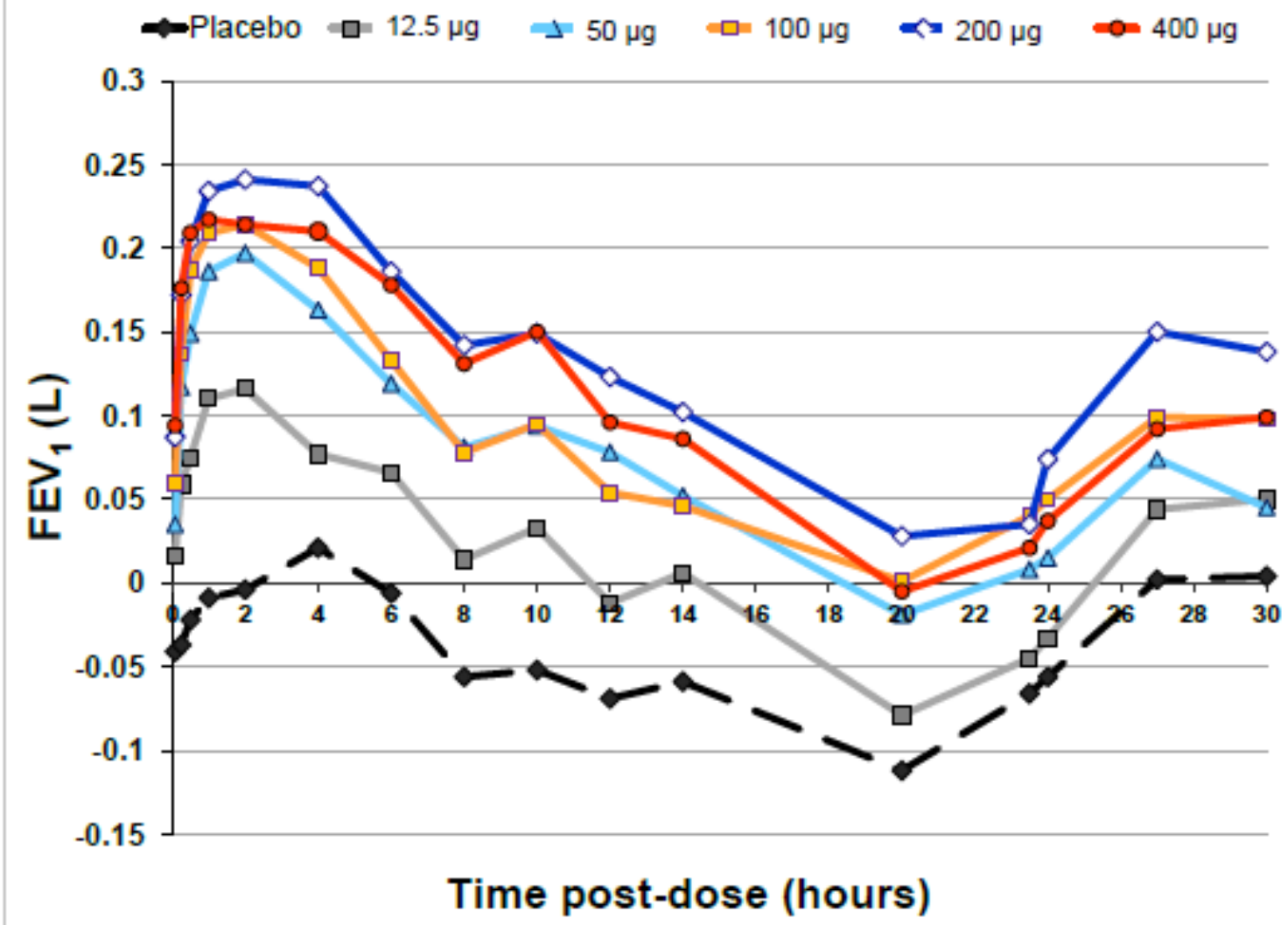
- To determine effects of EP 101 on bronchodilation up to 30 hrs post dose
  - Overnight stay in Unit
- 6 way cross over design (one week WO)
- Single Dose X 5 doses (12.5 – 200ug)
  - Placebo
- Patients
  - 40 COPD pts Gold stage 2 & 3
  - FEV1 30-75% post bronchodilator
  - Reversibility >12% (150mls)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

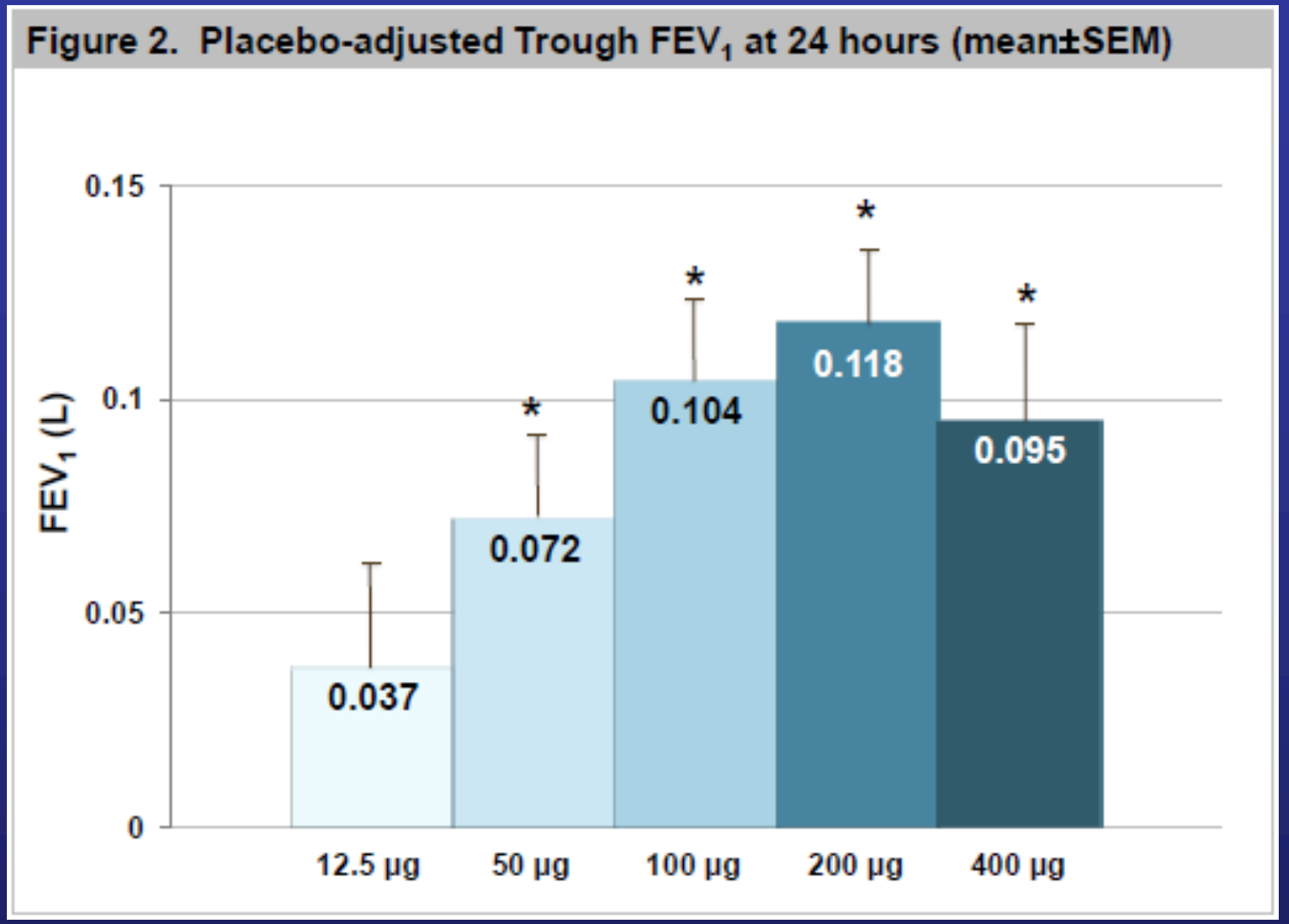
Risk Rating for Clinical Studies in Drug Development

Risk	IMP	Methods	Intended population
1	Product with known good safety profile based on exposure in population of thousands of patients.	Non-invasive except for venepuncture and low risk e.g. spirometry, psychometrics, most tests of CVS, imaging with low radiation exposure	Healthy young volunteers
2	Drug in development with good safety record based on exposure at relevant doses and route of administration in ≥200 subjects.	Non-invasive procedures of low risk but with potential for undesired effects e.g. tilt table, exercise testing, methacholine and other bronchial challenges.	Healthy elderly, and patients with mild, non-life threatening conditions, requiring intermittent medication e.g. hayfever mild asthma, osteoarthritis.
3	Novel NME in early development with no or very limited previous exposure in humans e.g. <200 healthy volunteers/patients, including those at doses lower than considered of therapeutic interest. No preclinical or clinical evidence of high risk.	Invasive procedures generally of low risk if performed by a skilled operator e.g. arterial puncture, bronchoscopy, gastroscopy and / or non-invasive procedures which carry significant risk e.g. allergen bronchial challenge, influenza challenge, anticoagulation administration.	Patients with disease of moderate severity, typically requiring regular medication, e.g. moderate asthma, COPD, renal impairment, hepatitis, inflammatory bowel disease or significant past medical history e.g. MI, head injury > 1 year previously.
4	Novel NME with very limited or no previous exposure in humans and / or uncertain mechanism of action and / or known high risk features such as possible involvement of cascades, agonist activity, effects on the immune system	Invasive procedures with known incidence of complications even when performed by skilled operators e.g. liver biopsy, lumbar puncture, bronchial biopsy, urinary bladder catheterisation.	Patients with advanced disease e.g. severe COPD, interstitial pulmonary fibrosis, asthma, unstable CAD, hypertension, rheumatoid arthritiis

