KOL Insight: Chronic obstructive pulmonary disease

Combination therapies to drive significant market growth

A FirstWord Therapy Trends Report
KOL Insight: Chronic obstructive pulmonary disease (COPD)

Combination therapies to drive significant market growth

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Executive summary

This report examines the most prominent insights gained from interviews with twelve key opinion leaders (KOLs) based in the US or Europe. The results of FirstWord's research and analysis for KOL Insight: Chronic obstructive pulmonary disease (COPD) identified the following findings:

- **The $10 billion COPD market is dominated by four brands** – these are Boehringer Ingelheim's Spiriva (tiotropium) and Combivent (salbutamol/ipratropium), GlaxoSmithKline's Advair/Seretide (fluticasone/salmeterol), and AstraZeneca’s Symbicort (budesonide/formoterol). Spiriva is the top selling COPD drug with global sales of $4.6 billion in 2012. Global Advair/Seretide sales in asthma and COPD were $8 billion in 2012; COPD comprised 35 percent, or $2.8 billion, of total sales. AstraZeneca’s Symbicort had global sales of $3.2 billion in 2012. COPD comprised 35 percent, or $1.1 billion, of total sales.

- **LAMA/LABAs provide maximum bronchodilation, although there are resistors to their uptake** – fixed-dose Long-Acting Muscarinic Antagonists (LAMAs) and Long-Acting Beta2 Agonists (LABAs) combinations may bring benefits to many patients. KOLs believe LAMA/LABAs will become the “premier drug for the treatment of COPD” representing a “a major shift” with the potential to become “Super Combivents” although they are “just more of the same” given the therapeutic goal of dual therapy with two classes of bronchodilator can be achieved with current drugs (i.e. free-dose LAMA and LABA). Pricing and reimbursement, launch sequence, dosing and device will play a role in determining the market share of the five LAMA/LABAs in development, although all face two key resistors to uptake: Inhaled Corticosteroid (ICS) withdrawal and lack of head-to-head studies with ICS/LABAs.

- **Switching patients to a LAMA/LABA means ICS withdrawal** – although some KOLs firmly believe ICS are ineffective in COPD, they are a commonly used maintenance treatment, with 40 percent to 80 percent of COPD patients using such therapies. A high uptake of LAMA/LABAs will require ICS withdrawal in many COPD patients, a decision physicians may be reluctant to take due to the fear of increasing exacerbations. If free-dose ICS were already approved for COPD, confidence in LAMA/LABA uptake would be greater because ICS could be added to LAMA/LABAs as required.

- **LAMA/LABAs need to demonstrate non-inferiority to ICS/LABAs** – data from head-to-head studies demonstrating that LAMA/LABAs are as effective in reducing
exacerbations as ICS/LABAs will not be available until 2015 or later, meaning significant changes in guideline recommendations and treatment practice may not occur for several years. As a consequence, LAMA/LABAs sales, at least initially, may not be as great as hoped for by pharmaceutical companies. A key “watch out” is whether payers will require evidence that LAMA/LABAs are as effective as triple therapy with ICS/LABA + free-dose LAMA.

- **A novel anti-inflammatory would have a powerful marketing position as an add-on to LAMA/LABA therapy** – the COPD treatment algorithm adds additional drugs if symptoms or exacerbations persist and LAMA/LABAs introduce a drug sequencing issue when physicians wish to add an ICS. Free-dose ICS (off-label) could be added but to treat within label recommendations, a switch to ICS/LABA plus free-dose LAMA is required. A third option is to add the oral PDE-IV inhibitor, Daliresp/Daxas (roflumilast) as an alternative to ICS. A novel oral or inhaled anti-inflammatory that is more effective and better tolerated than Daliresp/Daxas could be a valuable add-on therapy to LAMA/LABAs.

- **GlaxoSmithKline’s Breo/Relvar may need SUMMIT data to drive sales** – Breo/Relvar (fluticasone furoate/vilanterol) adds uncertain clinical value compared to Advair/Seretide; once-daily dosing is unlikely to be sufficient to gain favourable formulary decisions in the US. Clinical differentiation to Advair would be achieved if the US Food and Drug Administration (FDA) grants a mortality claim (possibly in 2016) based on the ongoing SUMMIT trial, which would also differentiate Breo/Relvar from generic ICS/LABAs, which may be launched in Europe in 2014 (substitutable) and the US in 2015 (non-substitutable). Furthermore, a Breo/Relvar mortality benefit could influence treatment practice beyond the expected label claim in COPD patients with moderate disease who have cardiovascular disease or cardiovascular risk factors.

- **Reducing exacerbations are desirable, attainable and commercially attractive** – interventions that reduce the frequency of COPD exacerbations, which are a key cause of hospitalisations (with associated costs), may be the optimal strategy to reduce the financial burden of COPD and therefore would be welcomed by payers. Strategies to reduce COPD exacerbations include novel vaccines, prophylactic anti-viral therapies such as inhaled interferon beta, and add-on anti-inflammatories.

- **No improvement in COPD diagnosis is anticipated** - COPD diagnosis is often delayed due to late presentation. Screening spirometry is the only present way to
diagnose COPD earlier; payers are unlikely to fund screening until treatments are available that can slow disease progression, making earlier detection beneficial. Increasing the use of spirometry, which is necessary to confirm a COPD diagnosis, will largely depend on continued efforts by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and other organisations to raise awareness (financial incentives can accelerate this process).
Introduction

Chronic obstructive pulmonary disease (COPD) is a common condition associated with a significant economic burden. In the US, approximately six percent of adults (approximately 15 million individuals) have been diagnosed with COPD, resulting in 10.3 million physician office visits, 1.5 million emergency room visits, and 699,000 hospital discharges in 2010\(^1\).\(^2\). In the UK, COPD is the second largest cause of emergency admission and one of the most costly inpatient conditions treated by the National Health Service (NHS)\(^3\).

The global COPD market, valued at $10 billion in 2012, is dominated by Boehringer Ingleheim’s Spiriva (tiotropium) and GlaxoSmithKline’s Advair/Seretide (fluticasone propionate/salmeterol), accounting for 75 percent of global COPD sales. Spiriva and Advair/Seretide provide symptomatic relief and reduce the frequency of exacerbations but do not modify the long-term decline in lung function, the hallmark of COPD. The main change in COPD treatment practice to 2016 will be driven by fixed-dose Long-Acting Muscarinic Antagonists/Long-Acting Beta2 Agonists (LAMA/LABA) combinations, which will bring benefits to many patients, although there are several resistors to market uptake.

From 2017 onwards, additional treatments may become available, such as novel anti-inflammatory, anti-oxidants, vaccines and anti-viral therapies. Those that reduce the frequency of COPD exacerbations would have significant market potential, while nicotine vaccines may improve smoking cessation rates. Towards the end of the decade, novel fixed-dose combination Inhaled Corticosteroid (ICS)/LAMA/LABA triple combinations may be approved which would simplify treatment sequencing and improve adherence. The Ellipta device provides a powerful, flexible platform for GlaxoSmithKline to bring triple-action combinations to market. Novel treatments that modify the decline in lung function are a long-term goal, although the failure of many novel COPD drugs to progress into Phase III development underlines the challenge of bringing COPD products to market.

FirstWord’s research is designed to understand the current and future COPD treatment landscape. Using insights from COPD Key Opinion Leaders (KOLs), medical journals, clinialtrials.gov and FirstWord news stories, this report aims to provide an independent view on the most important new evidence and what it means for the future of COPD.

Methodology

This FirstWord Therapy Trends report provides a qualitative overview of the current and future chronic obstructive pulmonary disease (COPD) market. Information was gathered from telephone discussions of 40 to 60 minutes held with twelve US/EU KOLs who were selected based on each KOL’s clinical experience, scientific publications, involvement in clinical trials and in the Pharma industry, and their record of presenting at high profile international conferences. Interviews covered COPD diagnosis, current therapeutic strategies and the Research & Development (R&D) pipeline structured around six questions (Figure 1)

<table>
<thead>
<tr>
<th>Figure 1: Research questions underpinning KOL Insight: COPD</th>
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<tbody>
<tr>
<td>What is your opinion of current therapies?</td>
</tr>
<tr>
<td>What are the unmet needs in COPD?</td>
</tr>
<tr>
<td>What is your opinion of pipeline therapies?</td>
</tr>
<tr>
<td>How can COPD diagnosis be improved?</td>
</tr>
<tr>
<td>What future developments will occur in clinical trials?</td>
</tr>
<tr>
<td>How will future treatment practice evolve?</td>
</tr>
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Source: FirstWord
Current chronic obstructive pulmonary disease marketplace

This section provides an overview of chronic obstructive pulmonary disease (COPD) and the current treatment landscape.

Figure 2 highlights key insights from the current COPD treatment landscape.

**Figure 2: Key insights from the current COPD treatment landscape**

- **Global COPD sales were $10 billion in 2012**
- **Spiriva and Advair/Seretide account for 75% of global COPD sales**
- **Spiriva is the top-selling COPD therapy with 2012 global sales of $4.6 billion**
- **Tudorza and Arcapta have not received favourable formulary decisions in the US**
- **Ultibro is the first fixed-dose LABA/LAMA to be approved**
- **No disease-modifier has been approved**

*Source: FirstWord*
Chronic obstructive pulmonary disease overview

Epidemiology

Chronic obstructive pulmonary disease (COPD) is not usually diagnosed until it is clinically apparent and moderately advanced, resulting in underdiagnosis. Over diagnosis can also occur as spirometry (the measuring of breath), which is required to confirm a COPD diagnosis, is under-used in clinical practice; patients with chronic bronchitis without airflow limitation may be incorrectly assumed to have COPD (many patients with chronic bronchitis may go on to develop COPD but these diseases are not interchangeable).

In the US, 6.3 percent of adults (around 15 million individuals), or 4.8 percent of the national population (including children), have been diagnosed with COPD based on the 2011 Behavioral Risk Factor Surveillance System (BRFSS) in which respondents were asked, "have you ever been told by a doctor or health professional that you have COPD, emphysema, or chronic bronchitis?"\(^4\)

In England, the prevalence of diagnosed and undiagnosed COPD in all age groups is approximately 3 percent based on a modelled COPD prevalence of 1.6 million persons\(^5\). There are around 940,000 registered COPD patients in England, indicating a diagnosed prevalence of 1.8 percent\(^6\). This is lower than the US (4.8 percent) possibly because the BRFSS used chronic bronchitis to define COPD. In England, 60 percent of the estimated 1.6 million patients with COPD have been diagnosed. As primary care physicians in England are financially incentivised to diagnose COPD, diagnosis rates are likely to be lower in other markets.

Applying the lower and upper estimates of diagnosed COPD (1.8 percent in England and 4.8 percent in the US) to the combined population of 636 million persons (all ages) in the US and five major EU markets (the UK, Spain, Italy, France and Germany), the prevalence of diagnosed COPD in these six markets ranges from 11.5 million to 30.5 million.

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\(^4\) Chronic Obstructive Pulmonary Disease Among Adults — United States, 2011. MMWR. November 23, 2012 / 61(46);938-943. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6146a2.htm


Aetiology

Inhaled cigarette smoke, occupational exposure to noxious chemicals and indoor pollution (biomass burning) causes lung inflammation, which results in parenchymal tissue destruction and small airway fibrosis. Small airway fibrosis and obliteration are believed to be the main contributors to airway dysfunction, occurring earlier than parenchymal tissue destruction (emphysema). The chronic inflammatory response in chronic obstructive pulmonary disease (COPD) patients is driven by neutrophils, CD8+ T-lymphocytes, and macrophages.

Risk factors

Chronic obstructive pulmonary disease (COPD) is mostly associated with smoking. There are an estimated 37 million daily smokers in the US and 95 million daily smokers in Europe. China has more daily smokers than the US and Europe combined (at approximately 260 million) and unlike most high- and middle-income countries, such as Mexico and Brazil, the number of smokers in China is increasing.

Over a 25-year time-frame, population models suggest reducing smoking prevalence has only a modest benefit in reducing COPD healthcare costs due to the time lag between exposure to smoke and the onset of COPD and evidence that airway inflammation can persist for many years after smoking cessation (reducing COPD exacerbations was the optimal strategy to reduce costs).

Not all smokers develop COPD. In a Danish study, approximately 25 percent of smokers developed clinically significant COPD after 25 years of continuous smoking, pointing to genetic susceptibility, which may be confirmed by the COPD Gene Study (ClinicalTrials.gov identifier: NCT00608764). China will have an enormous future healthcare burden due to COPD unless smoking prevalence falls, even if only 25 percent of smokers develop COPD.

---

COPD also occurs in persons who have never smoked. A substantial burden of COPD is attributable to occupational exposures to dusts, chemicals\(^1\) and indoor pollution caused by biomass burning, a COPD risk factor especially relevant to women in developing countries.

“In developing countries COPD is commonly seen in non-smokers, and particularly in women who are exposed to cooking fumes which they call biomass smoke.”

Professor Peter Barnes (Europe)

“Over three billion people, that's over half the world's population, are exposed to those biomass fuels on a daily basis. That's what is going to fuel the epidemic of this going forward. If you look at countries like China, 70 percent of men over the age of 16 are actively smoking. The pollution in the metropolitan areas is beyond belief, and in rural China there is a tremendous amount of biomass fuels usage. If you look at where China is, whatever its economic strength is now, the health - the respiratory health - of China in the next 10 or 20 years is going to be staggering.”

Professor Byron Thomashow (US)

**Symptoms**

Common chronic obstructive pulmonary disease (COPD) symptoms are persistent dyspnea (breathlessness), excessive sputum production and chronic cough. COPD patients suffer from a progressive reduction in forced expiratory volume in 1 second (FEV\(_1\)) indicating increasing airflow limitation, combined with a gradual decline in health status and increase in symptoms. The rate of FEV\(_1\) decline can vary between patients. COPD exacerbations (worsening of respiratory symptoms) are the most common cause of hospital admissions among COPD patients; frequent exacerbations can permanently impact quality of life. Late presentation is common in COPD as persons may restrict physical activity and only seek medical care when they experience significant symptoms.

**Diagnosis**

Chronic obstructive pulmonary disease (COPD) is defined by airflow limitation. A COPD diagnosis is confirmed by spirometry based on the post-bronchodilator FEV₁ (air expelled in the first second) and the forced vital capacity (FVC). The FEV₁ is divided by the FVC (total amount of air exhaled). A FEV₁/FVC of less than 0.70 confirms the presence of persistent airflow limitation and COPD. In patients with FEV₁/FVC of less than 0.70, the FEV₁ is used to grade the severity of airflow limitation from mild to very severe (see Table 1). The grade of airflow obstruction is not equivalent to disease severity, which requires additional assessment of symptoms and exacerbation risk.

<table>
<thead>
<tr>
<th>Severity</th>
<th>FEV₁ % predicted*</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>FEV₁ ≥ 80%</td>
<td>GOLD 1</td>
</tr>
<tr>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80%</td>
<td>GOLD 2</td>
</tr>
<tr>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50%</td>
<td>GOLD 3</td>
</tr>
<tr>
<td>Very severe</td>
<td>FEV₁ &lt; 30%</td>
<td>GOLD 4</td>
</tr>
</tbody>
</table>

Chronic obstructive pulmonary disease treatments

Chronic obstructive pulmonary disease (COPD) therapies provide symptomatic relief, increase health status and exercise tolerance, and reduce the frequency of exacerbations. No current drugs modify the long-term decline in FEV1. Inhaled bronchodilators, which increase FEV1 by widening the airways, are available in four classes:

- Short-Acting Beta2 Agonists (SABAs);
- Long-Acting Beta2 Agonists (LABAs);
- Short-Acting Muscarinic Antagonists (SAMAs);
- Long-Acting Muscarinic Antagonists (LAMAs).

Beta2 agonists, including SABAs and LABAs, increase cyclic adenosine monophosphate (AMP) levels, resulting in relaxation of bronchial smooth muscle. Muscarinic antagonists (also known as anticholinergics) block acetylcholine’s effect on muscarinic receptors leading to bronchodilation. SAMAs, such as ipratropium, block M2 and M3 macrophage receptors. LAMAs, such as tiotropium and aclidinium, primarily inhibit M3 macrophage receptors.

Inhaled Corticosteroids (ICS) are the principle anti-inflammatory agents used to treat COPD, most often in a fixed-dose combination with a LABA (the only presentations of ICS approved for use in COPD in the US and EU). The effects of ICS in COPD patients are not well defined.

Other COPD treatments include roflumilast, an oral phosphodiesterase-IV inhibitor (PDE-IV), methylxanthines (e.g. theophylline, a non-selective PDE inhibitor) and mucolytics (e.g. carbocysteine). Roflumilast is believed to exert an anti-inflammatory by increasing intracellular cyclic AMP in lung cells although roflumilast’s specific mechanism of action is not well defined. Further details on the mechanism of action of COPD therapies are included in the GOLD guidelines12.

COPD treatment landscape

Since 2000, major therapeutic advances include the approval of Boehringer Ingelheim’s once-daily LAMA Spiriva (tiotropium) in 2001, followed by GlaxoSmithKline’s Advair/Seretide (fluticasone propionate/salmeterol) and AstraZeneca’s Symbicort (budesonide/formoterol) in 2003. Fixed-dose combinations in this report are denoted by the use of a forward slash; free-dose combinations are donated by the “+” sign (e.g. triple therapy with salmeterol/ fluticasone and tiotropium is ICS/LABA + LAMA).

In 2009, Novartis launched Onbrez/Arcapta (indacaterol), the first once-daily LABA to be approved for COPD. Takeda’s Daxas/Daliresp (roflumilast), approved in 2010 in the EU and the US in 2011, was the first, and remains the only, oral PDE-IV inhibitor available. In 2012, two additional LAMAs were approved: Seebri (glycopyrronium) developed by Novartis, and Eklira/Tudorza (aclidinium) developed by Almirall/Forest.

In May 2013, the US Food and Drug Administration (FDA) approved GlaxoSmithKline’s Breo/Relvar (fluticasone furoate/vilanterol), the first once-daily ICS/LABA. Novartis’s Ultibro (indacaterol/glycopyrronium) was the first LAMA/LABA to be approved, following clearance by European regulators in September 2013. GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca/Pearl Therapeutics and Almirall/Forest are also developing LAMA/LABA combination products.

Figure 3 summarises the COPD product approvals/filings from 2000 to 2015.
COPD market definition

FirstWord’s COPD market valuation is based on company reported sales between 2008 and 2012 of the following drugs:

- **ICS/LABAs**: Advair/Seretide (fluticasone propionate/salmeterol; GlaxoSmithKline) and Symbicort (budesonide/formoterol; AstraZeneca);
- **LAMAs**: Spiriva (tiotropium bromide; Boehringer Ingelheim/Pfizer); Seebri (glycopyrronium; Novartis) and Eklira/Tudorza (aclidinium bromide; Almirall/Forest)
- **LABAs**: Onbrez/Arcapta (indacaterol; Novartis), Foradil (formoterol; Novartis), Serevent (salmeterol; GlaxoSmithKline)
- **SAMA/SABA**: Combivent (salbutamol/ipratropium; Boehringer Ingelheim);
- **PDE-IV inhibitors**: Daxas/Daliresp (roflumilast; Takeda/Forest)

Estimating the market for COPD treatments is complicated as several drugs approved for COPD, such as Seretide, Symbicort and Serevent are also indicated for asthma. Based on prescribing practices in England, an estimated 35 percent of global Seretide and Symbicort sales and 15 percent of global Serevent and Foradil sales are generated in COPD (please see methodology in the appendix). All Spiriva and Onbrez/Arcapta sales are assumed to be generated in COPD, as both do not have an asthma indication. The same asthma/COPD sales split was applied over the five-year sales period. The market definition excludes sales of the following:

- Sunovion’s Brovana (arformoterol);
- AstraZeneca’s Oxis (formoterol);
- Off-label use of free-dose ICS, such as Flixotide/Flovent (fluticasone; GlaxoSmithKline);
- Leukotriene antagonists (e.g. montelukast);
- Fixed-dose ICS/LABAs which do not have a COPD indication, such as Merck’s Dulera (mometasone/formoterol);
- Free-dose SAMAs and SAMAs such as GlaxoSmithKline’s Ventolin (salbutamol) and Boehringer Ingelheim’s Atrovent (ipratropium).
Current market overview

Global COPD sales were $10 billion in 2012 (CAGR 2008-12 = 8 percent) based on drugs included in FirstWord’s market definition. The COPD market is dominated Spiriva and Advair/Seretide, which generated combined sales of $7.5 billion in 2012, or 75 percent of global COPD sales (see table and figure below). The other major brands are Combivent and Symbicort.

Table 2: COPD global sales by brand, 2008-2012.

<table>
<thead>
<tr>
<th>Brand</th>
<th>2008 ($m)</th>
<th>2009 ($m)</th>
<th>2010 ($m)</th>
<th>2011 ($)</th>
<th>2012 ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiriva</td>
<td>3,045</td>
<td>3,349</td>
<td>3,793</td>
<td>4,351</td>
<td>4,595</td>
</tr>
<tr>
<td>Advair/Seretide</td>
<td>2,693</td>
<td>2,717</td>
<td>2,788</td>
<td>2,852</td>
<td>2,808</td>
</tr>
<tr>
<td>Combivent</td>
<td>850</td>
<td>911</td>
<td>963</td>
<td>1,057</td>
<td>1,139</td>
</tr>
<tr>
<td>Symbicort</td>
<td>701</td>
<td>803</td>
<td>961</td>
<td>1,102</td>
<td>1,118</td>
</tr>
<tr>
<td>Arcapta/Onbrez</td>
<td>-</td>
<td>n/r</td>
<td>33</td>
<td>103</td>
<td>134</td>
</tr>
<tr>
<td>Daliresp</td>
<td>-</td>
<td>-</td>
<td>n/r</td>
<td>n/r</td>
<td>78</td>
</tr>
<tr>
<td>Eklira/Tudorza</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Foradil</td>
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<td>n/r</td>
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</tr>
<tr>
<td>Serevent</td>
<td>73</td>
<td>55</td>
<td>47</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>Seebri</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7,363</strong></td>
<td><strong>7,836</strong></td>
<td><strong>8,638</strong></td>
<td><strong>9,562</strong></td>
<td><strong>9,988</strong></td>
</tr>
</tbody>
</table>

35% of global Seretide and Symbicort sales and 15% of global Serevent and Foradil sales estimated to be generated in COPD; Combivent sales estimated in 2008; Eklira/Tudorza European sales only; Daliresp US sales only (Forest fiscal year April to March); n/r = not reported

Source: Company reported sales

Spiriva is the top selling COPD drug with sales of $4.6 billion in 2012. Around $2.3 billion, or about half of global sales, were in the US, where Spiriva is marketed by Pfizer.

GlaxoSmithKline’s Advair/Seretide sales in asthma and COPD were around $8 billion in 2012, or 25 percent of GlaxoSmithKline’s total pharmaceutical sales, including vaccines. COPD comprised 35 percent, or $2.8 billion, of Advair/Seretide sales. AstraZeneca’s Symbicort global sales were $3.2 billion in 2012, of which 35 percent, or $1.1 billion, were COPD sales. Symbicort’s global COPD sales are around one-third of Advair/Seretide’s COPD sales. Delays in gaining US approval of Symbicort is the primary reason why Advair/Seretide is the dominant ICS/LABA brand.
Figure 4 illustrates global sales of brands from 2008-2012.

**Figure 4: COPD global sales by brand, 2008-2012**

35% of global Seretide and Symbicort sales and 15% of global Serevent and Foradil sales estimated to be generated in COPD; Combitvent sales estimated in 2008; Eklira/Tudorza European sales only; Daliresp US sales only (Forest fiscal year April to March); Daliresp sales not reported in 2010 and 2011; Foradil sales not reported in 2008 and 2009; CAGR = compound annual growth rate

Source: Company reported sales

Novartis’s Arcapta/Onbrez sales were $134 million in 2012; sales of Novartis’s Seebri, which was approved in September 2012, were not reported. Almirall reported 2012 Tudorza sales of around $35 million in three European markets (Germany, Denmark and the UK). Forest’s US sales of Eklira were $23 million between December 2012 and March 2013. Forest’s US sales of Daliresp were around $80 million between April 2012 and March 2013; sales in other markets were not identified.
Formulary coverage of chronic obstructive pulmonary disease drugs

Formulary coverage of six maintenance chronic obstructive pulmonary disease (COPD) treatments was based on ten Medicare Prescription Drug Plans (PDPs). Medicare plans were selected, as a majority of patients with diagnosed COPD are aged 65 years or older. All the PDPs were selected from the Medicare.gov Website. All ten plans cover Advair, Symbicort and Spiriva as preferred brand-name drugs (see table below). Daliresp has more variable coverage as a preferred brand-name drug in six plans. Tudorza has not received favourable formulary decisions, with only two plans covering the drug as a preferred brand-name drug. Arcapta was a non-preferred brand, or was not covered, in all ten plans.

Table 3: COPD formulary coverage (Medicare Prescription Drug Plans).

<table>
<thead>
<tr>
<th>Plan name</th>
<th>Advair</th>
<th>Symbicort</th>
<th>Spiriva</th>
<th>Tudorza</th>
<th>Daliresp</th>
<th>Arcapta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigna Medicare Rx</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Plan One</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humana Enhanced</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Express Scripts</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Medicare - Choice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EnvisionRxPlus Gold</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
</tr>
<tr>
<td>United American -</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Enhanced</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Express Scripts</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
<td>Preferred Brand</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Medicare - Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BlueMedicare Rx</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
<td>Not on Formulary</td>
<td>Not on Formulary</td>
</tr>
<tr>
<td>Option 1</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Humana Walmart-</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
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<td>Not on Formulary</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>Preferred Rx Plan</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AARP MedicareRx Preferred</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Preferred Brand</td>
<td>Not on Formulary</td>
<td>Not on Formulary</td>
<td>Non-Preferred Brand</td>
</tr>
<tr>
<td>CVS/pharmacy Prescription Drug Plan</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Source: Medicare.gov

Monthly drug costs, based on the Cigna Medicare Rx Plan One, are $270 for Advair, $262 for Spiriva, $237 for Symbicort and $201 for Daliresp. The monthly drug cost of Tudorza at $219 and Arcapta at $175 are lower than Spiriva, but this discount has not resulted in favourable
formulary uptake. The annual out-of-pocket expense paid by patients varies depending on the plan; as a guide, a patient prescribed Advair and Spiriva could pay annual estimated drug costs ranging from $1,624 (Humana Gold Plus) to $3,354 (Express Scripts Medicare – Value). Annual estimated drugs costs include monthly premiums, annual deductibles and drug copayments.
**Current therapies**

The following section will provide an overview of the key products approved for the treatment of chronic obstructive pulmonary disease (COPD).

