# Meet the Respiratory management

*2 September 2016*

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# Agenda

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# Presenters biographies

## *Eric Dube, Senior Vice President and Head, Global Respiratory Franchise*

Eric started his career at GSK in 2000 as a Medical Science Liaison and has worked in a variety of marketing, sales, operations and strategy roles in the USA, Japan and UK. During his time within US Pharma, he served as VP Managed Markets for National Accounts, as well Head of the Oncology Business Unit where he helped to launch three new oncology medicines. He then served as the Senior VP of Strategy, Planning and Operations, where he led transformation initiatives across US and Global Pharma.

He then joined GSK Japan in 2013, as Head of the Respiratory Business Unit. He was a member of the GSK Japan leadership team, responsible for the sales and marketing of our respiratory portfolio. During his leadership, GSK Japan has gained approval for a number of our new respiratory medicines; *Relvar* Ellipta, *Anoro* Ellipta, and most recently *Encruse* Ellipta. His team has achieved significant success with Relvar, which is now the leading ICS/LABA for new patients in Japan.

In his current role, Eric leads the Global Respiratory Franchise, and is responsible for the global strategy for the portfolio of recently launched medicines *Relvar/Breo*, *Anoro*, *Incruse*, *Arnuity* and *Nucala*.

Eric earned a BS in Biopsychology from Santa Clara University, California, followed by a MA and PhD in Psychology from Cornell University, New York, USA.

# Presenters biographies

## *Neil Barnes, Respiratory Global Franchise Medical Head*

Professor Neil Barnes is Medical Head of the Global Respiratory Franchise at GSK. Until October 2013 he was Consultant Respiratory Physician at London Chest Hospital, Barts Health NHS Trust and Professor of Respiratory Medicine at Barts and the London School of Medicine and Dentistry, London, UK. He was joint R&D Director at Barts and the London School of Medicine and Dentistry from 2005–2009.

Neil trained at Cambridge University and Westminster Medical School. He specialised in respiratory medicine at King's College Hospital and the London Chest Hospital. His main clinical and research interests are in asthma, in particular, severe and difficult asthma and COPD. His research focuses on the mechanisms and pharmacology of asthma and COPD and clinical trial design and interpretation.

Neil has given invited lectures at most of the major respiratory meetings worldwide. He has served as Associate Editor for Thorax and has been a reviewer for a wide range of general and respiratory journals and has published over 250 peer-review papers, book chapters, editorials and reviews.

# Presenters biographies

## *Dave Allen, Senior Vice President and Head, Respiratory R&D*

Dave Allen is the head of the Respiratory Therapy Area at GSK and is responsible for the identification of novel differentiated medicines and their progression to registration and launch. He leads a group of over 200 scientists and clinicians who exploit scientific innovations that have the potential to address the major unmet needs in diseases such as COPD, severe asthma, acute lung injury and idiopathic pulmonary fibrosis.

Previously, Dave was head of Respiratory Drug Discovery and prior to that he led the respiratory chemistry department where he managed the lead optimisation portfolio. He retains a keen interest in chemistry issues and was appointed GSK's Chief Chemist in 2012. In this role he works with GSK's global community of chemists to continually enhance the quality of science and innovation within chemistry at GSK. In addition, Dave is a member of a number of GSK's senior decision-making boards within research and development. In November 2014, Dave was awarded an honorary Doctor of Science degree from the University of Strathclyde in recognition of his pioneering work in drug discovery.

Dave joined the company as a research chemist in 1981 after completing his MA and BA at Oriel College, Oxford. During his career he has also worked on discovering antibiotics and cardiovascular medicines, as both a medicinal chemist and project leader.

# Respiratory commercial perspectives

*Eric Dube*

# Respiratory commercial landscape

*Market trends highlight the need for truly innovative medicines*

**Key market trends**

- Deliver the right medicine for the right patient
- Intense competition in inhaled medication driving pricing and access pressure
- Technological / digital convergence to improve outcomes, efficiency and value
- Further innovation beyond asthma and COPD
- High level of unmet need remains

## Asthma

- ICS expected to remain the cornerstone of treatment
- Improve control through adherence and compliance
- Reduce exacerbations in severe asthma

## COPD

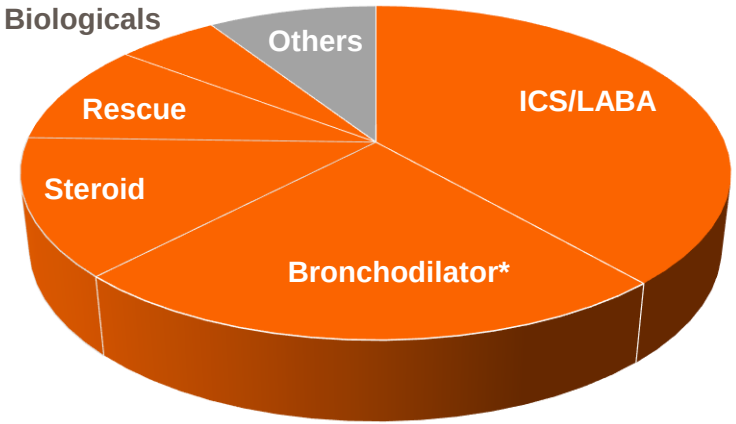
- Clarity of treatment choices to improve symptoms and reduce risk
- Further reduce exacerbations
- Slow disease progression

## Lung fibrosis & acute lung injury

- Bar for efficacy and safety is set for lung fibrosis
- Acute lung injury (ALI): hospital mortality rates of up to 50%

# Respiratory portfolio in transition – new portfolio provides platform for continued market leadership

*£24bn* global respiratory market (MAT Mar'16) with 8% growth over MAT Mar'15




*29%* GSK share of global market

*Bronchodilator market includes SAMAs and their combination in addition to LAMA, LABA and LAMA/LABAs
Source: IMS MIDAS, Rapier World Model, March 2016

***Relvar/Breo Ellipta™*** inhaler approved & launched
***Anoro Ellipta™*** inhaler approved & launched
***Incruse Ellipta™*** inhaler approved & launched
***Arnuity Ellipta™*** inhaler approved & launched
***Nucala™*** approved & launched

Additional products/indications in late stage development:

- **ICS/LABA/LAMA (Closed Triple) – Asthma and COPD**
- **Anti-IL5 mAb (COPD, HES, Nasal Polyps)**
- **MABA/ICS**

# GSK offers a broad portfolio across the spectrum of COPD and asthma treatment

## GSK Respiratory

### COPD

| Symptomatic patients / patients at lower risk of exacerbation | | Patients at higher risk of exacerbation | |
|---|---|---|---|
|  *Incruse* |  *Anoro* |  *Relvar/ Breo* |  *Incruse + Relvar/Breo* |
| LAMA | LAMA/LABA | ICS/LABA | LAMA+ ICS/LABA |

### Asthma

| Mild-moderate patients | Moderate-severe patients | Paediatric patients | Severe patients |
|---|---|---|---|
|  *Arnuity* |  *Relvar/Breo* |  *Seretide/ Advair* |  *Nucala* |
| ICS | ICS/LABA | ICS/LABA | anti-IL5 |

all available in the once-daily, easy to use *Ellipta* inhaler

# GSK well positioned to address the key unmet needs in asthma

**Mild asthma patients**

Consider low-dose ICS
Leukotriene receptor antagonist
Low-dose theophyline

**Moderate asthma patients**

Low-dose ICS/LABA
Med/high-dose ICS
Low-dose ICS+LTRA
(or +theophyline)

**Severe asthma patients**

Refer for add-on treatment
e.g. tiotropium, omalizumab,
*Nucala*

***Ventolin***


***Arnuity***


***Relvar/ Breo***

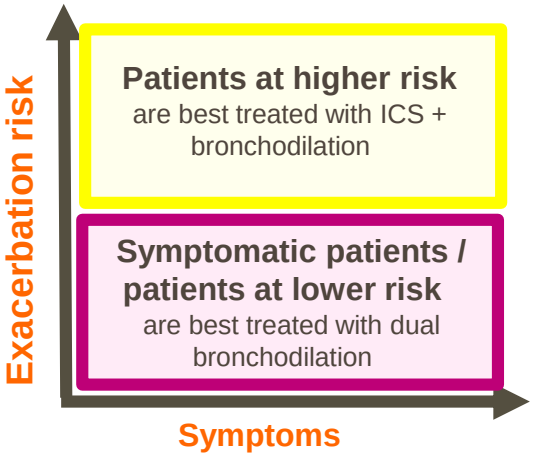
**Closed Triple***


***Nucala***

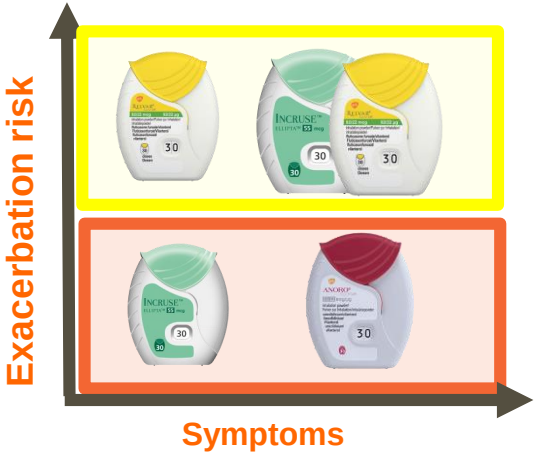
*An investigational product and not approved anywhere in the world

# GSK expects to maintain leadership in COPD segments

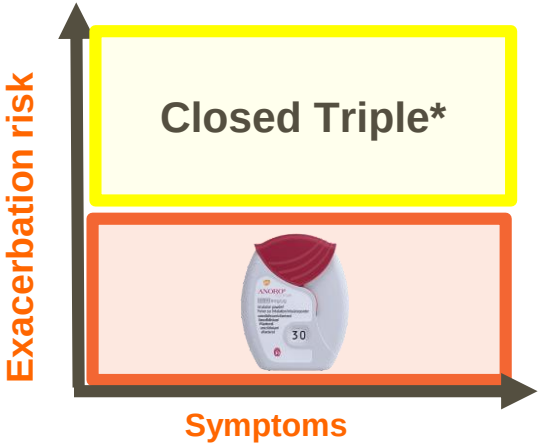
## Our belief




## Current opportunity




## Future priority opportunity

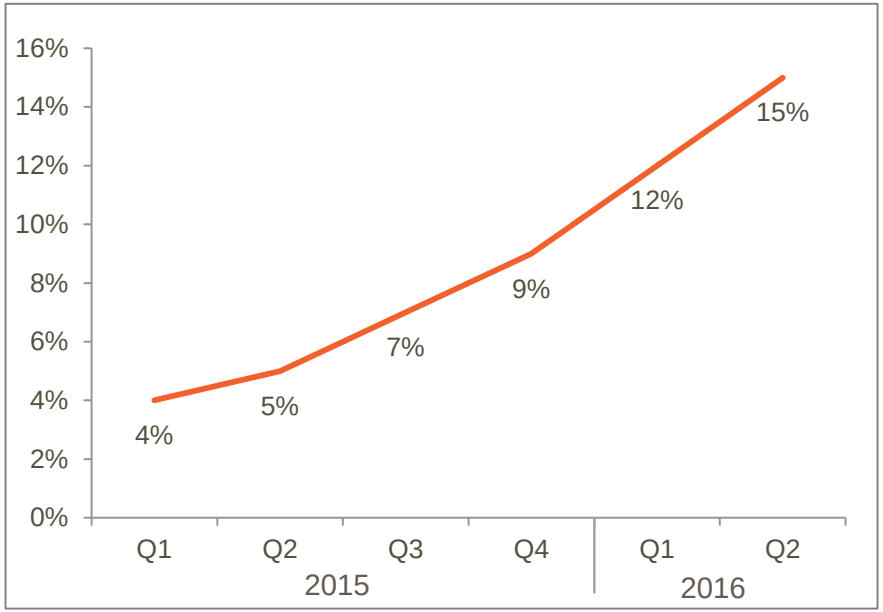



This framework is meant to visualise how we see the different classes of medicines used to treat patients optimally, based on the evolving evidence on risk and symptoms. It is not meant to describe treatment pathways or sequencing. *An investigational medicine and not approved anywhere in the world.