Add risks to max 12; Low risk = ≤ 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

Figure 1. Mean change in FEV_1





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

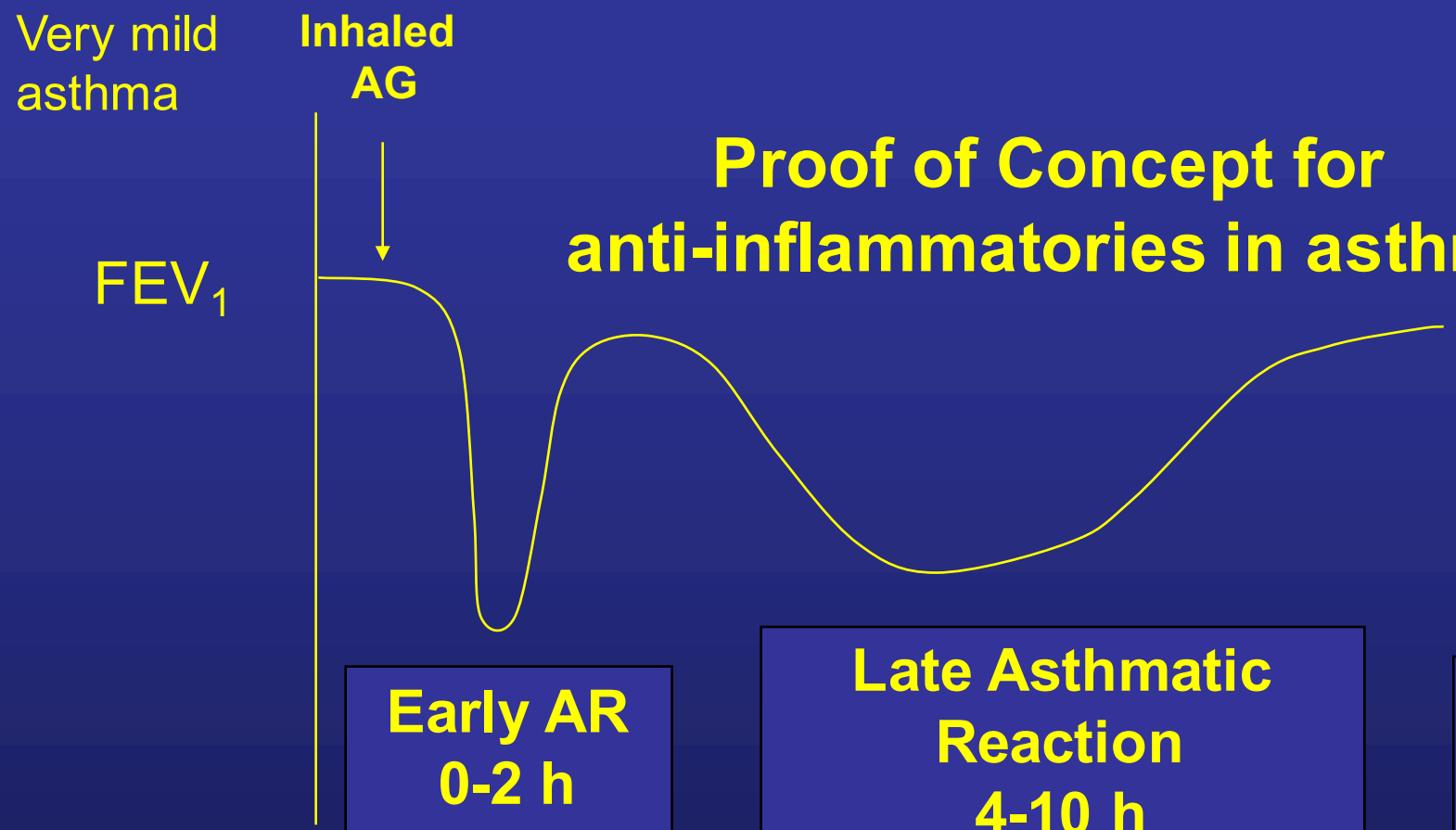
Brian Leaker,[1] Dave Singh,[2] Sam Lindgren,[3] Gun Almqvist,[3] Barbara Young,[4] Brian O'Connor[1]

