

# Key Events

## Respiratory

Last Updated: 1<sup>st</sup> June 2007

Date	Event	Status
25 <sup>th</sup> and 26 <sup>th</sup> April 2007	Asthma & COPD conference, London	Reported
18 <sup>th</sup> – 23 <sup>rd</sup> May 2007	American Thoracic Society, San Francisco	Reported

### Lack of Inspiring Data at ATS 2007 – UK KOL : “ATS very disappointing”

In our opinion, leading news is limited to additional TORCH data, and launch of AstraZeneca’s Symbicort

#### Other conference highlights:

- ICS / LABA combinations likely to dominate COPD / asthma markets in the near-to-mid term.
- Big pharma pipelines dominated by ICS / LABA therapies – truly novel therapeutics appear to be some way from the market.
- Both disease states remain poorly understood.

#### Wood Mackenzie View

In May 2007, Wood Mackenzie attended the 103<sup>rd</sup> American Thoracic Society (ATS) meeting in San Francisco. Despite expectations of breaking clinical data from the major pharmaceutical companies, and further insight into novel therapies in development for both COPD and asthma, we were surprised to discover that new clinical data was limited to the presentation of secondary analysis from GSK’s TORCH trial. There also appeared to be few, if any, novel compounds in development for either COPD or asthma – certainly from big pharma. Indeed, one UK key opinion leader described ATS 2007 as “very disappointing” – a perfect summation in our opinion.

ATS 2007 appeared to reinforce the perception that there remains a very poor understanding of the mechanisms of disease, underlying causes, and the best way to effectively treat asthma and COPD, particularly COPD. Truly novel approaches to treating these diseases appear to be limited to niche biotechnology companies – which ultimately rely on big pharma to ensure that such products fulfil their commercial potential.

#### Further Data from TORCH

GSK’s TORCH (Towards a Revolution in COPD Health) study was a three-year, 6,184 patient, randomised trial investigating the use of Advair (fluticasone / salmeterol) in treating COPD. The results, published in full in the *New England Medical Journal* in February 2007, showed that, while the drug did not show a statistically significant benefit over placebo in preventing all-cause mortality – the study’s primary endpoint – Advair was shown to reduce the number of exacerbations suffered, and improve the overall health of COPD patients.

Now, further data released from TORCH at ATS 2007 suggests that Advair slows the progressive decline in lung function in COPD patients. In the session entitled ‘**COPD Treatment III: Lessons from the TORCH and Others**’, Dr. Bartolome Celli presented data which showed that, versus placebo, Advair reduced the decline in FEV1 by 16ml per year ( $P<0.001$ ). However, compared to either salmeterol or fluticasone alone, Advair showed no statistically significant benefit in preventing lung function decline ( $P=0.441$  and  $P=0.445$  respectively).

This secondary analysis also showed that BMI played a role in lung function decline, with thinner patients doing worse. Patients in Asia and the Pacific region also had less decline than those from both Western Europe and the United States. As highlighted by Dr. Celli, the study showed that patients with milder disease (those with no, or few, exacerbations) benefited from therapeutic intervention, which may ultimately lead to changes in the guidelines for treatment of COPD.

Although TORCH failed to reach statistical significance in its primary endpoint – reduction in all-cause mortality ( $P=0.052$ ) – physicians at ATS indicated that they were likely to adopt the use of Advair in treating COPD based on the study results. Part of the reason for this was the feeling that TORCH was significantly underpowered, with an average drop-out rate of approximately 37% throughout the entire trial. Many physicians appeared to feel that, although statistical significance was not reached, clinical significance was.

However, these sentiments appear unlikely to be reciprocated by the FDA. In May 2007, an advisory board for the agency voted 9-2 that TORCH did not provide evidence to support survival benefit, although the board did agree that Advair showed a substantial reduction in the risk of exacerbation of COPD. Consequently, we expect the FDA to adopt the recommendations of its advisory board, probably by the end of Q3 2007. Although Advair will likely not be approved for use in reducing mortality, it should be licensed for reduction in the risk of exacerbations – providing an increase in sales for the product.

### **AstraZeneca uses ATS to launch Symbicort in US – product due to be shipped to wholesalers by end of June**

AstraZeneca formally announced the US launch of Symbicort (formoterol / budesonide), its combination therapy for the treatment of asthma, at ATS 2007. However, the product will not be shipped to wholesalers until the end of June 2007. Although we believe that Symbicort will garner sales in excess of \$1.5bn in the US by 2013 (Source: Wood Mackenzie's **Productview**), we expect Advair to retain its dominance in the combination therapy market (with projected US sales of over \$4.5bn by 2013, according to our forecasts).