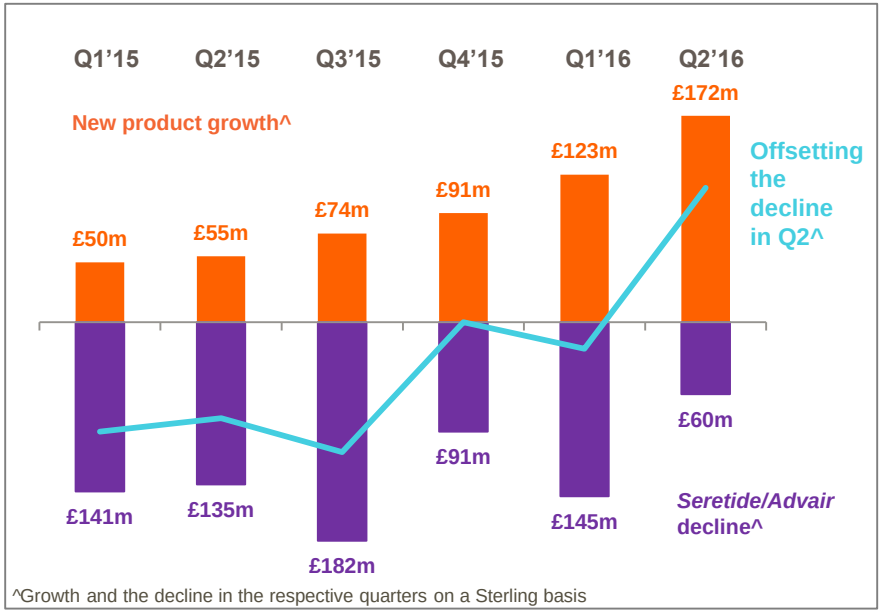
# Respiratory portfolio performance

*Return to growth driven by the performance of new medicines*

## Increasing proportion of sales from launches




## New Respiratory product growth offsetting *Seretide/Advair* decline

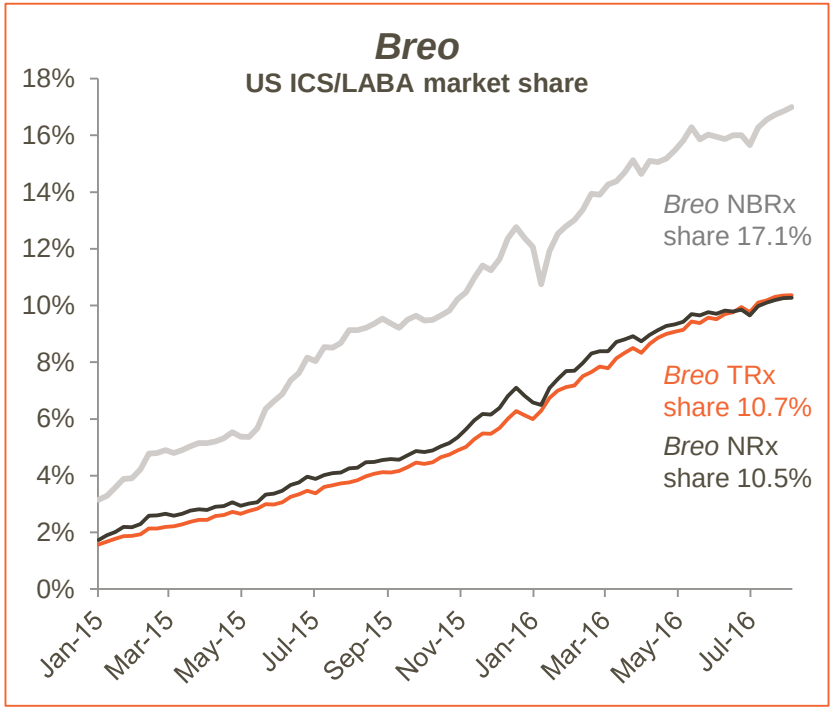


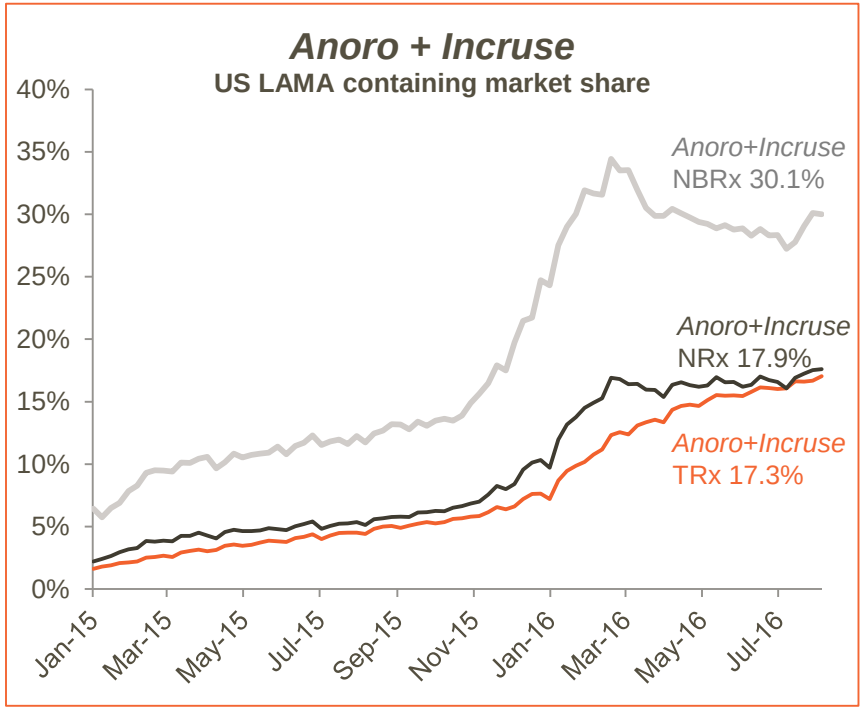

^Growth and the decline in the respective quarters on a Sterling basis

Source: GSK company slide. New products = *Relvar/Breo, Anoro, Incruse, Arnuity* and *Nucala*. All growth % are versus prior year quarter.

# Significant momentum in the US respiratory portfolio

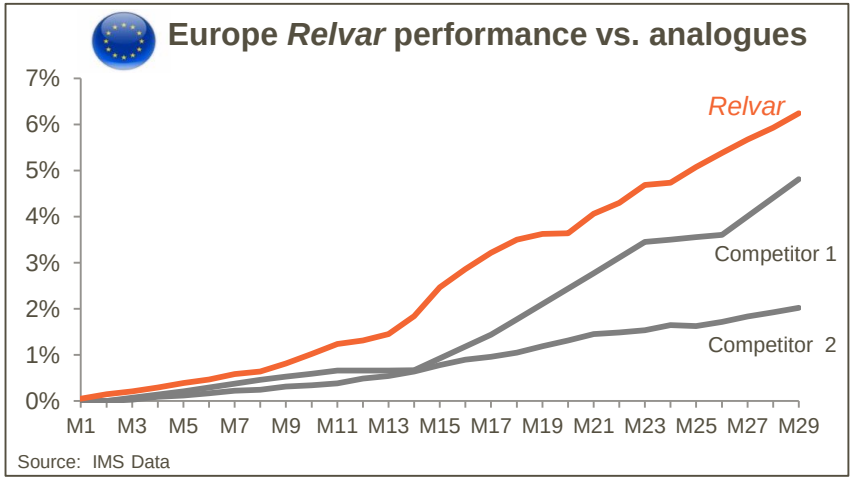
*Upward trajectory in US market share supporting respiratory growth*

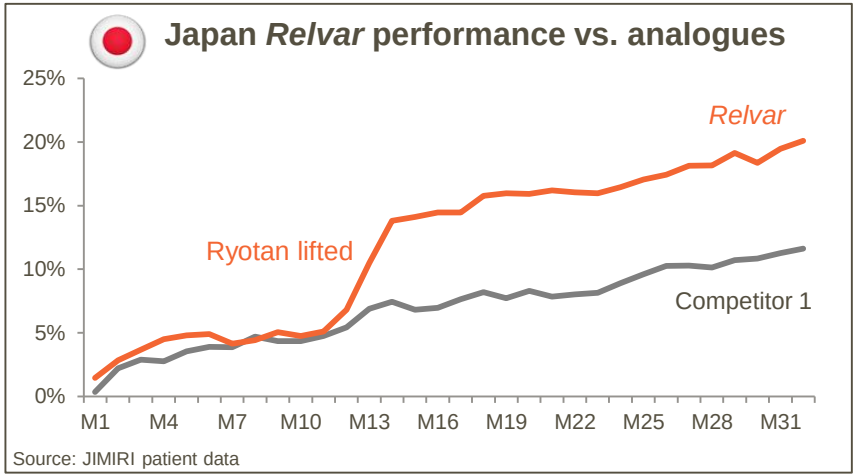



Source: IMS data to 19/08/16

# *Relvar* performance continues to exceed recent launch analogues, *Anoro* European launches underway



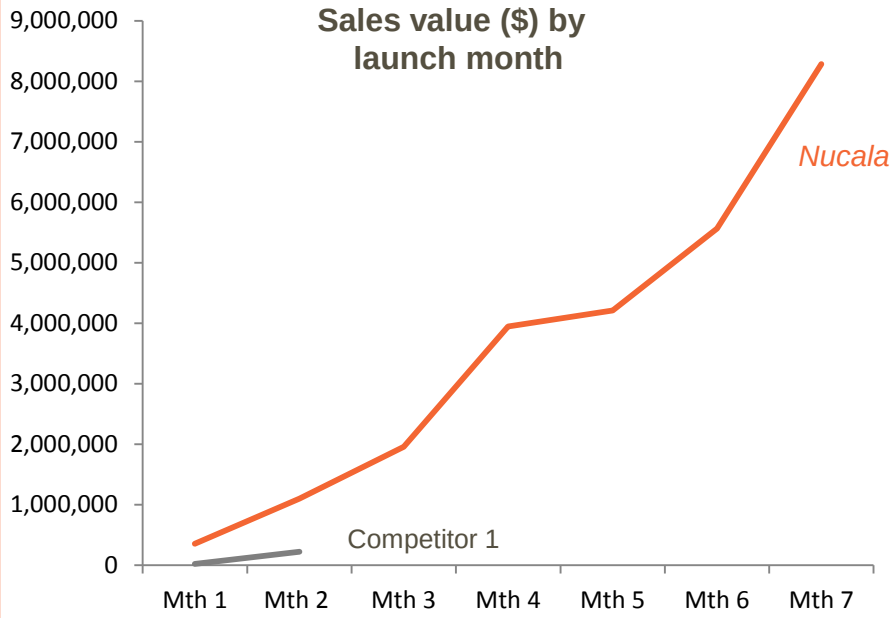




***Anoro* European performance:**

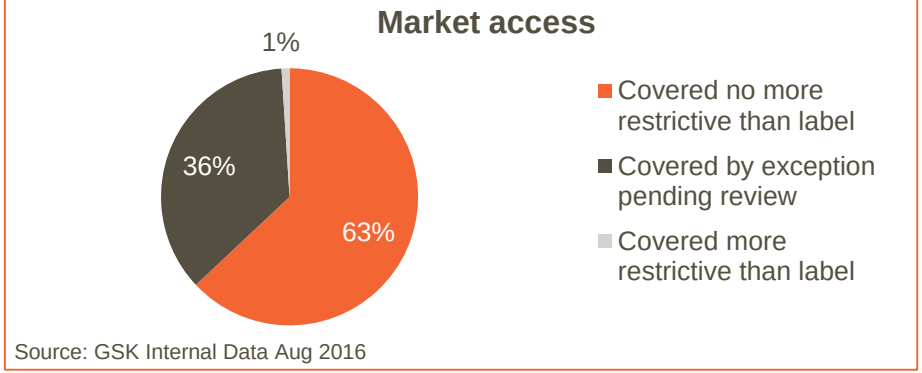
- *Anoro* has not experienced the same level of uptake as *Relvar* in Europe and Japan
- Second to market in the LAMA/LABA class and no component brand to convert
- The focus is on establishing *Anoro* as best in class
- Superiority of umeclidinium has been demonstrated versus tiotropium

# *Nucala* performance - US

*Strong patient demand and favourable access position driving volume growth*




Source: IMS NPS Data

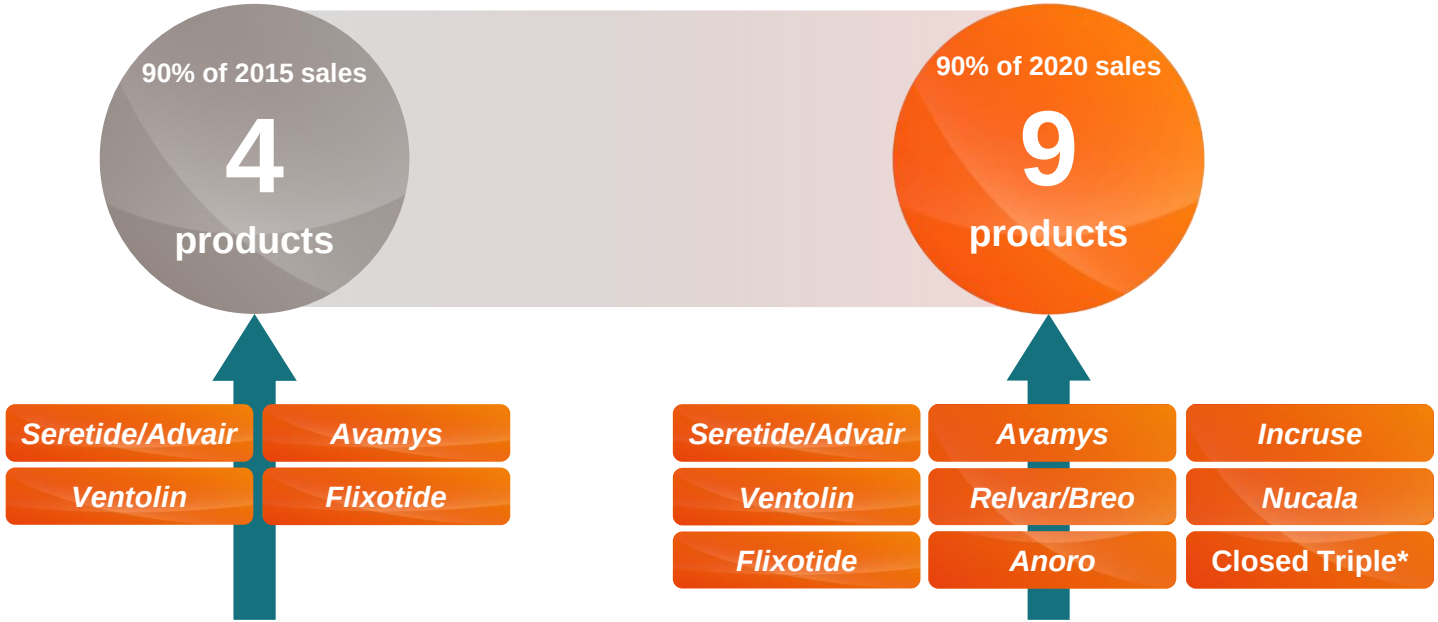



Source: GSK Internal Data Aug 2016

**US launch uptake:**

- J code to be available Jan 2017
- MUSCA study data showing QoL and lung function expected by end 2016
- Launch so far has received very strong feedback from physicians