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

ClinicalTrials.gov identifier: NCT00999466
AstraZeneca study code:D0540C00004

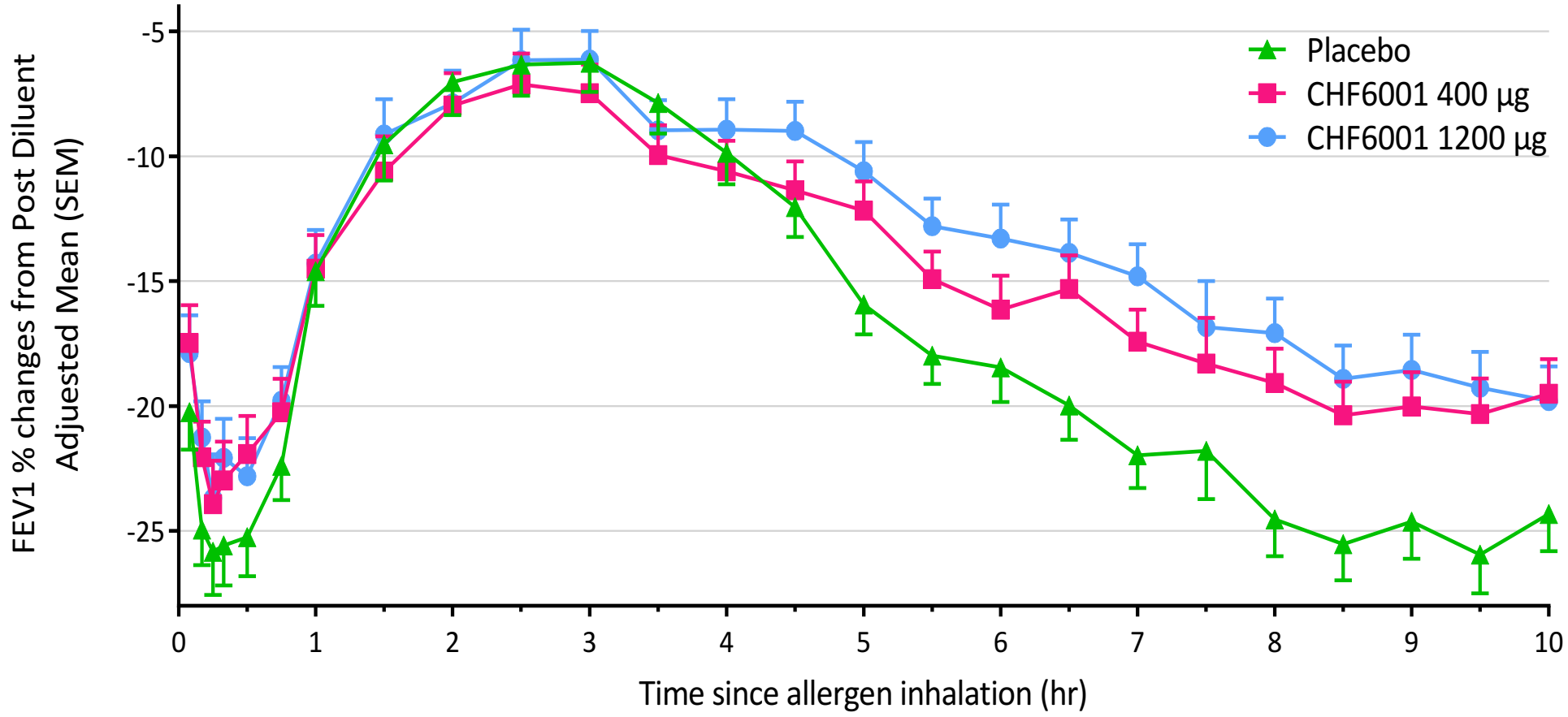
Leaker et al 2012

Inhaled Allergen Challenge



Clin Exp Allergy 2005; 35: 981-5

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

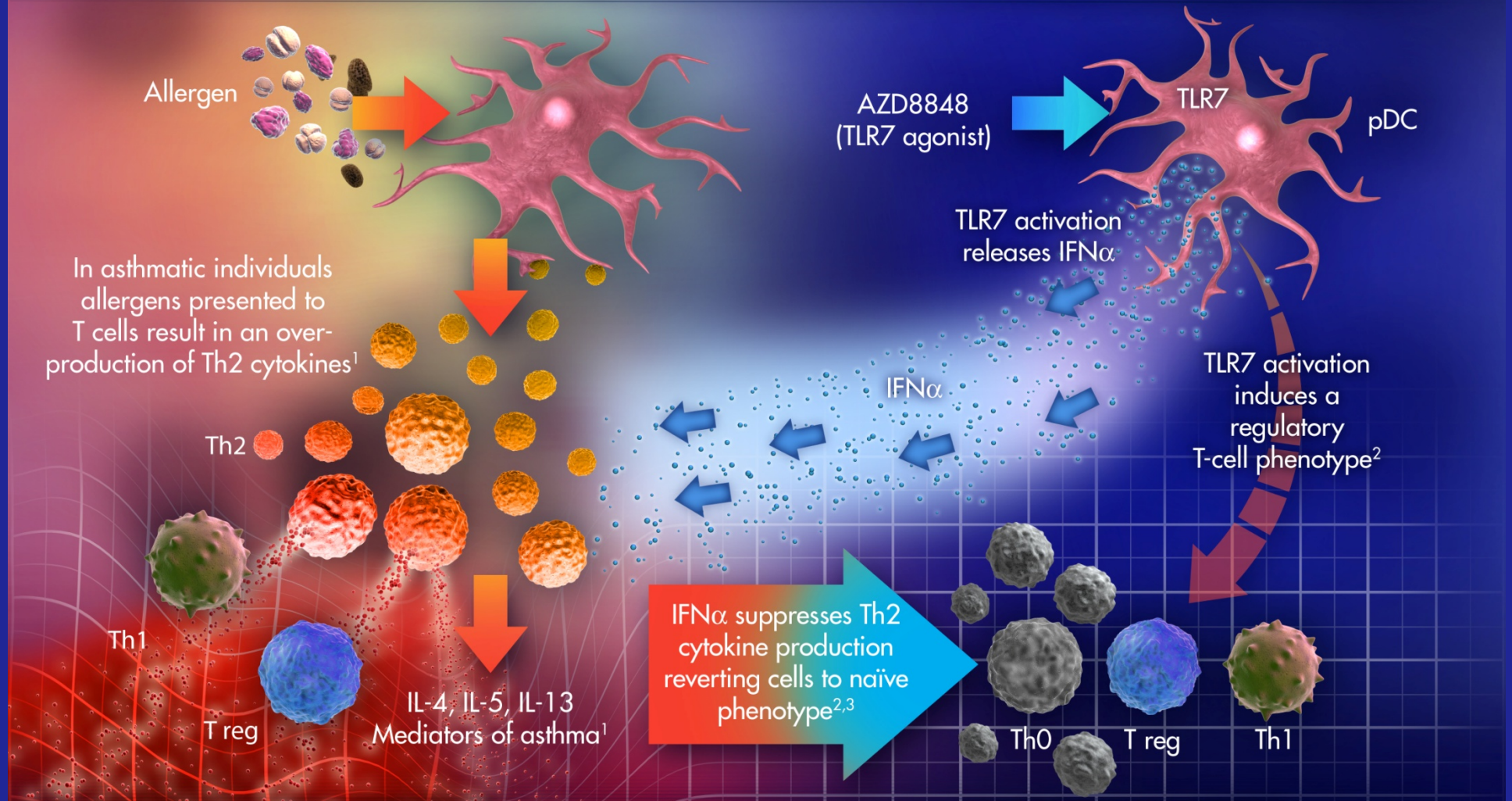
3. Biffen M, et al. *Br J Pharmacol* 2012; 166: 573–86.

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

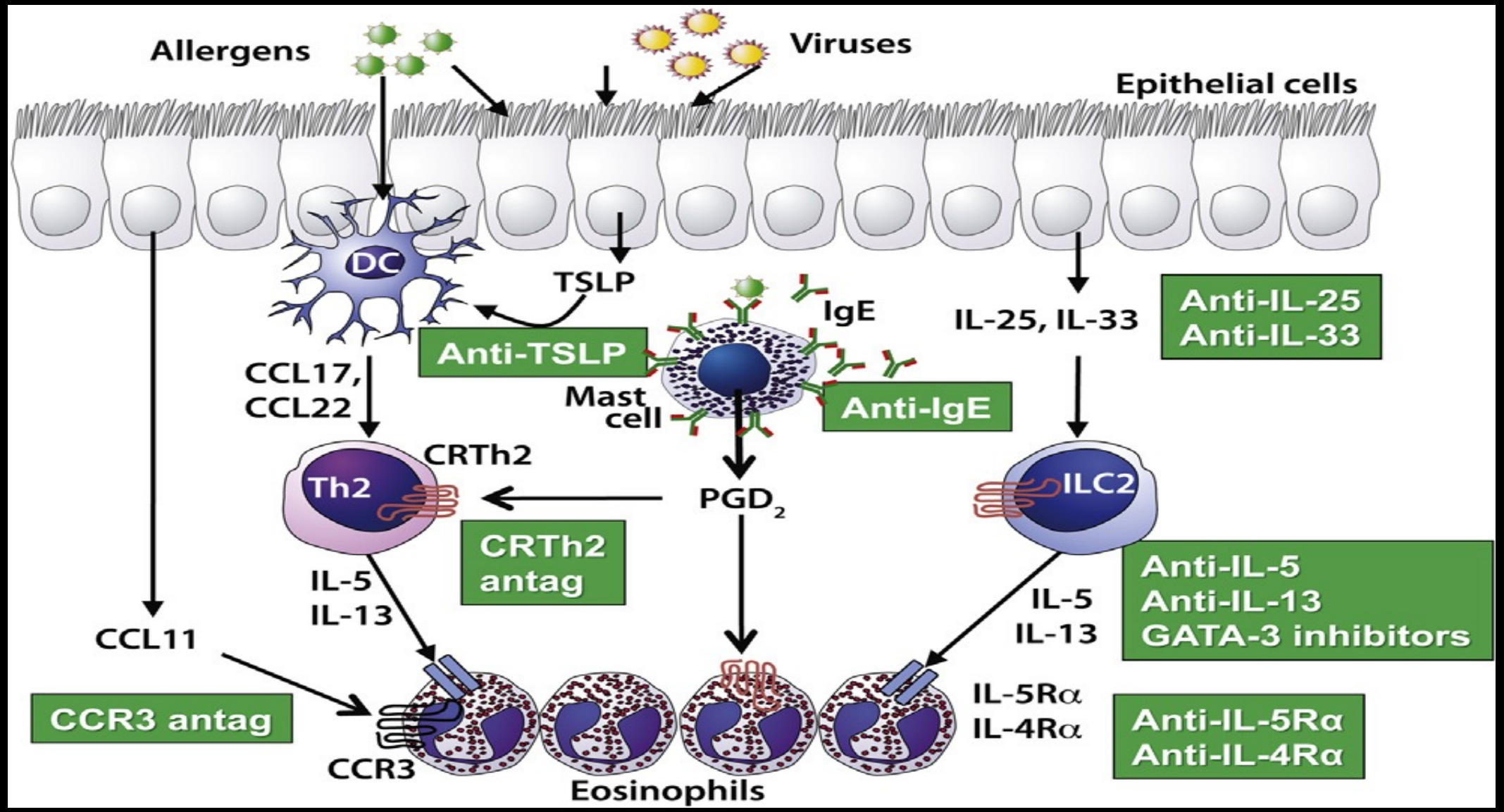
Proposed mechanism of action of AZD8848 in asthma

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



1. Holgate Clin Exp Allergy 2008; 38: 872-897. 2. Biffen et al Br J Pharmacology 2012; 166: 573-586. 3. Shibuya et al J Allergy Clin Immunol 2005; 116: 205-12.

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 PC_{20})
  - 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

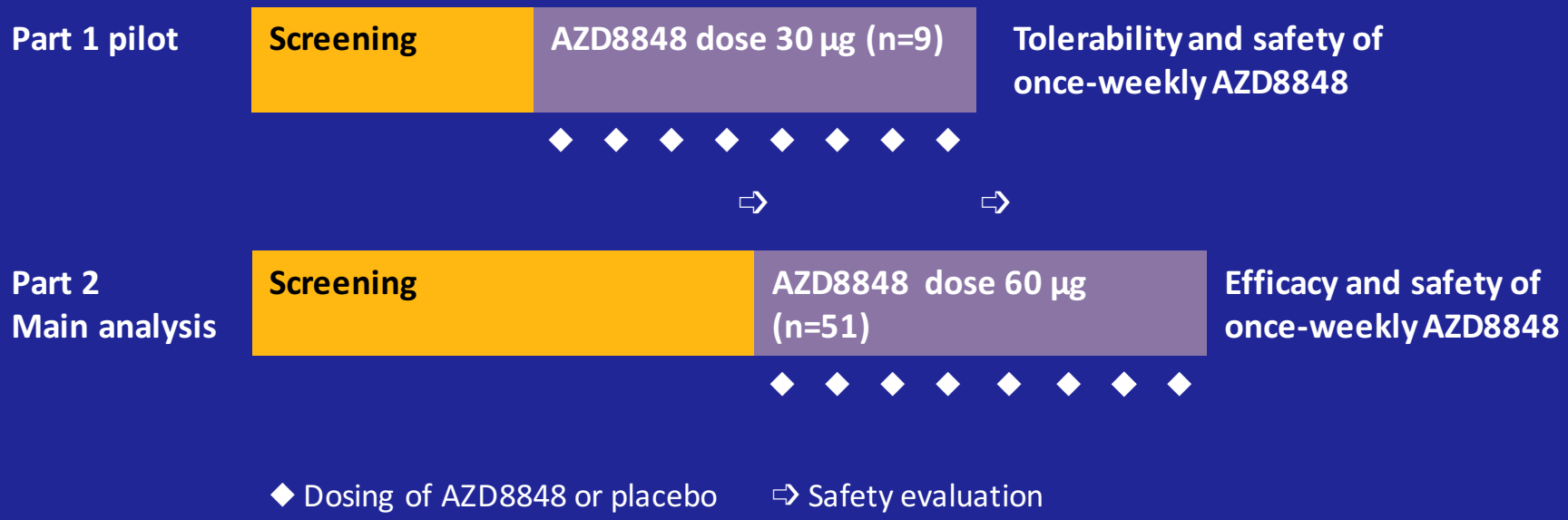
- Symptomatic allergic rhinitis
- Treatment with ICS ± LABA 4 weeks before first study visit
- Use of antihistamines within 1 week or systemic corticosteroids within 6 weeks
- Respiratory tract infection within 2 weeks
- Asthma exacerbation within 4 weeks