Indeed, AstraZeneca must ensure that it gains approval for the use of Symbicort in COPD in the US (currently in Phase III), as this market is expected to grow substantially in the coming years. Indeed, we believe that approximately 45% of Advair's current sales come from this indication. Despite its faster onset of action compared to Advair (15 minutes versus 60 minutes), we do not believe that this will provide AstraZeneca with a significant competitive advantage, given that these products are approved for maintenance therapy of asthma, rather than as rescue medication.

AstraZeneca may also find GSK using results from its 12-month CONCEPT (CONtrol CEntred Patient Treatment) trial to displace Symbicort in the US, much like it has done in the EU. Results from CONCEPT, a head-to-head between Advair and Symbicort, suggested that patients treated with Symbicort adjustable maintenance dosing were almost twice as likely to experience asthma attacks (exacerbations) requiring hospital admission or oral steroid treatment than patients treated with Advair stable dosing. However, AstraZeneca's earlier seven-month, head-to-head SUND (Symbicort Up aNd Down) study, suggested that Symbicort achieved a 40% reduction in asthma exacerbations compared to Advair.

The main difference between Symbicort and Advair is the ability of Symbicort patients to adjust the dose of the active drug based on their asthma conditions, as opposed to Advair's fixed dosing regime. However, while allowing differentiation from Advair, this approach does not appear to have gone down well with physicians, who point out that there is a minimum daily amount of maintenance therapy necessary to control symptoms in patients with persistent asthma.

In conclusion, there appears little to differentiate Symbicort and Advair in terms of clinical data, with both AZ and GSK claiming superiority. However, we believe that the delay in US launch for Symbicort will limit its full commercial potential, since physicians have little incentive to switch from Advair. Although we believe that Symbicort will experience healthy growth in the US, it will likely remain second to Advair in terms of market penetration and sales value. Indeed, with GSK developing 'Super-Advair', a once-daily formulation of the combination therapy, AstraZeneca may find the competitive landscape about to become even tougher. Although GSK has not announced when this once-daily version of Advair will be launched, we do not expect the product to reach the market before 2010.

### **Novel Therapies In Respiratory at ATS 2007**

A particular surprise at ATS 2007 was the apparent lack of novel therapies in development for many respiratory diseases, particularly in asthma and COPD. It would appear that many companies, certainly within big pharma, are content to develop inhaled corticosteroids, long-acting beta agonists, or a combination of both, to treat these disease states. It seems that many of the more novel drugs are limited to the pipelines of smaller biotechnology companies, and few talks within ATS 2007 covered such products. Of those products which we identified, we believe that the following were of particular interest:

- **MEDI-528** – In-licensed from Genaera Corporation, MedImmune is developing MEDI-528, an injectable anti-IL9 antibody for the treatment of moderate-to-severe persistent asthma. The product is currently in Phase II development in Canada (Phase I in the US), with clinical data presented at ATS 2007 suggesting that the product was well tolerated.
- **TPI-ASM8** – A truly novel therapy, which utilises RNA interference technology to target CCR3 and the  $\beta$ c-subunit of interleukin receptors. Developed by Topigen, the inhaled product is currently in Phase II development in Canada for the treatment of asthma.
- **INS-37217** – Developed by Inspire Pharmaceuticals, this Cystic Fibrosis drug is a P2Y2 agonist which had entered Phase III development in the US by July 2006.

Despite being a very limited list, we feel that this accurately reflects the current state of novel R&D, not only in the asthma and COPD arenas, but indeed in the entire area of respiratory.

### **Biomarkers in COPD**

A biomarker is defined in the *International Journal of Clinical Pharmacology & Therapeutics* as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Biomarkers such as HbA1c in diabetes help to identify disease progression and response to therapy. Some companies active in the respiratory arena now appear to be turning their attentions to identifying equivalent markers in asthma and COPD, albeit with limited success.