# Expect 2020 total respiratory sales to be at or above sales in 2015, whether or not there is US generic competition to *Advair*



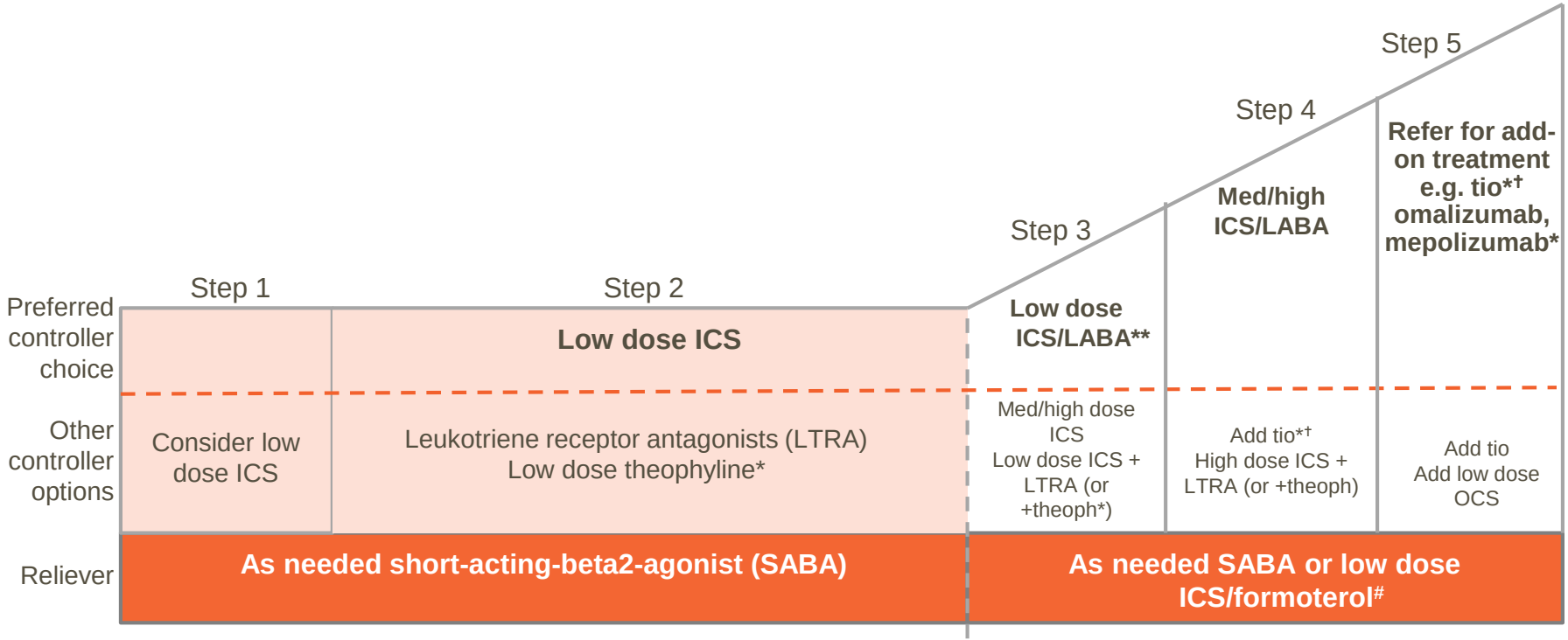

Internal financial data. All expectations and targets regarding future performance should be read together with the "2015-2020 Outlook" and "Assumptions and cautionary statement regarding forward-looking statements" sections of the Q1 Results Announcements dated 6 May 2015.
*An investigational product not approved anywhere in the world.

# Respiratory clinical perspectives

*Professor Neil Barnes*

# Asthma management – GINA guidelines

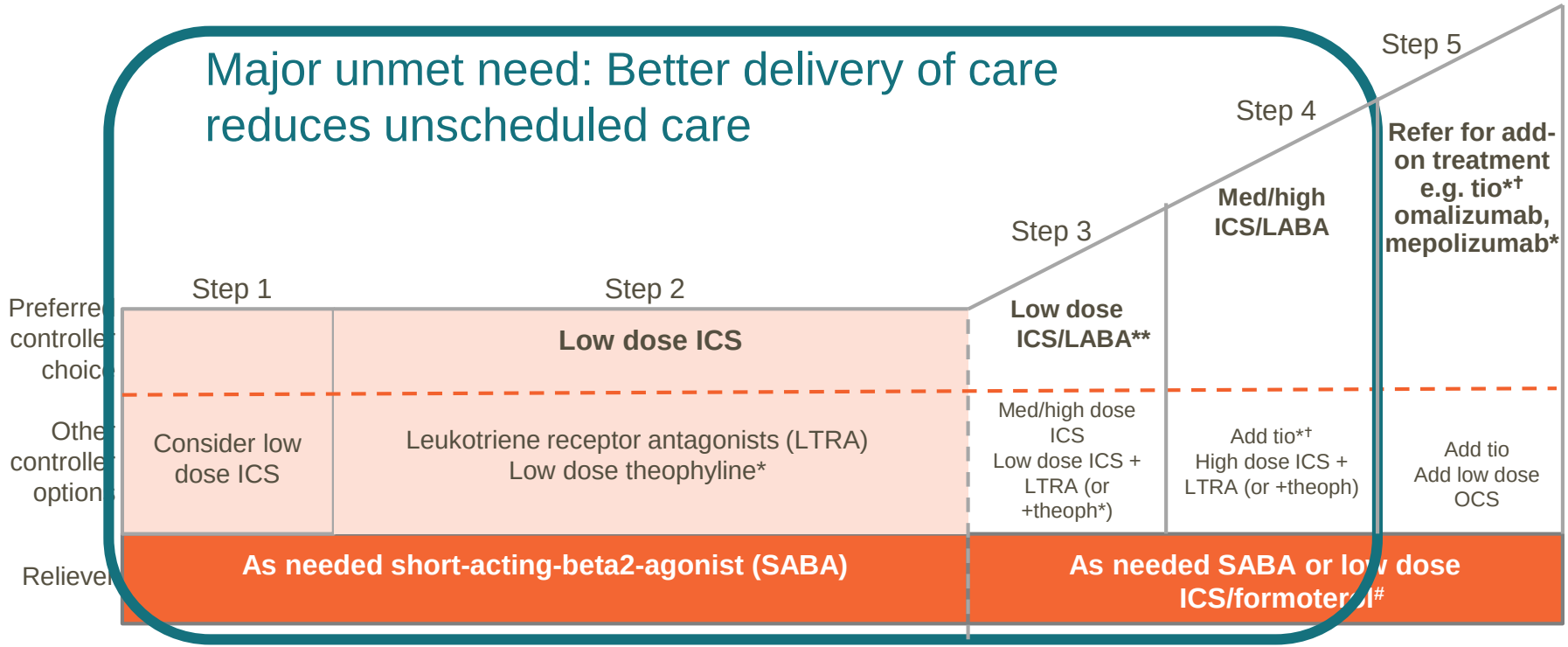
*Mild / moderate patients – focus on delivery of care*




*Not for children <12 years; **For children 6-11 years, the preferred Step 3 treatment is medium dose ICS; #For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy; †Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

# Asthma management – GINA guidelines

*Mild / moderate patients – focus on delivery of care*

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# Making asthma treatment effective

Get the diagnosis right

Address adherence and compliance

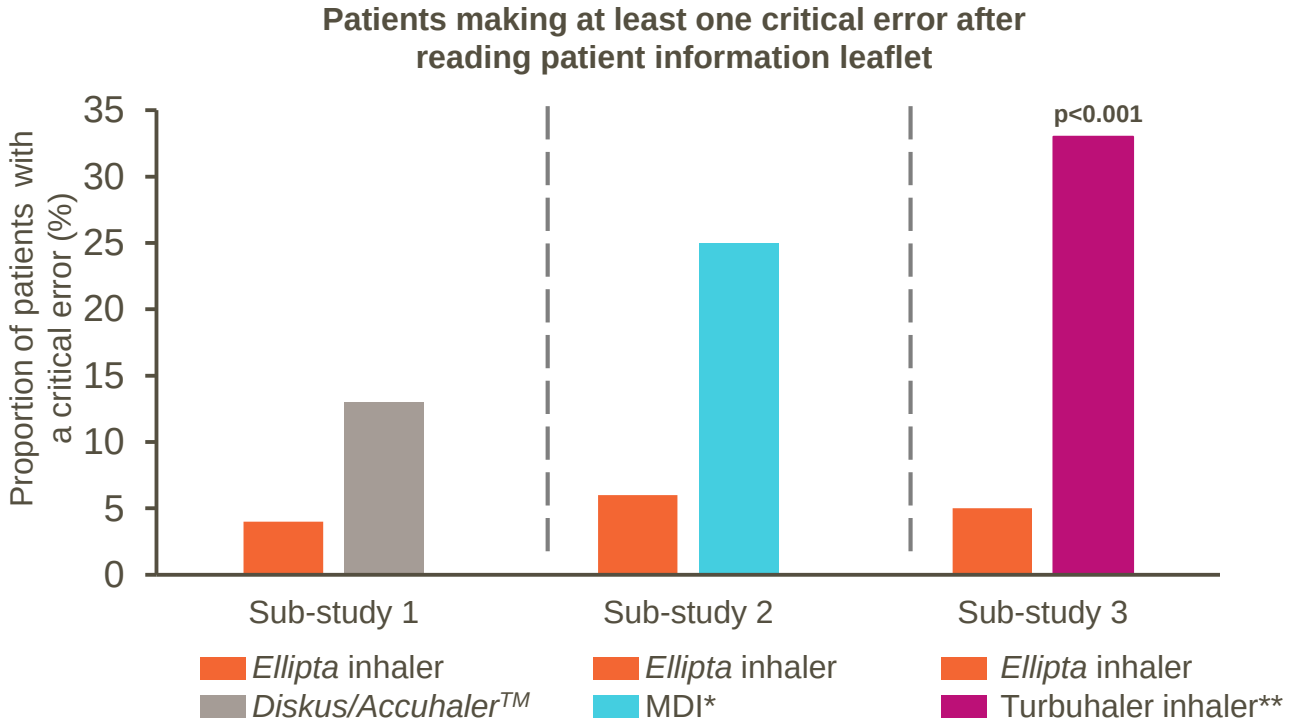
Get the treatment right

Get inhaler technique right

# Get inhaler technique right

*Critical error rates lower with Ellipta inhaler*

Critical error rates were consistently low with *Ellipta* inhaler; this finding was statistically significant compared with Turbuhaler inhaler**




Thomas M et al. *Am J Respir Crit Care Med* 2016;193:A1738
*MDI, metered dose inhaler
**Turbuhaler is a trade mark of AstraZeneca

# Connected inhaler system: integrated sensor model

3. Product with sensor/program given to patients via pharmacy; patient enrols and is required to enter HCP information from the prescription.

4. Patient uses sensors and app/ecosystem, which provides information via app, SMS, on-device signals, etc. that motivate behaviour change

**Patient**

5. Data are captured

**HCP**

2. HCP prescribes *Ellipta* inhaler with integrated sensor

1. GSK reps promote *Ellipta* inhaler with integrated sensor to HCPs

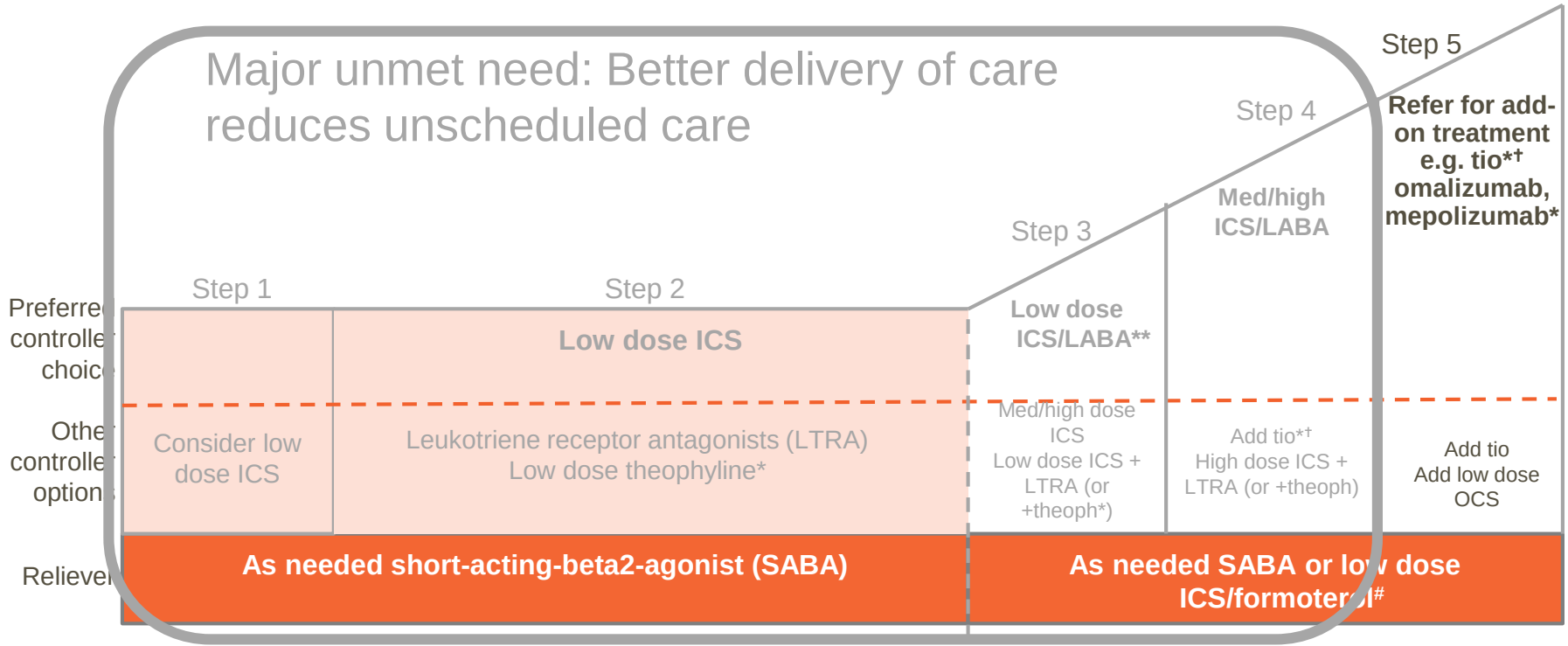
6. Data are integrated into EMR and shared with payers and HCPs who can intervene if they see a problem