Figure 5 highlights key insights from the current COPD therapies.

<table>
<thead>
<tr>
<th>Insight</th>
<th>Source: FirstWord</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIOSPIR trial does not show increased mortality risk with Spiriva Respimat (LAMA)</td>
<td></td>
</tr>
<tr>
<td>Almirall's Eklira/Tudorza (LAMA) twice-daily profile may be preferred in some patients</td>
<td></td>
</tr>
<tr>
<td>GlaxoSmithKline's Breo (ICS/LABA) adds uncertain clinical value compared to Advair and Symbicort</td>
<td></td>
</tr>
<tr>
<td>Novartis's Onbrez (LABA) EU sales are disappointing due in part to reimbursement issues</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca’s Symbicort (ICS/LABA) sales are lower than Seretide/Advair due to a significant delay in gaining US approval</td>
<td></td>
</tr>
<tr>
<td>DaiResp/Daxas sales are hampered by poor tolerability, variable US formulary coverage and restrictions on use in some EU markets</td>
<td></td>
</tr>
</tbody>
</table>
Key trials with approved therapies

Table 4 lists six landmark chronic obstructive pulmonary disease (COPD) trials, which examined various endpoints including decline in FEV1, mortality, symptoms, exacerbations and trough forced expiratory volume in 1 second (FEV1).

Table 4: Landmark chronic obstructive pulmonary disease clinical trials

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Name</th>
<th>Patients</th>
<th>Length</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium vs. placebo</td>
<td>UPLIFT</td>
<td>6,000</td>
<td>4 years</td>
<td>FEV1 decline, trough FEV1, exacerbations</td>
</tr>
<tr>
<td>Tiotropium vs. salmeterol</td>
<td>POET-COPD</td>
<td>7,400</td>
<td>1 year</td>
<td>Exacerbations</td>
</tr>
<tr>
<td>Salmeterol/fluticasone vs.</td>
<td>TORCH</td>
<td>6,000</td>
<td>3 years</td>
<td>Mortality, exacerbations, health status</td>
</tr>
<tr>
<td>salmeterol or fluticasone or placebo</td>
<td>TRISTAN</td>
<td>1,500</td>
<td>1 year</td>
<td>Trough FEV1, symptoms, exacerbations</td>
</tr>
<tr>
<td>Tiotropium vs. salmeterol or fluticasone</td>
<td>INSPIRE</td>
<td>1,300</td>
<td>2 years</td>
<td>Exacerbations, health status</td>
</tr>
<tr>
<td>Tiotropium vs. salmeterol+tiotropium</td>
<td>OPTIMAL</td>
<td>450</td>
<td>1 year</td>
<td>Exacerbation, health status</td>
</tr>
</tbody>
</table>

Source: various

Spiriva (UPLIFT); FEV1 decline and exacerbations

The 4-year UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial evaluated the long-term effects of Spiriva HandiHaler on disease progression (yearly rate of decline in FEV1) in approximately 6,000 patients with a mean FEV1 48 percent of predicted; around 2,800 patients had moderate COPD (GOLD grade 2) at randomisation. Patients were permitted to use Short-Acting Beta2 Agonists (SABAs), Long-Acting Beta2 Agonists (LABAs), Inhaled Corticosteroids (ICS) and theophylline. At screening, approximately 60 percent of patients were using an ICS and 40 percent a LABA.

There was no significant difference in the rate of decline of FEV1 between tiotropium and placebo, the primary endpoint of the trial. There was a sustained improvement in trough FEV1 between tiotropium and placebo over the four-year study period. The overall mean treatment difference was 94mL for pre-bronchodilator FEV1 and 57ml for post-bronchodilator FEV1.

Tiotropium reduced the risk of COPD exacerbation by 14 percent compared to placebo. The median time to first exacerbation was delayed from 12.5 months in the placebo group to...
16.7 months in the tiotropium group. In a subgroup analysis of the UPLIFT trial, patients with moderate COPD treated with tiotropium seemed to have a reduction in the rate of decline of post-bronchodilator FEV$_1$.\textsuperscript{13}

**Spiriva (POET-COPD): LAMA v LABA, exacerbations**

The 12-month POET-COPD study compared Spiriva HandiHaler (18mcg) once-daily versus salmeterol twice-daily (50mcg) in approximately 7,400 patients with mean FEV$_1$ 49 percent of predicted.\textsuperscript{14} The primary outcome was time to first COPD exacerbation. The POET-COPD study demonstrated the superiority of tiotropium over salmeterol in reducing the risk for COPD exacerbations. Specifically, tiotropium increased the time to the first exacerbation to 187 days, compared to 145 days with salmeterol and reduced the annual number of moderate or severe exacerbations by 0.64 and 0.72, respectively, marking a treatment difference of 0.08. As noted in the GOLD guidelines, this difference is considered “small.”

**Advair/Seretide (TORCH): mortality**

The three year TORCH (TOwards a Revolution in COPD Health) study compared survival in approximately 6,000 subjects with mean FEV$_1$ 44 percent of predicted treated with fluticasone propionate 500mcg/salmeterol 50mcg twice-daily compared with salmeterol alone, fluticasone propionate alone or placebo. The primary outcome was death from any cause; the frequency of exacerbations, health status and spirometric values were also assessed. The reduction in death from all causes in the fluticasone propionate/salmeterol group did not reach the predetermined level of statistical significance. Compared with placebo, fluticasone propionate/salmeterol reduced the annual rate of exacerbations from 1.13 to 0.85.

**Seretide (TRISTAN): lung function and exacerbations**

The 12 month lung-function TRISTAN (TRial of Inhaled STeroids ANd long-acting β2 agonists) trial compared fluticasone propionate 500mcg/salmeterol 50mcg twice-daily with salmeterol alone, fluticasone propionate alone or placebo.\textsuperscript{15} The primary outcome was trough FEV$_1$ after 12 months treatment. Secondary outcomes were symptoms and number of exacerbations. Combination therapy improved pretreatment FEV$_1$ significantly more than


placebo, with a treatment difference of 133mL, and by 73ml and 95ml over salmeterol and fluticasone alone. All treatments improved symptoms and frequency of exacerbations. The rate of exacerbations fell by 25 percent with combination therapy, 20 percent with salmeterol and 19 percent with fluticasone compared with placebo.

**Spiriva versus Seretide (INSPIRE): exacerbations**

The largest and longest study comparing Spiriva with Seretide is the two-year INSPIRE trial, which recruited approximately 1,300 patients with severe and very severe COPD (mean FEV\(_1\) 39 percent of predicted)\(^{16}\). The trial compared fluticasone propionate 500mcg/salmeterol 50mcg twice-daily with tiotropium (18mcg once-daily). The INSPIRE trial reported a small improvement in quality of life in persons taking Seretide compared to Spiriva, although the primary endpoint of exacerbation rates were similar and non-significant.

**Triple therapy (OPTIMAL): ICS/LABA plus LAMA**

The OPTIMAL study was designed to determine whether combining tiotropium with salmeterol or fluticasone/salmeterol improved clinical outcomes compared with tiotropium alone\(^{17}\). The study recruited around 500 patients with moderate to severe COPD and the primary endpoint was the proportion of patients who experienced an exacerbation after 12 months of treatment. At one year, triple therapy with fluticasone/salmeterol and tiotropium did not statistically influence rates of COPD exacerbation. Tiotropium plus fluticasone-salmeterol did significantly reduced hospitalisations for acute exacerbations and quality of life, as measured by total St George’s Respiratory Questionnaire (SGRQ) score.


**Long-Acting Muscarinic Antagonists (LAMAs)**

Long-Acting Muscarinic Antagonists (LAMAs) block the bronchoconstrictor action of acetylcholine on the smooth muscle in the airway to induce bronchodilation. LAMAs are recommended as first-line maintenance therapies in COPD patients with severe or very severe disease or those with mild to moderate airflow obstruction who have a history of exacerbations.

Three LAMAs are currently approved. The first was Spiriva (tiotropium; Boehringer Ingelheim/Pfizer), which was approved in Europe in 2001, becoming the first once-daily maintenance bronchodilator available for COPD. Spiriva has not had to compete with other drugs in the LAMA class for over ten years: it was only following the approval of Novartis's Seebri (glycopyrronium; Novartis) and Almirall's Eklira/Tudorza (aclidinium; Almirall/Forest) in 2012 that alternative LAMAs have become available.
Spiriva (tiotropium; Boehringer Ingelheim/Pfizer)

**Drug summary**

Spiriva was first approved in the HandiHaler DPI device in Europe in 2001, followed by approval in the US and Japan in 2004. A second formulation of tiotropium delivered using the Respimat device was approved in Europe in 2007 (Spiriva Respimat is not approved in the US). Spiriva Respimat was granted a US label claim for reduction of exacerbations in 2009, becoming the second drug (the first was GlaxoSmithKline’s Advair) to gain a reduction of exacerbations claim in the US.

Table 5 presents Spiriva (tiotropium, Boehringer Ingelheim/Pfizer) profile

<table>
<thead>
<tr>
<th>Table 5: Spiriva (tiotropium, Boehringer Ingelheim/Pfizer) profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecule</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td><strong>Originator</strong></td>
</tr>
</tbody>
</table>
| **Dosing (EU)** | Spiriva HandiHaler DPI: tiotropium 18mcg once daily  
Spiriva Respimat: tiotropium 2.5mcg once daily |
| **Approved indication (EU)** | Maintenance bronchodilator treatment to relieve symptoms in patients with COPD |
| **Dosing (US)** | Spiriva HandiHaler DPI: tiotropium 18mcg once daily |
| **Approved indication (US)** | Long-term, once daily, maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations |
| **Approval date** | 2004 (US); 2001 (EU); Japan (2004) |
| **Company reported global sales 2012** | $4.6 billion |

**Spiriva is considered the gold standard COPD monotherapy**

Upon Spiriva’s launch, as the first LAMA therapy, the drug has established itself as the number one therapy in COPD, generating $4.6 billion in 2012. Moreover, with the launch of a novel soft mist inhaler, the Respimat, to complement the dry powder inhaler, the HandiHaler, Boehringer Ingelheim have two devices that offer convenient administration. Key opinion leaders believe Spiriva offers clinical efficacy advantages over existing therapies, ease of use and safety.

“It is a very good bronchodilator; it works; patients feel better; a person’s lung function improves; it can stabilise (their COPD); so when you put all that together you see the medication works and I think that is pretty much the bottom line”

Dr Antonio Anzueto (US)
“I believe that tiotropium has a very important role in the treatment of COPD. Probably even more than LABAs. For instance, cholinergic tone plays an important role in COPD. I think that tiotropium might have a better effect on hyperinflation compared with LABAs and the effect of tiotropium on exacerbations is there.”

Professor Rene Aalbers (Europe)

“The patients love it; they don’t want to stop the treatment, and sometimes they even ask me why didn’t I prescribe the Spiriva before and I say, ’because it didn’t exist!’ The main issue is that it is a really good drug. I mean it changed the disease, and how the patients live with the disease. They tell you that they can do things that they could not do before. It changed their lives.”

Dr Marc Miravitlles (Europe)

“Spiriva is the first real effective bronchodilator developed for COPD and once-a-day. Some other drugs may have better activity because they are administered twice a day, but nevertheless, a patient may prefer a drug which is given just once a day.”

Professor Maurizio Luisetti (Europe)

**TIOSPIR does not show increased mortality risk with Respimat**

The TIOSPIR study was designed to determine if the Spiriva Respimat device (Boehringer Ingelheim’s preferred delivery device) is associated with increased mortality compared to the Spiriva HandiHaler device. During a mean follow-up of 2.3 years, Respimat was non-inferior to HandiHaler with respect to the risk of death.

The positive TIOSPIR trial result means Boehringer Ingelheim can seek US approval of Spiriva Respimat and the LAMA/LABA combination of tiotropium/olodaterol, which is also delivered using the Respimat inhaler.

**ICS withdrawal study paves way for tiotropium/olodaterol combination**

In July 2013, Boehringer Ingelheim completed a large study (trial NCT00975195) in approximately 2,500 patients to determine if ICS withdrawal results in a difference in time to first COPD exacerbation at 48 weeks in patients with severe to very severe COPD. Two treatment arms compared Spiriva and salmeterol and fluticasone (high dose), with Spiriva and salmeterol and fluticasone (high, medium or low dose or placebo). The study used free-dose combinations of salmeterol and fluticasone.

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As ICS are a commonly used maintenance treatment, a high uptake of Boehringer Ingelheim’s novel tiotropium/olodaterol fixed-dose LAMA/LABA combination (Phase III) will require ICS withdrawal, which physicians may be reluctant to do due to a fear of increasing exacerbations. If the study shows ICS withdrawal does not increase exacerbations in patients receiving a LAMA and a LABA, this may support switching of ICS/LABA to tiotropium/olodaterol.
Eklira/Tudorza (aclidinium; Almirall/Forest)

Drug summary

In July 2012, Almirall’s aclidinium (400mcg twice daily) was approved in Europe as Eklira/Bretaris and in the US as Tudorza, where is it marketed by Forest. In Japan, the Long-Acting Muscarinic Antagonists (LAMA) is being developed with Kyorin. The therapy is administered using Almirall’s Genuair DPI (the US trade name is Pressair). Eklira/Tudorza was the second LAMA to be approved in the US and Europe after Spiriva and was closely followed by Novartis’s Seebri (glycopyrronium) which was approved in Europe in September 2012.

Table 6: Eklira/Tudorza (aclidinium; Almirall/Forest)

<table>
<thead>
<tr>
<th>Table 6: Eklira/Tudorza (aclidinium; Almirall/Forest) profile</th>
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<tbody>
<tr>
<td>Molecule</td>
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<tr>
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<tr>
<td>Originator</td>
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<tr>
<td>Dosing (EU)</td>
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<tr>
<td>Approved indication (US)</td>
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<tr>
<td>Approval date</td>
</tr>
<tr>
<td>Company reported global sales 2012</td>
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</tbody>
</table>

Sources: Eklira/Tudorza prescribing information, company reported sales

Eklira/Tudorza has no added clinical benefit compared to Spiriva

Eklira/Tudorza (aclidinium) was initially developed as a once-daily LAMA. European registration was halted in 2010 following results from two Phase III trials in which the change in trough FEV1 was around half the size observed in the Phase II programme19.

Pivotal trials with aclidinium (400mcg twice-daily) demonstrated a treatment difference in trough FEV1 between aclidinium and placebo of 72ml to 124ml at week 12. The US Food and Drug Administration (FDA) required Forest to conduct a post-marketing study to evaluate

the risk of cardiac events, data from which will be submitted to the FDA in 2018. Tudorza does not have a label claim for reduction of COPD exacerbations in the US.

In January 2013, the German Institute for Quality and Efficiency in Health Care (IQWiG) concluded that Eklira had no added benefits compared to Spiriva20. Almirall submitted data from two studies comparing Eklira with Spiriva, which lasted two, and six weeks; the IQWiG required studies of at least six months.

Eklira/Tudorza lacks long-term trial data and a US exacerbation label claim. In an attempt to gain market share, Forest has priced Eklira/Tudorza at a discount to Spiriva although this has not resulted in significant formulary uptake. Twice-daily dosing (despite the intention to market a once-daily product) was perceived as an advantage by one KOL as this might be preferred to once-daily dosing with Spiriva in some patients.

“I think for most people, once-a-day is probably going to be better than twice-a-day, but that's not going to be true for everyone. That's why aclidinium, which is twice a day, probably will have considerable use even though there is tiotropium which is once a day.”

Dr Stephen Rennard (US)

“I suggested it [Tudorza] to a patient who developed urinary retention on tiotropium. With the availability of multiple new drugs there's going to be different pharmacological profiles to explore and altogether many different options for physicians and for patients as well.”

Professor Christopher Cooper (US)

“Almirall is trying to push a lot on nocturnal symptoms and variability in symptoms during the day and the need to consider more the night(-time), which is quite interesting to better understand the variability of the perceptions of the obstruction for these patients when they are at rest. But it's just a way to sell the drug twice-daily. Exercise is the main factor which drives symptoms in COPD.”

Professor Pascal Chanez (Europe)

“Almirall has a twice-daily anticholinergic. There are so many patients who are symptomatic during the night and they may profit. I would say this is a discussion that is ongoing and it is not clear at the moment who is right.”

Professor Claus Vogelmeier (Europe)

“I think it will not be easy for the new LAMAs to try to take the market of Spiriva because these drugs actually have very little [clinical] experience. Spiriva is a once-a-day and well-accepted by patients.”

Professor Maurizio Luisetti (Europe)
Seebri (glycopyrronium; Novartis)

Drug summary

Novartis’s once-daily Long-Acting Muscarinic Antagonists (LAMA) Seebri (glycopyrronium, also known as glycopyrrolate, and formerly NVA237), was approved in Europe in September 2012. Novartis licensed the formulation of glycopyrronium from Vectura/Sosei. Glycopyrronium is administered in the Breezhaler DPI, the same device used to deliver Novartis’s Arcapta/Onbrez (indacaterol). Several companies are developing glycopyrronium based products: these include Sunovion’s nebulised glycopyrronium (Phase II), Prosonix’s glycopyrronium pMDI (Phase I/II) and Pulmatrix glycopyrronium DPI (Phase I/II). In addition, AstraZeneca/Pearl Therapeutics are developing a fixed-dose combination of glycopyrronium/formoterol pMDI (Phase III).

In April 2013, Novartis announced that the GLOW5 study (NCT01613326) met its primary endpoint, demonstrating the non-inferiority of once-daily glycopyrronium 50mcg to once-daily tiotropium 18mcg based on trough FEV1 at 12 weeks.\(^{21}\)

Table 7: Seebri (glycopyrronium; Novartis profile

<table>
<thead>
<tr>
<th>Table 7: Seebri (glycopyrronium; Novartis profile</th>
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<tbody>
<tr>
<td><strong>Molecule</strong></td>
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<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td><strong>Dosing (US)</strong></td>
</tr>
<tr>
<td><strong>Approved indication (US)</strong></td>
</tr>
<tr>
<td><strong>Approval date</strong></td>
</tr>
<tr>
<td><strong>Company reported global sales 2012</strong></td>
</tr>
</tbody>
</table>

Sources: Seebri prescribing information

Rapid bronchodilation believed to be irrelevant

Glycopyrronium was approved in Europe based on the GLOW1 (6-month) and GLOW2 (12-month) studies. At 12 weeks (primary endpoint), glycopyrronium 50mcg increased trough FEV1 by 108ml in the 6-month study and by 97ml in the 12-month study compared to placebo. In the GLOW2 study, glycopyrronium reduced the rate of moderate or severe COPD exacerbations by 34 percent versus placebo. Glycopyrronium significantly prolonged the time to first moderate or severe COPD exacerbation compared to placebo. According to the GLOW2 study authors, glycopyrronium “provided rapid bronchodilation following the first dose,” although this was judged to be clinically irrelevant by one KOL.

“At the end of the day, if you have a rapid onset of action that doesn’t matter; you worry about day number three and on. By day number three when they are in the trough, they are achieving the same action and the same activity. The rapid onset of action at the end of the day does not mean anything.”

Dr Antonio Anzueto (US)

US submission expected in 2014; twice-daily dosing may be approved

Novartis did not use the GLOW1 and GLOW2 studies to file for approval of glycopyrronium in the US, as additional clinical data was necessary to support the submission, which is now anticipated in the first quarter of 2014.

Novartis may have reviewed the US glycopyrronium clinical programme in light of the prolonged the US Food and Drug Administration (FDA) review of indacaterol (the FDA rejected the doses of indacaterol proposed for marketing by Novartis as these were not supported by the submitted efficacy and safety data). The FDA will likely require evidence that Novartis has adequately explored the risk/benefit profile of glycopyrronium. Three ongoing US trials with glycopyrronium monotherapy began recruitment in the fourth quarter of 2012:

- A 12 month safety study is comparing the safety of glycopyrronium with indacaterol (study NCT01697696); the primary completion date is July 2013;
- Two 12-week lung function studies are comparing glycopyrronium with placebo (studies NCT01709864 and NCT01715298); the primary completion dates are in the fourth quarter of 2013.

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23 Novartis 2011 20-F annual report.
None of the studies disclose the exact dose of glycopyrronium used. Trial NCT01715298 is examining twice-daily dosing with glycopyrronium; trial NCT01709864 does not disclose the dosing frequency. One KOL believed the FDA will approve glycopyrronium as a twice-daily drug. This impacts the US glycopyrronium/indacaterol development programme, which is further complicated by the FDA approving a lower dose of indacaterol than in the rest of the world.

“In the US, glycopyrronium may be a twice-a-day medication. So that combination may end up being indacaterol 75mg with the glycopyrronium twice-a-day instead of once-a-day. This is the data that is coming across.”

Dr Antonio Anzueto (US)

“Information that I have received, and I don't know if it is correct or not, [is] that glycopyrronium will be licensed in the US as a twice-a-day.”

Professor Maurizio Luisetti (Europe)

In Europe, Seebri is the third LAMA to be approved after Spiriva and Eklira/Tudorza. Seebri has demonstrated non-inferiority to Spiriva in terms of FEV1 (there is no comparative data for exacerbations) and has the advantage of once-daily dosing compared to Eklira/Tudorza. In the UK, the net NHS price for a 30-day supply of Seebri is 27.50 pounds ($43.26) compared to 35.50 pounds ($55.85) for Spiriva25, a 20-percent discount. In the US, glycopyrronium may be the third or even fourth LAMA to be filed for approved. As with Eklira/Tudorza, Novartis may have difficulty gaining favourable formulary decisions for glycopyrronium as it lacks differentiation from Spiriva.

KOL Insight: COPD

Combination therapies to drive significant market growth

Fixed-dose Long-Acting Muscarinic Antagonists/Long-Acting Beta2 Agonists combinations

Clinical studies with fixed-dose Long-Acting Muscarinic Antagonists/Long-Acting Beta2 Agonists (LAMA/LABA) combinations have demonstrated the combination of two mechanisms of actions results in superior lung function as measured by FEV1 and exacerbation reduction compared to either agent alone. LAMA/LABA combination products should simplify treatment, as they will be more convenient than separate administration of a LAMA and LABA in two inhalers.

Novartis’s Ultibro (indacaterol/glycopyrronium once-daily) was the first LAMA/LABA to be approved following clearance by European regulators in September 2013; a US filing is expected in the fourth quarter of 2014. However, the US version of the therapy may be clinically inferior to the European version, as the dose of indacaterol in the combination product will be lower; further, the combination may have a twice-daily profile in the US. LAMA/LABA fixed-dose combinations are also being developed by GlaxoSmithKline, Almirall/Forest, AstraZeneca and Boehringer Ingelheim.
Ultibro (glycopyrronium/indacaterol; Novartis)

**Drug summary**

In September 2013, Ultibro (indacaterol 110mcg/50mcg glycopyrronium) was approved in the EU as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Five studies from the Phase III IGNITE clinical trial programme formed the basis of the Ultibro EU filing (ILLUMINATE, SHINE, SPARK, BRIGHT and ENLIGHTEN).

The pivotal lung function trial was the SHINE study, which recruited approximately 2,100 patients with moderate to severe COPD and a mean FEV$_1$ 55 percent predicted. The primary endpoint was trough FEV$_1$ at 26 weeks. The trial compared once-daily treatment with glycopyrronium 50mcg/indacaterol 110mg with the individual components, with open-label tiotropium serving as the active comparator arm. Concomitant ICS was allowed in all treatment arms. Trough FEV$_1$ at week 26 was significantly improved with the combination of glycopyrronium/indacaterol compared with indacaterol (mean difference 70mL) and glycopyrronium (mean difference 90mL).

Table 8 presents Ultibro (glycopyrronium/indacaterol; Novartis) profile.

<table>
<thead>
<tr>
<th>Table 8: Ultibro (glycopyrronium/indacaterol); Novartis profile</th>
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<tbody>
<tr>
<td><strong>Molecule</strong></td>
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<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td><strong>Company</strong></td>
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<tr>
<td><strong>Dosing</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Anticipated indication</strong></td>
</tr>
<tr>
<td><strong>Filing date</strong></td>
</tr>
<tr>
<td><strong>Sources:</strong> FirstWord</td>
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</table>

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**Positive response from SPARK and ENLIGHTEN Studies**

The other major trial was SPARK, a 64-week exacerbation trial, which recruited 2,224 patients with severe or very severe COPD and a history of exacerbations. Patients received glycopyrronium 50mcg/indacaterol 110mg, glycopyrronium 50mcg or open-label tiotropium, each once-daily. In the SPARK study, glycopyrronium/indacaterol significantly reduced the rate of moderate to severe exacerbations versus glycopyrronium by 12 percent. GlaxoSmithKline’s Breo (fluticasone furoate 100mcg/vilanterol 25mg) significantly reduced the rate of moderate to severe exacerbations by 21 percent compared to vilanterol 25mcg. The ENLIGHTEN study also reported significant improvements in lung function with the combination versus placebo which were sustained for 52 weeks.

“[Novartis] has shown us a very nice portfolio of development of the medication [Ultibro]. They have a really impressive development portfolio. The overall programme... is really very, very nice.”

Dr Antonio Anzueto (US)

“[Novartis] have done quite a big study portfolio; they have an exacerbation trial; they looked into several severities of the disease; they used an array of endpoints so I would say they will be number one for some time at least.”