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

1. GINA guidelines, 2008 revision. Available at: http://www.ginasthma.com/GuidelinesResources.asp?l1=2&l2=0

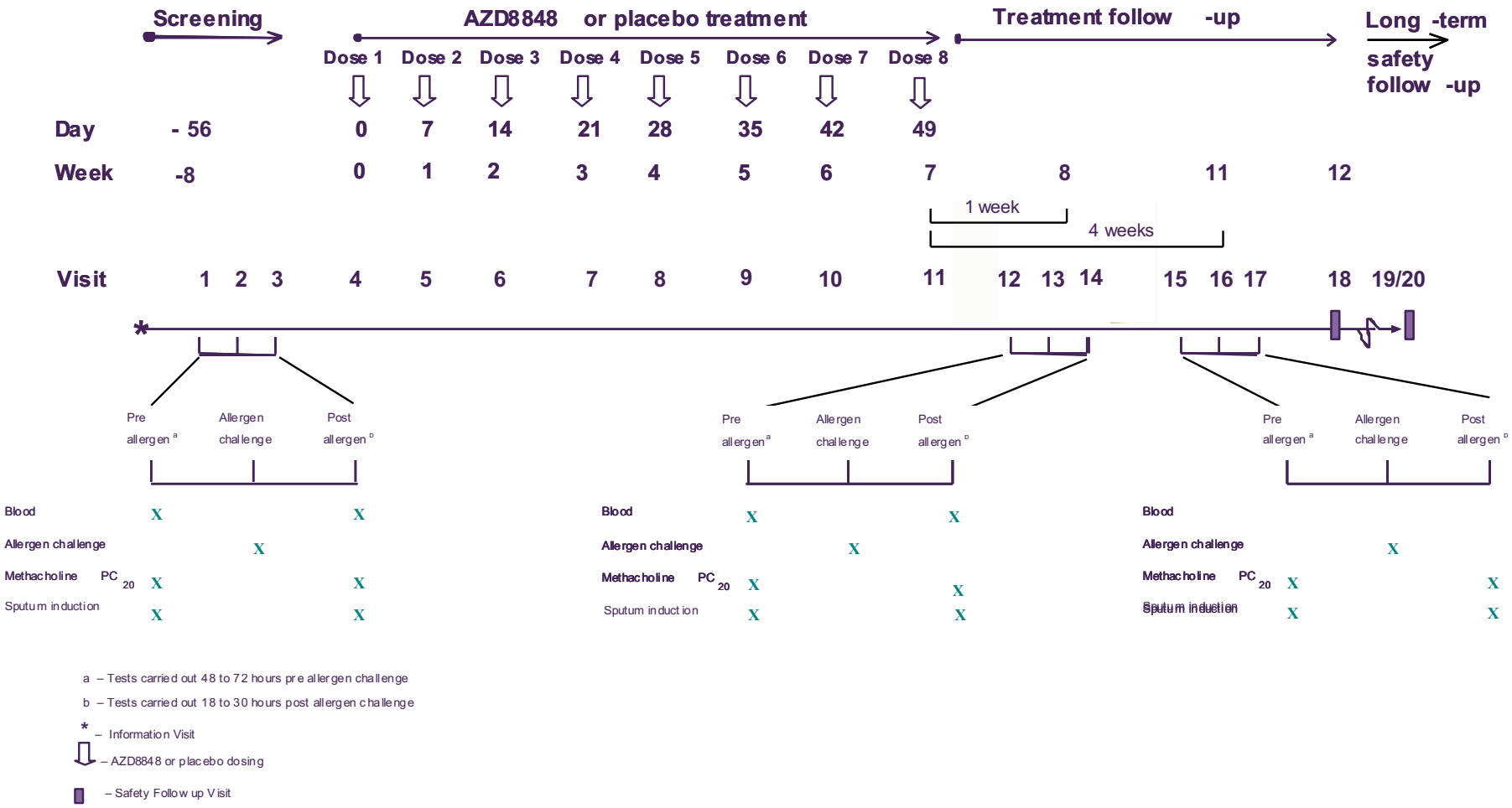
Double-blind, parallel, randomised, placebo-controlled, phase II study

- 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 β_2-agonists was permitted throughout the study.
SRC = Safety Review Committee

The POLAR study design



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

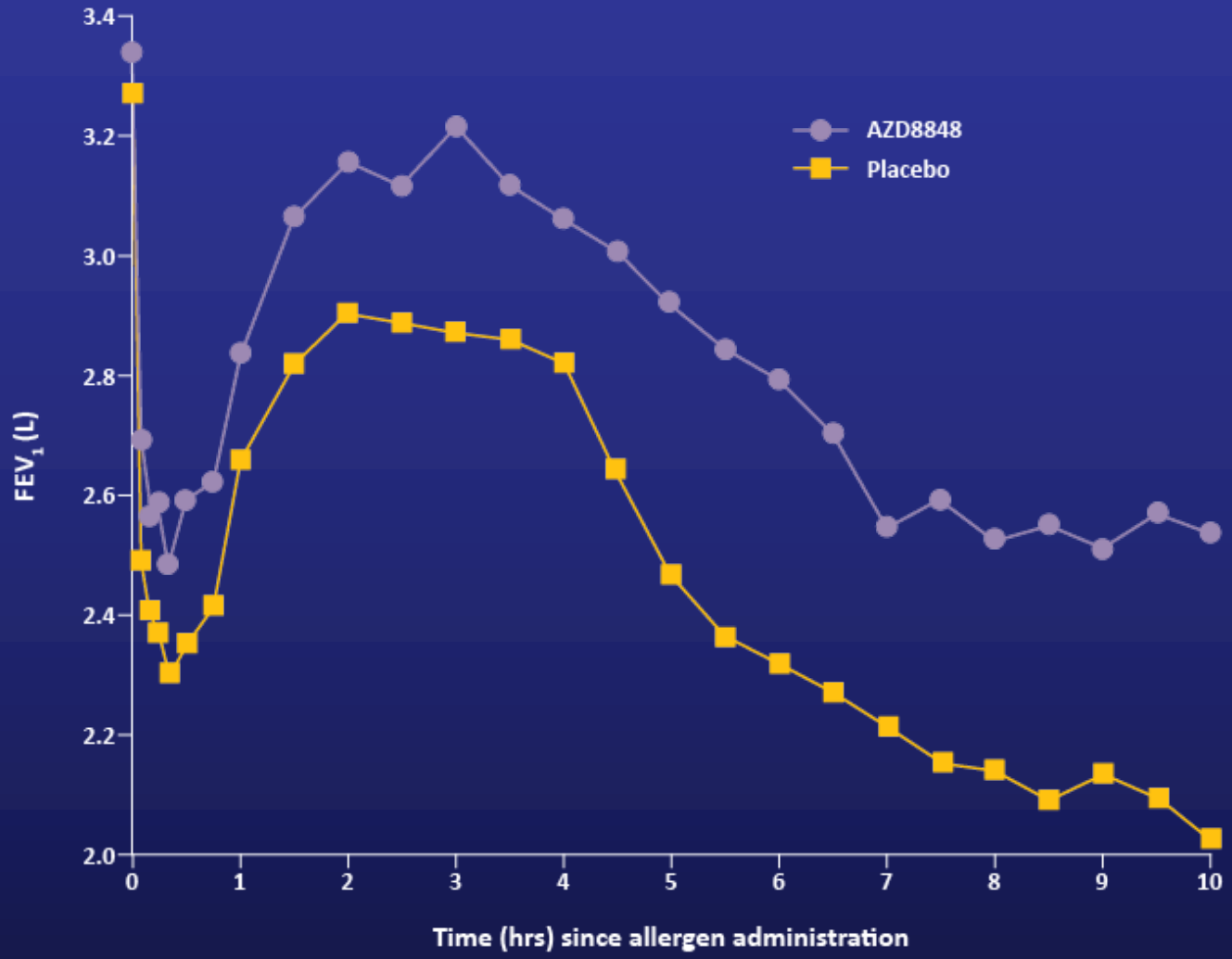
AUC = area under the drug concentration-time curve

Risk Rating for Clinical Studies in Drug Development

Risk	IMP	Methods	Intended population
1	Product with known good safety profile based on exposure in population of thousands of patients.	Non-invasive except for venepuncture and low risk e.g. spirometry, psychometrics, most tests of CVS, imaging with low radiation exposure	Healthy young volunteers
2	Drug in development with good safety record based on exposure at relevant doses and route of administration in ≥200 subjects.	Non-invasive procedures of low risk but with potential for undesired effects e.g. tilt table, exercise testing, methacholine and other bronchial challenges.	Healthy elderly, and patients with mild, non-life threatening conditions, requiring intermittent medication e.g. hayfever mild asthma, osteoarthritis.
3	Novel NME in early development with no or very limited previous exposure in humans e.g. <200 healthy volunteers/patients, including those at doses lower than considered of therapeutic interest. No preclinical or clinical evidence of high risk.	Invasive procedures generally of low risk if performed by a skilled operator e.g. arterial puncture, bronchoscopy, gastroscopy and / or non-invasive procedures which carry significant risk e.g. allergen bronchial challenge, influenza challenge, anticoagulation administration.	Patients with disease of moderate severity, typically requiring regular medication, e.g. moderate asthma, COPD, renal impairment, hepatitis, inflammatory bowel disease or significant past medical history e.g. MI, head injury > 1 year previously.
4	Novel NME with very limited or no previous exposure in humans and / or uncertain mechanism of action and / or known high risk features such as possible involvement of cascades, agonist activity, effects on the immune system	Invasive procedures with known incidence of complications even when performed by skilled operators e.g. liver biopsy, lumbar puncture, bronchial biopsy, urinary bladder catheterisation.	Patients with advanced disease e.g. severe COPD, interstitial pulmonary fibrosis, asthma, unstable CAD, hypertension, rheumatoid arthritiis