**Healthcare Systems**

**Information flow**

# Asthma management

*Severe patients – focus on drug discovery*

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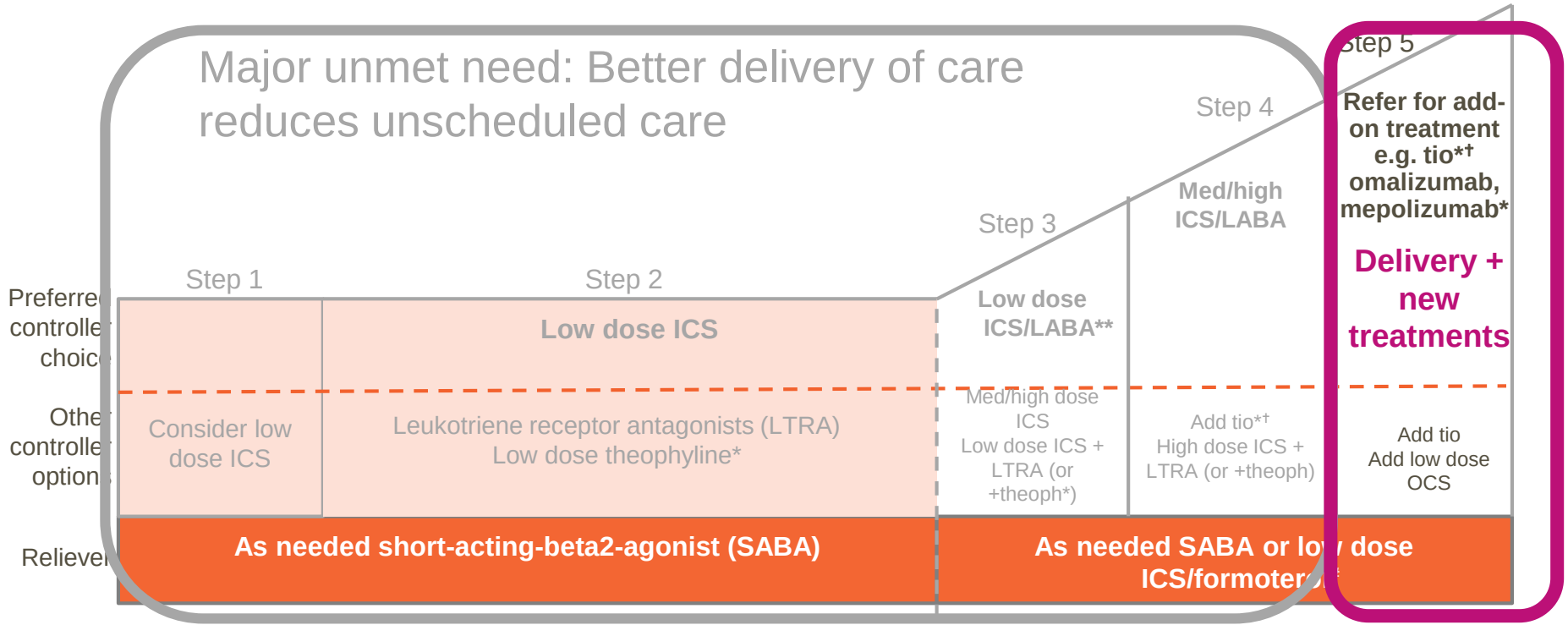
Source: www.ginasthma.org 

# Asthma management

*Severe patients – focus on drug discovery*

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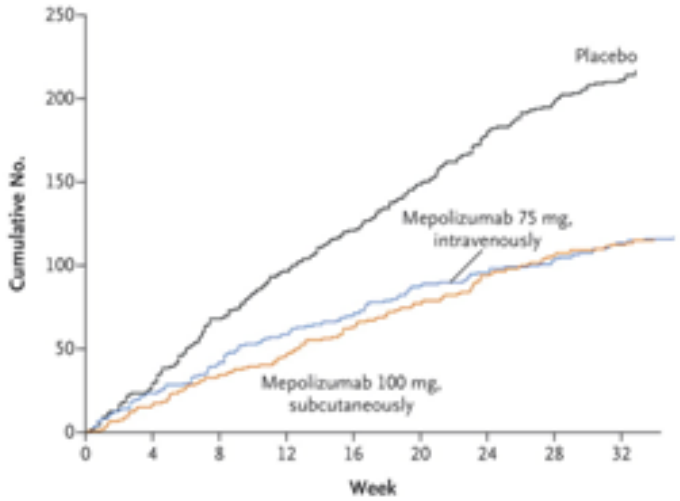
# *Nucala* pivotal studies

*MENSA and SIRIUS studies*

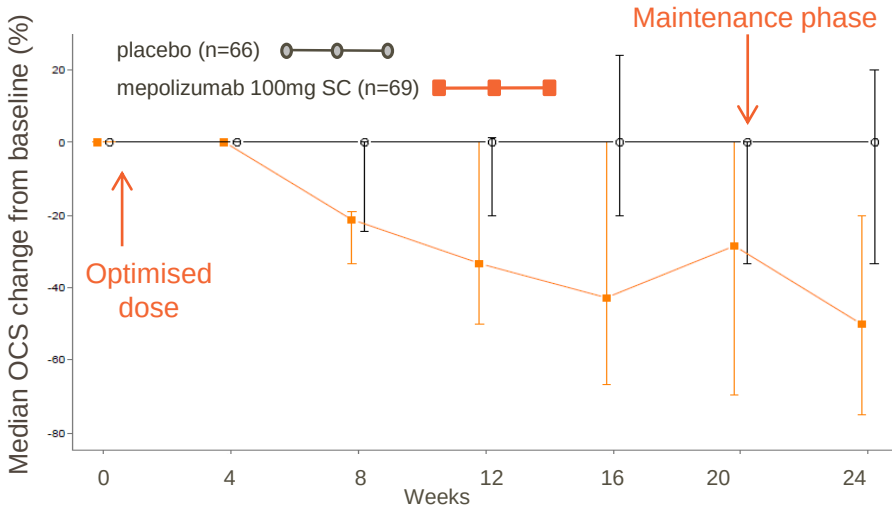
MENSA: asthma exacerbations at 32 weeks




**Rate of exacerbations was reduced by 47% among patients receiving iv mepolizumab and by 53% among those receiving sc mepolizumab, as compared with those receiving placebo (p<0.001 for both comparisons)**

Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.

SIRIUS: at 24 weeks, mepolizumab 50% placebo 0% p=0.007

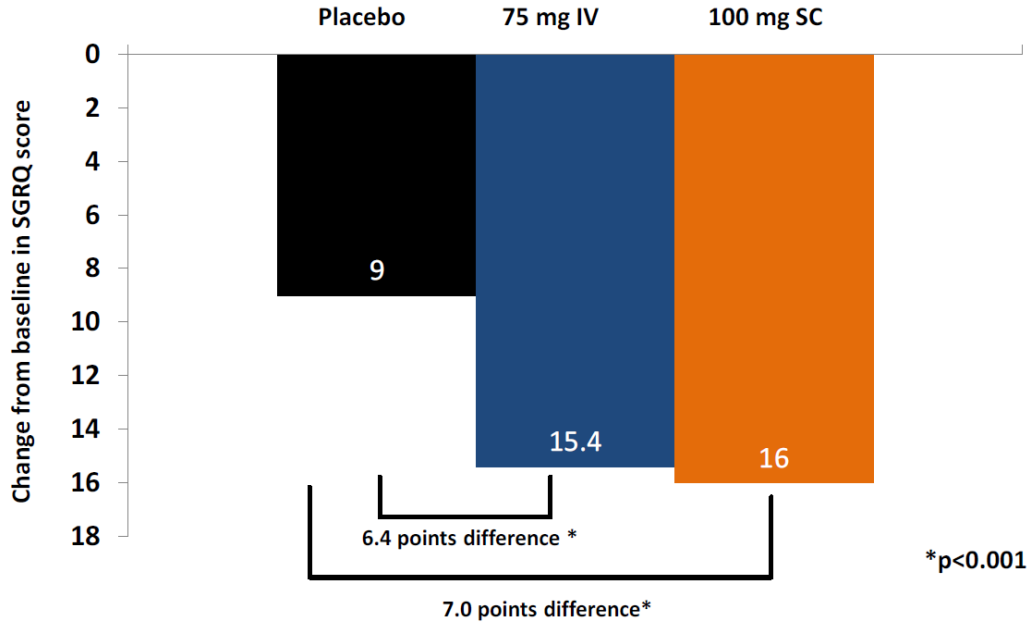



**Reduction in median daily OCS dose was marked in the mepolizumab group (10.0 to 3.1mg) compared to the placebo group (12.5 to 10.0mg)**

Bel EH, et al. *N Engl J Med.* 2014;371:1189-1197 and Supplement

# MENSA study: *Nucala* improves QoL

*Changes from baseline in the St George's Respiratory Questionnaire at week 32*




Ortega HG et al. *N Engl J Med* 2014;371:1198-1207.

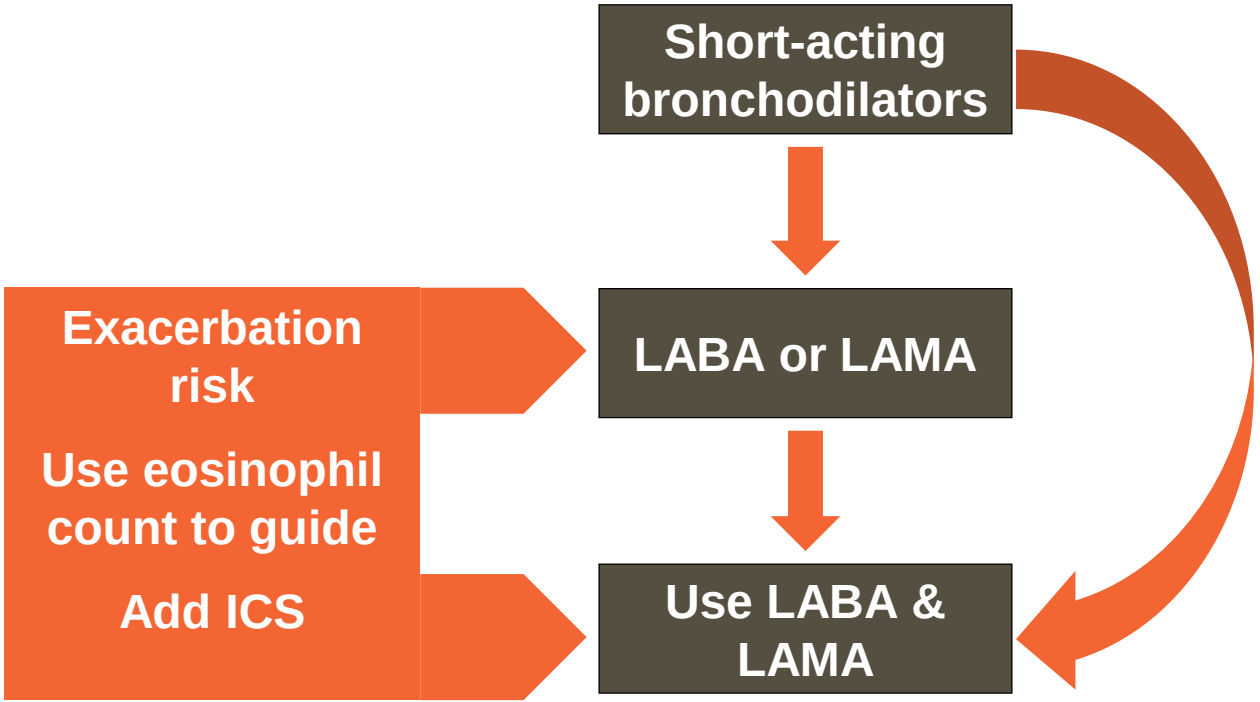
# COPD management – GOLD guidelines

*A complex treatment picture*

| Patient | Recommended first choice | Alternative choice | Other possible treatments |
|---|---|---|---|
| A | SAMA prn<br>or<br>SABA prn | LAMA or LABA<br>or<br>SABA and SAMA | theophylline |
| B | LAMA or LABA | LAMA and LABA | SABA and/or SAMA<br>theophylline |
| C | ICS + LABA<br>or LAMA | LAMA and LABA or<br>LAMA and PDE4-inh. or<br>LABA and PDE4-inh | SABA and/or SAMA<br>theophylline |
| D | ICS + LABA<br>and/or<br>LAMA | ICS and LABA and LAMA or<br>ICS+LABA and PDE4-inh. or<br>LAMA and LABA or<br>LAMA and PDE4-inh | carbocysteine<br>N-acetylcysteine<br>SABA and/or SAMA<br>theophylline |