Professor Claus Vogelmeier (Europe)

The ILLUMILATE study demonstrated a significantly higher improvement in lung function with glycopyrronium 50mcg/indacaterol 110mg compared to fluticasone propionate 500mcg/salmeterol 50mcg. The 26 week study was conducted primarily in patients with moderate COPD and a mean FEV₁ 60 percent of predicted with no history of exacerbations, a patient group that is not indicated for ICS/LABA treatment. The clinical relevance of the comparative study is unclear.

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“The only problem I have with that paper is that they restricted their patients to those without any exacerbations. What they should have done, and what they need to do, is to actually use exacerbations as an outcome. You are going to need to show that the LAMA/LABAs are at least as effective, maybe even more effective, compared to the LABA/ICS preparations in reducing exacerbations.”

Dr Donald P. Tashkin (US)

**Key LAMA/LABA verses ICS/LABA initiated by Novartis**

An ongoing 52-week, 3,300-patient exacerbation trial is comparing glycopyrronium/indacaterol with fluticasone/salmeterol (study number NCT01782326). The trial, which does not include US sites, is recruiting patients with moderate to very severe COPD and a history of at least one COPD exacerbation in the previous 12 months. A further, unusual inclusion criterion is that patients must have a modified Medical Research Council (mMRC) score of at least 2, which is indicative of a high impact of symptoms. Broadly speaking, the trial is recruiting GOLD group D patients as the restriction by mMRC excludes GOLD group C patients.

The trial, which is expected to be completed in 2015, is likely to be the first head-to-head trial between a LAMA/LABA and ICS/LABA that will determine which therapy is more effective in reducing exacerbations. The dosing of glycopyrronium/indacaterol is undisclosed but is probably the EU approved dose of indacaterol 110mcg/50mcg glycopyrronium once-daily. If so, Novartis will not be able to use the results to supporting US marketing.

“My own suspicion is that they will be first-line, but you will have to accumulate evidence. They will also have to be studied head-to-head against LABA/ICS in patients with moderate to severe disease and even very severe disease to see whether or not there’s comparable or not even greater reductions in exacerbations.”

Dr Donald P. Tashkin (US)

**US versions QVA-149 may be clinically inferior to EU version**

The US approved dose of indaceterol monotherapy is 75mcg, compared to 150mcg and 300mcg once-daily in the EU. The failure to gain approval of indacaterol 150mcg in the US meant Novartis had to conduct additional US clinical trials with QVA-149, which has delayed filing to the fourth quarter of 2014. There are three ongoing trials with QVA-149 with US recruitment centres:

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• Two 12-week lung function studies (study numbers NCT01727141 and NCT01712516) with an estimated completion date of March 2014;
• A one year safety study comparing QVA-149 with indacaterol with a completion date in July 2014 (study number NCT01682863).

The dose, and dosing frequency, of indacaterol/glycopyrronium used in the US QVA-149 clinical development programme is uncertain. The dose of indacaterol used in the combination must be lower than that of Novartis’ Onbrez/Arcapta (indacaterol 75mcg) due to the pharmacokinetic interaction of indacaterol with glycopyrronium.

“It’s not just the indacaterol dose, it’s the LAMA dose. There’s the pharmacokinetic interaction. So you have to go lower than 75 because the QVA [glycopyrronium] is not 150 for the indacaterol, its 110, because of the pharmacokinetic interaction with the anticholinergic.”

Dr Donald P. Tashkin (US)

Further complicating the QVA-149 clinical development programme is uncertainty around the expected approval and dosing frequency of glycopyrronium monotherapy. One KOL commented that glycopyrronium (and hence QVA-149) may be approved as a twice-daily product in the US.

“In the US, glycopyrronium may be a twice-a-day medication, so that combination (QVA-149) may end up being indacaterol 75mg with the glycopyrronium twice-a-day instead of once-a-day. This is the data that is coming across.”

Dr Antonio Anzueto (US)

Available evidence indicates that, if approved, the US version of QVA-149 may be clinically inferior to the European version, as the dose of indacaterol will likely be lower. Furthermore, Novartis cannot use data from the SHINE and SPARK trials, or any other data from past or ongoing trials that used the higher indacaterol 110mcg dose, to support US marketing. Although Novartis are likely to be the first company to gain approval of a LAMA/LABA combination in the EU, the delay in US approval, combined with a less than ideal combination and the prospect of potential approval of a twice daily product, curbs the competitiveness of QAB-149 in the US. The therapy may also be the fourth or fifth to be approved in this market.
Fixed-dose Inhaled Corticosteroid/Long-Acting Beta2 Agonists (ICS/LABA) combinations

These combination products pair two classes of chronic obstructive pulmonary disease (COPD) drugs, an ICS and a LABA, in a fixed-dose inhaler. LABAs increase cyclic adenosine monophosphate (AMP) levels, causing relaxation of bronchial smooth muscle. The precise mechanism through which ICS affects COPD symptoms is not known, although ICS have a range of actions on multiple cell types, including mast cells, eosinophils, neutrophils, macrophages and lymphocytes, as well as mediators involved in inflammation. No free-dose ICS have been approved for use in COPD.

ICS are recommended as first-line maintenance therapies in COPD patients with severe or very severe disease or those with mild to moderate airflow obstruction who have a history of exacerbations. Three fixed-dose ICS/LABA combinations have been approved in COPD, the most recent being GlaxoSmithKline’s Relvar/Breo (fluticasone furoate/vilanterol). The drugmaker’s other ICS/LABA product, Seretide/Advair (fluticasone propionate/salmeterol), and AstraZeneca’s Symbicort (budesonide/formoterol) are also approved to treat asthma; Breo is not approved for asthma in the US but may be in the EU. COPD is estimated to comprise 35 percent of global Seretide/Advair and Symbicort sales.
Seretide/Advair (fluticasone propionate/salmeterol; GlaxoSmithKline)

Drug summary

In the EU, Seretide Accuhaler DPI (fluticasone propionate 500mcg/salmeterol 50mcg twice-daily) was approved in 2003 in COPD patients with a FEV₁ <50 percent in 2003, this approval was extended to patients with a FEV₁ <60 percent in 2008 following a regulatory review of the TORCH study.

In the US, Advair Diskus DPI (fluticasone propionate 250mcg/salmeterol 50mcg twice-daily) was approved in 2003, and marked the first time the US Food and Drug Administration (FDA) approved an ICS for the treatment of COPD. In 2006, GlaxoSmithKline sought approval of a higher dose of Advair Diskus DPI (fluticasone propionate 500mcg/salmeterol 50mcg twice-daily) with a label claim to increase survival and reduce exacerbations.

The survival claim, which the FDA rejected, was based on data from the TORCH study. However, the FDA did grant Advair Diskus (fluticasone propionate 250mcg/salmeterol 50mcg twice-daily) a label claim for reduction of exacerbations in 2008 based on results from two identical 12 month trials which showed Advair reduced the annual rate of moderate/severe COPD exacerbations compared with salmeterol 50mcg twice-daily by around 30 percent.

Advair was the first COPD therapy to gain a US label claim for reduction of exacerbations, representing an advance in COPD treatment, given exacerbations are a common cause of COPD related hospitalisation.

Table 9- Seretide/Advair (fluticasone propionate/salmeterol; GSK)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Fluticasone propionate/salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhaled Corticosteroid/long-acting beta-2 agonist</td>
</tr>
<tr>
<td>Originator</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Dosing (EU)</td>
<td>Seretide Accuhaler DPI: fluticasone propionate 500mcg/salmeterol 50mcg twice daily</td>
</tr>
<tr>
<td>Approved indication (EU)</td>
<td>Symptomatic treatment of patients with COPD, with a FEV1 &lt;60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy</td>
</tr>
<tr>
<td>Dosing (US)</td>
<td>Advair Diskus DPI: fluticasone propionate 250mcg/salmeterol 50mcg twice daily</td>
</tr>
</tbody>
</table>
**Table 9 Seretide/Advair (fluticasone propionate/salmeterol; GSK)**

<table>
<thead>
<tr>
<th>Approved indication (US)</th>
<th>Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval date (COPD)</td>
<td>2003 (US), 2003 (Europe)</td>
</tr>
<tr>
<td>Global sales 2012 (total; COPD)</td>
<td>$8 billion; $2.8 billion (35 percent of total sales)</td>
</tr>
</tbody>
</table>

Source: Advair prescribing information, company reported sales

**Generic exclusivity**

Seretide’s patent has already expired in several countries, but the complexities of making both the powder and the “diskus” inhaler device have so far deterred generic manufacturers from taking a slice out of the drug’s £5bn-a-year sales. **Teva is developing a fluticasone/salmeterol DPI generic for Europe, which may be therapeutically equivalent to Seretide/Advair and could be approved in 2015.** Orion is also developing a fluticasone/salmeterol Easyhaler DPI generic for approval in Europe. Sweden approved Elpen’s fluticasone/salmeterol generic as therapeutically equivalent to Seretide/Advair in May 2011; the product does not yet appear to be approved in other EU Member states, except Greece, were it was first launched in November 2009 as the Rolenium Elpenhaler DPI.

In the US, the earliest that a product with the same active ingredients as Seretide/Advair could garner regulatory clearance is likely to be in 2015, when Teva’s Spiromax DPI may be approved. However, Teva’s Spiromax DPI (fluticasone/salmeterol) will not be interchangeable with Seretide/Advair: in 2010, Teva reported that US regulatory hurdles, including demonstrating bioequivalence, made development of a product that is substitutable for Advair “difficult.”
Relvar/Breo (fluticasone furoate/vilanterol; GlaxoSmithKline)

**Drug summary**

In May 2013, the US Food and Drug Administration (FDA) approved GlaxoSmithKline’s Breo (fluticasone furoate 100mcg/vilanterol 25mcg) for once-daily maintenance treatment of airflow obstruction in patients with COPD. Breo is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. GlaxoSmithKline did not seek an asthma indication for Breo in the US. Breo is delivered in the Ellipta DPI.

Table 10: Relvar/Breo (fluticasone furoate/vilanterol; GlaxoSmithKline)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Fluticasone furoate/vilanterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhaled Corticosteroid/long-acting beta-2 agonist</td>
</tr>
<tr>
<td>Originator</td>
<td>Fluticasone furoate (GSK); vilanterol (Theravance)</td>
</tr>
<tr>
<td>Dosing (EU)</td>
<td>Fluticasone furoate 100mcg/vilanterol 25mcg once-daily (proposed)</td>
</tr>
<tr>
<td>Approved indication (EU)</td>
<td>The symptomatic treatment of patients with COPD with a FEV1 &lt;70% predicted normal (post-bronchodilator) in patients with an exacerbation history (proposed)</td>
</tr>
<tr>
<td>Dosing (US)</td>
<td>Fluticasone furoate 100mcg/vilanterol 25mcg once-daily</td>
</tr>
<tr>
<td>Approved indication (US)</td>
<td>Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD</td>
</tr>
<tr>
<td>Approval date (COPD)</td>
<td>May 2013 (US); filed EU June 2012; COPD application in Japan withdrawn July 2013</td>
</tr>
<tr>
<td>Global sales 2012 (asthma and COPD)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Sources:** Breo prescribing information

*Breo successfully enters EU market*

An application for COPD and asthma (with the same dosage as in the US) was submitted to the European Medicines Agency (EMA) under the proposed trade name Relvar (previously Relovair) in June 2012. In September 2013, Relvar received a positive opinion from the EU Committee for Medicinal Products for Human Use (CHMP) as a symptomatic treatment for adults with COPD with a FEV1<70% predicted with an exacerbation history despite regular bronchodilator therapy (the CHMP also recommend approval of Relvar for the treatment of asthma). Relvar may be approved in the EU in December 2013, given Novartis’s Ultibro (glycopyrronium/indacaterol) was approved three months after receiving a positive CHMP opinion in July 2013. Relvar was approved in Japan for the treatment of asthma in September 2013; the COPD application was withdrawn in July 2013 and additional clinical studies may be required in Japanese patients.
Fluticasone furoate, a synthetic trifluorinated corticosteroid developed by GlaxoSmithKline, has a binding affinity for the human glucocorticoid receptor that is approximately 1.7 times that of fluticasone propionate. GlaxoSmithKline licensed vilanterol (formerly GSK642444) from Theravance. GlaxoSmithKline is not seeking approval of a free-dose presentation of fluticasone furoate for COPD.

**FDA regulatory review looks positive**

The Breo US Food and Drug Administration (FDA) filing included two 6-month lung-function studies and two one-year exacerbation studies. At the agency’s Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting held in April 2013, PADAC voting members strongly supported approval of Breo as a once-daily treatment for relief of airway obstruction, with a 12-1 vote in favour of the therapy. Support for the exacerbation claim was mixed (8 voted “Yes”, 5 voted “No”, none abstained) due to incomplete data stemming from a high dropout rate.

The primary end-points of the two 6-month lung function trials (studies 2206 and 2207) were weighted mean FEV\(_1\) 0–4 hours on day 168 and change from baseline in trough FEV\(_1\) on day 169. In trial 2206, there was a statistically significant treatment difference between fluticasone furoate 100mcg/vilanterol 25mg and placebo of 173ml (weighted mean FEV\(_1\)) and 115ml (trough FEV\(_1\)); there was numeric improvement in both endpoints in trial 2207. The exacerbation trials (studies 2871 and 2970) compared fluticasone furoate (50mcg, 100mcg and 200mcg) in combination with vilanterol 25mcg and vilanterol 25mcg alone. In trial 2970, the annual mean exacerbation rate for vilanterol 25mcg alone was 1.14 compared to 0.90 for fluticasone furoate 100mcg/vilanterol 25mg, marking a 21 percent reduction.

GlaxoSmithKline conducted three non-pivotal 12-week lung function superiority studies comparing Breo with Advair which all had the primary endpoint of change from baseline in weighted mean 0–24h FEV\(_1\) on Day 84. Two replicate trials (studies 3109 and 2352) compared fluticasone furoate 100mcg/vilanterol 25mcg with fluticasone propionate 250mcg/salmeterol 50mcg twice daily. The third trial (study 3107) compared fluticasone furoate 100mcg/vilanterol 25mcg with fluticasone propionate 500mcg/salmeterol 50mcg twice daily. In study 3019 there was a statistically significant difference in 24-hour weighted mean FEV\(_1\) between Breo and Advair of 80ml at day 84. There was numeric improvement for Breo versus Advair for the other two trials.

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31 Breo prescribing information, revised May 2013
32 Minutes for the April 17, 2013 Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC).
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm329187.htm
Breo adds uncertain clinical value compared to Advair and Symbicort

Breo has the same label claims as Advair and an anticipated launch in the fourth quarter of 2013, Breo’s primary point of differentiation is once-daily dosing. This may not be sufficient to gain favourable formulary decisions as a "preferred" brand based on previous experience with Aracpta (indacaterol) which is a non-preferred brand or off-formulary drug (based on ten Medicare Prescription Drug Plans) despite having the convenience of once-daily dosing compared to twice-daily alternatives (Serevent and Foradil).

“I think it will have a role, but it will not be a massive role.”

Dr Marc Miravitlles (Europe)

“Let’s assume it’s not a better drug than Advair and from what I've seen, it’s not likely to me that it’s going to be a better drug. It’s simply a once-a-day drug and will that have an impact? It may have some. Certainly, from the standpoint of COPD, if I could use a one-a-day Advair, Breo once a day, Spiriva once a day and that’s all I have to do, that has a potential role there. So, I think that’s a point that could be sold. Now it also has to do with cost. If they’re going to under-cost this, if they are going to undercut Advair, then it will do great.”

Professor Byron Thomashow (US)

“The problem with Relvar/Breo is when you look at the data when they compared their new drug with their old drug there are no convincing differences. From my point of view, it's a once-daily Advair. That's all it is.”

Professor Claus Vogelmeier (Europe)

GlaxoSmithKline could price Breo below Advair (Breo is priced at parity with Advair based on the Wholesale Acquisition Cost)\(^ {33}\) to offer improved value, although additional clinical data may be required to ensure Breo is added to plans as a ‘preferred’ brand.

There is no evidence from head-to-head trials that Breo is more effective than Advair with regard to quality of life, mortality, hospitalisations or exacerbations. The lung function superiority studies suggest, but do not provide compelling evidence, that Breo is superior efficacy to Advair. GlaxoSmithKline has not conducted any head-to-head exacerbation studies between Breo with Advair and no ongoing or planned comparative exacerbation studies were identified in Clinicaltrials.gov as of August 2013.

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**SUMMIT study may differentiate Breo from Advair**

The SUMMIT (Study to Understand Mortality and MorbidITy in COPD) study is recruiting about 16,000 COPD patients and is the largest outcomes study conducted in COPD patients to date (the UPLIFT and TORCH trials each recruited about 6,000 patients). The SUMMIT study is the first to assess the effect of an ICS/LABA on cardiovascular disease (CVD) outcomes.

SUMMIT is assessing the efficacy of fluticasone furoate 100mcg/vilanterol 25mcg, the individual components and placebo on survival in patients with moderate COPD who have a history of CVD or are at increased risk for CVD (study NCT01313676). Concomitant use of a LABA is not permitted over the study period. All cause mortality is the primary endpoint. Secondary endpoints include decline in FEV₁, cardiovascular death, heart attacks and strokes. Data may be available in 2015. The rational for the SUMMIT trial is based on the TORCH trial, which found that patients with an FEV₁>=50 percent predicted with an apparent history of demonstrated a “49 percent reduction in the risk of dying within 96 weeks for the comparison of Seretide with placebo,” according to researchers. The mechanism by which Seretide may reduce CVD mortality is through lessening systemic inflammation.

“The theory is that the inflammation in the lungs spills over into the blood, and that it is the systemic inflammation that increases the risk of cardiovascular disease, diabetes, osteoporosis etc., so that if you had an effective anti-inflammatory treatment, it should reduce the comorbidities as well.”

Professor Peter Barnes (Europe)

Assuming the SUMMIT data show a mortality benefit, Relvar/Breo could become the first COPD therapy to gain a mortality claim, possibly in 2016 or 2017, and patients with moderate COPD who have CVD or CVD risk factors and no history of exacerbations would be indicated an ICS/LABA.

“It will provide a new target for treatment. If patients have significant cardiac comorbidity then inhaled steroids will be indicated not for better breathing, but for preventing cardiac outcomes, which is an interesting option. Then it means that it will not be a decision to give double bronchodilator or LABA/ICS, but the ICS component should be added to any regimen in cases when a patient has an increased risk for cardiac events.”

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34 Study to Evaluate the Effect of Fluticasone Furoate/Vilanterol on Survival in Subjects With Chronic Obstructive Pulmonary Disease, NCT01313676
Dr Marc Miravitlles (Europe)

“They included patients with quite a good lung function but with a cardiovascular comorbidity. So they believe that their drug may affect cardiovascular mortality. Let’s assume that this study is positive. Then the whole field would change dramatically. This would cause an avalanche.”

Professor Claus Vogelmeier (Europe)

The SUMMIT trial will differentiate Relvar/Breo from Advair, Symbicort, and LAMA/LABAs and perhaps most significantly from ICS/LABA generics, which may be launched in Europe in 2014 and in the US in 2015. Furthermore, a Relvar/Breo mortality benefit could influence treatment practice beyond the expected label claim. Primary care physicians may prescribe Relvar/Breo in COPD patients with moderate disease who do not have CVD or CVD risk factors believing it may have some preventative benefit on CVD (e.g. in patients with asymptomatic/sub-clinical CVD). In addition, physicians may also extrapolate CVD benefits in moderate COPD patients to those with severe or very severe COPD.
Symbicort (budesonide/formoterol; AstraZeneca)

**Drug summary**

Symbicort Turbuhaler DPI was approved for COPD in Europe in 2003, the same year as GlaxoSmithKline’s Advair/Seretide. AstraZeneca had a significant delay in gaining US approval of Symbicort, which was finally approved as a pMDI in 2009, six years after Advair (Symbicort Turbohaler is not approved in the US).

<table>
<thead>
<tr>
<th>Table 11: Symbicort (budesonide/formoterol; AstraZeneca) profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecule</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td><strong>Originator</strong></td>
</tr>
<tr>
<td><strong>Dosing (EU)</strong></td>
</tr>
<tr>
<td><strong>Approved indication (EU)</strong></td>
</tr>
<tr>
<td><strong>Dosing (US)</strong></td>
</tr>
<tr>
<td><strong>Approved indication (US)</strong></td>
</tr>
<tr>
<td><strong>Approval date (COPD)</strong></td>
</tr>
<tr>
<td><strong>Global sales 2012 (total; COPD)</strong></td>
</tr>
</tbody>
</table>

Sources: Symbicort prescribing information, company reported sales

**Lack of exacerbation indication main issue**

Symbicort lacks an exacerbation claim in the US as the definition of COPD exacerbation used in the two pivotal SHINE and SUN studies was based upon oral corticosteroid use or hospitalisation, which the US Food and Drug Administration (FDA) felt was not sufficient.

“**Symbicort also reduces exacerbations, but doesn’t have the FDA indication because the FDA didn’t accept [AstraZeneca’s] definition of exacerbations unfortunately. But it does reduce exacerbations, so I think that –and since exacerbation is such an important event in the course of COPD – that, and one of the major goals is to prevent exacerbations, is that you are really going to need that indication**”

Dr Donald P. Tashkin (US)
“In the US, Symbicort came much, much later than Advair and it had to do with a lot of problems with the device. In the US, they had a totally new formulation and come up with a new concept because the FDA did not like the Turbohaler.”

Professor Claus Vogelmeier (Europe)

One KOL felt that Symbicort and Seretide/Advair were comparable in terms of efficacy, with Symbicort having a lower risk of pneumonia; whether this is sufficient to influence prescribing choice is unclear.

“Symbicort is at least equally as good [as Seretide/Advair] with regards to the effect on patients. One advantage of Symbicort compared to Seretide seems to be that the rate of patients that develop pneumonia is lower. And this may have to do with the fact that the steroid - budesonide - is not as potent as fluticasone.”

Professor Claus Vogelmeier (Europe)

AstraZeneca are currently conducting two US retrospective database analyses evaluating the comparative effectiveness in terms of exacerbations of Symbicort versus Spiriva (study NCT01917643) and Symbicort versus Advair (study NCT01921127).
**Long-Acting Beta2 Agonists (LABAs)**

LABAs increase cyclic adenosine monophosphate (AMP) levels causing relaxation of bronchial smooth muscle. Novartis’s Arcapta/Onbrez (indacaterol), approved in the EU in 2009 and in the US in 2011, was the first once-daily LABA to gain clearance. Arcapta/Onbrez is licensed only for COPD and is not indicated for asthma. The European Medicines Agency (EMA) approved indacaterol dosages of 150mcg and 300mcg once-daily, while the US Food and Drug Administration (FDA) approved the therapy in dosages of 75mcg once-daily. Twice-daily LABAs are approved for COPD, including GlaxoSmithKline’s Serevent (salmeterol), which was approved in the US in 1997, Novartis’s Foradil (formoterol, marketed in the US by Merck & Co.) and AstraZeneca’s Oxis (formoterol, marketed in the EU only). Sunovion’s Brovana (arformoterol, marketed in the US only) is a nebulised twice-daily inhalation solution approved for COPD.
KOL Insight: COPD

Combination therapies to drive significant market growth

**Arcapta/Onbrez (indacaterol; Novartis)**

**Drug summary**

Novartis’s (indacaterol, formerly QAB149), marketed as Arcapta in the US and Onbrez in Europe, is administered in the Breezhaler DPI (known as the Neohaler in the US).

Onbrez was approved in Europe in November 2009 at two dose strengths, 150mcg and 300mcg once-daily (the only LABA licensed at two dose levels in Europe). The EMA approved the two dose strengths based on data that the higher dose provided additional clinical benefit with regard to breathlessness. In July 2011, the FDA approved Arcapta 75mcg once-daily (a higher dose of 150mcg once daily was not cleared). In January 2013, Novartis and Eisai terminated a deal to co-promote Onbrez in Japan following a “review of sales strategies for the products,” which may mean sales were below expectations.

In 2012, Arcapta/Onbrez generated sales of $134 million. Arcapta/Onbrez is most likely cannibalising Novartis’s Foradil (formoterol) sales and taking share from GlaxoSmithKline’s Serevent (salmeterol), rather than expanding the market. Novartis do not provide Arcapta/Onbrez sales by region, although a majority of sales are assumed to be in Europe given the lack of formulary coverage in the US where the lower (less effective) dose is approved.

**Table 12: Arcapta/Onbrez (indacaterol, Novartis)**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Indacaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Long-acting beta2-agonist</td>
</tr>
<tr>
<td>Originator</td>
<td>Novartis</td>
</tr>
<tr>
<td>Dosing (EU)</td>
<td>Breezhaler DPI: indacaterol 150mcg or 300mcg once-daily</td>
</tr>
<tr>
<td>Approved indication (EU)</td>
<td>Maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD</td>
</tr>
<tr>
<td>Dosing (US)</td>
<td>Neohaler DPI: indacaterol 75mcg once-daily</td>
</tr>
<tr>
<td>Approved indication (US)</td>
<td>Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD</td>
</tr>
<tr>
<td>Approval date</td>
<td>2011 (US); 2009 (EU); Japan (2011)</td>
</tr>
<tr>
<td>Company reported global sales 2012</td>
<td>$134m</td>
</tr>
</tbody>
</table>

Source: Arcapta/Onbrez prescribing information, company reported sales
Poor efficacy and a lack of differentiation adversely affected sales in Europe. Sales of Onbrez in Germany were negatively impacted in 2011 following a reference pricing review by The Institute for Quality and Efficiency in Healthcare (IQWiG): the reimbursed price of Onbrez was reduced below that of generic LABAs.

“The problem with indacaterol was when it came into the market in Germany, Novartis made several mistakes. They want to fight against Spiriva, and from my point of view, this was not smart. The smarter approach would have been to show that indacaterol is better than formoterol. The only thing they [Novartis] embarked upon was to find out that they are non-inferior compared to tiotropium. And that, of course, is not a good argument. There were no data supporting that indacaterol is clearly better than formoterol, and because of that, they got a bad price when they introduced the drug into the German market. So it’s basically not used which is quite unfortunate because I think it is a good drug.”