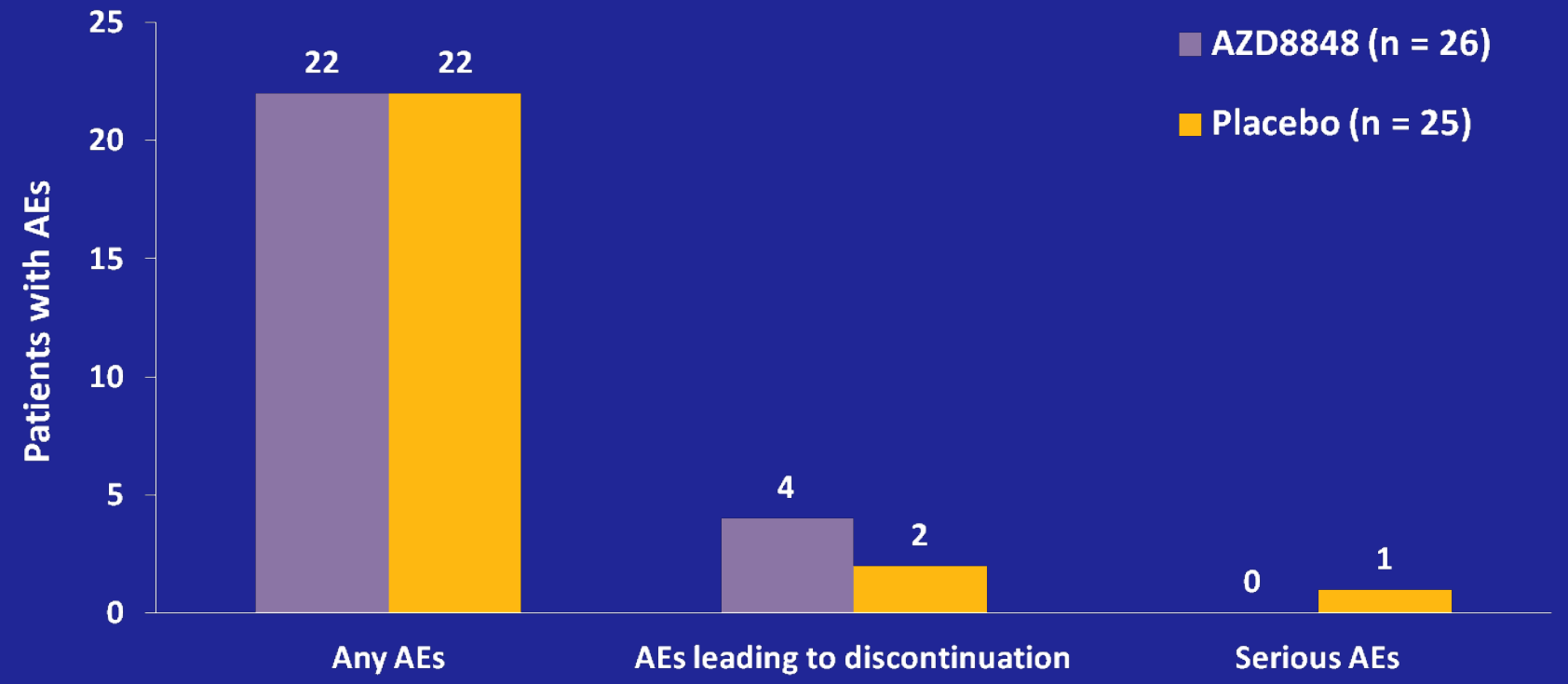
Add risks to max 12; Low risk = ≤ 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

Mean FEV_1 after allergen challenge 1 week after end of treatment



Safety and tolerability

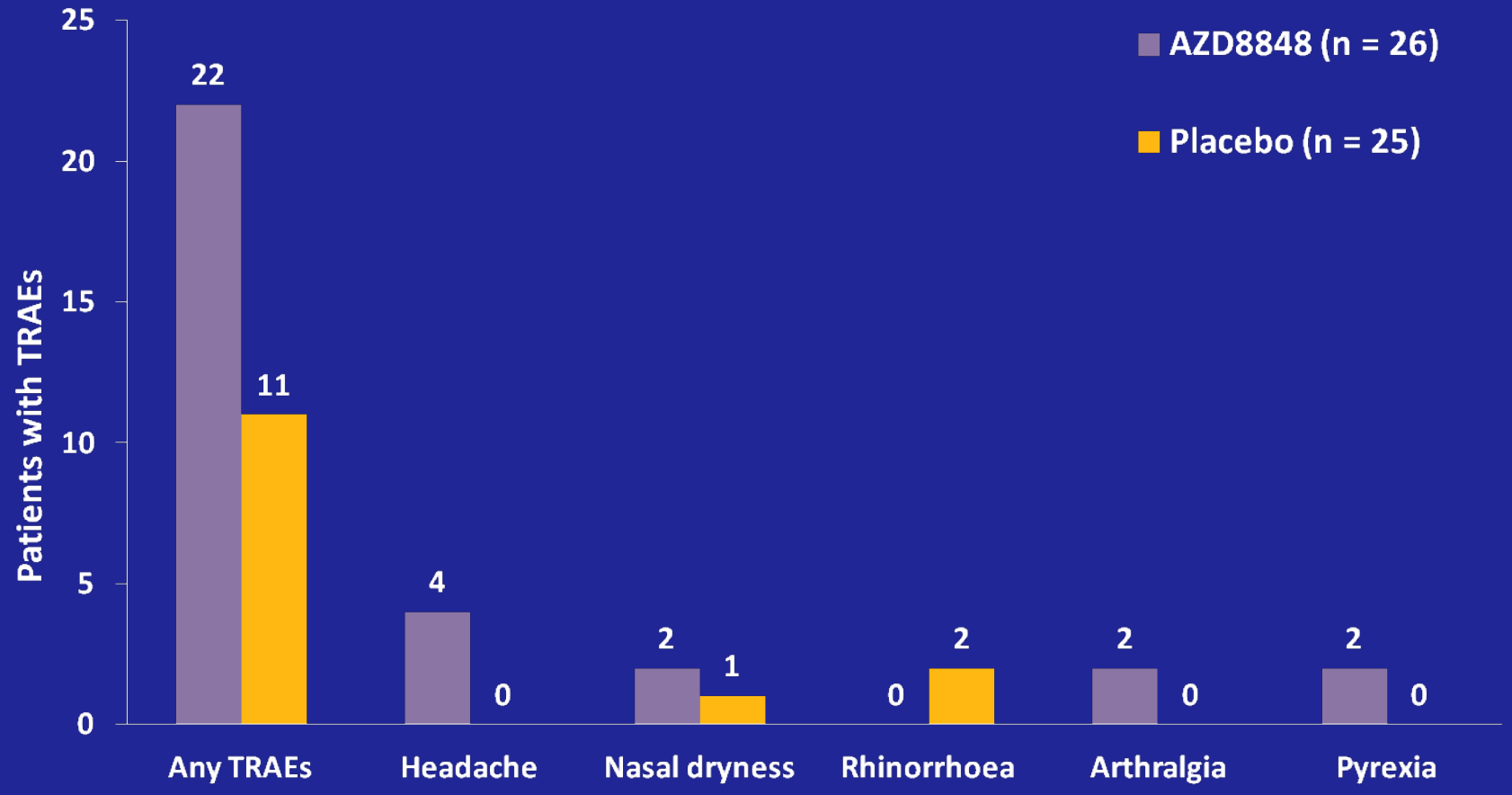
- AZD8848 was generally well tolerated
- A total of 178 AEs reported
- Serious AE in placebo group was severe bacterial tonsillitis
- No clinically relevant changes in ECG or vital signs