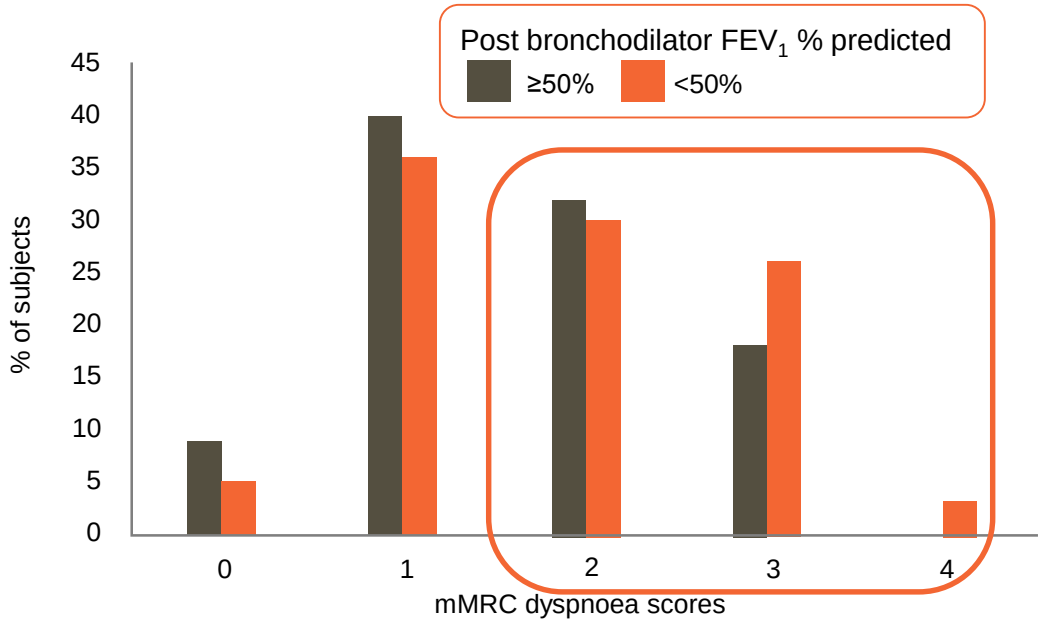
# Potential COPD treatment paradigm: reducing complexity

*Reduce symptoms, reduce risk*



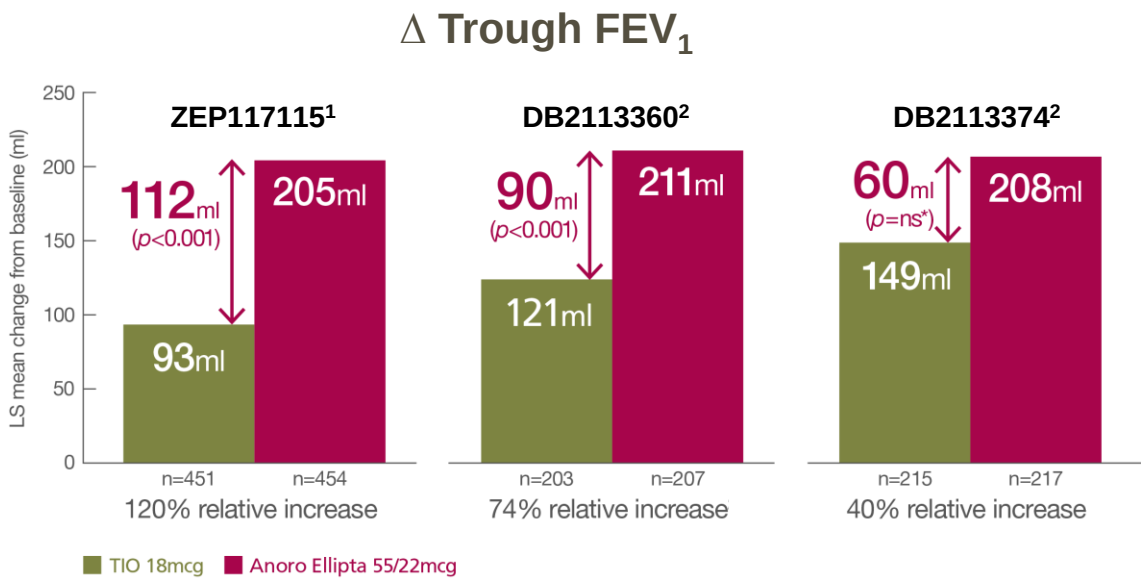
# Real world studies have shown that most COPD patients remain breathless when using only one long acting bronchodilator

- Patients treated with a single bronchodilator remain breathless
- Percent who are breathless has little relation to lung function




$FEV_1$ = forced expiratory volume in one second; mMRC = modified Medical Research Council
Source: Adapted from Dransfield MT et al. *Prim Care Respir J.* 2011;20:46-53

# Comparative studies of *Anoro* versus tiotropium



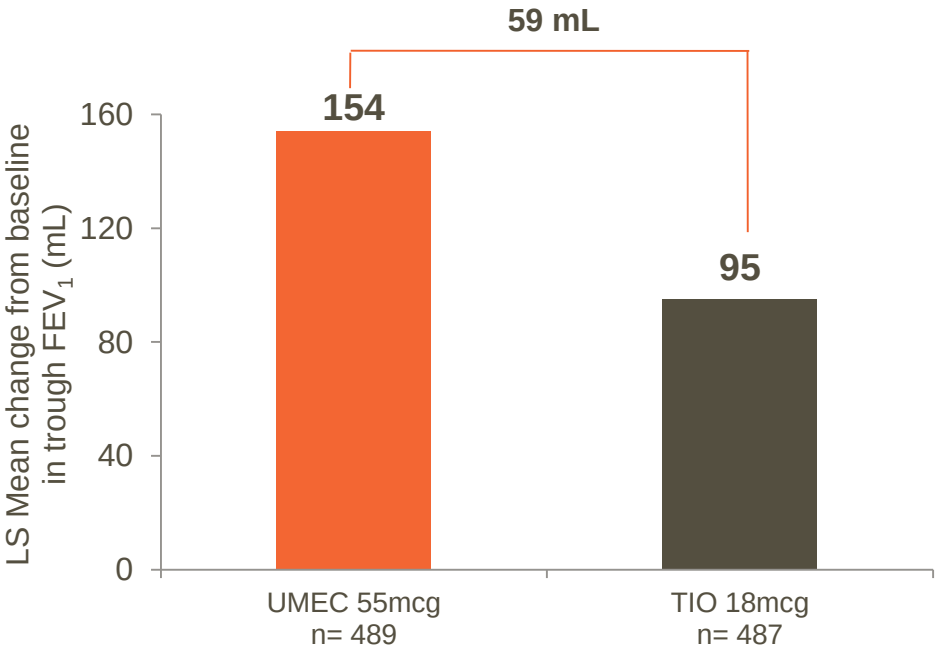

- 24-week, PhIII, multicentre, randomised, blinded, double-dummy, parallel-group study of UMEC/VI (62.5/25 mcg) versus tio (18 mcg) in patients with moderate-to-very severe COPD
- Primary endpoint: Trough FEV1 at Day 169: UMEC/VI vs tiotropium in moderate to very severe COPD patients (double-blind, double-dummy study†)
- There were no significant differences in safety findings. The ISI is available on the version of this slide deck posted to gsk.com

†Patients may not have been blind to tiotropium. *Not statistically significant due to hierarchical testing.
Adapted from: [1]Maleki-Yazdi M et al. *Respir Med* 2014; 108:1752–1760; [2]Decramer et al. *Lancet Resp Med* 2014;2 472-4486

# Trough $FEV_1$ at day 85 – PP population

*Umeclidinium was significantly superior to tiotropium (p<0.001) in the PP population*

LS mean change from baseline in trough $FEV_1$ at day 85




There were no significant differences in safety findings.

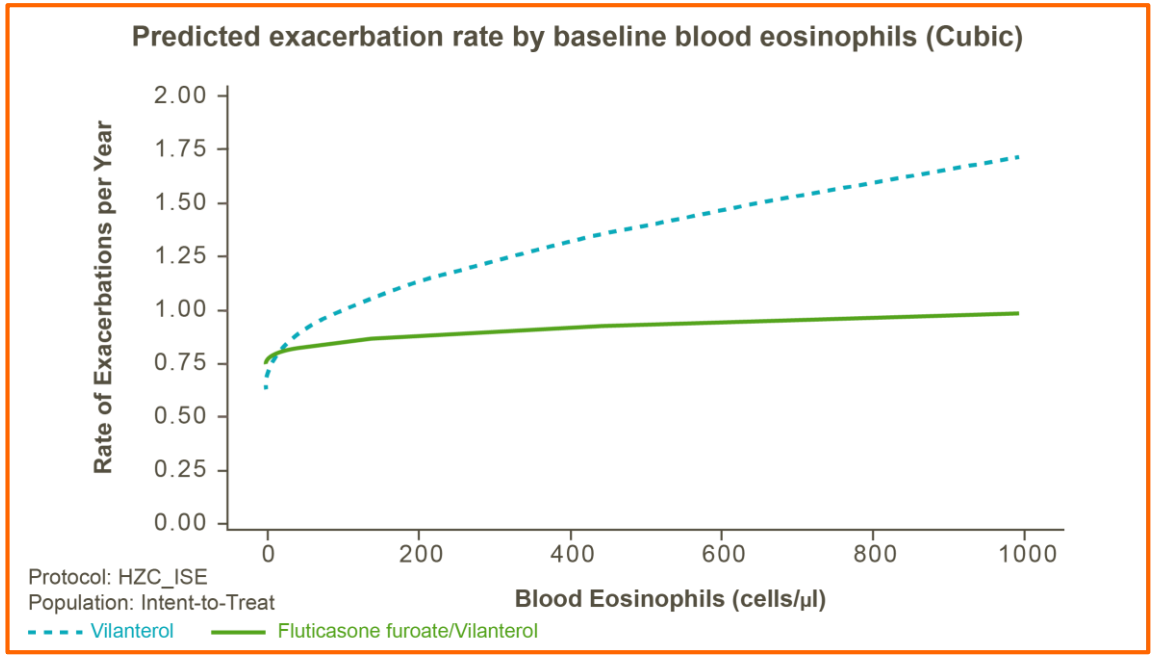
The ISI is available on the version of this slide deck posted to gsk.com

PP – per protocol population

Data on file. Study 201316. 2015. Available at: www.gsk-clinicalstudyregister.com

# Blood eosinophil count is associated with exacerbation frequency and predicts ICS response: post-hoc analysis

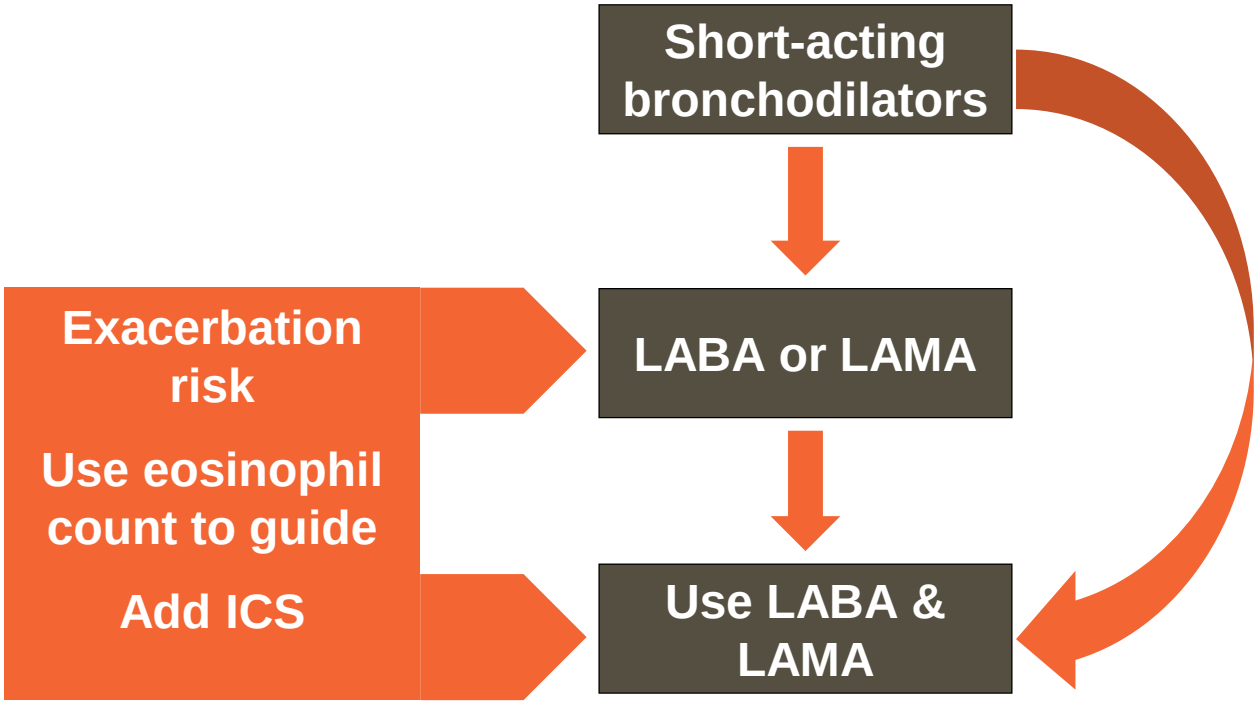
- In an exacerbating COPD patient population a higher blood eosinophil count is a predictor of exacerbation risk
- Blood eosinophils are a predictor of response to inhaled steroids




Source: Salman. S, Pavord. I, et al: Blood eosinophils are a biomarker of COPD exacerbation reduction with inhaled corticosteroids (ICS): an across-trials model-based approach. ERS 2016. Abstract number: OA1763

# Potential COPD treatment paradigm: reducing complexity

*Reduce symptoms, reduce risk*



# COPD Salford Lung Study with *Relvar/Breo*

*RCT in real world setting*

- Patients in primary care
- Aged 40+ years
- GP diagnosis of COPD
- Taking ICS and/or LABA and/or LAMA
- Exacerbation in last 3 years
- Consented

Constant real-time data collection of all interventions/safety monitoring

**FF/VI open label**

**Randomisation visit**
- Routine respiratory review
- Device instruction
- CAT

12 months of **usual care plan**

3 phone calls (if no regular visits)

**End of study visit**
- Routine respiratory review
- CAT

**Usual treatment**

- At baseline 86% were receiving an ICS containing regimen; 52% were on triple therapy
- In the past 3 years: at baseline 47% of patients had ≥ 2 moderate exacerbations, 33% had 1 exacerbation and 20% had not reported an exacerbation in the prior 12 months
- ~80% of comparative population patients were on *Seretide*: either LABA/ICS, or LABA/ICS with LAMA as well

**2,802** COPD patients

**1** electronic medical record system

**80** GP practices

**130** pharmacies

**3,000** people trained as part of study

**265 million** rows of data

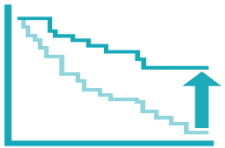
# What has the healthcare community asked for?