Professor Claus Vogelmeier (Europe)

“I was surprised that for some patients it was extremely difficult to support and to take it on a long-term basis, mostly for coughing or lack of efficacy. At the beginning, it was prescribed by a lot of physicians. For most of the patients, they are going back to old combinations using formoterol plus the LAMA. Some of the patients remain on indacaterol, but it was not the expected success.”

Professor Pascal Chanez (Europe)

Novartis are also developing QMF-149, a fixed-dose combination of indacaterol and Merck & Co.’s mometasone (which was originally developed by Schering-Plough). Phase II development for asthma and COPD is currently ongoing, with filings for both indications expected in the EU in 2015. Novartis/Merck & Co. have no plans to launch QMF-149 in the US.

**Indacaterol comparator trials use indacaterol 150mcg**

The US approved dose of indacaterol 75mcg is the minimum effective dose. The higher doses approved by the European Medicines Agency (EMA) according to Rossi and colleagues “significantly reduce pulmonary hyperinflation, thereby improving exercise tolerance.”

“It’s a great drug (indacaterol); it probably is at least equivalent to Spiriva. It may even be superior. There haven’t been any head-to-head comparisons with the dose approved

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In the US. In Europe, the higher doses seem to be more efficacious than Spiriva, so it's a reasonable choice.”

Dr Donald P. Tashkin (US)

Comparative studies with indacaterol, such as INVIGORATE, INTENSITY and INSTEAD, use indacaterol 150mcg and not the lower indacaterol 75mcg dose approved in the US. Novartis cannot use data from these studies to market Arcapta in the US.

The 52 week INVIGORATE study recruited approximately 3,500 patients with severe COPD who had at least one exacerbation within the previous year. Patients were randomised to receive indacaterol 150mcg once-daily or tiotropium 18mcg once-daily. The primary outcome was trough FEV₁ at 12 weeks with a secondary outcome of rate of COPD exacerbations at 52 weeks. As in the 12-week INTENSITY study, the INVIGORATE study found that indacaterol was non-inferior to tiotropium based on the mean trough FEV₁. Indacaterol, however, did not demonstrate non-inferiority to tiotropium based on the annual exacerbation rate of 0.79 with indacaterol and 0.61 with tiotropium). According to the INVIGORATE study authors, “tiotropium afforded greater protection from exacerbations, although the absolute number of events was small and the difference between treatments is of uncertain clinical importance.” The ongoing INSTEAD trial is comparing indacaterol 150mcg once-daily with Seretide (study NCT01555138) over 26 weeks. The trial is recruiting patients with moderate COPD with a primary endpoint of trough FEV₁ at 12 weeks. Results are expected in 2014.


Phosphodiesterase-IV (PDE-IV) inhibitors

Takeda’s Daxas/Daliresp (roflumilast) was the first, and remains the only, oral PDE-IV inhibitor available. Roflumilast was originally developed by Altana Pharma, which was acquired by Nycomed in 2007. Nycomed was subsequently acquired by Takeda in 2011. Roflumilast is believed to exert an anti-inflammatory by increasing intracellular cyclic AMP in lung cells although roflumilast’s specific mechanism of action is not well defined.
Daliresp/Daxas (roflumilast; Takeda/Forest)

**Drug summary**

Roflumilast (500mg once-daily) was approved in the EU in 2010 as Daxas and in the US in 2011 as Daliresp (where it is marketed by Forest). Daliresp/Daxas is approved as a maintenance treatment to reduce exacerbations in a narrow COPD population that includes individuals with severe COPD and chronic bronchitis with a history of COPD exacerbations. The US approval of roflumilast was based on two 52-week studies (studies 124 and 125) in patients with severe COPD and chronic bronchitis with a history of exacerbations. Concomitant use of ICS and LAMAs was not permitted; LABAs were permitted. Roflumilast reduced the rate of moderate or severe exacerbations by 15 percent and 18 percent in trial 124 and 125, respectively. The US Food and Drug Administration (FDA) required Forest to conduct a post-marketing 52-week study to demonstrate a clinically relevant effect of roflumilast on exacerbations as an add-on therapy to ICS/LABAs which should be completed in the first half of 2014 (study NCT01443845).

Table 13: Daliresp/Daxas (roflumilast; Takeda)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Roflumilast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Oral phosphodiesterase-IV inhibitor</td>
</tr>
<tr>
<td>Originator</td>
<td>Takeda (originally Altana)</td>
</tr>
<tr>
<td>Dosing (EU)</td>
<td>500mcg once daily</td>
</tr>
<tr>
<td>Approved indication (EU)</td>
<td>Maintenance treatment of severe COPD (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.</td>
</tr>
<tr>
<td>Dosing (US)</td>
<td>500mcg once daily</td>
</tr>
<tr>
<td>Approved indication (US)</td>
<td>A treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations</td>
</tr>
<tr>
<td>Approval date</td>
<td>2011 (US); 2010 (EU)</td>
</tr>
<tr>
<td>Company reported global sales 2012</td>
<td>$80m (US only, April 2012 to March 2013)</td>
</tr>
</tbody>
</table>

Source: Daliresp/Daxas prescribing information, company reported sales

**Daliresp/Daxas has poor tolerability and a restricted label**

An oral route of administration and non-steroidal mechanism are potentially powerful marketing positions in respiratory therapy, as demonstrated by Merck & Co.’s success with Singulair (montelukast) in asthma. Daliresp/Daxas sales have been hampered by a
restricted label; poor tolerability, with side effects including diarrhoea and nausea; variable US formulary coverage; and restrictions on use in some European markets.

In England, the National Institute for Health and Care Excellence (NICE) did not make a recommendation for the use of Daxas as no clinical data was available which examined the benefit of adding Daxas to triple therapy of LAMA and ICS/LABA (the patient group in which NICE believed Daxas was most likely to be used). NICE recommended a clinical trial of Daxas as an add-on therapy in patients with LAMA and ICS/LABA.

“NICE considered the benefits were not big enough against the adverse effects. I think it’s been a very disappointing treatment. Side effects are quite unpleasant. Patients don’t really want to go on with the treatment. There is a very small reduction in exacerbations, so the patient is not going to notice any benefit”

Professor Peter Barnes (Europe)

“The committees who have to approve whether a medication is being admitted to the market in the Netherlands or not were not convinced from the data, so roflumilast is not available in the Netherlands. You can’t prescribe it.”

Professor Rene Aalbers (Europe)

“Roflumilast is an interesting drug; I certainly use a fair amount of it as an add-on therapy when my triple drugs have not been controlling exacerbations. The major problem with roflumilast is that it has limited benefit as far as lung function is concerned, which is why the FDA didn’t approve it for lung function, and it has significant GI side effects. I would estimate that about a third of people can’t tolerate the 500mcg dose.”

Professor Byron Thomashow (US)
Pipeline therapies

The following section provides an overview of pipeline products currently in late-stage development for the treatment of COPD.

Fixed-dose Long-Acting Muscarinic Antagonists/Long-Acting Beta Agonist (LAMA/LABA) combinations

Novartis’s Ultibro (indacaterol/glycopyrronium once-daily) was approved in Europe in September 2013; a US filing is expected in the fourth quarter of 2014. GlaxoSmithKline’s Anoro (umeclidinium/Vilanterol) is likely to be the first LAMA/LABA to become available in the US market. A possible delay in the completion of Phase III trials with Boehringer Ingelheim’s tiotropium/olodaterol may mean US/EU filings are unlikely until the first half of 2014. The US filing of Almirall/Forest’s aclidinium/formoterol, which was expected in the fourth quarter of 2013, has been delayed following a pre-new drug application (NDA) meeting. AstraZeneca’s glycopyrronium/formoterol combination is likely to be the fourth or fifth LAMA/LABA to be filed for approval.

Table 14 presents the fixed-dose LAMA/LABA combinations in development, and estimated US and EU filing dates.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>US filing</th>
<th>EU filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrronium/formoterol</td>
<td>Novartis</td>
<td>Q4 2014</td>
<td>Approved (September 2013)</td>
</tr>
<tr>
<td>Umeclidinium/vilanterol</td>
<td>GlaxoSmithKline</td>
<td>Filed (December 2012)</td>
<td>Filed (January 2013)</td>
</tr>
<tr>
<td>Tiotropium/olodaterol</td>
<td>Boehringer Ingelheim</td>
<td>1H 2014</td>
<td>1H 2014</td>
</tr>
<tr>
<td>Aclidinium/formoterol</td>
<td>Forest/Almirall</td>
<td>Uncertain (was Q4 2013)*</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Glycopyrronium/formoterol</td>
<td>AstraZeneca (Pearl Therapeutics)</td>
<td>1H 2015</td>
<td>1H 2015</td>
</tr>
</tbody>
</table>

* in August 2013, Forest/Almirall announced the US filing would be delayed following a pre-NDA meeting.

Source: company reports; clinicaltrial.gov
**Anoro (umeclidinium/vilanterol; GlaxoSmithKline)**

**Drug summary**
GlaxoSmithKline submitted a new drug application (NDA) with US regulators for Anoro, a once-daily Long-Acting Muscarinic Antagonists/Long-Acting Beta Agonist (LAMA/LABA) fixed dose combination of umeclidinium and vilanterol, in December 2012. Anoro is administered using the Ellipta device, which is the same device used in the company’s Relvar/Breo. GlaxoSmithKline licensed vilanterol, a LABA, from Theravance, but developed umeclidinium in-house. GlaxoSmithKline is seeking approval of two dose strengths: umeclidinium 62.5mg/vilanterol 25mcg and umeclidinium 125mg/vilanterol 25mcg. An application was made to the European Medicines Agency (EMA) in January 2013 with the same dose strengths.

<table>
<thead>
<tr>
<th>Table 15: Anoro (umeclidinium/vilanterol); GlaxoSmithKline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecule</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td><strong>Company</strong></td>
</tr>
</tbody>
</table>
| **Dosing *** | Umeclidinium 62.5mg/vilanterol 25mcg once-daily  
Umeclidinium 125mg/vilanterol 25mcg once-daily |
| **Anticipated indication** | Maintenance bronchodilator treatment to relieve symptoms in patients with COPD |
| **Filing date** | Filed (EU); filed (US) |
| **Source:** FirstWord |

**Higher dose approval possible in the EU but may not in the US**
In September 2013, the umeclidinium/vilanterol NDA was discussed at an FDA advisory panel meeting, which voted 13-0 in favour of approval of umeclidinium 62.5mg/vilanterol 25mcg once-daily as a long-term maintenance treatment of airflow obstruction in COPD patients (13 yes, 0 no).

The FDA did not request the advisory panel to vote on the higher-dose umeclidinium 125mg/vilanterol 25mcg combination. The decisive panel vote means it is most likely that the FDA will approve Anoro by 18 December 2013, the US Prescription Drug User Fee Act (PDUFA) goal date. Although the FDA did not consider the higher dose, the EMA may do so given that the regulator approved higher doses of GlaxoSmithKline’s Seretide/Advair and Novartis’s Arcapta/Onbrez than the FDA.
One KOL felt that the Anoro clinical development programme was “poor” and did not include exacerbation studies (the Breo FDA filing included two one-year exacerbation studies).

“The problem with the GlaxoSmithKline combination is they have a very good anticholinergic - that’s theumeclidinium - and they have a mediocre LABA. A severe mistake that GlaxoSmithKline made is that they did a very poor study programme.

When you compare the programme - the Relvar programme - with the programme that they did for the LABA/LAMA combination, there’s no comparison. There were no exacerbation data.”

Professor Claus Vogelmeier (Europe)

The EU filing of Novartis’s LAMA/LABA, Ultibro, included exacerbation data from the SPARK trial; ongoing pivotal trials with LAMA/LABAs developed by Boehringer Ingelheim, Almirall/Forest and AstraZeneca do not include exacerbation endpoints.

GlaxoSmithKline may have derived some advantages by not including exacerbation data in the initial filing for Anoro. As the Anoro pivotal trials only included a lung-function endpoint, filing was possible perhaps 6 to 12 months earlier than if exacerbation endpoints were included, meaning Anoro is able to enter the market sooner. In addition, as Anoro will not have an exacerbation claim, this differentiates the product from GlaxoSmithKline’s ICS/LABA products, Breo and Seretide/Advair, which both have exacerbation claims. GlaxoSmithKline may position Anoro as the treatment of choice in COPD patients with moderate disease (where an exacerbation claim is not required in most patients) and Breo as the preferred treatment in COPD patients with severe or very severe COPD.

**Impressive Umeclidinium/vilanterol clinical trial data**

In July 2012, GlaxoSmithKline announced the completion of four 6-month lung-function pivotal studies with umclidinium/vilanterol. The primary endpoint for all studies was trough FEV1 on day 169.

Two studies compared umclidinium/vilanterol with the individual components and placebo; in both trials, the efficacy of umclidinium/vilanterol was superior to the individual components. The first evaluated umclidinium 125mg/vilanterol 25mcg with component and placebo once-daily\(^\text{38}\). All active treatments produced statistically significant improvements in trough FEV1 versus placebo; the greatest difference relative to placebo was 238mL with umclidinium/vilanterol. The second evaluated umclidinium 62.5mcg/vilanterol 25mcg,

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umeclidinium 62.5mg, vilanterol 25mcg or placebo\textsuperscript{39}. All active treatments produced statistically significant improvements in trough FEV\textsubscript{1} versus placebo; the greatest difference relative to placebo was 167mL with umeclidinium/vilanterol. The other two studies had an active comparator arm using tiotropium, in which umeclidinium 125mg/vilanterol 25mcg and umeclidinium 62.5mg/vilanterol 25mcg both showed statistically significant improvements in trough FEV\textsubscript{1} compared with tiotropium\textsuperscript{40}.

In January 2013, GlaxoSmithKline began a 900 patient study of umeclidinium 62.5mg/vilanterol 25mcg versus tiotropium with a primary endpoint of trough FEV\textsubscript{1} on day 169 (study number NCT01777334). In March 2013, GlaxoSmithKline began a second study comparing umeclidinium 62.5mg/vilanterol 25mcg to Advair (fluticasone 250mcg/salmeterol 50mcg) with a primary endpoint of 24-hour weighted-mean serial FEV\textsubscript{1} on day 84 (study number NCT01817764).


\textsuperscript{40} Anzueto, MD et al. The Efficacy And Safety Of Umeclidinium/Vilanterol Compared With Tiotropium Or Vilanterol Over 24 Weeks In Subjects With COPD [A4268] American Thoracic Society 2013, May 17-22, Philadelphia.
Tiotropium/olodaterol (Boehringer Ingelheim)

**Drug summary**

Boehringer Ingelheim is developing a once-daily combination of tiotropium/olodaterol, which uses the Respimat device. Two ongoing replicate Phase III trials (TONado 1 and TONado 2) involving approximately 5,100 patients are examining tiotropium/olodaterol compared with the individual components (study numbers NCT01431287 and NCT01431274). The primary endpoints for both studies are trough FEV1, FEV1 AUC0-3h and St George’s Respiratory Questionnaire (SGRQ) score at 6-months (week 24). The SGRQ endpoint will combine data from the two studies.

**Table 16: tiotropium/olodaterol (Boehringer Ingelheim)**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Tiotropium/olodaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Long-acting beta2-agonist/Long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>Company</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Dosing</td>
<td>Tiotropium (2.5mg of 5mcg)/olodaterol 5mcg once-daily</td>
</tr>
<tr>
<td>Anticipated indication</td>
<td>Maintenance bronchodilator treatment to relieve symptoms in patients with COPD</td>
</tr>
<tr>
<td>Filing date</td>
<td>EU (1H 2014); US (1H 2014)</td>
</tr>
</tbody>
</table>

**KOLS positive about the outcomes of the trials and filing expected to be in Q1 2014**

The two trials started recruitment in September 2011 and, based on the length of other pivotal trials with LAMA/LABA combinations (around 18 months), a completion date in the first half of 2013 would be anticipated. According to clinicaltrials.gov, both trials were still ongoing in September 2013 (although recruitment has closed), which suggests the earliest filing could be in the first half of 2014. KOLs were positive about the data from Phase II studies with tiotropium/olodaterol.

“There is an absolute synergistic effect of this combination in terms of benefit. From the beginning it starts already, within half an hour, and this effect continues at least six, seven, eight hours. If you look to the picture you have the feeling it is synergistic, and not additive.”

Professor Rene Aalbers (Europe)

“Olodaterol and tiotropium would be a good combination, I think. That clinical data are quite convincing. I think the others would probably be as good. So umclidinium/vilanterol are probably going to be similar ... and indacaterol—well the
**KOL Insight: COPD**

*Combination therapies to drive significant market growth*

*QVA-149 will be similar. So I think they are all going to be pretty much competing with each other.*

Professor Peter Barnes (Europe)

Olodaterol received a positive vote from an US Food and Drug Administration (FDA) panel and is expected to be approved by the regulator. Tiotropium has more than a decade of clinical use. Barring any safety signals emerging from the combination of the two drugs, the chance of approval of olodaterol/tiotropium is high given the positive result from the TIOSPIR study with Spiriva Respimat. If TIOSPIR had show the Respimat device raised mortality with tiotropium monotherapy, the FDA would not have approved the olodaterol/tiotropium combination as this also uses the Respimat device.
Aclidinium/formoterol (Almirall/Forest)

Drug summary
Almirall and Forest are developing a twice-daily combination of aclidinium/formoterol delivered in the Pressair DPI, which is known as the Genuair DPI outside the US. Filings in the US and EU were expected in the fourth quarter of 2013. In August 2013, Forest/Almirall announced that the FDA filing would be delayed following a pre-new drug application (NDA) meeting in which the regulator identified deficiencies in the chemistry, manufacturing and control (CMC) portion of the submission.

The aclidinium and formoterol clinical development programme included two pivotal studies (ACLIFORM COPD in Europe and AUGMENT COPD in the US). The trials examined two dosage forms: aclidinium 400mcg/formoterol 6mcg and aclidinium 400mcg/formoterol 12mcg. In the AUGMENT study, aclidinium 400mcg/formoterol 12mcg demonstrated statistically significant improvement in FEV1 versus formoterol 12mcg at week 24 of 45mL; aclidinium 400mcg/formoterol 6mcg did not.

Almirall is planning a 900-patient, 6-month lung-function study comparing aclidinium 400mcg/formoterol 12mcg with fluticasone/salmeterol (study NCT01908140). The trial, which does not include US recruitment sites, has a primary outcome of FEV1 at week 24.

Table 17: aclidinium/formoterol; Almirall/Forest

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Aclidinium/formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Long-acting beta2-agonist/Long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>Company</td>
<td>Almirall/Forest</td>
</tr>
<tr>
<td>Dosing</td>
<td>Aclidinium 400mcg/formoterol 12mcg twice-daily</td>
</tr>
<tr>
<td>Anticipated indication</td>
<td>Maintenance bronchodilator treatment to relieve symptoms in patients with COPD</td>
</tr>
<tr>
<td>Filing date</td>
<td>Uncertain; in August 2013, Forest/Almirall announced the US filing would be delayed following a pre-NDA</td>
</tr>
</tbody>
</table>

Source: FirstWord
Glycopyrronium/formoterol (AstraZeneca/Pearl Therapeutics)

Drug summary
In June 2013, AstraZeneca completed the acquisition of Pearl Therapeutics in a deal valued at $1 billion, which included a $560 million upfront payment with potential future payments of $450 million. Pearl Therapeutics’ lead product, PT003, is a twice-daily combination of glycopyrronium/formoterol delivered with a pMDI, which uses “novel co-suspension formulation technology,” according to Pearl Therapeutics. Glycopyrronium is the same Long-Acting Muscarinic Antagonists (LAMA) used in Novartis’s Seebri and combination product, QAB-149.

Table 18: glycopyrronium/formoterol; AstraZeneca/Pearl Therapeutics

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Glycopyrronium/formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Long-acting beta2-agonist/Long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>Company</td>
<td>AstraZeneca/Pearl Therapeutics</td>
</tr>
<tr>
<td>Dosing</td>
<td>Unknown. Twice-daily.</td>
</tr>
<tr>
<td>Anticipated indication</td>
<td>Maintenance bronchodilator treatment to relieve symptoms in patients with COPD</td>
</tr>
<tr>
<td>Filing date</td>
<td>EU (1H 2015); US (1H 2015)</td>
</tr>
</tbody>
</table>

Source: FirstWord

PT003 will enter into competitive market
AstraZeneca are conducting two Phase III trials with PT003 comparing glycopyrronium/formoterol with the individual components and placebo; the PINNACLE 1 trial has an open-label tiotropium arm. The primary endpoint for both the PINNACLE 1 and PINNACLE 2 studies is trough FEV₁ at 6-months; both have a primary completion date in the fourth quarter of 2014, indicating potential US/EU filings in 2015. Phase II dose ranging studies examined twice-daily dosing of glycopyrronium 1.2mcg to 18mcg combined with 9.6mcg of formoterol.

Barring any safety signals emerging from the combination of the two drugs, the chance of approval of glycopyrronium/formoterol is high as the LABA component, formoterol, is already approved in the US, which is an advantage given the US Food and Drug Administration’s (FDA) safety concerns with LABAs. The LAMA component, glycopyrronium, has been approved in the EU as Novartis’s Seebri.
Long-Acting Beta2 Agonists (LABAs)

Striverdi (olodaterol; Boehringer Ingelheim)

Drug summary

Striverdi (olodaterol) is a once-daily Long-Acting Beta2 Agonist (LABAs) developed by Boehringer Ingelheim and delivered using the Respimat device.

Table 19: Striverdi (olodaterol; Boehringer Ingelheim)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Olodaterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Long-acting beta2-agonist</td>
</tr>
<tr>
<td>Company</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Dosing</td>
<td>Olodaterol 5mcg once-daily</td>
</tr>
<tr>
<td>Anticipated indication</td>
<td>Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD</td>
</tr>
<tr>
<td>Filing date</td>
<td>EU (uncertain, assumed filed); US (filed)</td>
</tr>
</tbody>
</table>

Source: FirstWord

FDA may request for postmarketing surveillance

The olodaterol NDA was discussed at an FDA panel meeting in January 2013, which voted 15-0 with one abstention in favour of approval in terms of efficacy and safety. Although the panel vote does not bind the FDA to any decision, it is almost certain that the FDA will approve Striverdi, as it would be unprecedented for the agency to refuse approval when an advisory committee vote is so strongly in favour of approval. The panel felt that the safety profile was similar to other LABAs, but there was concern regarding the occurrence of lung related malignant neoplasms, and several members of the committee thought that post-marketing surveillance was warranted.

"Olodaterol seems to be okay, but I am not sure that it is as good as indacaterol. The problem is that there are so far very few published data with regards to olodaterol, whereas when you compare that with indacaterol there have been a bunch of studies that have been published and that tells you there is a very robust signal."

Professor Claus Vogelmeier (Europe)
Pivotal trials with Striverdi allowed concomitant tiotropium

The olodaterol filing included four 48-week spirometry trials (studies 11-14), four six-week spirometry trials (studies 24, 25, 39 and 40) and two 6-week exercise tolerance trials. The pivotal 48-week spirometry trials included olodaterol 5mcg, olodaterol 10mcg and placebo arms, and trials 13 and 14 also included the active comparator formoterol. The co-primary endpoints were FEV1 area under curve (AUC) 0-3hrs and trough FEV1 measured at 12 weeks in trials 11 and 12 and at 24 weeks in trials 13 and 14. Trials 39 and 40 included the active comparator tiotropium. Giving patients a higher dose of olodaterol did not provide greater benefits.

The week 12 trough FEV1 response to olodaterol once-daily 5mcg compared to placebo was an average of 65ml. Although olodaterol had a modest bronchodilatory effect, the pivotal trials allowed background maintenance therapy, including LAMAs and ICS, but not a LABA. As shown in the figure below, the bronchodilatory response to olodaterol was lower in trials that allowed maintenance therapy including tiotropium (trials 11-14) compared to trials in which patients were on tiotropium, olodaterol or formoterol but no other maintenance bronchodilator therapy (trials 39 and 40); in these trials, the trough FEV1 response was similar for olodaterol and tiotropium.

Figure 6: Background Maintenance Bronchodilator Therapy Influences Response to Olodaterol

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Fixed-dose Inhaled Corticosteroid/Long-Acting Muscarinic Antagonists/Long-Acting Beta (ICS/LAMA/LABA) combinations

Currently, triple therapy of an ICS/LABA plus a free-dose LAMA is relatively common, used in approximately 30 percent of US COPD patients. A fixed-dose ICS/LAMA/LABA combination could improve adherence and simplify treatment sequencing, as therapy could be stepped-up from LAMA to LAMA/LABA to ICS/LAMA/LABA.

The main drawback of combining three actives in one inhaler, aside from a complex clinical development and regulatory approval process, is dose-flexibility and tolerability issues.

“My general therapeutic approach in COPD or in fact in any pulmonary disorder, is to shy away from combination treatment and the reason I do that is because if patients get side effects, you are not sure which it is so you’ve got to stop both. The other thing is that the doses are fixed and if you want to change it for whatever reason - side effect profile or effectiveness or an asthma component - what are you going to use? And that’s why I am not really too much in favour of these long-acting combination treatments. It’s not like treating hypertension.”

Dr Edward Eden (US)

As the combination of an ICS/LABA and free-dose LAMA can already achieve the therapeutic goal of triple therapy, the rationale for developing triple fixed-dose combinations was questioned by one KOL.
“Personally, I think that is a waste of everybody's time and effort because from my standpoint, a combination of Spiriva and Advair, for example, works perfectly well. And unless the triple drug is going to be less expensive than that combination - and there is no way that is going to happen - this is a waste of everybody's time and effort. From my standpoint, it has been a tremendous waste of time, effort and money in this push to get a triple agent. My patients have no problem using a combination of Spiriva and Advair so I think that has been a waste of time.”