AEs = adverse events; ECG, electrocardiography

Treatment-related adverse events

- Most AEs attributable to AZD8848 were mild in severity



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

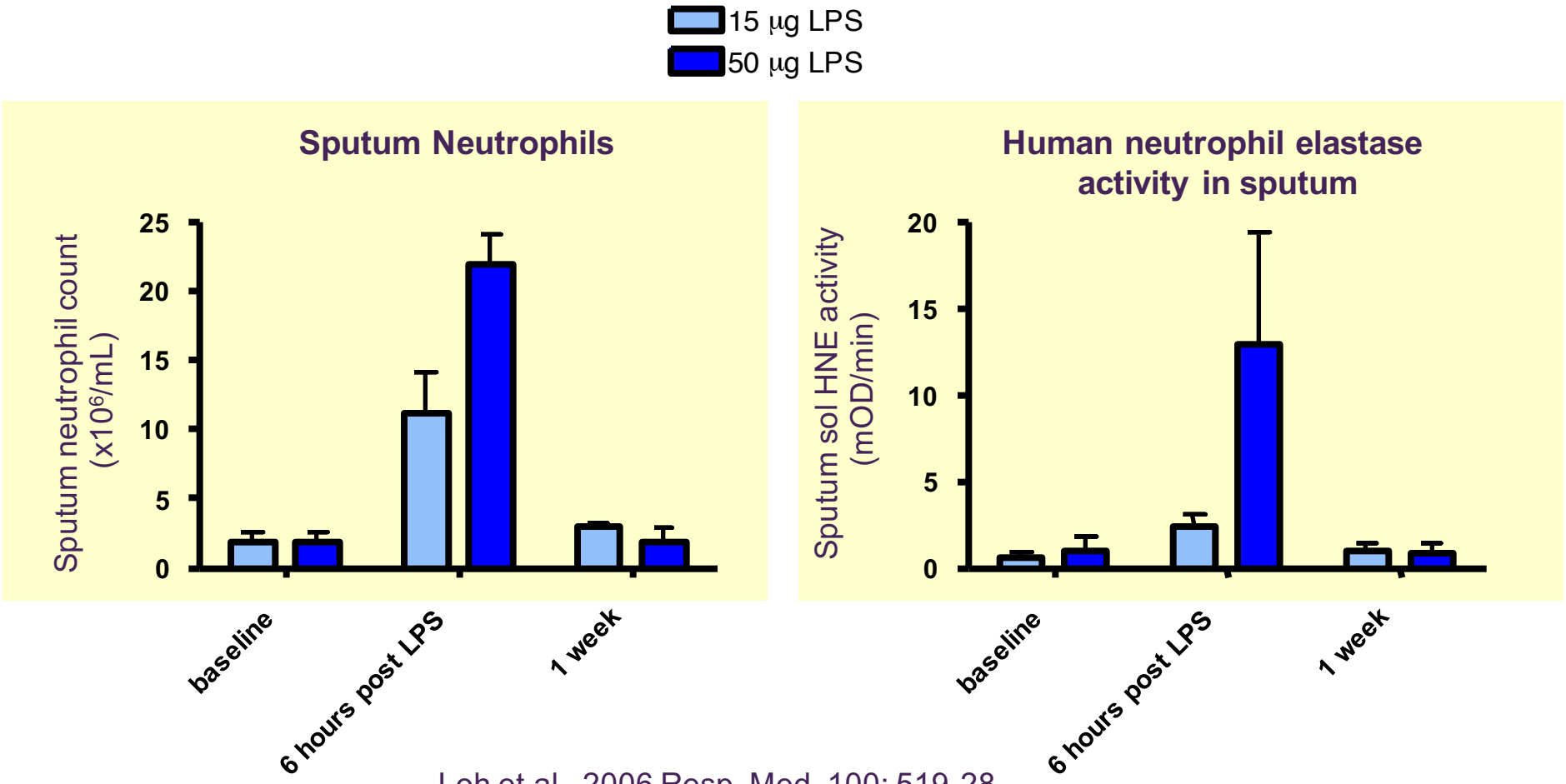
Respiratory
Clinical Trials

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

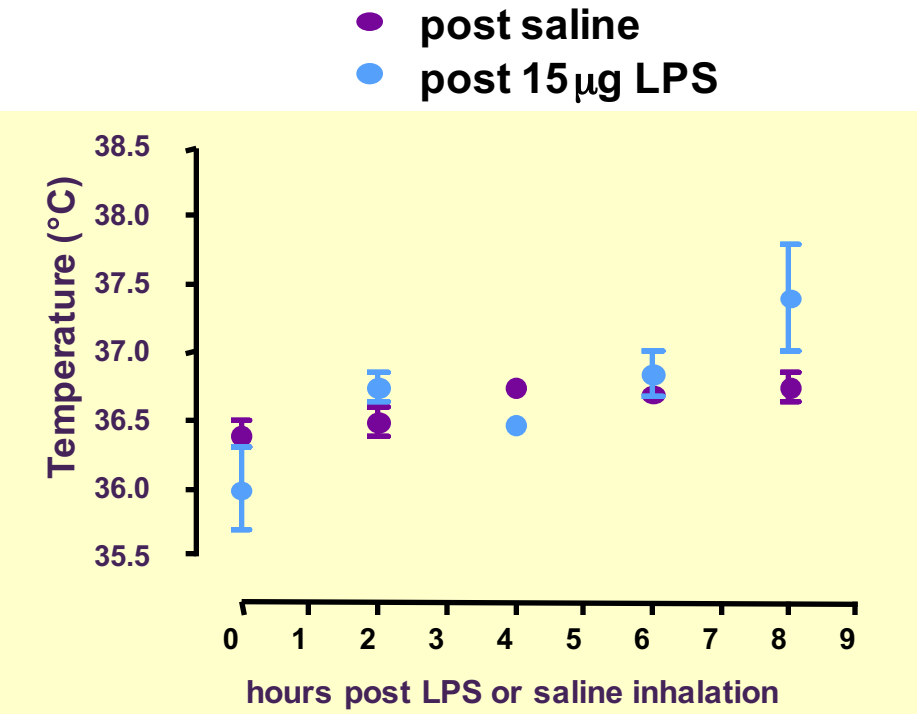
- LPS gives a dose-dependent, transient increase in neutrophil numbers and inflammatory mediators in sputum

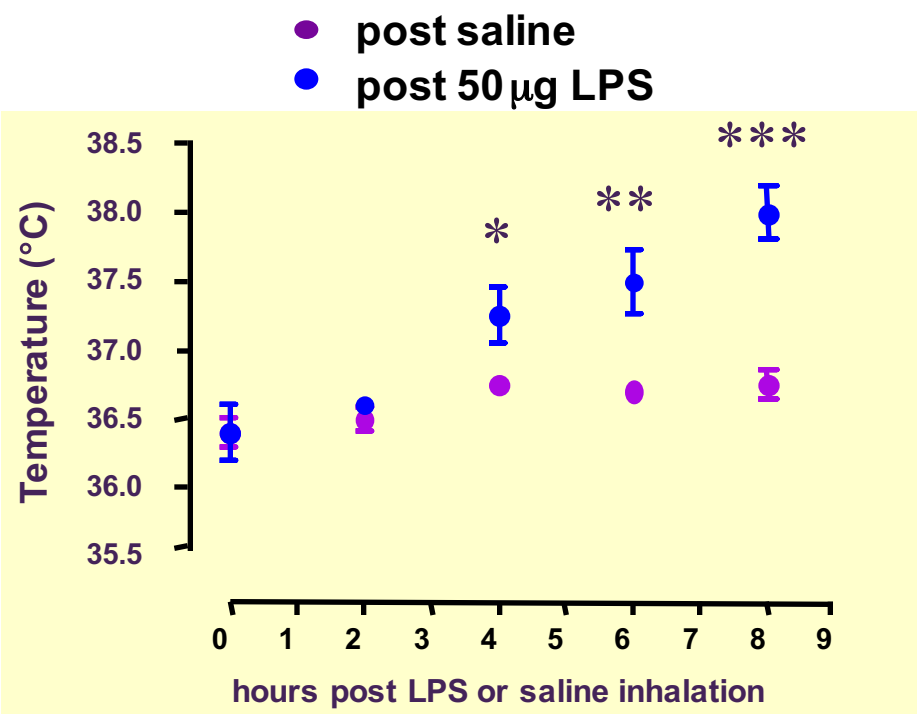


Loh et al., 2006 Resp. Med. 100: 519-28.