*Data that provides understanding about effectiveness and value of medicines*

## Traditional randomised control trial

Focus on **EFFICACY** by measuring a medicine's impact under

**controlled conditions**



**Selected population**

population – likely to respond to the medication

## Salford Lung Study

Focus on **EFFECTIVENESS** by measuring a medicine's impact under close to

**normal conditions**

**Non-selective**

population - broad and inclusive group with varied lifestyles and comorbidities

# COPD Salford Lung Study with *Relvar/Breo*

*Primary endpoint: rate of moderate and severe on-treatment exacerbations*

Primary Efficacy Analysis (PEA) Population

| | Usual Care (n=1134) | *Relvar/Breo* (n=1135) |
|---|---|---|
| LS Mean Annual Rate | 1.90 | 1.74 |
| FF/VI vs Usual Care<br>Ratio<br>95% CI<br>p-value | | <br>0.92<br>(0.85, 0.99)<br>0.025 |
| Percent reduction<br>95% CI | | 8.41<br>(1.12, 15.17) |

Data reported May 2016. To be presented at ERS on 4 September 2016

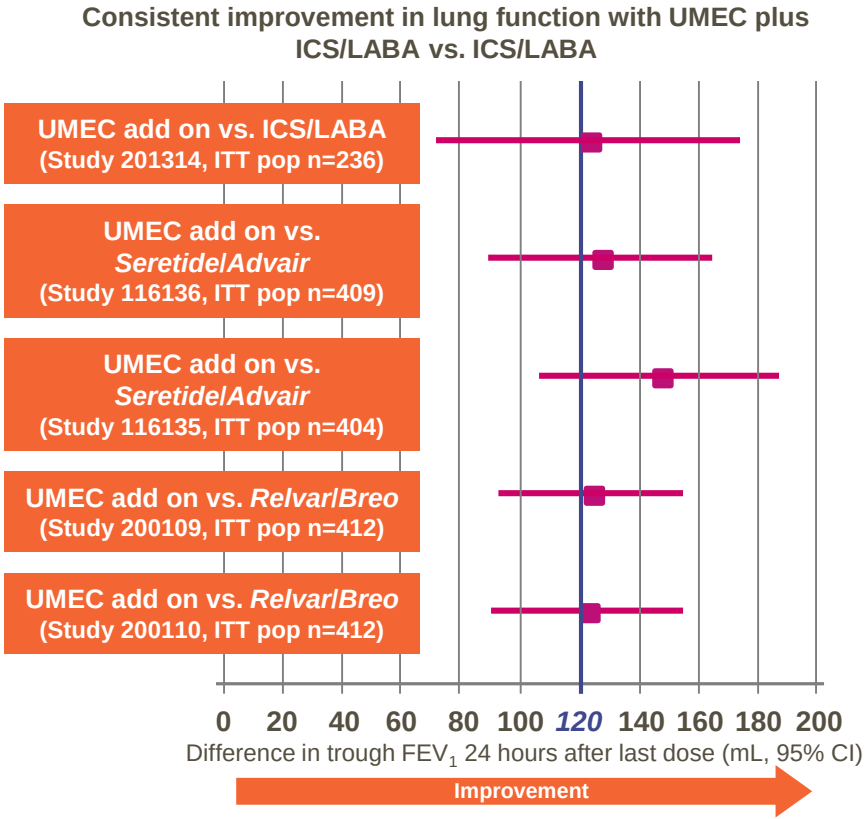
**Conclusion:**

Initiating treatment with *Relvar/Breo* 100/25mcg statistically significantly decreased the annual rate of moderate and severe exacerbations vs. continuing treatment with Usual Care

The ISI is available on the version of this slide deck posted to gsk.com

# Late phase inhaled COPD portfolio

*Understanding the role of triple therapy in COPD*

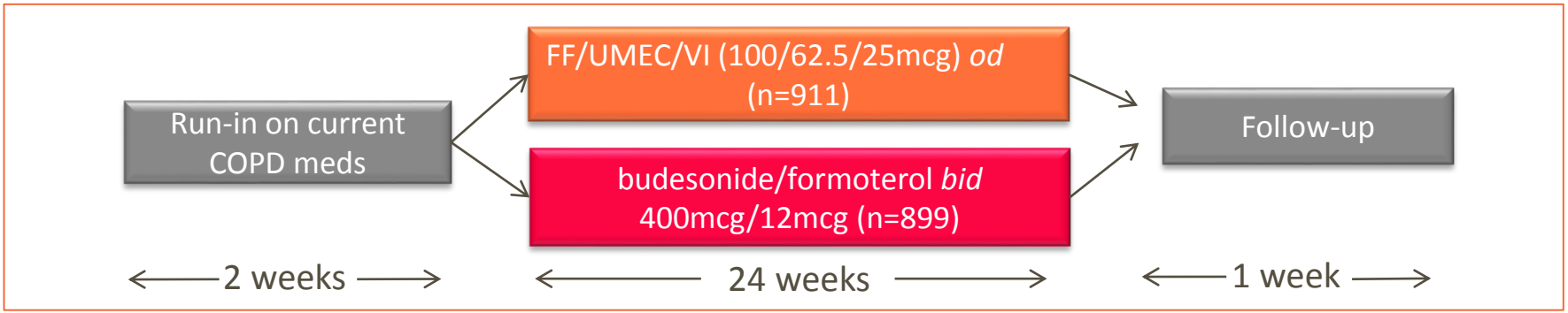



- Triple therapy already part of clinical practice[1]
- Open triple with *Incruse* launched in the US at end of 2015
- PhIII lung function study (FULFIL) reported and will be presented at ERS on 6 Sept
- Closed Triple filing in US & EU: end 2016
- PhIII exacerbation study (IMPACT) to read out by end 2017

[1]Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2015

# FULFIL study design

*Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy**




**Population (COPD GOLD D)**

- $FEV_1$ <50% + CAT ≥10; ***OR***
- $FEV_1$ ≥50% to <80% + (≥2 moderate exacerbations in past year OR ≥1 severe exacerbations) + CAT ≥10

**Co-primary endpoints**

- Change from baseline in trough $FEV_1$ at week 24
- Change from baseline in SGRQ total score at week 24

Total randomised subjects n=1800, recruited from 162 centres across 15 countries
~400 subjects continue up to week 52 in extension study

* Closed triple is an investigational product and not approved anywhere in the world.

# FULFIL efficacy data

*Co-primary efficacy endpoints: trough $FEV_1$ and SGRQ week 24 – ITT population*

FF/UMEC/VI 100/62.5/25 vs BUD/FOR 400/12

| | Difference | Standard error | p-value |
|---|---|---|---|
| $FEV_1$ | 171mL | 12 | <0.001 |
| SGRQ | -2.2 | 0.64 | <0.001 |

| Annual rate of COPD exacerbations (Moderate and severe exacerbations) | Up to 24 weeks | | Up to 52 weeks | |
|---|---|---|---|---|
| | FF/UMEC/VI 100/62.5/25 n=911 | BUD/FOR 400/12 n=899 | FF/UMEC/VI 100/62.5/25 n=210 | BUD/FOR 400/12 n=220 |
| Population, n | 907 | 892 | 210 | 219 |
| Mean rate | 0.22 | 0.34 | 0.20 | 0.36 |
| Ratio (95% CI); p-value<br>Reduction in rate, % (95% CI) | 0.65 (0.49 to 0.85); **0.002**<br>**35** (14 to 51) | | 0.56 (0.37 to 0.85); 0.006<br>44 (15 to 63) | |

# FULFIL safety data

*Overview of on-treatment adverse event up to week 24 – ITT population*

| Number (%) of subjects with: | FF/UMEC/VI (100/62.5/25 mcg) (n=911 ) | BUD/FOR (400/12 mcg) (n=899 ) |
|---|---|---|
| Any on treatment AE | 354 (39%) | 339 (38%) |
| Any on treatment SAE | 49 (5.4%) | 51 (5.7%) |
| Any on treatment non-fatal SAE | 45 (4.9%) | 47 (5.2%) |
| Any on treatment fatal SAE | 4 (0.4%) | 6 (0.7%) |
| Pneumonia SAE | 9 (1.0%) | 3 (0.3%) |
| Cardiac disorders: any event | 3 (0.3%) | 9 (1.0%) |

# Journey to personalised medicine

| Yesterday: Traditional Medicine | Today: Stratified Medicine | Tomorrow: Personalised Medicine |
| --- | --- | --- |
| All patients with a given disease | Groups of relatively homogenous patients (biomarkers; phenotypes) | Single individuals with a disease or risk of a disease |

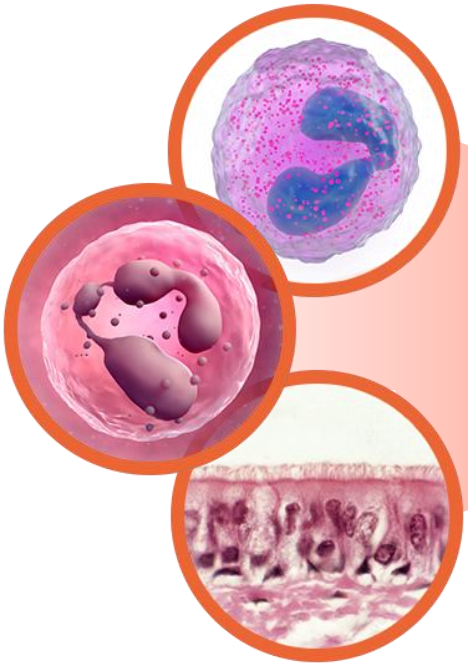
- Emerging scientific evidence is enabling a more personalised approach to treatment of airway diseases to better meet the needs of patients
- This has been an important emphasis in the evolution of guidelines over recent years
- GSK is well-positioned for this shift towards personalised medicine as we have products in all classes

# Respiratory R&D

*Dave Allen*

# COPD R&D strategy

*Targeting the fundamental drivers of disease*



GSK Pipeline

## Once Daily Inhaled

- *Anoro Ellipta* inhaler
- *Relvar/Breo Ellipta* inhaler (Japan file)
- *Incruse Ellipta* inhaler
- Closed Triple (EU/US file 2016)
- MABA (PhIIb data imminent)

## Infection Driven Exacerbations

- PI3Kδ (interim PhIIa data)
- danirixin (interim PhIIa data)

## Targeted Biologicals

- mepolizumab (PhIII data due 2017)

## Preserve Lung Function

- PI3Kδ
- danirixin

# GSK2269557: Inhaled PI3Kδ inhibitor

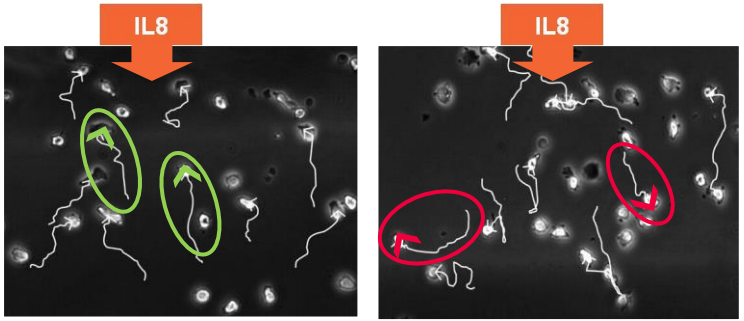
*Two PhIIa studies in COPD patients, completed August 2016**

- PI3Kδ over-activation causes human rare disease (APDS) with severe, recurrent COPD-like bacterial infections
- Inhaled delivery offers potential efficacy/safety advantage and opportunity for combination therapy
- Target engagement demonstrated in healthy smokers (PIP3)
- GSK2269557 is well tolerated and reduces markers of inflammation (IL6 and IL8) in stable COPD patients on top of standard of care
- Interim PhIIa data in exacerbating COPD patients shows improvement in high resolution CT (HRCT) lung imaging parameters for GSK2269557 on top of standard of care
- PhIIb studies to start 2017

| | |
|---|---|
| Status: | PhIIa dosing complete |
| Indication: | COPD exacerbation |
| Planned filing: | 2021-2025 |

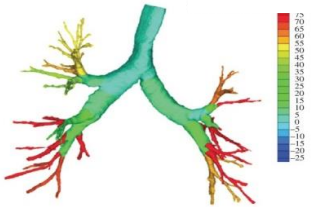
*Data in-house and being analysed
Sapey et al, *AJRCCM* 2011; 183: 1176
Burrowes et al. *Interface Focus* 2013;3:20120057 (Fluidda)