Professor Byron Thomashow (US)

**Chiesi’s triple fixed-dose ICS/LAMA/LABA combination**

Chiesi’s fixed-dose triple combination therapy product combines glycopyrronium, beclometasone and formoterol in the Modulite MDI device. A Phase II dose-finding study was completed in 2012 which assessed a free-dose of glycopyrronium of 12.5mcg, 25mcg and 50mcg; one inhalation twice daily) added to Foster/Fostair (beclometasone 100mcg/formoterol 6mcg, two inhalations twice daily). Foster/Fostair is currently approved for asthma in Europe but not in the US; Chiesi plans to file for European Marketing Agency (EMA) marketing authorisation of Foster in COPD in 2013.

Table 20: Beclometasone/formoterol/glycopyrronium (Chiesi)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Beclometasone/formoterol/glycopyrronium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhaled Corticosteroid/Long-acting beta2-agonist/Long-acting muscarinic antagonist</td>
</tr>
<tr>
<td>Company</td>
<td>Chiesi</td>
</tr>
<tr>
<td>Dosing</td>
<td>Unknown. Twice daily</td>
</tr>
<tr>
<td>Anticipated indication</td>
<td>Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD</td>
</tr>
<tr>
<td>Filing date</td>
<td>EU (2017); US (n/a)</td>
</tr>
</tbody>
</table>

Chiesi have added two Phase III studies with the triple combination to clinicaltrials.gov (study numbers NCT01917331 and NCT01911364) which plan to recruit patients with severe or very severe COPD and at least one exacerbation in the last 12 months. NCT01917331 is a 52-week study comparing the triple combination with beclometasone/formoterol with a primary outcome of trough FEV1 at week 26; a secondary outcome is exacerbations at week 52. NCT01911364 is a 52-week trial comparing the triple combination with tiotropium and the combination of beclometasone/formoterol plus free-
dose tiotropium. The primary outcome is COPD exacerbation rate at week 52 with a secondary outcome of trough FEV₁ at week 52. The trials, which are expected to open for recruitment in the first quarter of 2014, have a completion date in 2016.

**GlaxoSmithKline’s Ellipta device: a platform for triple therapies**

GlaxoSmithKline’s Ellipta DPI has a unique dual-strip feature, which may facilitate the development of triple therapy combination products, as it is possible to combine two actives in one strip, and a third active in the other strip. This should allow greater dosing flexibility and may overcome some of the technical challenges in co-formulating three actives. In March 2013, GlaxoSmithKline completed a Phase I study with fluticasone furoate, umeclidinium, and vilanterol (study number NCT01691547). One of the study arms investigated a “new blend” of umeclidinium/vilanterol within a single strip combined with fluticasone furoate delivered via the second strip.

**Muscarinic antagonist/beta2 agonists (MABAs)**

Inhaled MABAs are bi-functional single molecules that combine the properties of a LABA and a LAMA. The most clinically advanced MABA is GlaxoSmithKline’s GSK961081, which was licensed from Theravance. A Phase II study examined GSK961081 twice-daily or once-daily in 436 patients with moderate or severe COPD. The improvement in day 29 trough FEV₁ was 215mL for the 400mcg once-daily arm and 249mL for the 200mcg twice-daily arm. A second trial evaluated GSK961081 400mcg compared with a combination of tiotropium once-daily plus salmeterol twice-daily in 50 patients with moderate COPD. The mean trough FEV₁ values relative to placebo were 115mL for GSK961081 and 103mL for the combination of tiotropium plus salmeterol. In August 2013, Theravance reported that GlaxoSmithKline had “recently initiated preclinical Phase III enabling studies” which will examine the combination of GSK961081 with fluticasone furoate. GlaxoSmithKline informed Theravance that a Phase III study with GSK961081 monotherapy will not be initiated in 2013.

AstraZeneca is developing a MABA, AZD2115, which completed a Phase II trial in March 2012; Almirall’s preclinical candidate, LAS190792, is expected to enter clinical trials in 2013.

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42 Wielders PL et al. A new class of bronchodilator improves lung function in COPD: a trial with GSK961081. Eur Respir J. 2013 Mar 21


44 Theravance 10-Q. August 2013.
As monotherapies, MABAs will compete with LAMA/LABAs: the greatest potential of MABAs may lie in a fixed-dose combination with an inflammatory agent: at present, this would most likely be an ICS, although other inhaled inflammatory agents, such as PDE-IV inhibitors, could be an alternative. A fixed-dose MABA/ICS combination product may have a simpler clinical development programme and lower regulatory bar compared with LAMA/LABA/ICS fixed-dose combinations. A disadvantage of MABAs is that they have a fixed ratio of muscarinic antagonist and beta2-agonist activity.

“It’s actually really a cool concept in the same molecule, I mean it would be very interesting from a mechanistic perspective if there was a synergy due to the same molecule, but I think that remains to be seen.”

Dr Stephen Rennard (US)

“Yes, probably this will be a revolution…the single drug with a dual action.”

Professor Maurizio Luisetti (Europe)

“One advantage is that it would be simpler to combine it (a MABA) with a third molecule to make a triple, so a triple would essentially be a double – it is easier to make, you don’t have to worry about three drugs interacting; just two. I really don’t see any other advantage.”

Dr Donald P. Tashkin (US)

“I think MABAs have been very difficult because it is extremely difficult to balance the anti-cholinergic and the beta agonist effects in the same molecule. And of course, once you’ve made the molecule, you can’t change it because it’s a fixed ratio. I would think that the only role for them is that it would be easier to make a triple combination.”

Professor Peter Barnes (Europe)

“I think it is a very nice possibility. If this MABA is really as good as a combination of two bronchodilators then this would be the obvious step for a triple; that would be a MABA/ICS instead of LAMA/LABA/ICS. Yes, but it is dangerous too, because by having this combination we - again - maybe are using inhaled steroids for a majority of patients and some of them may not need it.”

Dr Marc Miravitlles (Europe)
Novel anti-inflammatory and anti-oxidants

FirstWord identified 11 novel anti-inflammatory and anti-oxidant drugs that are in active Phase I/II development or completed Phase I/II trials in 2012 or 2013 as shown in the table below. The earliest potential filing for these drugs is likely to be from 2016.

KOLs were positive about the potential of p38 kinase inhibitors, phosphoinositide 3 kinase inhibitors and PDE-IV inhibitors. KOLs were supportive of drugs that reduce oxidative stress; as several antioxidant mechanisms are involved in COPD pathogenesis, it is uncertain how effective antioxidants such as GlaxoSmithKline’s oral soluble epoxide hydrolase inhibitor and Otsuka’s tetomilast will be.

Other drugs, not specifically commented on by KOLs, include AstraZeneca/Bayer’s AZD5423 and AZD7594, which target the glucocorticoid receptor (the aim is to develop a nonsteroidal COPD treatment). Johnson & Johnson are developing the inhaled “narrow spectrum” kinase inhibitor, JNJ 49095397 (RV568); Johnson & Johnson acquired the originator, RespiVert, in 2010. AstraZeneca are developing two biological agents—benralizumab, an anti-IL-5R monoclonal antibody, and MEDI8968, an anti-IL-1R monoclonal antibody —which could be positioned as add-on therapies to reduce the frequency of COPD exacerbations. Novartis’s oral BCT197, which has an unknown mechanism, appears to be a novel treatment for COPD exacerbations, rather than preventing exacerbations.

Table 21: Phase I/II trials of novel anti-inflammatory COPD drugs: Phase I/II trials of novel anti-inflammatory COPD drugs

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drug</th>
<th>Mechanism</th>
<th>Route</th>
<th>Phase</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>AZD7624</td>
<td>p38 kinase inhibitor</td>
<td>Inhaled</td>
<td>I</td>
<td>72</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>MEDI8968</td>
<td>Anti-IL-1R mAb</td>
<td>Subcutaneous</td>
<td>II</td>
<td>300</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AZD5423</td>
<td>Non-steroidal anti-inflammatory</td>
<td>Inhaled</td>
<td>II</td>
<td>353</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>benralizumab</td>
<td>Anti-IL-5R mAb</td>
<td>Subcutaneous</td>
<td>II</td>
<td>90</td>
</tr>
<tr>
<td>Chiesi</td>
<td>CHF6001</td>
<td>PDE-IV inhibitor</td>
<td>Inhaled</td>
<td>II</td>
<td>65</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>GSK2256294</td>
<td>Soluble epoxide hydrolase inhibitor</td>
<td>Oral</td>
<td>I</td>
<td>54</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>GSK2269557</td>
<td>Phosphoinositide 3 kinase inhibitor</td>
<td>Inhaled</td>
<td>I</td>
<td>28</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>JNJ 49095397</td>
<td>Kinase inhibitor</td>
<td>Inhaled</td>
<td>II</td>
<td>200</td>
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<tr>
<td>Novartis</td>
<td>BCT197</td>
<td>Unknown</td>
<td>Oral</td>
<td>II</td>
<td>183</td>
</tr>
<tr>
<td>Otsuka</td>
<td>tetomilast</td>
<td>Superoxide anion inhibitor</td>
<td>Oral</td>
<td>II</td>
<td>720</td>
</tr>
</tbody>
</table>
A 12-week study with Pfizer’s oral p38 kinase inhibitor, which examined PH-797804 6mg once-daily, or placebo added onto salmeterol/fluticasone in 377 persons with moderate-severe COPD reported a mean improvement in FEV₁ of 27mL compared with placebo. As PH-797804 is not a bronchodilator, the minor improvement in FEV₁ that is not clinically relevant, is expected; perhaps more significantly, high sensitivity C-reactive protein was decreased indicating an anti-inflammatory effect. Mild-moderate rash was observed in 8 percent of PH-797804 treated patients. Pfizer have also investigated an inhaled p38 kinase inhibitor, PF-03715455, which completed a Phase I trial in December 2011. Recruitment in a Phase I trial of AstraZeneca’s inhaled p38 kinase inhibitor, AZD7624, was suspended in January 2013; recruitment has since restarted. GlaxoSmithKline’s losmapimod, an oral p38 kinase inhibitor, which completed a Phase II trial December 2011, is unlikely to progress due to side effects (liver toxicity).

“I think there’s been a lot of information about the p38s over the years, and it’s just getting more exciting. My personal opinion is that it is extremely promising.”

Dr Stephen Rennard (US)

“p38 MAP kinase play a role in orchestrating the inflammatory response and so, again, the potential hazard would be increasing infection, and there is at least one of them that is being developed for inhalation. GlaxoSmithKline’s drug - liver toxicity was a big issue in that one.”

Dr Donald P. Tashkin (US)

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“There's a good rationale for them, because we know that p38 is activated in COPD, and that it switches on many of the genes that are known to be involved in the disease.”

Professor Peter Barnes (Europe)

GlaxoSmithKline's inhaled phosphoinositide 3 kinase (PI3K-delta) inhibitor, currently in Phase I development, was regarded as promising a promising approach.

“I think PI3 kinase delta inhibitors are quite promising because we've shown that PI3 kinase delta is activated by oxidative stress, and it is the main mechanism for steroid resistance in COPD. So if you inhibit this enzyme, then you might reverse steroid resistance and I think several companies are developing oral or inhaled inhibitors of that.”

Professor Peter Barnes (Europe)

Chiesi's CHF 6001 is an inhaled PDE-IV inhibitor in Phase II trials (study number NCT01730404), which according to Chiesi is more potent than roflumilast and was "extremely well tolerated in extended safety studies." Verona Pharma's RPL554, an inhaled dual PDE-III/IV, has completed Phase II studies in COPD patients.

“I think there is still interest (in PDE). It is true that PDE4 inhibitors have a broad anti-inflammatory effect, so if you could get around the side effect problem, it would potentially be a good treatment.”

Professor Peter Barnes (Europe)

“I don't think that anybody believes that roflumilast is the last generation PDE4 inhibitor. There's four different PDE4 subtypes and it may be that the next generation will be selective and be able to get more benefits and less side effects. I think there's lots and lots of room to expect future studies with phosphodiesterase inhibitors.”

Dr Stephen Rennard (US)

“Chiesi is working on an inhaled PDE4 inhibitor and there are data that I have seen that suggest that they may have a more favourable drug than roflumilast that is capable of reducing side effects. This is early phase and it's too early to say if this concept works.”

Professor Claus Vogelmeier (Europe)

Another novel potential mechanism of action is to reduce oxidative stress. A decrease in Nrf2 (nuclear erythroid-related factor 2) signalling in COPD patients may reduce their ability to defend against oxidative stress. In 2010, AbbVie licensed bardoxolone methyl, a synthetic triterpenoid that reduces oxidative stress and inflammation through Nrf2 activation, from Reata Pharmaceuticals. Bardoxolone methyl was being developed as a potential treatment
for chronic kidney disease. In October 2012, Reata halted a Phase III trial due to safety concerns.

“I think a promising general approach is to reduce oxidative stress, but that has proved difficult to do at the moment, so people are looking at trying to understand why the antioxidants do not increase in COPD and there is a lot of interest in a transcription factor called NRF2 looking at drugs that activate NRF2. It has proved to be quite difficult. I think Abbott was developing one of those drugs, but it failed because it was called bardoxolone methyl ester and it failed because there was a high toxicity.

Professor Peter Barnes (Europe)

One KOL was uncertain about the prospects for GlaxoSmithKline’s GSK2256294, an oral soluble epoxide hydrolase inhibitor that is in Phase I development.

“Well I think there is hope for the strategy of reducing oxidative stress, but whether having an effect on epoxide hydrolase would be relevant is not clear...because there are several antioxidant mechanisms and presumably they are trying to stimulate epoxide hydrolase because it seems to be defective in COPD, but I don’t know what their strategy is with that.”

Professor Peter Barnes (Europe)
Treatment focus

The following section describes unmet needs in COPD and the current and future COPD treatment algorithms, summarized in the figure below (Figure 7)

Figure 7: Key insights from the unmet needs and current and future treatment algorithms

- No novel anti-inflammatory, anti-oxidant or vaccines are likely to influence treatment practice within the next five years
- Screening spirometry in high-risk patients may enable the earlier detection and treatment of COPD
- Once-daily dosing may improve adherence but twice-daily dosing is not a significant competitive disadvantage
- Widespread use of ICS means a high uptake of LAMA/LABAs will require ICS withdrawal in many COPD patients
- LAMA/LABA sales, at least initially, may not be as great as hoped for by pharmaceutical companies
- Changes in guidelines and treatment practice may require further LAMA/LABA exacerbation data

Source: FirstWord
Unmet needs in Current chronic obstructive pulmonary disease

Five unmet needs were identified by KOLs:

- Novel agents that modify disease progression and/or reduce exacerbations;
- Early detection of COPD;
- Improving patient drug adherence;
- Confirming COPD diagnosis;
- Understanding of the mechanism of action of COPD drugs.

Unmet need 1: Novel agents that modify disease progression and/or reduce exacerbations

A disease-modifier would slow, and ideally halt, the progressive decline in FEV₁ such that COPD patients had the same natural decline in FEV₁ as persons without COPD. Drugs that reduce exacerbations more effectively are also required. Ideally, novel drugs would be delivered orally, which is the most effective delivery route to reach the lung parenchyma and small airways, although oral administration can increase the risk of side effects⁴⁶.

“I think the great unmet need is for an anti-inflammatory treatment that is safe and effective in order to more effectively reduce exacerbations and disease progression. The trouble is there is nothing very close to market outside the bronchodilators.”

Professor Peter Barnes (Europe)

“We do need more effective anti-inflammatories in COPD. Not only anti-inflammatories, maybe antifibrotics, because in some respects COPD is a fibrotic disease laying down collagen in the airway wall that contributes to fixed-airflow obstruction.”

Dr Donald P. Tashkin (US)

“I would say number one from my point of view, is that we do not have a really good anti-inflammatory.”

Professor Claus Vogelmeier (Europe)

“Inflammatory processes, especially ones that involve neutrophilic inflammation and macrophage inflammation, and probably lymphocytic inflammation as well, all contribute to the progression of the disease. And so anything that interrupts any of those pathways has the potential to modify disease progression.”

Dr Stephen Rennard (US)

“Patients now have less exacerbations than they used to have in the last decade. The new treatments are more effective and it is clear that we do not see so many exacerbations and they are not so severe, but, still, this is the main problem of our patients. This is what drives patients to the hospitals. So still we have not eradicated exacerbations”

Dr Marc Miravitlles (Europe)

“I think the medications we are using now are basically what we were using 30 years ago. There’s been nothing to prevent or modify - in any significant way - the course of the disease. What we are doing is we are treating people, essentially, in the end stage of their disease. So there has been very little that has been accomplished.”

Dr Edward Eden (US)

“To interfere with the natural history of the disease you need to restore to some point some new alveoli; you need to have stem cells. The main issue is to know exactly where you are going to graft this new tissue.”

Professor Pascal Chanez (Europe)

In an attempt to address the unmet need for novel therapies, pharmaceutical companies have made a considerable R&D investment in COPD. Unfortunately, of 14 drugs with novel mechanisms of action that entered clinical development from 2007 onwards, none has progressed into Phase III trials. AstraZeneca terminated development of AZD1236, (a matrix metalloproteinase inhibitor), AZD9668 and AZD9819 (neutrophil elastase inhibitors), AZD6553 (a protease inhibitor), MEDI2338 (an anti-IL-18 monoclonal antibody), and MEDI7814 (an anti-C5/C5a antibody). Roche’s palovarotene (gamma-selective retinoid agonist) and Boehringer Ingelheim’s inhaled epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor BIBW2948, also failed to progress.

Chemokine antagonists held initial promise although none have entered Phase III development, including CXCR2 antagonists developed by Schering-Plough (navarixin), AstraZeneca (AZD5069) and GlaxoSmithKline (GSK1325756/GSK656933). Development of AstraZeneca’s inhaled CCR1 antagonist, AZD4818, and oral CCR2b antagonist, AZD2423, have not progressed.

“CXCR2 antagonists reduce neutrophils in COPD lungs, but when they came to do long term clinical studies over a year they didn’t see any clinical improvement (with navarixin). GlaxoSmithKline has a similar drug and it looks pretty much similar to the Schering-Plough drug, so I wouldn’t be optimistic that that’s going to work.”

Professor Peter Barnes (Europe)
“(navarixin) was very disappointing; they are not going forward in Phase III. So the problem with the CXCR2 antagonist is that it may not be enough to just antagonise a single chemokine receptor; you may have to block more than one. So you really need some broad spectrum chemokine inhibitor. I don't think that just a single CXCR2 antagonist is going to make it.”

Dr Donald P. Tashkin (US)

“One of the problems is we don't have a real biomarker so what kind of study do you do? How do you find out in the early phase if the drug works? How do you define a dose/effect relationship? If you have a drug which is purely anti-inflammatory, you may not see an immediate lung function signal.”

Professor Claus Vogelmeier (Europe)

**Unmet need 2: Early detection of COPD**

In a US study, 30 percent of COPD patients had an FEV₁ of 50 percent or less of predicted at spirometry-confirmed diagnosis, reflecting a significant delay in COPD diagnosis. Of these patients, 75 percent were aged 65 years or older at diagnosis, compared to 5 percent under the age of 50 years.

Figure 8 GOLD grade of airflow obstruction at diagnosis (US)

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The delay in COPD diagnosis is due to late presentation: persons with COPD may gradually restrict physical activity, only seeking medical care when they experience significant symptoms. In smokers, the early signs of COPD, such as chronic cough or dyspnea, may be accepted as an expected consequence of smoking.

“People with COPD adjust to their physiologic compromise by reducing their activity, and so as a result they don't have complaints because they're not doing anything that precipitates shortness of breath.”

Dr Stephen Rennard (US)

“COPD is linked to tobacco smoking and it’s a kind of stigma. If they smoke, they have a disease related to smoking so ‘that’s life’.”

Professor Pascal Chanez (Europe)

“Patients will not report these symptoms to their physicians. They do not even recognise that they are short of breath. They simply adapt their lifestyle to live within the limits of...”
their physiologic impairment. So I think this is a real, real problem and I don’t know if it's going to go away.”

Dr Donald P. Tashkin (US)

“People think it's normal they feel a little breathless and say ‘well it's normal, it's the age we are talking about.’ So, yes, underdiagnosis is absolutely another point.”

Professor Rene Aalbers (Europe)

“A lot of COPD is hidden, is undiagnosed, especially in its early stages. I think that primary care physicians who are the first line are not always screening patients for airflow obstruction and I think that patients are falling through the cracks. And then five or ten years later they are developing shortness of breath and the options are limited.”

Dr Edward Eden (US)

“There is a reluctance to present with the symptoms of COPD because there is still a stigma and that it is a self-inflicted disease caused by smoking.”

Professor Christopher Cooper (US)

There are no national screening spirometry programmes to detect COPD in the general population. GOLD advocates active case finding but not screening spirometry. KOLs believed screening spirometry is currently the only way to diagnose COPD earlier.

“It has been controversial about whether everyone should be screened primarily because a large number of people without disease would be screened - and that’s an expense. I think that the general consensus is that spirometry should be performed if people have symptoms.”

Dr Stephen Rennard (US)

“Screening is not recommended by the GOLD guidelines. I disagree with that position. I believe that [screening spirometry] is probably the only way, or the major way, in which we can increase the ability of physicians to diagnose this disease.”

Dr Donald P. Tashkin (US)

Screening spirometry to identify patients with mild disease would not necessarily increase treatment rates. There is no evidence that earlier intervention in patients with mild COPD changes long-term outcomes. This is because of lack of clinical trial data in patients with mild COPD. Treatment benefits in patients with moderate disease, however, have been demonstrated in the UPLIFT (Understanding Potential Long-Term Impacts on Function with
Tiotropium) trial\(^{48}\) and TORCH (TOwards a Revolution in COPD Health) trial\(^{49}\). Screening spirometry in high-risk patients (those who smoke or who have respiratory symptoms) has detected undiagnosed COPD in around 1 in 5 screened persons and a majority are GOLD grade 2\(^{50,51}\).

“All the data is pointing out that we should start patients with moderate disease and don’t wait until the disease is more severe. So diagnose early, and start treatment early - don’t wait until the disease has advanced.”

Dr Antonio Anzueto (US)

“We need to try to intervene before the problems emerge. We have seen data from clinical studies – the TORCH, the UPLIFT – [that] clearly has pointed out that for people who had a milder form of the disease, these bronchodilators have a tremendous impact on them. We learned from ECLIPSE too, that the decline in lung function is not necessarily the person who has more severe disease. So putting all those together really tells us...we really need to try to intervene sooner’.

Dr Antonio Anzueto (US)

“I believe to get really optimal results we have to start early. Early case finding is probably the right strategy. This strategy has the advantage that you only test a few, and have a very high rate of people that you detect.”

Professor Claus Vogelmeier (Europe)

The position of GOLD is unlikely to change until novel treatments are available that prevent or slow disease progression, making early detection beneficial.

“In the future, if we had anti-inflammatory treatments we might try to pick patients up before they get symptoms to treat them with some type of drug that would stop them developing symptoms. Just like we now treat high cholesterol with drugs that don’t have any effect on symptoms, but they prevent future disease development.”

Professor Peter Barnes (Europe)


“If you could protect the airway from the effects of cigarette smoking in some way, it would require people to take medications when they actually don’t have the disease yet, which is a difficult thing for people to do. But the sort of approaches that would inhibit the effects of cigarette smoke on the airway, these would be things that could be considered.”

Dr Edward Eden (US)

Unmet need 3: Improving patient drug adherence

Adherence to therapy is low in COPD patients as with other chronic conditions. One approach to improve adherence is to reduce the frequency of dosing. Of the four main inhaled products (by sales) used to treat COPD, Spiriva is taken once-daily, Seretide and Symbicort are taken twice-daily, and Combivent is taken four-times a day.

Based on a US administrative claims database, the proportion of days (PDC) covered over 12 months was 43 percent for once-daily, 37 percent for twice-daily and 23 percent for drugs taken four times a day. There was a large difference in PDC between once-daily and four-times daily drugs (20 percentage points), but the difference between once-daily and twice-daily drugs, however, was six percentage points.

“The big difference is between once or twice compared to three and four times a day.”

Professor Peter Barnes (Europe)

Although once-daily dosing may improve adherence, this dosing frequency may not automatically be preferred by all patients, as confirmed in a study of 2,138 COPD patients which found that although approximately half of the patients expressed a preference for once-daily dosing, one-quarter preferred twice-daily dosing and one-quarter were unsure.

A high self-perceived need for controller medication was associated with a once-daily dosing preference; dosing preferences were not associated with disease severity or frequency of exacerbations.

The reasons for non-adherence are varied and include out-of-pocket expense, as well as perceptions of efficacy; patients may stop taking effective drugs once symptoms improve, or may not persist with a treatment they feel is ineffective.

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“Where they get the medication for free, the issue of compliance comes down to if they have the perception of the efficacy of the medication. And they feel the medication is working, and they are feeling much better they say, ‘well it’s time for me to stop; I don’t need to continue to take my medication because I am better.’”

Dr Antonio Anzueto (US)

“People are extending their prescriptions to save on costs. They are taking the medication once a day instead of twice a day. They are missing out an inhalation dose to extend it out so they are not having to spend the money to buy the drugs.”

Dr Edward Eden (US)

“There are several things working against regular compliance: cost is one, convenience of use, ease of device and appreciation of effectiveness. That’s why the short-acting bronchodilators give much more a therapeutic advantage because they are easily appreciated by the patient.”

Dr Edward Eden (US)

“If they have relief of their symptoms I think that they usually stay on the treatment prescribed. The problem I think is that some patients don’t think that the treatment is a long term treatment and they just use the treatment as a cycle during exacerbations and then they may stop the treatment.”

Professor Maurizio Luisetti (Europe)

KOLs agreed, on the whole, that once-daily dosing is more convenient for patients, although twice-daily dosing was not regarded as a significant competitive disadvantage.

“Now the biggest difference is between Relvar and the two twice-a-day drugs and it’s a once a day agent. And for most people, I think, it’s going to be more convenient than twice-a-day. Some people may prefer twice-a-day. So I think that the advent of once a day LABA/ICS combinations is likely to replace to a very large extent, the twice-a-day drugs.”