Systemic effects

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



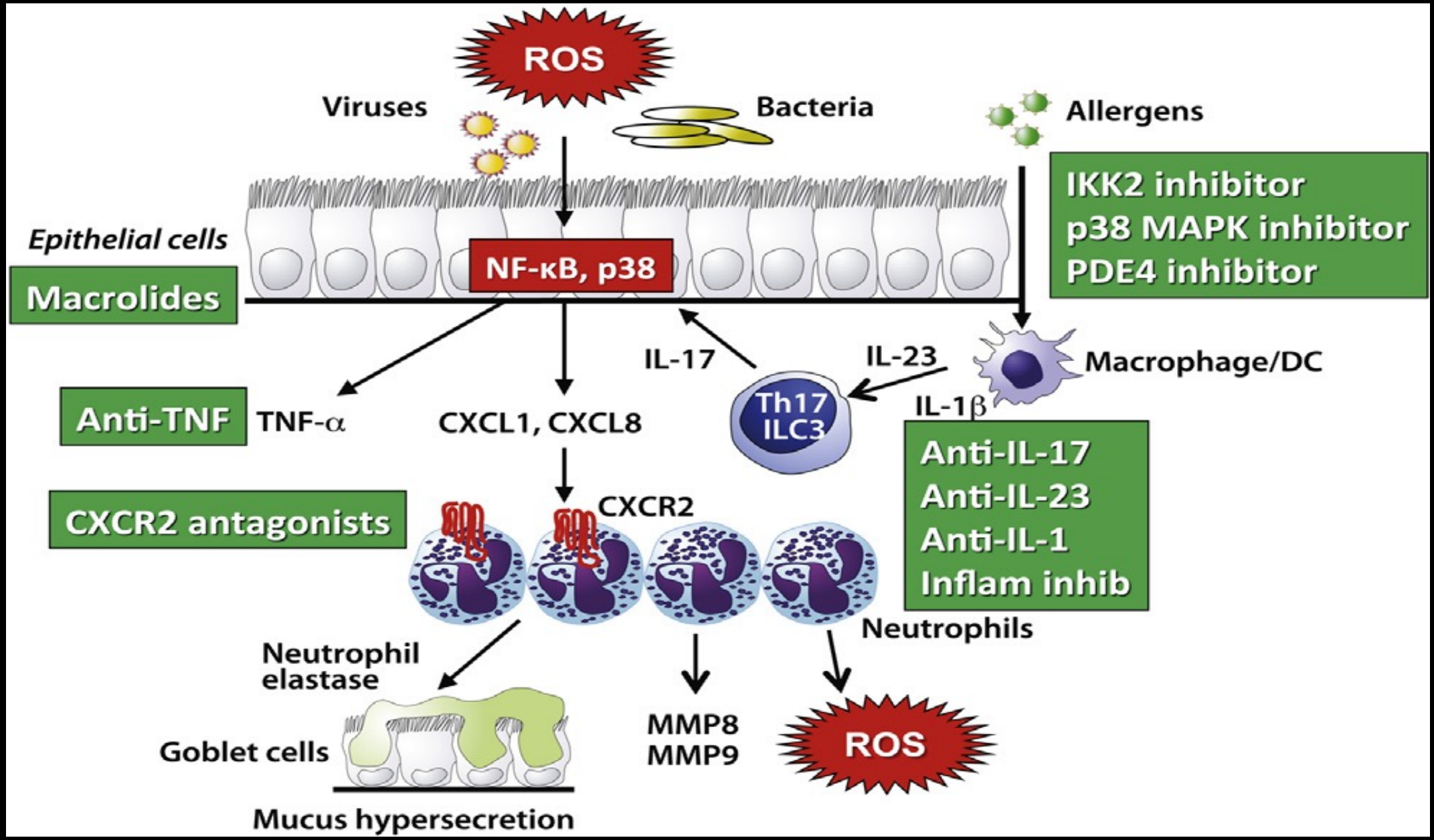


Loh et al., 2006 Resp. Med. 100: 519-28.

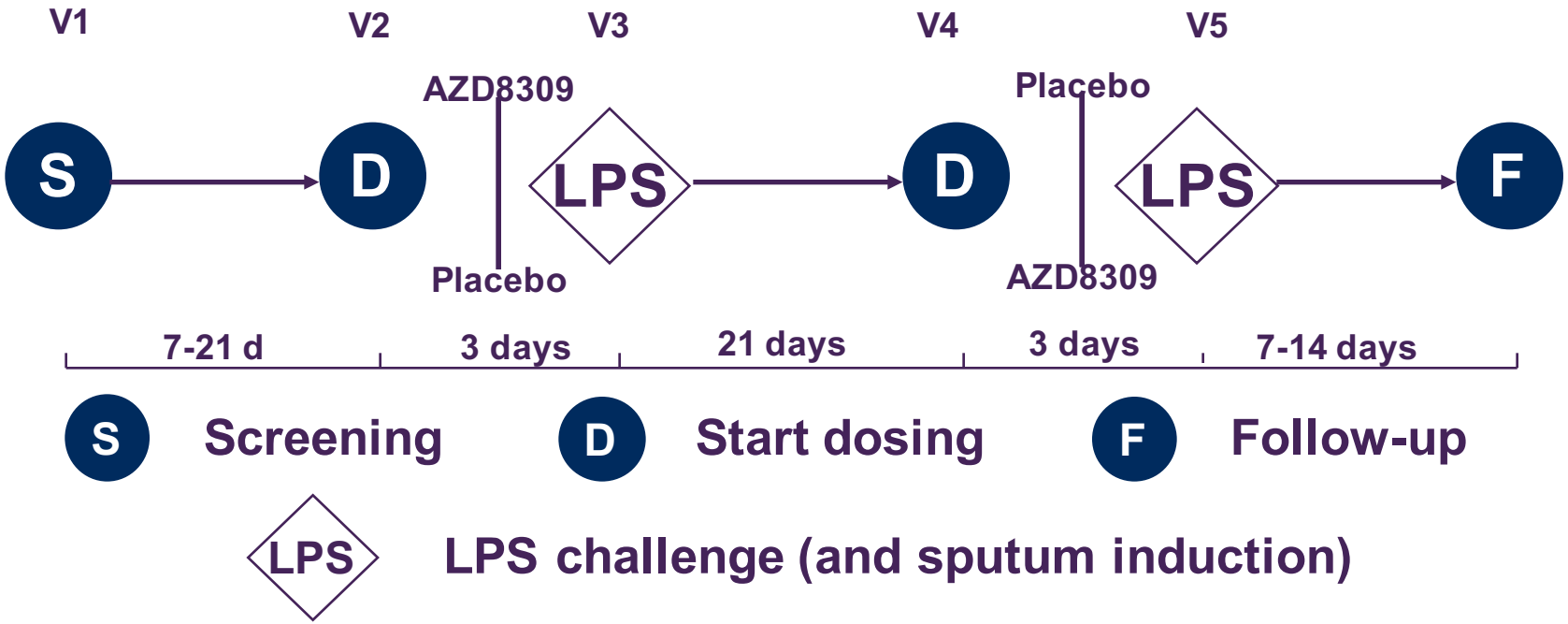
Utility of the LPS challenge model

- 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



Study design



- 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%

Risk Rating of Human Pharmacology Studies in Drug Development

Risk	IMP	Methods	Intended population
1	Product with known good safety profile based on exposure in population of thousands of patients.	Non-invasive except for venepuncture and low risk e.g. spirometry, psychometrics, most tests of CVS, imaging with low radiation exposure	Healthy young volunteers
2	Drug in development with good safety record based on exposure at relevant doses and route of administration in ≥200 subjects.	Non-invasive procedures of low risk but with potential for undesired effects e.g. tilt table, exercise testing, methacholine and other bronchial challenges.	Healthy elderly, and patients with mild, non-life threatening conditions, requiring intermittent medication e.g. hayfever mild asthma, osteoarthritis.
3	Novel NME in early development with no or very limited previous exposure in humans e.g. <200 healthy volunteers/patients, including those at doses lower than considered of therapeutic interest. No preclinical or clinical evidence of high risk.	Invasive procedures generally of low risk if performed by a skilled operator e.g. arterial puncture, bronchoscopy, gastroscopy and / or non-invasive procedures which carry significant risk e.g. allergen bronchial challenge, influenza challenge, anticoagulation administration.	Patients with disease of moderate severity, typically requiring regular medication, e.g. moderate asthma, COPD, renal impairment, hepatitis, inflammatory bowel disease or significant past medical history e.g. MI, head injury > 1 year previously.
4	Novel NME with very limited or no previous exposure in humans and / or uncertain mechanism of action and / or known high risk features such as possible involvement of cascades, agonist activity, effects on the immune system	Invasive procedures with known incidence of complications even when performed by skilled operators e.g. liver biopsy, lumbar puncture, bronchial biopsy, urinary bladder catheterisation.	Patients with advanced disease e.g. severe COPD, interstitial pulmonary fibrosis, asthma, unstable CAD, hypertension, rheumatoid arthritiis

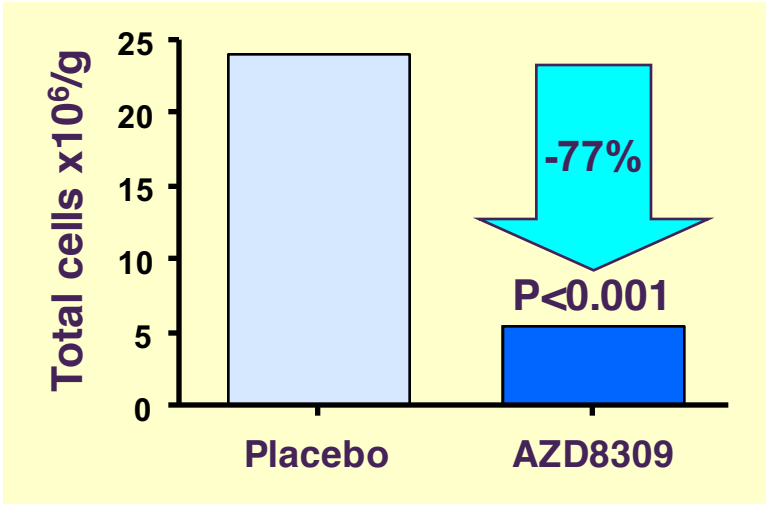
Add risks to max 12; Low risk = ≤ 4, Moderate risk = 5-6, Higher risk = 7-8, High risk = 9-12

Study Demographics

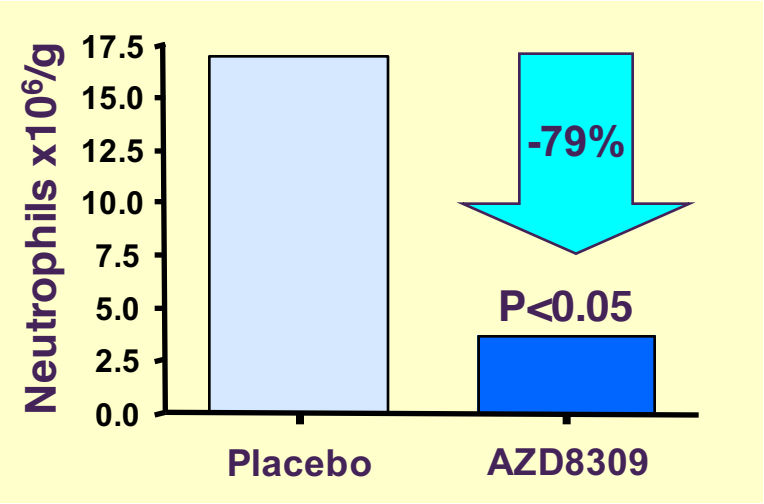
- 20 subjects randomised
  - 3 past smokers
- 16 subjects completed
- No subjects withdrew due to adverse effects of AZD8309 or the LPS challenge
  - 2 for entering other trials
  - 1 on placebo with migraine
  - 1 withdrew prior to dosing