**Directionality of neutrophil migration is aberrant in COPD patients and corrected by PI3Kδ inhibition - *in vitro***




Healthy control | COPD

**HRCT imaging used in PhIIa to measure regional improvements in airway volumes and resistances**

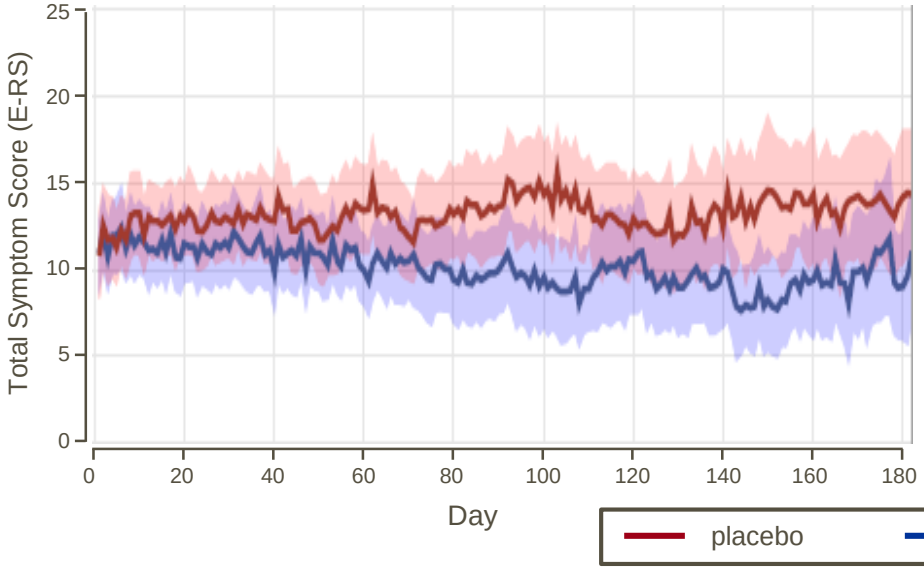


*Representative change in airway volume in a COPD patient after treatment with ipratropium bromide*

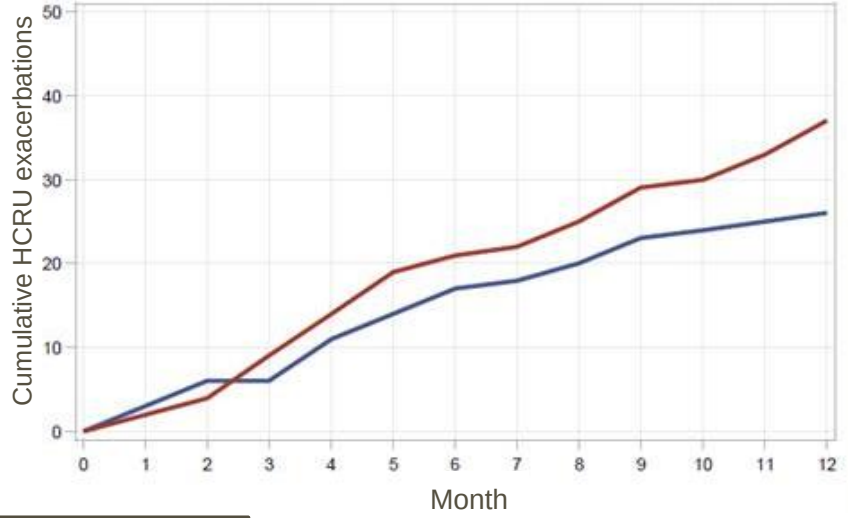
# Danirixin (GSK1325756): oral CXCR2 antagonist

*Interim PhIIa data in symptomatic COPD, completed August 2016*

**Real-time data demonstrate improvement of symptoms with danirixin in symptomatic COPD (frequent exacerbators)**




**Trend for reduction in COPD exacerbations requiring health care resource utilisation (HCRU) with danirixin***




placebo — danirixin 75mg

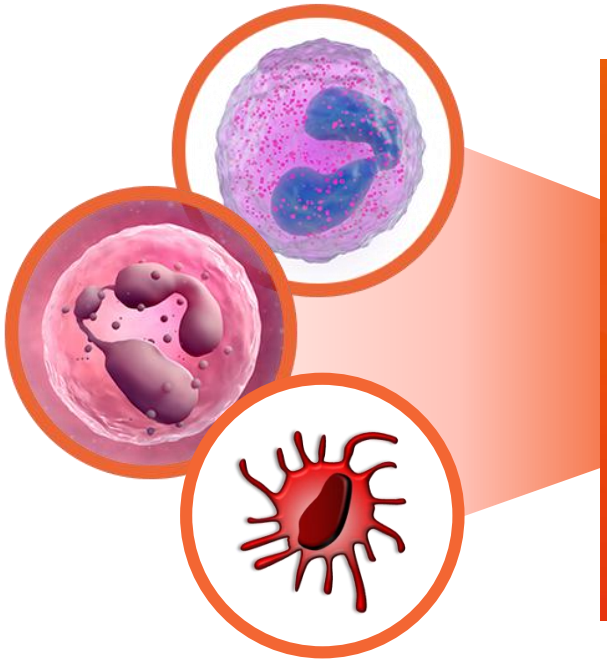
| | |
|---|---|
| Status: | PhIIb 2017 |
| Indication: | Symptomatic COPD |
| Planned filing: | 2021-2025 |

- 93 COPD patients, first time in patient study on top of inhaled standard of care
- Similar trends on CAT, lung function (FVC) and blood biomarkers of matrix turnover

GSK, data on file (study 200163). *Interim PhIII data in symptomatic COPD

# Asthma R&D strategy

*From secondary prevention to primary disease modification*



GSK Pipeline

## Once Daily Inhaled

- ***Relvar/Breo Ellipta*** **inhaler (paediatrics)**
- ***Arnuity Ellipta*** **inhaler (Japan file)**
- **Closed Triple (PhIIb data)**

## Extended Duration Biologicals

- **long-acting anti-IL-5**
- **anti-IL-5/13**

## Targeted Biologicals

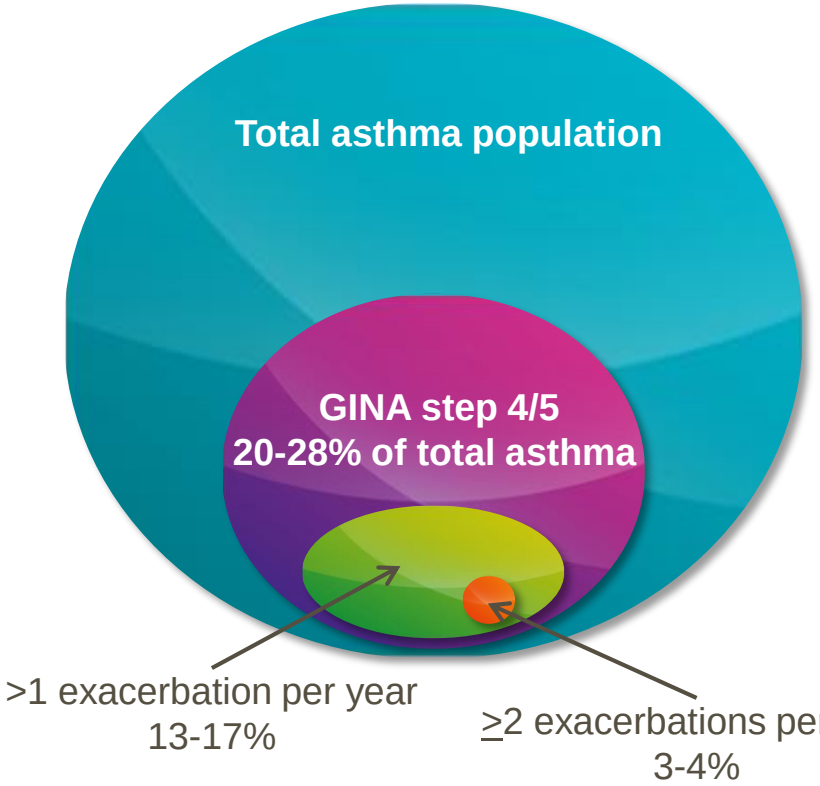
- ***Nucala***
- **sirukumab (PhIIa FSFV imminent)**
- **anti-IL-33r (in-license)**
- **anti-TSLP dAb**

## Immunomodulatory / Remission

- **TLR7 agonist (PhIIa FSFV imminent)**

# Asthma population

*Opportunity for biologics and improved symptom control*




>80% of GINA step 4/5 patients do not exacerbate

At least 50% are uncontrolled

Exacerbations / severe asthma

Role for biologics

# Closed Triple for asthma

*PhIIb data support progression, completed May 2016*

**UMEC add-on: study of asthma-COPD overlap syndrome**

| | Change from baseline in trough $FEV_1$ vs FF 100µg, mL | | |
|---|---|---|---|
| **Dose combined with FF 100µg** | **ITT population (N=338)** | **Asthma (n=183)** | **COPD (n=155)** |
| UMEC 15.6µg | 85 | 67 | 92 |
| UMEC 62.5µg | 140 | 136 | 127 |
| UMEC 125µg | 120 | 96 | 146 |
| UMEC 250µg | 85 | 51 | 129 |
| VI 25µg | 72 | 101 | 49 |

- Assessing all the data, it is likely FF/UMEC/VI will have significant benefit compared to FF/VI (approx 120mL trough $FEV_1$) in asthma uncontrolled by LABA/ICS
- Additional bronchodilator to improve lung function, asthma control and health-related quality of life compared to dual ICS/LABA
- Potential to improve patient adherence, reduce inhaler complexity compared to open triple therapy (ICS/LABA/LAMA)
- Pivotal PhIII study (CAPTAIN) FSFD Dec 2016

Status: On track for PhIII start 2016
Indication: Symptomatic asthma
Planned filing: 2018

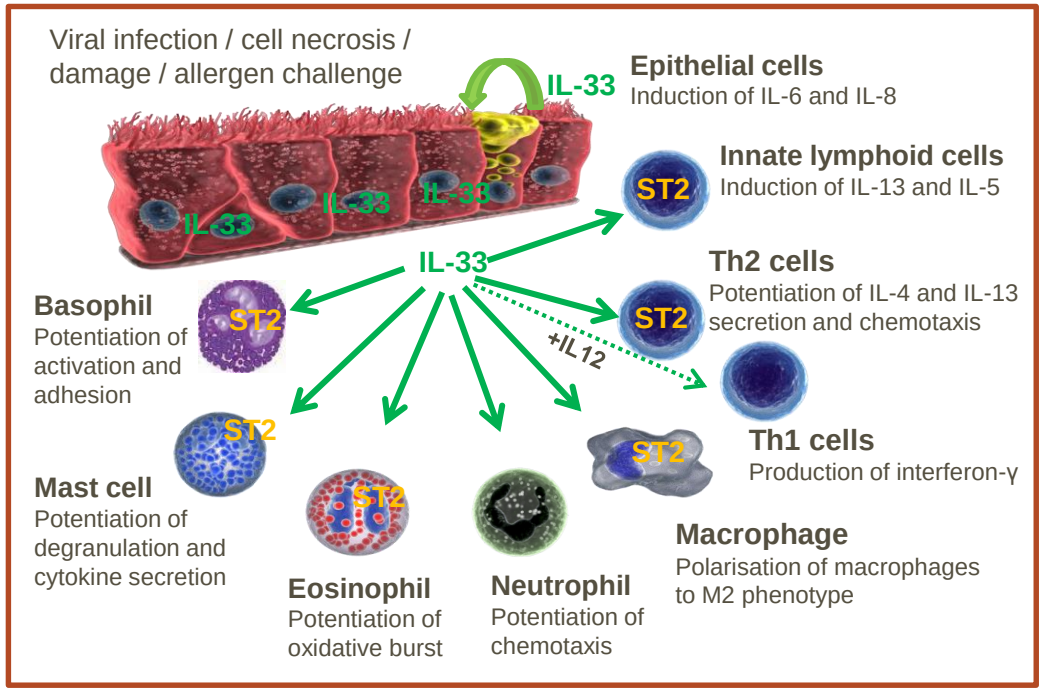
# Diverse asthma biologic pipeline continues to develop

| | ***Nucala*** *anti-IL-5* | **sirukumab** *anti-IL-6* | *GSK3772847 anti-IL-33r* | *long acting anti-IL-5 (NBE)* | *anti-TSLP dAb* | *anti-IL-5/13* |
|---|---|---|---|---|---|---|
| **Modality** | mAb | mAb | mAb | Extended pharmacology mAb | Inhaled dAb in Ellipta | Bispecific dAb-mAb extended pharmacology |
| **Expected file** | 2014 | 2021-25 | 2021-25 | 2021-25 | 2021-25 | 2021-25 |
| **Status** | Launched | PhII start 2016 | PhII start 2017-18 | PhI/II start 2017 | PhI start 2017 | Preclinical |
| **Asthma segment** | Severe eosinophilic | Severe without elevated eosinophils | Severe neutrophilic and eosinophilic | Moderate-severe eosinophilic | Moderate-severe eosinophilic and neutrophilic | Moderate-severe eosinophilic |
| **Reason to believe** | Clinical data and strong mechanism rationale | IL-6 is key driver of non-eosinophilic inflammation | Genetic and biological link to regulation of cells that drive inflammation | Extended pharmacology allows six monthly dosing | Key cytokine in epithelial immune response; Inhaled - directly targets site of action | Additive efficacy of two complimentary mechanisms, in six monthly dosing |