Dr Stephen Rennard (US)

“I think that once daily will make the medication-taking more convenient; you only have to do it once a day.”

Dr Donald P. Tashkin (US)

“You know twice-a-day, there are going to be many, many medications at twice-a-day, so being twice-a-day may not be that bad. Like aclidinium and formoterol and this other
medication [AstraZeneca/Pearl Therapeutics glycopyrronium/formoterol], these may not be, at the end of the day, that bad.”

Dr Antonio Anzueto (US)

“I think once a day treatments are usually more effective than twice a day because it means that the effect carries over to the next day whereas twice a day treatment tend to wear off before the next dose. For example, indacaterol, which is once a day, seems to work better than salmeterol twice a day.”

Professor Peter Barnes (Europe)

“In COPD, this is a chronic long term disease and...taking a drug once or twice a day is, in my view, of very little importance.”

Dr Edward Eden (US)

“It's still an open question as to whether once-daily [dosing] is truly superior. It may be preferred; it maybe better patient adherence, but whether it's truly better for medical management is still an open question.”

Professor Christopher Cooper (US)

“You can use twice-daily drugs and there are companies that tell you that this is much better because patients may get worse in the evening, and then you need another dose. You know this is an open field from my point of view and it's not clear which one is right.”

Professor Claus Vogelmeier (Europe)

“In some patients once-a-day is okay, in other patients they need the twice-a-day to control their symptoms. It is difficult, of course to preview which are the patients who are responders and non-responders.”

Professor Maurizio Luisetti (Europe)

Once-daily dosing may be preferred on the grounds of patient convenience but this does not necessarily mean the drug will be perceived as offering increased value by payers. In the US, Tudorza (twice-daily) did not receive favourable formulary decisions despite being priced at a discount to Spiriva (once-daily). Clinical differentiation, rather than dosing frequency, is likely to be key to favourable reimbursement decisions for GlaxoSmithKline’s Breo/Relvar, as well as LAMA/LABAs. Market share will also be determined by pricing.
“I think everything is going to come down to price. This is going to be a huge price fight. All over the world we have price becoming a big issue. So everything is going to come down to price.”

Dr Antonio Anzueto (US)

Unmet need 4: Confirming COPD diagnosis

A US study reported that only 32 percent of patients with a new diagnosis of COPD had undergone spirometry. As the study authors note, “while most physicians would not think of prescribing antihypertensives without measuring BP [blood pressure], many seem comfortable prescribing bronchodilators without spirometric evidence of airway obstruction.” A second study of US primary care physicians reported that only 17 percent ordered pulmonary function test or spirometry in smokers with shortness of breath, citing time constraints and/or lack of awareness of GOLD recommendations (less than 50 percent of respondents were aware of the existence of the GOLD guidelines).

“I think the main problem is lack of time, because spirometry requires at least 10 to 15 minutes and a primary care physician has about eight minutes per patient. I mean, most GPs [general practitioners] have been provided with the spirometers, but they have not been provided with a person to perform the spirometries. They just don’t have time.”

Dr Marc Miravitlles (Europe)

“It is an extremely difficult disease for the general practitioners because they have no clear avenue to cure the disease. And at least in France they do not have access to lung function measurements and they are scared to do it and they don’t earn any money by doing lung function measurements. So all smokers with any respiratory symptoms are called ‘COPD’ whatever their lung function.”

Professor Pascal Chanez (Europe)

The under-utility of spirometry means that in clinical practice, a COPD diagnosis is based on clinical grounds without confirming the presence, or severity, of airflow limitation; the consequence is potential inappropriate prescribing.

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“In at least 50 percent of patients with a diagnosis of COPD, they never receive a lung function test in Italy. So the diagnosis is based only on symptoms and that means that the patient has not been correctly assessed for the severity of the disease. I think probably a majority of general practitioners still diagnose COPD like they did 20, 25 or 30 years ago.”

Professor Maurizio Luisetti (Europe)

“They have not done the proper diagnosis and they may have heart failure or they may have other conditions, and that is the reason they don't feel the benefit of the medication. There are patients referred to me because of severe COPD - not improving on treatment, and then I find out that it is not that they are not improving on treatment, (it) is because they don’t have COPD.

Dr Antonio Anzueto (US)

“There may be misdiagnosis which means the patients get treated as if they are asthmatic, which is what tends to happen, or they may not be diagnosed at all which means they are not getting any treatment.”

Professor Peter Barnes (Europe)

“Confusion can arise in trying to determine whether someone has COPD or asthma. I think that it’s important, and some have argued it doesn’t matter, the treatment is going to be similar. But I think they are entirely different disease mechanisms and I think they warrant a different therapeutic approach.”

Professor Christopher Cooper (US)

“COPD is defined in terms of spirometric features; it's not an expensive test and it easily can be done in primary physicians' offices. It's about as difficult to do as blood pressure measurement, but it isn't done in all offices.”

Dr Stephen Rennard (US)

“I think in general with all these LABA/LAMA combinations coming up I would think that doctors will think more about the question - is this COPD?”

Professor Claus Vogelmeier (Europe)

“The only way to make the diagnosis is spirometry. And don't rely on symptoms; we need to rely on spirometry.”

Dr Antonio Anzueto (US)
“It is certainly clear that many people [with COPD] are being over-treated who probably don’t have the disease, and many people who have the disease are being under-treated. So it’s both too much and too little therapy.”

Professor Byron Thomashow (US)

“Although we have a number of drugs available for COPD now and there is more attention to the treatment and to the prescription of the drugs... I don't see the same attention to the improvement of the diagnosis and the general assessment of the disease. So I think at this point needs still to be largely improved.”

Professor Maurizio Luisetti (Europe)

Increasing the use of spirometry will depend on continued efforts by GOLD and other organisations to raise awareness, although providing financial incentives (and possibly penalties) can accelerate this process. In England, primary care physicians are paid to confirm diagnosis by spirometry with the result that in 2011-12, 71 percent of patients had spirometry confirmed initial diagnosis56.

“The government has a scheme that rewards GPs [general practitioners] for measuring spirometry. They actually get paid for doing it. They hope that the take-up of spirometry is going to be much greater in general practice.”

Professor Peter Barnes (Europe)

**Unmet need 5: Understanding the mechanism of action of COPD drugs**

KOLs noted the need to better characterise the mechanism of action of COPD drugs, including newer agents such as PDE-IV inhibitors, as well as older COPD drugs such as theophylline.

“I think we are going to have this incredible amount of bronchodilators, and I think the unmet need is to fully understand what else they do, and what is the impact on bronchodilation. We are seeing more and more data that, for example, tiotropium may not only be antimuscarinic [but] may have some important anti-inflammatory effects. We have learned over the years the LABAs do have significant anti-inflammatory effects, so the unmet need is to further characterise what are the proper mechanisms: roflumilast (for example), ...how does it decrease exacerbations; how does it impact the disease?”

Dr Antonio Anzueto (US)

“You may have heard of the selective PDE4 inhibitor, roflumilast. That is a very interesting drug because it is a pill and it affects a central pro-inflammatory mechanism in the body that is not restricted to COPD. This may play a role in diabetes; this may play a role in coronary artery disease and others. Takeda is not very...aggressive with regards to finding out what the drug’s potential really is.”

Professor Claus Vogelmeier (Europe)

Theophylline, a bronchodilator with anti-inflammatory properties, is not a preferred treatment for COPD due to associated toxicities due to the relatively high doses required. In the future, low-dose theophylline could potentially be useful in reversing corticosteroid-resistance in COPD and severe asthma. Inhaled theophylline is being studied as a potential novel therapy, although no further clinical development has been reported by sponsor Pulmagen Therapeutics since 2009.

“We are scratching our heads and saying, 'how does this work? What's going to happen at the end of the day with theophylline?' And theophylline is one of these medications that keep coming and keep coming and keep coming and it's surprising everybody because it does something. We are learning with theophylline is the fact that the medication may do other things that we do not understand. For example, the effect on the up-regulated 'steroid' receptor.”

Dr Antonio Anzueto (US)
Current chronic obstructive pulmonary disease treatment algorithm

The principle international COPD clinical guideline is published by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)\textsuperscript{57} and was last updated in February 2013; a major revision was published in 2011. In England and Wales, The National Clinical Guideline Centre published an updated COPD guideline in 2010 that was commissioned by NICE\textsuperscript{58}. NICE guidelines include a clinical and cost-effectiveness evaluation of treatments; GOLD recommendations are not guided by cost-effectiveness.

In other countries, such as in Germany, Switzerland, Canada, Australia, Spain, the Czech Republic and Argentina, national COPD guidelines are published which may diverge from GOLD guidelines. For example, Spanish COPD guidelines, unlike GOLD, recommend treatment options based on clinical phenotypes, such as “mixed COPD-asthma” and “frequent exacerbator.”

“Not all guidelines are going in the same direction. I mean GOLD has moved in one direction; in Spain we have been moving in another direction. In my opinion, the guidelines should be moving in differentiating responders to different treatments. So I think the guidelines should move in the sense of identifying—since we have more drugs we need to identify which patients will respond to which drug. I mean it's not that all drugs may work in everybody.”

Dr Marc Miravitlles (Europe)

GOLD guidelines

In 2011, the GOLD guidelines changed the terminology of COPD severity based on FEV\textsubscript{1} from a staging system (GOLD stage 1 to 4) to a grading system (GOLD grade 1 to 4) to emphasise that FEV\textsubscript{1} refers purely to the grade of airflow obstruction, rather than clinical severity or disease stage. The 2011 update also introduced a new clinical evaluation assessment which categorised COPD patients into four groups (A to D) based on a combination of FEV\textsubscript{1}, symptoms and exacerbation risk or history (patients with more severe COPD and/or history of exacerbations have a higher risk of exacerbations\textsuperscript{59}).


\textsuperscript{59} Hurst JR et al., et al Susceptibility to exacerbation in chronic obstructive pulmonary disease. NEJM. 2010;363:1128-38.
COPD patients are classified into those having “less” or “more” symptoms based on the assessed modified Medical Research Council Dyspnoea Scale (mMRC) and/or COPD Assessment Tool (CAT). An mMRC score of >=2 or a CAT score of >=10 is indicative of a high impact of symptoms. Patients are categorized as high risk if they have two or more exacerbations within the last year or FEV₁ <50 percent of predicted value.

Table 22: Initial recommended therapies by GOLD patient group (A-D)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Characteristics</th>
<th>Initial recommended therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk, less symptoms</td>
<td>SAMA or SABA</td>
</tr>
<tr>
<td>B</td>
<td>Low risk, more symptoms</td>
<td>LABA or LAMA (choice depends on patient preference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LABA + LAMA (patients with severe breathlessness)</td>
</tr>
<tr>
<td>C*</td>
<td>High risk, less symptoms</td>
<td>ICS/LABA or LAMA monotherapy</td>
</tr>
<tr>
<td>D*</td>
<td>High risk, more symptoms</td>
<td>ICS/LABA or LAMA monotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICS/LABA + LAMA (some evidence for triple therapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*roflumilast can be added in patients with chronic bronchitis</td>
</tr>
</tbody>
</table>

*Source: adapted from GOLD. Global Strategy for Diagnosis, Management, and Prevention of COPD (2013)

The GOLD clinical evaluation assessment reduces the reliance on spirometry to grade COPD severity, although it requires a more comprehensive and more time-consuming assessment of each individual patient. One KOL believed the new assessment system was imperfect.

“You’ve made a classification that was previously simple - the GOLD classification - to now one that is more complex and that is a disservice, in my feeling, because what you have now are three elements, whereas previously you had one element... It might be a better fidelity measure for epidemiological purposes, but in terms of management and approach, I don’t think it is helpful to the [general practitioner], particularly to be told you have to measure dyspnoea index and exacerbation rate when neither of these things are well defined.”

Dr Edward Eden (US)
The figure below overlays Seretide, Symbicort, Spiriva and Combivent onto GOLD A-D patients groups.

Figure 9 shows the key brands (by sales) by GOLD patient group (A-D).

![Figure 9: Key brands (by sales) by GOLD patient group (A-D)](image)

\[mMRC = \text{Medical Research Council Dyspnoea Scale; CAT = COPD Assessment Tool.}
\]

Source: adapted from GOLD. Global Strategy for Diagnosis, Management, and Prevention of COPD (2013)

A consequence of the A-D patient system is that patients with mild to moderate airflow obstruction (FEV\(_1\) >= 50% of predicted), which would be Group A or B patients based on severity of airflow obstruction alone, are moved into Group C or D based on exacerbation risk. The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate...
Endpoints) study found that only a minority (about 22 percent) of COPD patients with moderate airflow obstruction have frequent exacerbations.\(^{60}\)

The recommended therapy for Group A patients is a short-acting bronchodilator (SABA or SAMA). For Group B patients, a long-acting bronchodilator (LABA or LAMA) is recommended; there is no strong evidence to favour one over the other for initial maintenance bronchodilator therapy. In Group B patients with severe breathlessness, a combination treatment with a LABA and LAMA “can be considered.” GOLD based this recommendation on two lung-function studies that compared the combination of tiotropium and formoterol with tiotropium alone\(^{61,62}\).

The recommended first-line therapies for Group C patients are ICS/LABA or a LAMA. For Group D patients, the recommended first-line therapies are similar to Group C patients: ICS/LABA or a LAMA with some evidence from the OPTIMAL study supporting use of triple therapy (ICS/LABA and LAMA) as this improves lung function, quality of life and “may further reduce exacerbations.”

An alternative treatment option in group C and D patients is dual treatment with a LAMA and LABA, based on evidence that both reduce the risk of exacerbations and although “good long-term” studies are lacking, the principle of combination treatment with a LAMA and LABA “seems sound.” GOLD will likely recommend LAMA/LABAs as alternative treatment options. For GOLD to recommend LAMA/LABAs as first-choice therapies, it is probable that evidence of non-inferiority (and ideally superiority) versus ICS/LABAs in terms of reduction in exacerbations will be required.

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NICE guidelines (England and Wales)

NICE guidelines, updated in 2010, do not group patients into categories the way GOLD does, although the clinical assessment is the same (assess FEV₁, symptoms and exacerbation risk). The clinical assessment underpins the treatment algorithm, which adds additional drugs if symptoms or exacerbation persist:

- Use SABA or SAMA as required to alleviate symptoms

In people who remain breathless or have exacerbations despite use of SABA or SAMA, the guidelines suggest that:

- if FEV₁ is >= 50 percent of predicted offer either LAMA or LABA;
- if FEV₁ is < 50 percent of predicted, offer either a LAMA or a fixed-dose ICS/LABA;
- In any patient, irrespective of their FEV₁, who remains breathless or continues to have exacerbations despite taking ICS/LABA, triple therapy with a fixed-dose ICS/LABA plus a LAMA should be used.

In formulating the NICE guidelines, there are three points to note:

- A recommendation to move to a LABA + LAMA combination in those already taking a LAMA as sole maintenance therapy could not be made as clinical effectiveness data was considered insufficient;
- Triple therapy (ICS/LABA + LAMA) is recommended as a step-up treatment if symptoms or exacerbations persist on current therapy;
- NICE considered recommending that all patients with an FEV₁ < 50 percent should be started on triple therapy based on the reduction in exacerbations, but there was insufficient evidence to support this.

Figure 11 presents NICE’s COPD treatment algorithm.
Combination therapies to drive significant market growth

**Figure 10: NICE COPD Treatment algorithm**

- **Breathlessness and/or exercise limitation**
  - SABA or SAMA as required*

- **Exacerbations or persistent breathlessness**
  - FEV₁ ≥ 50%
    - LABA
    - LAMA**
      - Offer LAMA in preference to regular SAMA four times a day
  - FEV₁ < 50%
    - LABA + ICS**
      - Consider LABA + LAMA if ICS declined or not tolerated
      - Offer LAMA in preference to regular SAMA four times a day

- **Persistent exacerbations or breathlessness**
  - LABA + ICS in a combination inhaler
    - Consider LABA + LAMA if ICS declined or not tolerated

*SABA as required may continue at all stages; **discontinue SAMA

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta₂ agonist; ICS = Inhaled Corticosteroid; SABA = short-acting beta₂ agonists; SAMA = short-acting muscarinic antagonists

Device is not a deciding factor in selecting treatments

COPD drugs are delivered using dry power inhalers (DPIs), metered dose inhalers (MDIs) and the Respimat, a propellant-free inhaler (some SABAs, SAMAs and LAMAs may also be given using a nebulizer). A majority of COPD therapies use DPIs including:

- GlaxoSmithKline’s Accuhaler/Diskus DPI (Advair/Seretide) and Ellipta DPI (Relvar/Breo);
- AstraZeneca’s Turbohaler DPI (Symbicort);
- Boehringer Ingelheim’s HandiHaler DPI (Spiriva);
- Novartis’s Breezhaler/Neohaler DPI (Onbrez and Seebri);
- Almirall’s Genuair/Pressair DPI (Eklira/Tudorza).

AstraZeneca’s Symbicort is also approved as a metered dose inhaler (MDI) and Boehringer Ingelheim’s market the Respimat “soft mist” device (Spiriva and Combivent).

Most of the currently available devices were judged to be user-friendly and were not a deciding factor is selecting treatments.

“Most of them offer good features. Some people who have difficulty with one device or another - that’s rather individualised, but these devices are much, much easier to use than the kind of inhalational devices that were available 20 or 25 years ago so they are all pretty easy at this point.”

Dr Stephen Rennard (US)

“There is no ideal device around. There are pros and cons for each of them. The only thing that counts is what percentage of patients can deal with that device in a way that it works.”

Professor Claus Vogelmeier (Europe)

“For me, the preferred device is where the patients may have a perception of something... I don't care about dry powder or capsules. It's good to have variety of different inhalers but I have no favourite.”

Professor Pascal Chanez (Europe)
Figure 11 shows devices used in COPD treatment.

<table>
<thead>
<tr>
<th>Device/Brand</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim Respimat (Spiriva)</td>
<td>GlaxoSmithKline Accuhaler/Diskus DPI (Seretide)</td>
</tr>
<tr>
<td>AstraZeneca Turbohaler DPI (Symbicort)</td>
<td>Almirall Genuair/Pressair DPI (Eklira/Tudorza)</td>
</tr>
<tr>
<td>GlaxoSmithKline Ellipta DPI (Relvar/Breo)</td>
<td>Novartis Breezhaler/Neohaler DPI (Onbrez)</td>
</tr>
</tbody>
</table>

The Respimat device, a propellant-free inhaler that relies on energy released from a spring, was regarded by KOLs as effective in delivering drugs to the lower respiratory tract. The dose delivered by the Respimat, unlike DPIs, is not dependent on a patient’s inspiratory capacity.

“I think the simplest device, not only the most convenient, but the device most conducive to effective delivery to the lower respiratory tract is the Respimat.”

Dr Donald P. Tashkin (US)

“If the olodaterol/tiotropium combination goes to the Respimat, this is a much nicer device. It's a much easier to use device any way you look at it.”

Dr Antonio Anzueto (US)

“I think (Respimat) it is a superior delivery (compared to Ellipta or Breezhaler). It is superior in the availability of the delivery of the medications.”

Dr Antonio Anzueto (US)
“I think the soft-mist delivery systems are very interesting in terms of the emission velocity and the particle size. I think the Respimat is an excellent device.”

Professor Christopher Cooper (US)

“The Respimat is a very, very interesting device. It is typical German engineering. I mean very complicated and very sophisticated...and the patients love it. It gives you a very good feeling because it has this soft mist that comes out of it and it gives you time to inhale. It’s not faultless. For example, you have to turn it, and for turning it, you need quite some force. And there may be patients that cannot do that, but leaving that aside, this is a very user-friendly device.”

Professor Claus Vogelmeier (Europe)

DPIs are more reliable in delivering the required dose compared to MDIs, as DPIs are less dependent on inhaler technique (i.e. coordinating actuation with inhalation).

“We know that many patients don’t use inhalers correctly, particularly MDIs because when they don’t breathe in at the same time that they activate the aerosol. So dry powder inhalers tend to be taken more consistently. We think once a day is better than twice a day. Twice a day is much better than three times a day or four times a day.”

Professor Peter Barnes (Europe)

“The Advair Diskus. Well, of course, that’s very easy to use – breath-activated. Timing of actuation to inhalation is not important. It obviated that problem with the MDI, which is very technique-dependent. There are errors even with the DPI: not inhaling forcibly enough to deaggregate the powder, because you have to generate a certain inspiratory flow rate against the resistance of the device, and or not inhaling deeply enough; not holding your breath for a full ten seconds to allow the finer particles to settle by gravity.”

Dr Donald P. Tashkin (US)

“I think the Diskus is an incredible device. I think it’s a great device. Ellipta - it seems like a twist of the Diskus; it’s just a little easier to use. It's pretty much under the Diskus; it falls under the Diskus, but it is a little easier to use.”

Dr Antonio Anzueto (US)
For once-daily medications, the actual choice of device was not as critical as a twice-daily medication.

“For these once-a-day inhalers, it’s not such a big issue because they don’t need to take the inhaler out with them so they can do it at home and the HandiHaler is okay, it’s just rather primitive, but it works and the patients don’t mind it.”

Professor Peter Barnes (Europe)

Compared to other DPIs, GlaxoSmithKline’s Ellipta has a dual strip. GlaxoSmithKline is employing this novel feature to develop an Ellipta based triple-therapy product, which combines fluticasone furoate in the first strip with vilanterol/umeclidinium in the second strip.

“Yes, it’s a good device, there’s no question; it’s easy to use; you can use it for triple already. It’s made that way.”

Professor Claus Vogelmeier (Europe)
Current chronic obstructive pulmonary disease treatment practice

Inhaled Corticosteroid (ICS) are commonly used to treat COPD, with use ranging from 39 percent of patients in England to 80 percent of patients in Spain and Italy. ICS are most commonly prescribed as a fixed-dose ICS/LABA combination (the use of free-dose ICS to treat COPD is off-label), which are used in 62 percent of Spanish patients, 53 percent of US patients, 30 percent of French patients and 25 percent of English patients. Spiriva is also a commonly used maintenance treatment: around 40 percent to 50 percent of COPD patients are prescribed Spiriva, either as sole maintenance therapy or as triple therapy in combination with ICS and LABA; triple therapy is more common in the US, with 27 percent of patients following such a regimen, compared with 13 percent of patients in England.

GOLD and NICE recommend either a LAMA or LABA for initial maintenance bronchodilator therapy, although in practice, LABAs are used in only around 1 percent to 2 percent of COPD patients (which compares to 10 percent to 30 percent with Spiriva).

“You have a choice between a LAMA or a LABA. We would prefer tiotropium, just because it’s been around for a long time and we know it’s safe, so we tend to start people on tiotropium.”

Professor Peter Barnes (Europe)

“Single therapy, only the LABAs are very, very low [in Germany]. LABA/LAMA free combination is, at the moment, not very popular. The three most popular strategies are either: Spiriva alone, LABA/ICS or triple.”

Professor Claus Vogelmeier (Europe)

KOLs noted that GlaxoSmithKline and AstraZeneca (who both market ICS/LABA combinations) have not promoted their respective LABA monotherapies (Serevent and Oxis) in COPD.

“The companies who had these LABAs, with a few exceptions, also have the combination and they put all their effort in the combination. That was their priority, and they were not promoting at all the mono components.”

Dr Marc Miravitlles (Europe)

“For the longest time, we didn’t have a good one-a-day LABA. Serevent is not a great drug, and GlaxoSmithKline never really pushed it as a sole agent. So we never had a really good single-dose LABA until Arcapta was approved.”

Professor Byron Thomashow (US)
The use of the free-dose combination of LAMA + LABA (without an ICS) is uncommon in clinical practice, with use in only about 1 percent of patients. NICE could not recommend stepping up treatment from LAMA monotherapy to LABA + LAMA, as clinical data was considered insufficient. KOLs noted that the step-up to LAMA + LABA is “skipped” in clinical practice.

“We skipped the LAMA/LABA step in this disease. We sort of went directly from a single agent to a combined therapy. And that's a step that we shouldn't have skipped.”

Professor Byron Thomashow (US)

“Many patients with COPD receive the combination of LABA and Inhaled Corticosteroids even if they don’t have the severity requiring this combination. I usually try to add as a second step the LABA plus LAMA. This is not very common. It is much more common that the physician prescribes the LABA/Inhaled Corticosteroid.”

Professor Maurizio Luisetti (Europe)

Treatment practice: US

In the 2010 US National Health and Wellness Survey (NHWS), a self-administered online survey of 75,000 adults, 1,369 persons reported a diagnosis of COPD or emphysema; patients with co-morbid asthma were not excluded. The self-reported perception of disease severity was 45 percent, 44 percent and 12 percent for mild, moderate and severe COPD, respectively. Of the 1,369 patients, 64 percent reported use of at least one prescription medication. The reasons for lack of treatment were not explored in the study; the study did not examine prescribing by COPD severity.

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Figure 12 shows COPD prescribing practice in the US.

**Figure 12: COPD prescribing practice US, (2010)**

<table>
<thead>
<tr>
<th>Prescribing Practice</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMA only, 11%</td>
<td></td>
</tr>
<tr>
<td>LABA + LAMA only, 1%</td>
<td></td>
</tr>
<tr>
<td>LABA only, 2%</td>
<td></td>
</tr>
<tr>
<td>SABA or SAMA only, 24%</td>
<td></td>
</tr>
<tr>
<td>Any ICS, 62%</td>
<td></td>
</tr>
<tr>
<td>ICS/LABA only, 26%</td>
<td></td>
</tr>
<tr>
<td>ICS/LABA + LAMA, 27%</td>
<td></td>
</tr>
<tr>
<td>ICS only, 4%</td>
<td></td>
</tr>
<tr>
<td>ICS + LAMA, 5%</td>
<td></td>
</tr>
<tr>
<td>Any ICS, 62%</td>
<td></td>
</tr>
</tbody>
</table>

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta2 agonist; ICS = Inhaled Corticosteroid; SABA = short-acting beta2 agonists; SAMA = short-acting muscarinic antagonists


Based on the 879 patients who received a prescription medication, the percentage who reported use of LAMAs, LABAs, ICS and ICS/LABAs were as follows:

- Spiriva was used by 44 percent of patients, either as monotherapy (11 percent) or in combination with other maintenance therapies;
- Advair or Symbicort were used in 53 percent of patients;
- Triple therapy (ICS/LABA + LAMA) were prescribed for 27 percent of patients;
- LABA monotherapy was used by 2 percent of patients and free-dose LABA + LAMA therapy was used in 1 percent of patients;
- ICS was prescribed in 62 percent of COPD patients, mainly as a fixed-dose ICS/LABA combination;
In addition, 4 percent of patients were prescribed an ICS without a long-acting bronchodilator, which is not recommended.