Results: Sputum Cells

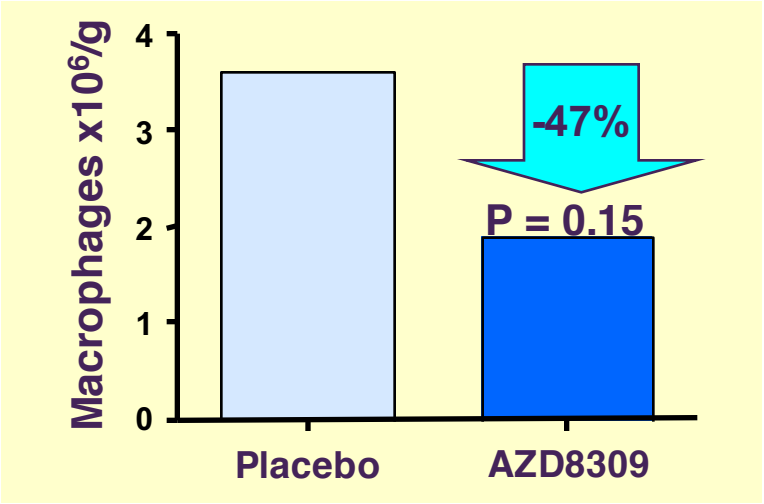
Total Cells



Neutrophils

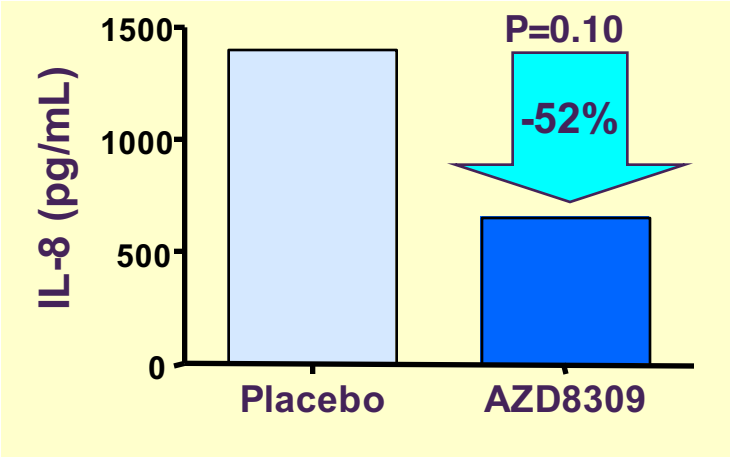


Macrophages

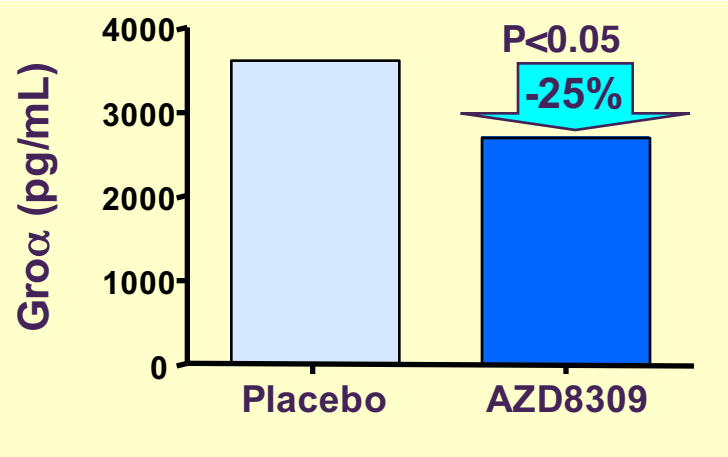


Results: Inflammatory Markers

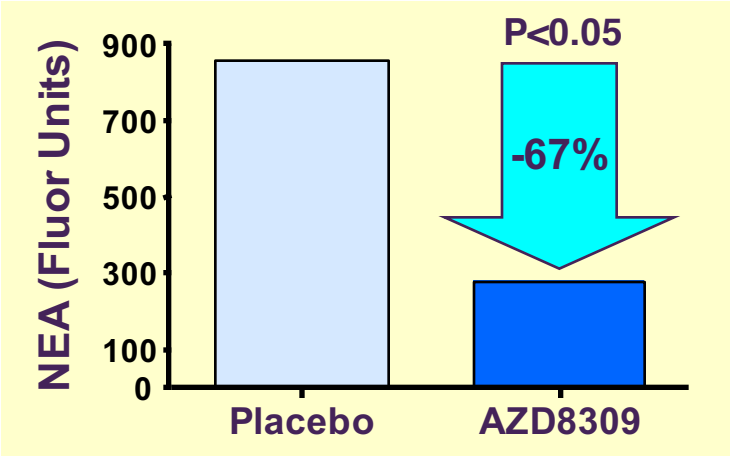
IL-8



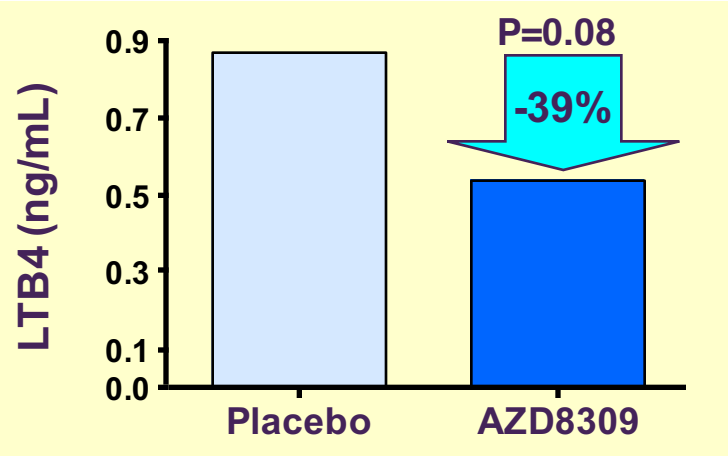
Groα



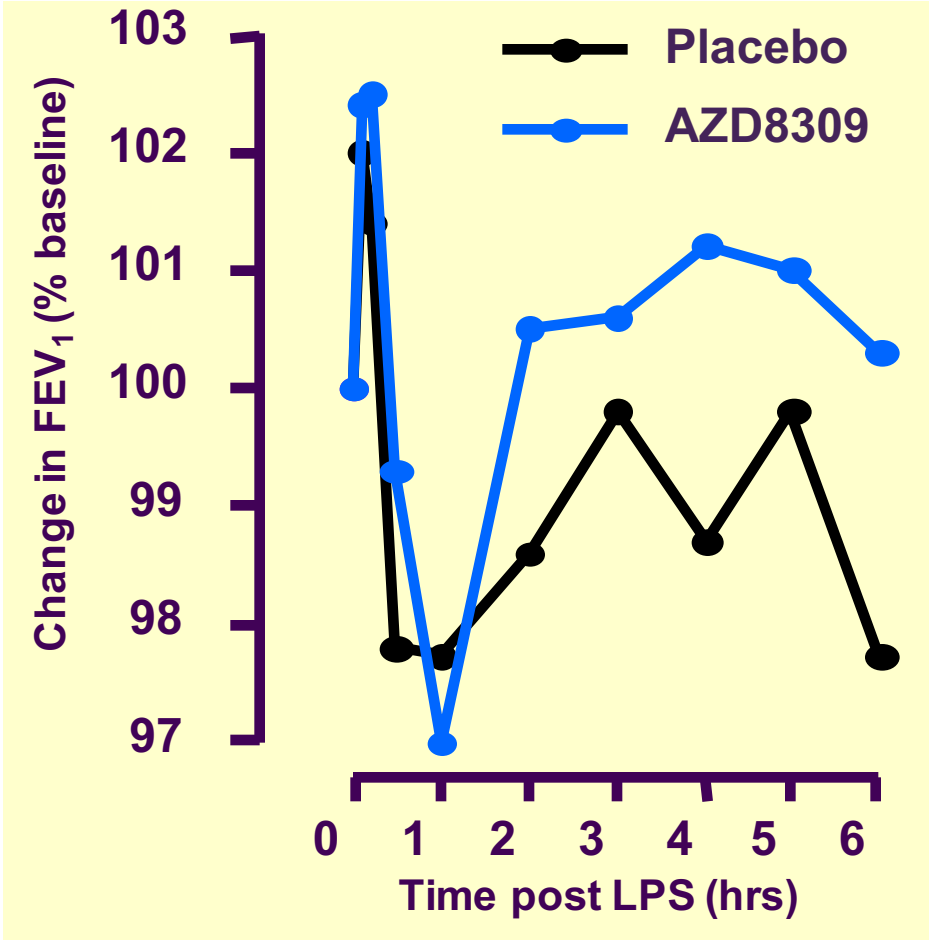
NEA



LTB4



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

	AZD8309 (N=18)	Placebo (N=19)
No. (%) of subjects with DAE	0	1 (5%)
No. AEs	19	28
No. (%) of subjects with AEs	14 (61%)	10 (53%)
AEs by preferred term	N=18	N=18
pyrexia	5 (28%)	3 (17%)
headache	2 (11%)	4 (22%)
dizziness	0	3 (17%)
nasal congestion	2 (11%)	3 (17%)
diarrhoea	3 (17%)	1 (6%)
rhinitis	0	2 (11%)
pharyngolaryngeal pain	0	2 (11%)

Summary

- 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 (30μg LPS) well tolerated

CXCR2 antagonists in COPD (Navarixin)

Respiratory Clinical Trials

- Dose response study versus placebo n=616.
- Reduction in sputum neutrophils by >50% at3/12
  - 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