# Anti-IL33r mAb for severe asthma

*In-licensed from Janssen, July 2016*

**IL33 engages with a wide range of immune cells amplifying a mixed inflammatory response**




- Biological therapy that prevents IL33 binding to the ST2 receptor (IL33r)
- Strong human genetic evidence and target biology link the IL33/IL33r axis to asthma and regulation of cells that drive inflammation in asthma
- Significant unmet need in neutrophilic asthma population at time of launch
- PhI ongoing at Janssen (part 1 in healthy volunteers complete; part 2 in asthma and atopic dermatitis ongoing)
- Fit with GSK's respiratory portfolio and adds to our pipeline of targeted biologicals

| | |
|---|---|
| Status: | PhI ongoing |
| Indication: | Severe neutrophilic and eosinophilic asthma |
| Planned filing: | 2021-25 |

# Beyond asthma and COPD

*Other disease areas of interest*

## Eosinophilic disorders

- mepolizumab EGPA (PhIII results this year)
- mepolizumab nasal polyposis (PhIIa data)
- mepolizumab HES (PhIII start 2016)

## Acute lung injury

- TNFR1 dAb (PhIIa underway)

## Idiopathic pulmonary fibrosis

- inhaled αvβ6 antagonist (PET data)

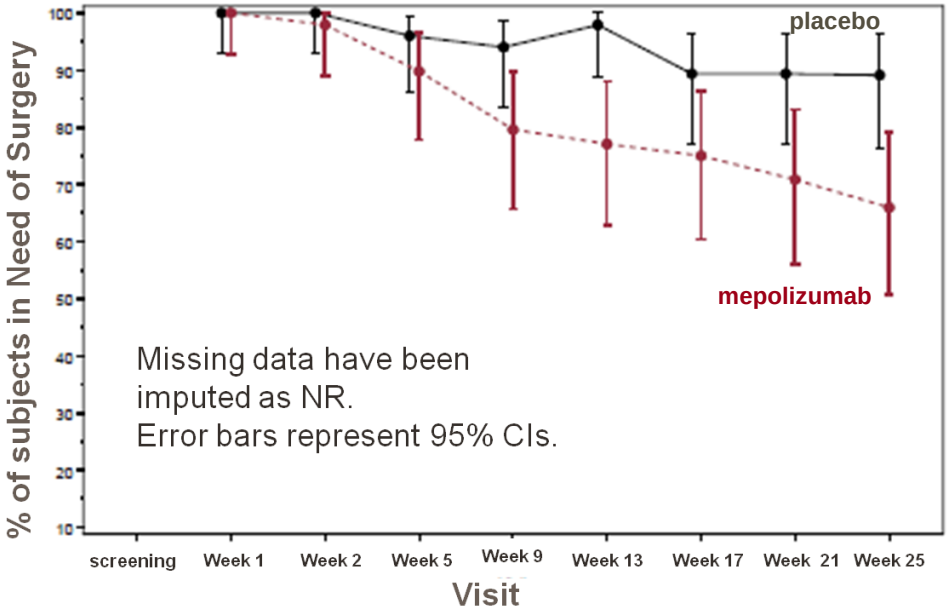
# Mepolizumab, severe nasal polyposis

*Reduction in polyp size/symptoms and in the need for surgery in PhIIb study*

- Mepolizumab (n=54) vs placebo (n=51): 6 doses 750mg i.v. patients with severe refractory nasal polyposis, all had previous surgery
- Response maintained in those who continued with 6 month follow on period, but low numbers of patients (7 placebo, 14 mepolizumab)
- Health related quality of life using SNOT 22 (sinonasal related outcomes) improved (-13.2/100) vs placebo (MCID is 8). EQ-5D (general health outcomes) did not improve

| Group | Primary endpoint: no longer need surgery at 6 months | Any improvement in visual analogue score (VAS) or polyp score | Actual surgeries + those on waiting list + withdrawals for lack of efficacy |
|---|---|---|---|
| mepolizumab | 19 (35%) | 40 (74%) | 6 (11%) |
| placebo | 8 (16%) | 21 (41%) | 20 (39%) |

**Improvement in the % subjects in need of surgery at 6 months**




| | |
|---|---|
| Status: | On track for PhIII start 2017 |
| Indication: | Severe nasal polyposis |
| Planned filing: | 2019 |

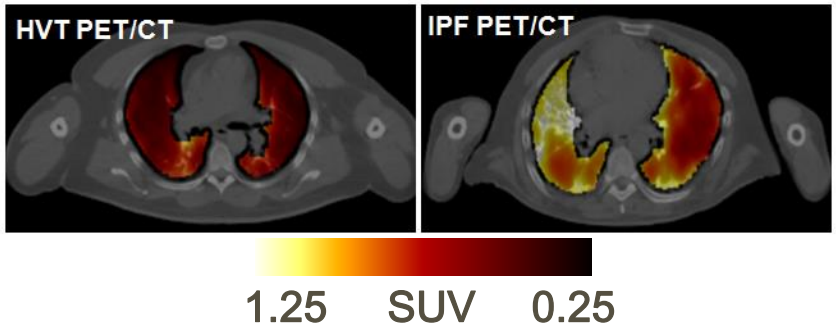
# GSK3008348 inhaled αvβ6 inhibitor

*FTIH commenced, December 2015*

- Inhibits αvβ6 integrin-mediated activation TGFβ on myofibroblasts, so may slow progression of fibrosis
- FTIH outcome: GSK3008348 was well tolerated in healthy volunteers, PK profile consistent with expectations
- Next: evaluate safety in IPF patients, and show target engagement using PET imaging
- PETAL study demonstrated PET ligand is well tolerated

| | |
|---|---|
| Status: | PhI |
| Indication: | Idiopathic pulmonary fibrosis (IPF) |
| Planned filing: | 2025 |

**PET/CT clinical enabling, [18F]-A20FMDV2 binds to αvβ6 in fibrotic regions of IPF lungs**




Source: RES116235/PETAL
HVT - healthy volunteers; SUV - standardised uptake value

# Digital ecosystem: real-time full patient experience

*Potential for acceleration and de-risking clinical development*

**Adherence monitor**

*Ellipta* clip-on or other e-sensor

**Rescue medicine use**

Clip-on monitor

**Biosensors**

Physical activity, sleep, lung function

**Digital e-diary, ePRO**

Patient Reported Outcomes
e.g. symptoms, activity, health status

**EHR/Patient registries**

Help identify appropriate patients
Link to long-term outcomes

**Data integration**

- Did the patient take the medicine?
- Did the markers of the patient's disease improve?
- Did the patient feel better?
- What else was impacting the patient's health?
- Was it the right medicine for the right patient?

# Q&A

# Appendix – additional safety information

# Important Safety Information (ISI) for FF/VI (Breo Ellipta) in the US

The following ISI is based on the Highlights section of the US Prescribing Information for Breo Ellipta. Please consult the full Prescribing Information for all the labelled safety information for Breo Ellipta.

**Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**

Breo Ellipta is contraindicated for primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required and in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

Breo Ellipta should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma, or used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

Breo Ellipta should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result.

Oropharyngeal candidiasis has occurred in patients treated with Breo Ellipta. Patients should be advised to rinse their mouth with water without swallowing after inhalation to help reduce this risk.

An increase in the incidence of pneumonia has been observed in subjects with COPD receiving the fluticasone furoate/vilanterol combination, including Breo Ellipta 100 mcg/25 mcg, in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal.

Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.

Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals.

Caution should be exercised when considering the coadministration of Breo Ellipta with long-term ketoconazole and other known strong CYP3A4 inhibitors because increased systemic corticosteroid and cardiovascular adverse effects may occur.

Breo Ellipta can produce paradoxical bronchospasm which may be life-threatening.

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of Breo Ellipta.

Vilanterol, the LABA in Breo Ellipta, can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias. Breo Ellipta should be used with caution in patients with cardiovascular disorders.

Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids, as have glaucoma, increased intraocular pressure, and cataracts.

Breo Ellipta should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients. Beta-adrenergic agonist medicines may produce transient hyperglycemia in some patients.

For COPD, the most common adverse reactions (≥3% and more common than in placebo) reported in two 6-month clinical trials with Breo Ellipta 100/25 (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%). In addition to the reactions reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects treated with Breo Ellipta 100/25 in two 1-year studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

# Anoro v tiotropium head to head safety results (study 117115)

The most commonly reported side effects for both UMEC/VI and tiotropium included headache (9% UMEC/VI; 7% tiotropium), nasopharyngitis (6% UMEC/VI; 7% tiotropium), cough (3% UMEC/VI; 3% tiotropium) and back pain (2% UMEC/VI; 3% tiotropium).

The incidence of any on-treatment serious adverse events was 4% for UMEC/VI 4% and 4% for tiotropium. The incidence of cardiovascular events of special interest on both treatment arms was 2%. Both LAMAs and LABAs have previously been associated with adverse effects on the cardiovascular system and therefore incidence of these effects was considered to be of interest in this study.

Pneumonia is a common event in the COPD population. In this study, the incidence of pneumonia and LRTIs were UMEC/VI <1% and tiotropium 1% treatment groups.

## Important Safety Information for Anoro Ellipta

The following Important Safety Information (ISI) is based on the Highlights section of the Prescribing Information for Anoro Ellipta. Please consult the full Prescribing Information for all the labelled safety information for Anoro Ellipta.

Long-acting beta2-adrenergic agonists (LABAs), such as vilanterol, one of the active ingredients in Anoro Ellipta, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. The safety and efficacy of Anoro Ellipta in patients with asthma have not been established. Anoro Ellipta is not indicated for the treatment of asthma.

Anoro Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either umeclidinium, vilanterol, or any of the other ingredients.

Anoro Ellipta should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD, or as rescue therapy for the treatment of acute episodes of bronchospasm, which should be treated with an inhaled, short-acting beta2-agonist.

Anoro Ellipta should not be used more often than recommended, at higher doses than recommended, or in conjunction with additional medicine containing a LABA, as an overdose may result.

Anoro Ellipta should be used with caution when considering coadministration with long-term ketoconazole and other known strong cytochrome P450 3A4 inhibitors because increased cardiovascular adverse effects may occur.

As with other inhaled medicines, Anoro Ellipta can produce paradoxical bronchospasm, which may be life-threatening.

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of Anoro Ellipta. Discontinue Anoro Ellipta if such reactions occur.

Anoro Ellipta should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Anoro Ellipta should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

Anoro Ellipta should be used with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately should any signs or symptoms of narrow-angle glaucoma occur.

Anoro Ellipta should be used with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to contact a physician immediately should any signs or symptoms of urinary retention occur.

Beta-adrenergic agonist medicines may produce significant hypokalemia and transient hyperglycemia in some patients.

The most common adverse reactions (incidence ≥1% and more common than placebo) reported in four 6-month clinical trials with Anoro Ellipta (and placebo) were pharyngitis, 2% (<1%); sinusitis 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain 1% (<1%). In addition to the 6-month efficacy trials with Anoro Ellipta, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

Beta2-agonists, such as vilanterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated.

Use beta blockers with caution as they not only block the pulmonary effect of beta2-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.

Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

Avoid co-administration of Anoro Ellipta with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects such as cardiovascular effects, worsening of narrow-angle glaucoma, and worsening of urinary retention.

## Important Safety Information for Umeclidinium (Incruse Ellipta)

The following Important Safety Information is based on the Highlights section of the Prescribing Information for Incruse Ellipta. Please consult the full Prescribing Information for all the labeled safety information for Incruse Ellipta.

Incruse Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either umeclidinium, or any of the other ingredients.

Incruse Ellipta should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD, or as rescue therapy for the treatment of acute episodes of bronchospasm, which should be treated with an inhaled, short-acting beta2-agonist.

As with other inhaled medicines, Incruse Ellipta can produce paradoxical bronchospasm, which may be life-threatening.

Incruse Ellipta should be used with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately should any signs or symptoms of narrow-angle glaucoma occur.

Incruse Ellipta should be used with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to contact a physician immediately should any signs or symptoms of urinary retention occur.

The most common adverse reactions (incidence ≥2% and more common than placebo) with Incruse Ellipta (and placebo) were nasopharyngitis, 8% (7%); upper respiratory tract infection, 5% (4%); cough, 3% (2%); and arthralgia, 2% (1%). Other adverse reactions with Incruse Ellipta observed with an incidence less than 1% but more common than placebo included atrial fibrillation.

Avoid co-administration of Incruse Ellipta with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects such as worsening of narrow-angle glaucoma, and worsening of urinary retention.

# Mepolizumab safety information

**MENSA**

Adverse events reported in the study were similar across all treatment groups, including placebo. The most common reported adverse events across all treatment groups were nasopharyngitis, headache, upper respiratory tract infection and asthma. The frequency of adverse events considered to be related to study drug was 16% in the placebo group, 17% in the mepolizumab IV group and 9% in the mepolizumab SC group. The frequency of serious adverse events after excluding asthma-related events was 9% in the placebo group, 4% in the mepolizumab IV group and 6% in the mepolizumab SC group. Positive anti-mepolizumab antibodies were found in 19 patients: 2% in the placebo group, 4% in mepolizumab IV and 5% in the mepolizumab SC group at least one visit after randomisation. None of these patients had neutralizing antibodies.

**SIRIUS**

Adverse events were similar across treatment groups. The most common reported adverse events in the two treatment groups were headache, nasopharyngitis, bronchitis, sinusitis, fatigue and asthma. The frequency of adverse events was 92% in the placebo and 84% in the mepolizumab treatment group. Frequency of serious adverse events was 18% in the placebo group and 1% in the mepolizumab group.

Serious Adverse Events were infrequent and the imbalance was related to respiratory events in the placebo group.  The incidence of non-asthma- related adverse events was 83% in the mepolizumab arm and 91% in the placebo arm.