Table 23: COPD prescribing practice (US), 2010

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Proportion treated, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA or SAMA only</td>
<td>Salbutamol and/or ipratropium</td>
<td>24</td>
</tr>
<tr>
<td>LAMA only</td>
<td>Spiriva</td>
<td>11</td>
</tr>
<tr>
<td>LABA only</td>
<td>Arformoterol or formoterol or salmeterol</td>
<td>2</td>
</tr>
<tr>
<td>LABA + LAMA only</td>
<td>Spiriva + arformoterol or formoterol or salmeterol</td>
<td>1</td>
</tr>
<tr>
<td>ICS/LABA only</td>
<td>Seretide or Symbicort</td>
<td>26</td>
</tr>
<tr>
<td>ICS/LABA + LAMA</td>
<td>Seretide or Symbicort + Spiriva</td>
<td>27</td>
</tr>
<tr>
<td>ICS only</td>
<td>Various</td>
<td>4</td>
</tr>
<tr>
<td>ICS + LABA (free-dose)</td>
<td>ICS + arformoterol or formoterol or salmeterol</td>
<td>0</td>
</tr>
<tr>
<td>ICS + LAMA</td>
<td>ICS + Spiriva</td>
<td>5</td>
</tr>
<tr>
<td>Grand totals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA (any combination)</td>
<td>Spiriva</td>
<td>44</td>
</tr>
<tr>
<td>ICS/LABA (any combination)</td>
<td>Seretide or Symbicort</td>
<td>53</td>
</tr>
<tr>
<td>ICS (free and fixed-dose combinations)</td>
<td>Total Seretide or Symbicort or free-dose ICS</td>
<td>62</td>
</tr>
</tbody>
</table>

LAMA = Long-Acting Muscarinic Antagonist; LABA = Long-Acting Beta2 Agonist; ICS = Inhaled Corticosteroid (which included flunisolide, mometasone, triamcinolone, fluticasone propionate and budesonide)

**Treatment practice: England**

An analysis of COPD prescribing practices in England linked prescriptions to individual patients\(^6^4\); prescribing was not analysed by COPD severity. It is unclear if patients with co-morbid asthma were excluded. Spiriva was prescribed in 44 percent of COPD patients, either as monotherapy in 28 percent of patients or in combination with other maintenance therapies.

Table 24: COPD prescribing practice, England, 2010

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Proportion treated, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA or SAMA only</td>
<td>Salbutamol and/or ipratropium</td>
<td>31</td>
</tr>
<tr>
<td>LAMA only</td>
<td>Spiriva</td>
<td>28</td>
</tr>
<tr>
<td>LABA only</td>
<td>Serevent</td>
<td>2</td>
</tr>
<tr>
<td>LABA + LAMA only</td>
<td>Spiriva + Serevent</td>
<td>0</td>
</tr>
<tr>
<td>ICS/LABA only</td>
<td>Seretide or Symbicort</td>
<td>12</td>
</tr>
<tr>
<td>ICS/LABA + LAMA</td>
<td>Seretide or Symbicort + Spiriva</td>
<td>13</td>
</tr>
<tr>
<td>ICS only</td>
<td>Beclometasone</td>
<td>10</td>
</tr>
<tr>
<td>ICS + LABA (free-dose)</td>
<td>Beclometasone + Serevent</td>
<td>1</td>
</tr>
<tr>
<td>ICS + LAMA</td>
<td>Beclometasone + Spiriva</td>
<td>3</td>
</tr>
<tr>
<td><strong>Grand totals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAMA (any combination)</td>
<td>Total Spiriva</td>
<td>44</td>
</tr>
<tr>
<td>ICS/LABA (any combination)</td>
<td>Total Seretide or Symbicort</td>
<td>25</td>
</tr>
<tr>
<td>ICS (free and fixed-dose combinations)</td>
<td>Total Seretide or Symbicort or beclometasone</td>
<td>39</td>
</tr>
</tbody>
</table>

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta2 agonist; ICS = Inhaled Corticosteroid; SABA = short-acting beta2-agonists; SAMA = short-acting muscarinic antagonist

Source: adapted from NICE. CG101: Chronic obstructive pulmonary disease (update): costing report. 23 February 2011.

LABA monotherapy was used infrequently with only 2 percent of patients prescribed Serevent alone; no patients were reported to use a free-dose LABA + LAMA combination. Seretide or Symbicort was prescribed in 25 percent of COPD patients. Further, 13 percent of COPD patients were prescribed triple therapy of ICS/LABA + LAMA and 39 percent were

prescribed an ICS, either as a fixed-dose ICS/LABA combination or free-dose ICS. The major inappropriate therapy was the off-label use of beclometasone without a long-acting bronchodilator in 10 percent of patients.

**Treatment practice: Spain, France, Italy**

In Spain, a 2008 study examined prescribing in approximately 4,000 COPD patients treated in primary health care facilities; 17.3 percent of patients had mild COPD, 55.3 percent had moderate, 24.1 percent had severe, and 3.2 percent had very severe COPD based on spirometry. The results were:

- 86 percent of patients received an ICS (either as an ICS/LABA or free-dose ICS)
- 40 percent of patients were prescribed Spiriva (either as monotherapy or in combination with other agents);
- 62 percent of patients were prescribed Seretide or Symbicort;
- 24 percent of patients were prescribed free-dose ICS and 24 percent were prescribed free-dose LABA, most likely co-prescribed but this is not made clear.

In France, ICS were used in 55 percent of patients with GOLD grade 1, 59 percent of patients with grade 2, 77 percent of grade 3 and 85 percent of grade 4 COPD. In addition, 30 percent of patients with any grade of airflow obstruction used Seretide or Symbicort. In Italy, a study of 4,094 COPD patients, of which 18 percent had mild COPD, 42 percent had moderate, 23 percent had severe and 17 percent had very severe disease, it was reported that 82 percent received an ICS, with 67 percent receiving the therapy in combination with LABA and 15 percent as a standalone.

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Prescribing point 1: ICS are widely used to treat COPD

GOLD recommends the use of ICS in patients with severe or very severe disease (FEV₁ < 50 percent of predicted) regardless of exacerbation history; ICS are also indicated in patients with mild to moderate airflow obstruction (FEV₁ ≥ 50 percent of predicted) who have a history of exacerbations. GOLD also recommended LAMA as a first line therapy in the same patient groups indicated an ICS, and dual treatment with a LAMA and LABA as an alternative.

Despite GOLD recommendations supporting LAMA monotherapy and LAMA + LABA therapy, ICS (largely ICS/LABA combinations) are the preferred maintenance treatment in most markets, ranging from 39 percent of patients in England, 62 percent in the US, 82 percent in Italy and 86 percent in Spain. As noted in the GOLD guidelines, the lack of comparative studies of ICS/LABA versus LAMA makes “differentiation difficult” – a recent systematic review concluded that the relative efficacy of ICS/LABA versus tiotropium alone is uncertain.

The dominance of ICS/LABAs was attributed by KOLs to primary care physicians (who also treat asthma patients) prescribing ICS based on the extrapolation of their anti-inflammatory effects in asthma.

“The problem with COPD is that inhaled steroids are very widely used because they are anti-inflammatory in asthma, but we know they are not anti-inflammatory in COPD and yet they are still used. So a big problem is really the misuse of inhaled steroids.”

Professor Peter Barnes (Europe)

“The doctors may think that...they can’t cure the disease so they want to control it as much as possible and they say, ‘well, in the same inhaler I can prescribe two drugs, so why use a bronchodilator alone if I’ve been told that by adding inhaled steroids I may have some added benefits, so I can just prescribe one inhaler with both.’”

Dr Marc Miravitlles (Europe)

“The role of Inhaled Corticosteroids in COPD is still not clearly resolved. Inhaled Corticosteroids are highly effective in allergic airway inflammation but they are unproven in toxic airway inflammation.”

Professor Christopher Cooper (US)

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In addition, an ICS/LABA may be preferred over LAMA or LAMA + LABA when there is diagnostic uncertainty that asthma is present, given that LABAs are contra-indicated without an ICS in asthma patients.

“I think a LABA/ICS is often used when there is some question as to whether people have asthma or not. This puts clinicians at a very awkward position: if somebody says, 'yeah, I used to have asthma,' then how do you deny them Inhaled Corticosteroid therapy? If something bad happens then you could be culpable.”

Dr Stephen Rennard (US)

“I think the issue here is the fact that why are people using that because they are concerned that the patient may have asthma. There may be an asthma component and that’s what really drives (that).”

Dr Antonio Anzueto (US)

“Since they are told not to use LABAs alone in asthma, and not to use inhaled steroids alone in COPD, to be on the safe side they say, 'well, if we combine both I am more ways doing right even if it’s asthma or COPD; it doesn’t matter'. So, it’s easy to prescribe a combination.”

Dr Marc Miravitlles (Europe)

The variation in ICS use between markets, and lack of uptake of LAMA monotherapy or LAMA + LABA as alternative treatments to ICS/LABAs, may stem from a lack of physician familiarity or agreement with guideline recommendations. A study of US primary care physicians reported that 50 percent were unaware of the existence of the GOLD guidelines69. Of note, in England, which has the lowest use of ICS, treatment practice may more closely follow guideline recommendations due to the centralised healthcare system which permits a national, top-down treatment strategy.

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Prescribing point 2: Free-dose ICS are not approved for COPD in the US or EU

In the US and EU, no free-dose ICS is approved for use in COPD: ICS are only approved for use in COPD as fixed-dose combinations with a LABA (Seretide and Symbicort).

GlaxoSmithKline did seek a COPD indication for Flovent (fluticasone propionate) for COPD in the US in 2001. However, the drugmaker withdrew the application in 2002, meaning any COPD patient indicated an ICS must be prescribed a fixed-dose ICS/LABA combination. No evidence that pharmaceutical companies are seeking approval of a free-dose ICS for approval in COPD was identified and GlaxoSmithKline is not seeking approval of free-dose fluticasone furoate for COPD.

As a majority of clinical trial data with ICS is based on ICS/LABA combinations, clinical guidelines lack an evidence base for free-dose ICS+LABA, or free-dose ICS+LAMA combinations. The latter is noted by GOLD as potentially effective but the “lack of evidence seems to be a result of lack of interest from the pharmaceutical industry rather than doubts about the rationale.”

As clinical guidelines generally only recommend drugs within the approved label, ICS/LABA combinations, and not free-dose ICS+LABA, are the recommend first-line therapy. There is ambiguity in the GOLD guidelines regarding free-dose ICS+LABA: the full GOLD guidelines do specifically recommend the use of fixed-dose ICS/LABA products in Group C patients but in Group D patients, the first choice therapy is “Inhaled Corticosteroid plus long-acting beta2-agonst.” This is open to interpretation as to whether a free-dose ICS+LABA can be used, although the evidence base supporting the recommendation was entirely based on fixed-dose ICS/LABA combinations. In the GOLD pocket guide, which is aimed at healthcare professionals, the distinction to use a fixed-dose ICS/LABA in group C patients is omitted.

The absence of approved free-dose ICS preparations for COPD, meaning the “decoupling” of ICS from LABAs in treatment practice is currently not possible, poses the question as to how drug switching will evolve in the future with regard to LAMA/LABA fixed-dose combinations. A patient cannot receive a fixed-dose LAMA/LABA combination and an ICS/LABA, which are mutually exclusive, and a switch from ICS/LABA to LAMA/LABA would mean withdrawal of the ICS, which physicians may be reluctant to do. Further, this change would be contraindicated in COPD patients with asthma. The alternative would be to prescribe a LAMA/LABA + ICS, although this would be off-label.
Prescribing point 3: FDA’s heightened risk attitude towards LABAs

In the US, all LABAs and fixed-dose ICS/LABA combinations include a boxed warning that LABAs increase the risk of asthma-related death. The labelling changes followed results from the Salmeterol Multi-center Asthma Research Trial (SMART), which showed an increase in asthma-related deaths in US patients receiving salmeterol. The finding with salmeterol is considered a class effect by the US Food and Drug Administration (FDA) and applies to all LABAs. GlaxoSmithKline’s Breo (fluticasone furoate/vilanterol) and Novartis’s Arcapta (indacaterol), which are only indicated for COPD in the US, include a boxed warning that LABAs increase the risk of asthma-related death.

“Most of my colleagues both in pulmonary medicine and in allergy—because I do asthma studies as well—are appalled at the bias, the anti-LABA bias of the FDA, and based on very poorly-designed studies, the FDA has put this box warning indicating LABA use does increase asthma related deaths. Of course COPD is not asthma, although there is a certain overlap, the extent of the overlap is unclear. In the literature, it varies from 10 percent to 50 percent—probably more like 20 percent—and that scares physicians. That’s the impact: It scares physicians. LABA monotherapy is a ‘no-no’ in asthma and since there is a certain overlap and since physicians are sometimes confused as to whether patients have COPD, or maybe an asthmatic component, if they respond significantly to a bronchodilator, they shy away from LABA monotherapy in COPD even though it has been shown to be safe”

Dr Donald P. Tashkin (US)

“LABAs are not dangerous in themselves, but they are dangerous because patients stop using the steroid, whereas in COPD the steroid doesn’t work anyway so it’s not an issue. And, as far as we know, LABAs are quite safe in COPD. There’s no evidence for cardiovascular problems or deaths. Outside America no one is concerned about this.”

Professor Peter Barnes (Europe)

A consequence of the boxed warning is that US physicians may be more cautious about prescribing LABA monotherapy in COPD patients who they suspect may have asthma. As LABA monotherapy is used in only around 1 percent to 2 percent of patients in the US, this should not significantly change existing COPD treatment practice: when LABA or LAMA monotherapy is indicated, physicians are likely to continue to opt for a LAMA, constraining growth of LABA monotherapy. Less certain is the impact on uptake of LAMA/LABAs, which will all include the boxed warning. As with LABA monotherapy, primary care physicians may be cautious about prescribing a LAMA/LABA (without an ICS) in COPD patients who they suspect may have asthma because prescribing a LAMA/LABA without an ICS in COPD patients with asthma would be contraindicated.
The FDA’s stance on LABAs resulted in Almirall/Forest discontinuing US development of the novel once-daily LABA abediterol in May 2012. Almirall intends to develop an abediterol/ICS combination for ex-US markets70; the ICS is undisclosed.

**Prescribing point 4: EMA and FDA have approved different doses**

The two main regulating agencies, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), have approved different dosages of GlaxoSmithKline’s Seretide/Advair and Novartis’s Arcapta/Onbrez. The doses of both product approved by EMA are higher than the FDA, which approved the lowest dose submitted in each NDA. In 2001, GlaxoSmithKline submitted a supplemental new drug application (sNDA) for fluticasone propionate 250mcg/salmeterol 50mcg twice daily and fluticasone propionate 500mcg/salmeterol 50mcg twice daily. The FDA issued a complete response letter because of lack of convincing evidence of efficacy, balanced against safety concerns with the use of ICS in COPD. Following receipt of a second completed response letter, GlaxoSmithKline in 2003 decided not to pursue the higher strength of the therapy. The EMA approved the higher dose of fluticasone propionate 500mcg/salmeterol 50mcg twice-daily in 2003.

In 2008, Novartis sought FDA approval of Arcapta (indacaterol 150mcg and 300mcg once daily) which resulted in a complete response letter requesting that Novartis establish the safety of lower doses and provide data showing a clinically meaningful advantage of a higher dose compared to a lower dose. Novartis resubmitted an application in October 2010 with results from additional clinical studies to address deficiencies in the original NDA and lowered the proposed dose to indacaterol 75mcg or 150mcg once daily. The lowest 75mcg indacaterol dose was chosen by the FDA for licence in the US, as the added benefit of indacaterol 150mcg was not demonstrated. Onbrez was approved in Europe in November 2009 at two dose strengths, 150mcg and 300mcg once-daily.

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Future chronic obstructive pulmonary disease treatment algorithm

Within the next five years, up to 2018, the main change in COPD treatment practice will be the introduction of LAMA/LABAs. Novartis’s Ultibro (indacaterol/glycopyrronium) was the first LAMA/LABA to be approved in September 2013; approval of four other LAMA/LABAs may follow from 2014 to 2016. As no novel anti-inflammatory, anti-oxidant, vaccines or anti-viral therapies have entered Phase III COPD trials, none are likely to influence treatment practice within the next five years. The figure below lists some of the drivers and resistors to uptake of LAMA/LABAs.

Figure 13: Resistors and drivers to LAMA/LABA uptake

Maximum bronchodilation
Simplifies treatment when LABA and LAMA indicated
“Super-Combivent”
Physicians want to “try something new"
Boehringer Ingelheim’s ICS withdrawal study may reassure physicians

Entrenched use of ICS
ICS withdrawal – fear it will increase exacerbations
Unclear drug sequencing when ICS indicated: no free-dose ICS approved for COPD
LAMA/LABA boxed warning in US
Can achieve treatment goal of dual LABA and LAMA therapy with existing drugs
Payers may need equivalence to ICS/LABA + free-dose LAMA

Source: FirstWord
Potentially the most significant barrier is the widespread use of ICS to treat COPD, meaning uptake of LAMA/LABAs will require ICS withdrawal in many COPD patients. LAMA/LABAs will also need to demonstrate non-inferiority, and ideally, superiority, in head-to-head trials against ICS/LABAs in terms of exacerbation reduction, which will not be available until 2015 or later, meaning significant changes in guideline recommendations and treatment practice may not occur for several years. The consequence is LAMA/LABAs sales, at least initially, may not be as great as hoped for by pharmaceutical companies.

An unknown element is the behaviour of primary care physicians, who may make decisions that are not evidence based. One KOL noted that some physicians might simply wish to try “something new,” although therapeutic inertia is likely to play a role.

“There are some doctors who are more conservative and they know very well Spiriva, and they want to stick with what they know. Others, they like to try new things. It may sound like a joke, but it’s true, perhaps some doctors are tired of Spiriva and saying, ‘well we have been using the same for ten or eleven years, so I want to change and try something new”

Dr Marc Miravitlles (Europe)

In addition, although several LAMA/LABAs may be approved, they may not receive favourable reimbursement/pricing in some markets, such as France.

“In France, perhaps they will be on the market, but the price may not be what the companies are expecting and the reimbursement is crucial in that country.”

Professor Pascal Chanez (Europe)

**LAMA/LABAs provide maximum bronchodilation**

Clinical studies with LAMA/LABAs have demonstrated the combination of two mechanism of actions results in superior lung function as measured by FEV₁ and exacerbation reduction compared to either agent alone. LAMA/LABA combination products should simplify treatment, as they will be more convenient than separate administration of a LAMA and LABA in two inhalers.

“I think there is more and more evidence that using two bronchodilators may be a better option for many patients.”

Dr Marc Miravitlles (Europe)

“I think what will be in the best interest of the COPD population is that the LABA/LAMA combination becomes accepted as foundation therapy for anyone with more than mild COPD. Patients who have moderate COPD would benefit most from being on a LABA/LAMA combination.”
KOL Insight: COPD

Combination therapies to drive significant market growth

Professor Christopher Cooper (US)
“I think we are looking at a major shift. The name of the game here is maximum bronchodilation. We need to provide the maximum bronchodilation as possible. We are working with two different mechanisms of action; so two mechanisms that complement each other so they are not excluding each other, so that they complement. And that's the market; the way the market is looking and the way the market is shaping up. Everybody is like, 'well, this is probably the way for us to go.'”

Dr Antonio Anzueto (US)

“Over time there will be a shift. There will be a shift in the direction of LABA/LAMA combinations, and this will be the cornerstone of therapy in the foreseeable future for COPD - that's my feeling. And it will be a COPD-specific medication. That's the other issue.”

Professor Claus Vogelmeier (Europe)

“In terms of efficacy, these drugs are all going to be fairly similar. It will be very hard for any company to claim that their drug has superior efficacy over other drugs in this same class. A lot is going to depend on the sequence of availability and what patients are already taking: for people already on tiotropium, physicians may wait for the availability of a LABA/LAMA with tiotropium so that can be added to what they are already taking”.

Professor Christopher Cooper (US)

“This should be the ideal prescription for a patient with COPD; it should be the LAMA and the LABA, especially if the patient has hyperinflation.”

Professor Maurizio Luisetti (Europe)

The therapeutic goal of dual therapy with two classes of bronchodilator can already be achieved with current drugs (i.e. free-dose LAMA and LABA), although this is rarely used in clinical practice without an ICS. Approximately 30 percent of US COPD patients are, however, prescribed a LAMA and a LABA through triple therapy with an ICS/LABA and free-dose LAMA, meaning current treatment practice already reflects the principle of combining two bronchodilator with different mechanism of action, with the caveat that this is always in combination with an ICS.

“What they're doing is repackaging the LABA and the LAMA in a single inhaler. This is just more of the same.”

Professor Peter Barnes (Europe)
“None of these new bronchodilators or bronchodilator/ICS combinations represent a shift in the management paradigms.”

Dr Stephen Rennard (US)

“We desperately need new anti-inflammatory agents. That’s what will take us to the next level. And this almost lemming rush that pharmaceutical companies have of doing the same thing as somebody else does so you can be the first to the market with it.”

Professor Byron Thomashow (US)

“If you have this treatment it’s just a way to have a better quality of life, and I don’t know at the end of the day, if they will do better than tiotropium. With all these treatments we are just trying to increase by 100ml the FEV1, but what does it mean?”

Professor Pascal Chanez (Europe)

LAMA/LABAs introduce a drug sequencing issue

The uptake of LAMA/LABA as initial maintenance therapy will probably be highest in COPD patients with moderate disease, especially those patients who have persistent symptoms with either LABA or LAMA monotherapy and require a second bronchodilator. Based on GOLD patients groups, this is principally group B patients (where no exacerbation claim is required). LAMA/LABA combinations are unlikely to expand the COPD market, as they will take market share from existing LABA or LAMA monotherapy products.

“We will have a combination without corticosteroids for the stages of the disease in which the corticosteroids are not suggested, so I think it will be very useful for the physician to prescribe a fixed combination of LABA/LAMA.”

Professor Maurizio Luisetti (Europe)

If LAMA/LABAs have significant uptake in patients with moderate COPD, this introduces a drug sequencing issue. KOLs were uncertain as to how treatment would be stepped-up when an ICS is required.

“The interesting thing is if they [LAMA/LABA] will become available on the market, will we stop to prescribe the combination of Long-Acting Beta2 Agonists with an inhaled steroid? And start with the Long-Acting Beta Agonist and anti-cholinergic medication and give in certain circumstances, in special patients, additional steroids? That’s very interesting. I don’t know.”

Professor Rene Aalbers (Europe)
“We will then have to address the question as to whether Inhaled Corticosteroids add anything in terms of reducing exacerbations [to LABA/LAMA therapy]. That's the key question.”

Professor Christopher Cooper (US)

Off-label free-dose ICS could be added to a LAMA/LABA, although to treat within label recommendation, patients would need to be switched to ICS/LABA plus free-dose LAMA.

“If you need to prescribe the corticosteroid, it would be changing totally the prescription to a LABA/Inhaled Corticosteroid and LAMA alone.”

Professor Maurizio Luisetti (Europe)

Daliresp/Daxas (roflumilast; Takeda/Forest), an oral PDE-IV inhibitor, could be added as an alternative to ICS although this may not be suitable, or possible, for many patients, given Daliresp/Daxas restricted label for COPD patients with bronchitis, poor tolerability, variable US formulary coverage and restrictions on use in some European markets.

“If somebody is on a fixed combination of a LAMA/LABA and you want to add something else to control exacerbations, the choice would be to, if you wanted to add an ICS, then you have to add either an ICS by itself, which would be off-label, and another inhaler to take OR switch them to two inhalers. That's a LAMA and a LABA/ICS - at least until there's a triple inhaler available. Or add a pill. In that case it might be more convenient to just add roflumilast. I think we really don't have any specific guidance on if something is going to be added to maximal bronchodilator therapy, to further control exacerbations.”

Dr Stephen Rennard (US)

“[For] those patients with dual bronchodilators [who] still have exacerbations, and then you think that you need something else. One option is...off-label inhaled steroids. That is frequently used. I would not be surprised at all, if many doctors add an inhaled steroid to a combination of bronchodilators. That's one option. The second option is to change to triple therapy with a combination LABA/ICS, plus a LAMA.”

Dr Marc Miravitlles (Europe)
“When a patient is established on a LABA/LAMA combination, there may be a role for roflumilast in reducing exacerbations. It would be interesting if someone compared the addition of roflumilast to LABA/LAMA versus the addition of ICS to LABA/LAMA.”

Professor Christopher Cooper (US)

Fixed-dose ICS/LAMA/LABA triple combinations could potentially address this treatment sequencing issue, as step-up therapy would be LAMA followed by LAMA/LABA followed by ICS/LAMA/LABA.

ICS withdrawal is a key resistor to LAMA/LABA uptake

Physician acceptance of LAMA/LABAs as maintenance therapy in patients with severe or very severe COPD is uncertain. This is not because LAMA/LABAs may be less effective than ICS/LABA combinations in reducing exacerbations or improving lung function, rather it is a consequence of how the COPD market has developed historically. Further, only ICS/LABA fixed-dose combinations have been approved for COPD.

If free-dose ICS agents were approved for COPD, confidence in the uptake of LAMA/LABAs would be much higher, as in this scenario, an ICS could be added to LABA/LAMA as required. The fact that “decoupling” of ICS from LABAs in treatment practice is currently not possible presents a major resistor to LAMA/LABA uptake. If a physician switched a patient from ICS/LABA to LAMA/LABA, this would mean withdrawal of the ICS, which physicians may be reluctant to do given ICS reduce exacerbations (and would be contraindicated in COPD patients with asthma). The alternative would be to prescribe a LAMA/LABA + ICS, although this would be off-label.

Commercial success of Combivent supports LAMA/LABA US uptake

US KOLs pointed to the commercial success of Boehringer Ingelheim’s Combivent, a fixed-dose combination of salbutamol and ipratropium, with sales of $1.1 billion in 2012. Combivent was first approved in the US in 1996 in an MDI device; a formulation using the Respimat device was approved in 2012, which will replace the MDI formulation. As with LAMA/LABAs, the combination of salbutamol/ipratropium obtained greater bronchodilation than either drug used alone71.

“I am a firm believer, this is my own personal opinion, not based on any data, that when the LAMA/LABA fixed-dose combinations become available, they will be the premier drug for the treatment of COPD when initiating patients on treatment. It will be ‘Super Combivents.’”

“I think the LAMA/LABAs, combinations, the fixed combinations in one inhaler are going to be extremely popular, basing that on the experience with Combivent. Combivent is way more popular with both clinicians and patients than you would have believed from the sort of pharmacological effects of individual drugs or the combination. So, if you expect that to play out with fixed combinations, it’s going to be extremely popular. I think everybody’s enthusiastic to have them available. How they will be used in practice will probably be very complicated.”

Dr Stephen Rennard (US)

Combivent is not a maintenance COPD therapy and for LAMA/LABAs to emulate Combivent sales, they will need to challenge the dominance of ICS/LABAs, which are used in around half of US COPD patients.

In the US, all LAMA/LABAs will include a boxed warning that LABAs increase the risk of asthma-related death. In clinical practice, COPD diagnosis may be clinical grounds alone without confirming the presence of airflow limitation, meaning there is diagnostic uncertainty around whether a patient with COPD also has asthma.

A consequence is that unless asthma is conclusively ruled out, US primary care physicians may be reluctant to prescribe a LAMA/LABA without an ICS, meaning ICS/LABA could remain the preferred initial maintenance therapy.

“If you are giving a LABA without an ICS - is it safe if there is an asthmatic component [in a COPD patient]?”

Dr Donald P. Tashkin (US)

Comparative data with ICS/LABAs could accelerate clinical adoption of LAMA/LABAs

Head-to-head trials of LAMA/LABAs are required to demonstrate non-inferiority (and ideally superiority) to ICS/LABAs, particularly in terms of exacerbation reduction.

“You would have to show significantly greater effectiveness of the LAMA/LABA combination compared to existing therapy to justify a switch over. Non-inferiority is not a very high standard. I think they have to be shown to be superior than existing treatments (Advair or Symbicort).”

Dr Edward Eden (US)

“So far there has been no direct comparison with regard to exacerbations between LABA/LAMA and LABA/ICS, so we cannot be sure if there is really a difference between the two concepts.”
At present, there are few data comparing ICS/LABA with LAMA/LABA in terms of exacerbation reduction. Novartis’s ILLUMILATE study, the first study to compare an ICS/LABA with a LAMA/LABA, was conducted in patients with no history of exacerbations. Novartis is now conducting a head-to-head study with glycopyrronium/indacaterol and fluticasone/salmeterol (study number NCT01782326) which is recruiting patients with a history of COPD exacerbations. This trial, which is expected to be completed in 2015, will likely be the first to determine which therapy is more effective in reducing exacerbations.

Data from studies comparing ICS/LABA with LAMA/LABA may be insufficient as payers may require evidence that LAMA/LABA are as effective as triple therapy with ICS/LABA + LAMA. One KOL believed a LAMA/LABA would be inferior to ICS/LABA + LAMA.

“A LAMA/LABA cannot be better than a LAMA/LABA/inhaled steroid. It can’t be better. Since you are not, I don’t think, going to get a benefit from using a LAMA/LABA over a LAMA/LABA/inhaled steroid. It will be interesting to see how the companies approach this. And so how they advertise their LAMA/LABA will be intriguing because they are not going to want to shoot themselves in the foot knowing that they’ve got a triple that’s probably coming down the path.”

Professor Byron Thomashow (US)
Future treatment landscape

This section examines the future developments in prescribing trends in COPD as summarised in the figure below.

Figure 14: Future developments in COPD

**Figure 14: Key insights from future developments in COPD**

- LABA/LAMAs only near-term approvals (2013-16)
- No "disease modifiers" anticipated in next ten years
- GlaxoSmithKline’s Breo (ICS/LABA) adds uncertain clinical value compared to Advair and Symbicort
- Novartis’s Onbrez (LABA) EU sales are disappointing due in part to reimbursement issues
- AstraZeneca’s Symbicort (ICS/LABA) sales are lower than Seretide/Advair due to a significant delay in gaining US approval
- Daliresp/Daxas sales are hampered by poor tolerability, variable US formulary coverage and restrictions on use in some EU markets

Source: FirstWord

Over the next three years to 2016, LAMA/LABAs combinations are the only new COPD therapies likely to be approved. Widespread uptake of LAMA/LABAs will require ICS withdrawal in many COPD patients, a decision many physicians may be reluctant to take due to the fear of increasing exacerbations. Chiesi’s fixed-dose ICS/LAMA/LABA triple therapy could potentially be approved in 2017 in Europe, although GlaxoSmithKline will likely shape the triple therapy market though the Ellipta device. ICS/LAMA/LABA would offer improve adherence, simplify treatment sequencing and would not require ICS withdrawal. Inhaled MABAs, which combine the properties of a LABA and a LAMA, offer another potential route to developing a triple-action product through combination with an ICS (or other inhaled inflammatory agents, such as a PDE-IV inhibitor).

From 2017 onwards, additional treatment may become available, although the failure of so many novel drugs to progress into Phase III development (at least 14 in the last five years) underlines the challenge facing pharmaceutical companies in bringing new COPD products to market. The COPD R&D pipeline primarily consists of novel anti-inflammatories and antioxidants although whether any will be approved as “disease modifiers” which slow or halt the progressive decline in FEV1 is unknown at present. Novel interventions that reduce the
Frequency of COPD exacerbations, a key cause of hospitalisations—with associated costs—could have significant market potential. Strategies to reduce COPD exacerbations include novel vaccines (e.g. GlaxoSmithKline’s respiratory syncytial virus (RSV) vaccines and non-typeable *Haemophilus influenza* vaccines) and prophylactic anti-viral therapies such as inhaled interferon beta, which could be taken by nebulizer for COPD at home at the onset of respiratory symptoms. Smoking cessation vaccines are also in clinical development that may improve cessation rates. Generic ICS/LABA combinations become available from 2014.

“We desperately need new drugs, particularly anti-inflammatory agents that can really make a difference here, and those are years away. We are probably five to ten years away from a new class of agents as best as I can tell.”

Professor Byron Thomashow (US)

**Smoking cessation vaccines**

A means to reducing the burden of COPD is to reduce the prevalence of smoking in the general population.

“The main therapeutic approach to COPD is prevention of cigarette smoking. And so the pharmaceutical industry is somewhat responsible for that because they focus on bronchodilators and inhaled steroids, whereas they should be turning their attention to prevention.”

Dr Edward Eden (US)

Several pharmacologic therapies for smoking cessation are available, including nicotine replacement therapy (NRT) and two prescription only medications: Pfizer’s Chantix/Champix (varenicline) and GlaxoSmithKline’s Zyban (bupropion). Pfizer reported sales of Chantix of $670 million in 2012. In the US and the UK, NRT products are available via any retail outlet, although in most other European markets, NRT is only available in pharmacies and must be sold under the supervision of a pharmacist. In the US, UK and Japan, smoking cessation treatments are reimbursed, or provided free of charge. In other markets, smokers must fund the full or partial costs of treatments. These include Germany, Italy, France and Spain.

“In Spain, these treatments are not reimbursed. The specialists are struggling with authorities to reimburse these treatments for patients at least with severe disease. I mean, the rate of relapse in smoking is high, even after quitting so smoking is really very addictive and still we do not have the ideal drug, or the ideal help, for our patients.”

Dr Marc Miravitlles (Europe)
Nicotine vaccines offer a potential novel smoking cessation treatment by diminishing the pleasurable effects of nicotine. Two nicotine vaccines are in Phase I/II trials: Pfizer’s NIC7-001/NIC7-003 and Selecta Biosciences’s SEL-068. Development of three other nicotine vaccines has been discontinued: NABI’s NicVAX, Cytos’s NicQb/NIC002 and Celtic Pharma’s TA-NIC. These vaccine candidates failed, in part, as they did not achieve sufficiently high anti-nicotine antibody levels to increase smoking cessation rates above placebo in a majority of smokers. Pfizer and Selecta Biosciences’s vaccines may achieve higher and more sustained antibody levels than previous candidates, resulting in improved efficacy.

**Novel vaccines and anti-virals to reduce exacerbations**

One of the main objectives of COPD treatment is to reduce the frequency and severity of exacerbations. A common cause of COPD exacerbations are bacterial and viral respiratory tract infections: according to a clinical audit of COPD exacerbations in patients admitted to acute NHS trusts across the UK in 2008, 68 percent of patients reported a respiratory infection or flu-like symptoms in the month prior to admission\(^\text{72}\) and 83 percent reported frequent exacerbation of their COPD.

Various pathogens are implicated in COPD exacerbations. The most common bacteria associated with COPD exacerbations are nontypeable *Haemophilus influenza* (*NTHi*), *Streptococcus pneumonia*, and *Moraxella catarrhalis*; the most common respiratory viruses are rhinoviruses (the common cold), influenza, parainfluenza, respiratory syncytial virus (RSV) and adenoviruses\(^\text{73}\). Annual influenza vaccination and pneumococcal polysaccharide vaccine are already indicated in COPD patients; novel vaccines, which reduce the severity of RSV and NTHi infections in COPD patients, may reduce the frequency of exacerbations.

NTHi is the dominant bacterium isolated from the lungs of patients with COPD\(^\text{74}\). NTHi activates lung T cells in patients with COPD, which may result in inflammation. GlaxoSmithKline’s NTHi vaccine is being investigated in current and former smokers aged 50 to 70 years old (study number NCT01678677).

A RSV vaccine could reduce the number of hospitalisations in patients with COPD, particularly among those with congestive heart failure: an analysis of RSV among 379 patients with COPD reported the rate of symptomatic RSV illness was 11 percent; congestive


heart failure was the only significant risk factor for developing medically attended RSV illness\textsuperscript{75}.

Novavax is conducting a Phase I trial in a healthy elderly population with a virus-like particle (VLP) recombinant RSV-F fusion protein vaccine candidate (study number NCT01709019). The trial is expected to be completed in October 2013. Okairos is conducting a trial with two novel live viral vector vaccines (study NCT01805921), which is expected to be completed in 2014. Both vaccines encode the F (Fusion), N (Nucleocapsid) and M2-1 (Matrix) RSV proteins but use different vectors, a simian adenoviruses (PanAd3) and Modified Vaccinia virus Ankara (MVA). In July 2013, GlaxoSmithKline began a trial with a RSV vaccine, GSK3003892A, in healthy adults (study NCT01905215). Evidence suggest that neutralising antibody responses to RSV wane after one year, hence annual immunisation, possibly administered at the same time as the an influenza vaccine, may be required to ensure seasonal protection.

Synairgen is developing inhaled SNG001 (interferon beta) as a broad-spectrum anti-viral therapy to be taken at the onset of cold (or influenza) symptoms in asthma and COPD patients. The objective is to limit the spread of viral infections to the lung and prevent exacerbations. A Phase II trial in asthma patients has being completed (study NCT01126177); Synairgen is currently designing a Phase II COPD proof of concept study. An intervention such as SNG001 could possible prevent hospital admission in COPD patients who experience frequent exacerbations, although this would require early recognition of cold or influenza symptoms and prompt self-management or presentation to healthcare professionals.

**Novel endpoints**

COPD drugs have been approved based on improvements in lung function or exacerbations. Trough FEV\textsubscript{1} is the principal endpoint of lung function used in clinical trials. Trough FEV\textsubscript{1} measured at 12 weeks is standard for US Food and Drug Administration (FDA) approval; trough FEV\textsubscript{1} measured at 24 weeks is standard for European Medicines Agency (EMA) approval. An inclusion of an active comparator arm is generally required for approval in the EU. A minimum clinically important difference (MCID), the smallest difference that patients perceive as beneficial, has not been defined for FEV\textsubscript{1}, although an improvement of 100–140mL in trough FEV\textsubscript{1} has been suggested as a benchmark\textsuperscript{76}.


The principle endpoints used to evaluate exacerbations are the annual rate of moderate and severe exacerbations and/or time to first COPD exacerbation. There is no established MCID for COPD exacerbations.

Other endpoints, such as endurance time and inspiratory capacity have not yet been accepted by regulators to support label claims. Boehringer Ingelheim requested a claim that Striverdi (olodaterol) improves exercise endurance time and increases inspiratory capacity, indicative of a reduction in hyperinflation. If approved, Striverdi would be the first COPD product to have such a claim. Some FDA panel members noted the data were not supportive of an exercise tolerance claim, but the committee was not asked to vote on whether the claim should be granted.

In 2011, the COPD Biomarkers Qualification Consortium, was initiated, which is pooling data from clinical trials conducted by GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca and Pfizer to identify additional biomarkers which may be accepted by regulators, such as hyperinflation.

“Are we going to start being clever and using other endpoints, and the FDA is in a situation of ‘wait and see?’ There is this huge network together working on biomarkers - and I think that is what the judge is going to be”.

Dr Antonio Anzueto (US)

“I believe the work on biomarkers is extremely important. I think we have to make progress here because one day there will be a very interesting anti-inflammatory drug and we will not be able to find out that it works. That’s a major problem”.

Professor Claus Vogelmeier (Europe)

“I believe that biomarkers of COPD are very, very important. But, it is very, very difficult to find suitable biomarkers. Once we are able to identify the pathway of the disease, we will be able to identify suitable biomarkers.”

Professor Maurizio Luisetti (Europe)

Generic drugs

The first generic ICS/LABA products are likely to be approved in Europe. In January 2013, Teva filed for approval of a budesonide/formoterol Spiromax DPI generic in Europe, which according to Teva is bio-equivalent to AstraZeneca’s Symbicort Turbhaler. Teva is developing a fluticasone/salmeterol DPI generic for Europe, which may be therapeutically

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equivalent to GlaxoSmithKline's Seretide/Advair and could be approved in 2015. Teva are also developing a generic version of Boehringer Ingelheim and Pfizer's Spiriva (tiotropium) generic, which uses a breath-actuated inhaler, although Teva has not provided guidance on likely approval. In March 2013, Orion submitted an application for approval of a Symbicort (budesonide/formoterol; AstraZeneca) Easyhaler DPI generic in Europe and are also developing an Advair/Seretide (fluticasone/salmeterol; GlaxoSmithKline) Easyhaler DPI generic.

Sweden approved Elpen's fluticasone/salmeterol generic as therapeutically equivalent to GlaxoSmithKline's Seretide/Advair in May 2011, although the product does not yet appear to be approved in other EU Member states (except Greece, were it was first launched in November 2009 as the Rolenium Elpenhaler DPI). Elpen is also developing a budesonide/formoterol combination (the proposed trade name is Pulmoton) and a generic tiotropium DPI.

In the US, the earliest that a product with the same active ingredients as Seretide/Advair (fluticasone/salmeterol) could garner regulatory clearance is likely to be in 2015, when Teva's Spiromax DPI may be approved. Teva's Spiromax DPI (fluticasone/salmeterol) will not be interchangeable with Seretide/Advair: in 2010, Teva reported that US regulatory hurdles (i.e. demonstrating bioequivalence) made development of a product that is substitutable for Advair “difficult.” Generic competition for Spiriva (Boehringer Ingelheim/Pfizer) may occur in the US from 2018, when the Spiriva Handihaler patent expires.

Appendix

Estimating indication specific sales

FirstWord examined chronic obstructive pulmonary disease (COPD) prescribing practice in England in 2009 based on an analysis of 1 million primary care patients. Total primary care prescribing costs for COPD therapies were estimated at 268 million pounds ($424 million) based on 2011 prices. Spiriva COPD sales were 141 million pounds ($223 million), Seretide sales were 80 million pounds ($127 million) and Symbicort 20 million pounds ($63 million).

The Prescription Cost Analysis (PCA) database provides details of all retail prescriptions dispensed in England. In 2011, sales of respiratory drugs across all indications were 941 million pounds ($1.5 billion). Approximately 92 percent of this value was attributable to six drugs: Spiriva, Seretide, Symbicort, beclometasone and salbutamol. Sales of COPD therapies based on the COPD prescribing practice analysis were compared with sales in the PCA data. The analysis suggests that, by sales, approximately 26 percent of respiratory drugs are used to treat COPD.

As shown in the table below, Spiriva is used almost entirely in COPD patients, representing about 94 percent of sales by value. Only 22 percent of Seretide and 14 percent of Symbicort sales were used in COPD patients.

Table 25 Respiratory drug sales (all indications and COPD), England, 2011

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**KOL Insight: COPD**

Combination therapies to drive significant market growth

### Table 25: Respiratory drug sales (all indications and COPD), England, 2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sales (£m), all indications</th>
<th>Sales (£m), COPD only</th>
<th>COPD sales (% of sales in all indications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiriva</td>
<td>150</td>
<td>141</td>
<td>94</td>
</tr>
<tr>
<td>Seretide</td>
<td>371</td>
<td>80</td>
<td>22</td>
</tr>
<tr>
<td>Symbicort</td>
<td>149</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Serevent</td>
<td>42</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>90</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>63</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>All respiratory drugs</td>
<td>941</td>
<td>248</td>
<td>26</td>
</tr>
</tbody>
</table>

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta2 agonist; ICS = Inhaled Corticosteroid

SABA = short-acting beta2-agonists; SAMA = short-acting muscarinic antagonist

Source: adapted from NICE. CG101: Chronic obstructive pulmonary disease (update): costing report. 23 February 2011.

Sales of Seretide Accuhaler (fluticasone 500mcg/50mcg) which is the only approved formulation of Seretide approved for treatment of COPD in England were 70 million pounds ($110 million) in 2011 based on the PCA database. This is close to Seretide COPD sales of 80 million pounds ($127 million) calculated using the above methodology, indicating a 78 percent/22 percent asthma/COPD sales mix is a reasonable estimate.

Applying the sales mix to global sales of these products should take into account differences in asthma and COPD prescribing practice and epidemiology (such as prevalence and diagnosis rates) between markets. In England, ICS/LABAs are prescribed in about 25 percent of COPD patients, which is similar to the 30 percent rate in France but much lower than the 50 percent rate in the US and 60 percent rate in Spain. As a greater percentage of ICS/LABAs total sales are likely to be generated in these markets than in England, FirstWord estimates that approximately 35 percent of global Seretide and Symbicort sales are generated in COPD. For LABAs, it is assumed that approximately 15 percent of sales are generated in COPD.
Table 26: Estimated percentage of global sales generated in COPD

<table>
<thead>
<tr>
<th>Company</th>
<th>Brand</th>
<th>Drug</th>
<th>COPD sales (% of global sales)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>Advair/Seretide</td>
<td>Salmeterol/fluticasone</td>
<td>35</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Serevent</td>
<td>Salmeterol</td>
<td>15</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Symbicort</td>
<td>Formoterol/budesonide</td>
<td>35</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Combivent</td>
<td>Salbutamol/ipratropium</td>
<td>100</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Spiriva</td>
<td>Tiotropium</td>
<td>100</td>
</tr>
<tr>
<td>Novartis</td>
<td>Seebri</td>
<td>Glycopyrronium</td>
<td>100</td>
</tr>
<tr>
<td>Novartis</td>
<td>Arcapta/Onbrez</td>
<td>Indacaterol</td>
<td>100</td>
</tr>
<tr>
<td>Novartis</td>
<td>Foradil</td>
<td>Formoterol</td>
<td>15</td>
</tr>
<tr>
<td>Almirall/Forest</td>
<td>Eklira/Tudorza</td>
<td>Aclidinium</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: FirstWord
KOL biographies

KOLs from US

Dr Stephen Rennard is Larson Professor in the Department of Internal Medicine and Professor (courtesy) in the Department of Pathology and Microbiology at the University of Nebraska Medical Center. Professor Rennard has served on numerous national and international committees including the Respiratory and Allergic Disease Foundation Steering Committee, the Scientific and Ethics Advisory Committee for the Veterans Affairs Rheumatoid Arthritis (VARA) Registry, the Editorial Board of the Proceedings of the American Thoracic Society, the National Emphysema COPD Association (NECA), the Medical Advisory Panel, the National Emphysema COPD Association, the American Thoracic Society COPD Standards Committee, the National Heart Lung Education Program Executive Committee, and the World Health Organization/National Institutes of Health Task Force on COPD.

Dr Antonio Anzueto is Professor of Medicine, Pulmonary/Critical Care Medicine at University of Texas Health Science Center, San Antonio. Specialising in the field of Pulmonology, Dr Anzueto has 30 years of experience treating disorders of the respiratory tract including asthma, pulmonary fibrosis, lung cancer and COPD, among other diseases and complications.

Dr Donald P. Tashkin is Emeritus Professor of Medicine, Division of Pulmonary and Critical Care Medicine at David Geffen School of Medicine at University of California Los Angeles. His area of interest include early intervention in COPD, microelectronic monitoring of medication adherence in asthma and COPD, and novel pharmacologic approaches to treatment of asthma and COPD.

Dr Edward Eden is Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons. Dr Eden’s major interest is in chronic obstructive pulmonary disease (COPD) and emphysema. He has published extensively on the relationship between COPD and asthma especially in a genetic condition, alpha-1 antitrypsin deficiency, which predisposes patients to early emphysema. Dr Eden is a fellow of the American College of Physicians and the American College of Chest Physicians. He is a member of the American Thoracic Society, the Society of Critical Care Medicine and the New York Academy of Sciences.
Dr Byron Thomashow is a Clinical Professor of Medicine at Columbia University Medical Center and an Attending Physician at the New York-Presbyterian Hospital. He presently chairs the Respiratory Disease Council of the New York-Presbyterian Healthcare Network and co-chairs the New York Presbyterian smoking cessation initiative. He helped found and is now chairman of the board of directors of the COPD Foundation. He is the co-chair for the NY State COPD Summit and co-chair of the COPD Coalition National Meeting. He was a member of the steering committee and the co-primary investigator at the Columbia site for the National Emphysema Treatment Trial and has been and remains actively involved in multiple national clinical research projects.

Professor Christopher Cooper is a Professor of Medicine and Physiology at David Geffen School of Medicine, University of California, Los Angeles. His areas of interest include COPD, pulmonary rehabilitation, neuromuscular diseases that affect the respiratory system, oxygen therapy, and exercise testing and interpretation.

KOLs from Europe

Professor Peter Barnes is a Professor of Thoracic Medicine at the National Heart and Lung Institute, Head of Respiratory Medicine at Imperial College and Honorary Consultant Physician at Royal Brompton Hospital, London. In 2007, he became the first respiratory researcher to be elected a Fellow of the Royal Society for over 150 years. He is currently a member of the World Health Organization/National Institutes of Health Scientific Committee of Global Initiative on Asthma (GINA) and Global Initiative on Obstructive Lung Disease (GOLD). He also serves on the editorial boards of over 30 journals and is currently an Associate Editor of Chest and respiratory editor of PLoS Medicine. Professor Barnes has published more than 1000 peer-reviewed papers on asthma, chronic obstructive pulmonary disease and related topics, and has edited more than 40 books.

Dr Marc Miravitlles is Chest Physician & Senior Researcher, Department of Pneumology, Hospital Clinic, Barcelona, Spain. His primary research interests include COPD, chronic bronchitis, alpha-1-antitripsin deficiency, lung defence mechanisms and respiratory infections. Dr Miravitlles serves on various medical committees and is a member of numerous professional societies, including the Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Currently, he has been elected Chair of the Respiratory Infections Group of the European Respiratory Society (ERS) and was a member of the ERS task force in the redaction of the American Thoracic Society/European Respiratory Society task force on
outcomes of COPD (ERJ 2008). He has acted as a consultant for the development of the Spanish, Central American, Latin American and Canadian guidelines on the management of exacerbations of COPD and has participated in the development of Spanish and Brazilian guidelines on the management of COPD.

**Dr Rene Aalbers** is Consultant Physician, Respiratory Medicine at Martini Hospital, Groningen, The Netherlands. Dr Albers was a lead author of the Phase II clinical trial investigating lung function using tiotropium and olodaterol fixed-dose combination in COPD patients.

**Professor Claus Vogelmeier** is a Professor of Medicine and Head of Pulmonary Division at Marburg University Hospital, Germany. Professor Vogelmeier is also chair of the European Alpha-1-Antitrypsin Laurell’s Training Award (eALTA) and was the lead author of the landmark POET-COPD study, which compared tiotropium and salmeterol for the prevention of exacerbations of COPD.

**Professor Maurizio Luisetti** is a Professor of Respiratory Medicine at the University of Pavia, Italy. He is coordinator of the Italian Alpha-1 antitrypsin deficiency registry and Director of the Centre for the Diagnosis of Alpha-1 antitrypsin deficiency. He also serves on the Honorary Editorial Board of International Journal of Chronic Obstructive Pulmonary Disease and has research interests that include the role of desmosines as COPD biomarkers.

**Professor Pascal Chanez** is a Professor of Medicine, Departement des Maladies Respiratoires, INSERM, Aix Marseille Universite, Marseille, France. He has published numerous peer-reviewed papers on airway inflammation and remodelling, COPD, Inhaled Corticosteroids and severe refractory asthma. His research interests include the role of bronchial epithelial cells in the development of airway obstruction in asthma and COPD patients and the epigenetics of COPD.