In the session entitled '**COPD assessment: Novel approaches to identify response to therapy**', Dr. Clive Page, London, highlighted the fact that very few biomarkers exist in COPD and that FEV1 remains the most robust measure of disease progression. Indeed, Dr. Page pointed out that many clinical biomarkers don't correlate with an increase in the progression of COPD. Despite this, Dr. Page highlighted C-reactive protein, local neutrophils and local macrophages as possible biomarkers in COPD. However, we believe that the lack of identification of possible biomarkers highlights the complexities of both asthma and COPD, and that a clear understanding of the underlying mechanisms of these disease states remains elusive.

However, in an attempt to identify novel endpoints in COPD, and compare them to FEV1, GSK is conducting its ECLIPSE (Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints) trial. This ongoing three-year, Phase III study, will try and identify novel endpoints as predictors of COPD severity, and its progression over time. We expect the results sometime in 2009.

### Other Highlights of ATS 2007

- Many physicians now view COPD as a co-morbid disease. Indeed, data from ATS 2007 suggested that up to 64% of COPD patients have cardiovascular problems, and up to 48% have gastro-intestinal conditions. A 10% reduction in FEV1 is also associated with a similar increase in cardiovascular mortality. As such, COPD is now being viewed as a part of an overall 'holistic disease state'. Potential therapies may therefore include the statins, as highlighted by *Mancini et al* in the Journal of the American College of Cardiology in 2006.

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## Wood Mackenzie attends SMI's Asthma and COPD conference, London

COPD and asthma are chronic obstructive diseases of the airways, which are both treated with similar types of drugs (bronchodilators and inhaled corticosteroids). But there remains a number of key differences between these disease states, including age of onset, effectiveness of treatment and ultimate morbidity outcome. In fact, COPD is set to become the fifth leading cause of death in the world by 2020. Despite this, the condition remains under-diagnosed and poorly understood by the public, whilst therapeutic intervention is both limited and lacking in efficacy. Like COPD, asthma rates continue to rise globally and, although prophylactic therapies are proving effective in controlling the disease, asthma remains a major cause of chronic morbidity and mortality.

It therefore remains a major challenge for the pharmaceutical industry to develop drugs to treat both conditions, which are both efficacious and safe. SMI's Asthma and COPD conference in London on the 25<sup>th</sup> and 26<sup>th</sup> April 2007, which Wood Mackenzie attended, sought to address such issues by bringing together some of the leading figures from the pharmaceutical and biotechnology industries.

### Wood Mackenzie View

Although topics included the use of biomarkers to help accelerate drug development, and the development of novel delivery systems which can effectively deliver therapeutic intervention, the conference was dominated by the identification of novel targets to treat both COPD and asthma. A number of companies, including those which do not have a significant presence in the COPD/asthma markets, are attempting to develop therapeutics against novel targets such as interleukin-13 (IL-13), CC Receptor-3 (CCR-3) and chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTH2). However, we would note that many of these programmes are at the pre-clinical stage of development, with potential novel therapeutics many years from the market. Although we believe that such drugs will eventually play a role in treating both asthma and COPD, we believe that the inhaled corticosteroids and long-acting beta-2 agonists will continue to dominate the market for some time to come.

### Overview of Asthma and COPD

As highlighted by Dr. Craig Conoscenti, Senior Associate Director, Medical Affairs, **Boehringer Ingelheim**, approximately 70% of COPD patients are under 65, with some 12.6 million new diagnoses in 2004. Although COPD prevalence, morbidity and mortality varies across countries and groups, smoking remains the main cause of the disease. While many people focus on the human cost of COPD, the economic costs are also considerable, with indirect and direct costs amounting to approximately \$37.2bn in 2004. Unlike COPD, Dr. Conoscenti highlighted the fact that deaths from asthma continue to plateau or decline, although prevalence increases by approximately 10% each decade, with an estimated 300 million people worldwide living with what continues to be a debilitating disease. Like COPD, the economic burden of asthma is significant, with indirect and direct costs amounting to approximately \$16.1bn annually.

In terms of market dynamics, Dr. Conoscenti estimated that the global COPD and asthma markets were currently worth approximately \$20bn (we estimate this figure to be approximately \$24bn in 2006). Future market growth was likely to be driven by increasing disease awareness in both asthma and COPD, as well as an increase in the paediatric asthma sector, and an ageing population susceptible to COPD. We estimate that the global asthma market will grow from \$21bn in 2006 to \$32bn in 2013 (CAGR of 6.2%), whilst the COPD market will grow from \$3bn in 2006 to \$7bn in 2013 (CAGR of 12.6%).

## Novel Targets for Therapeutic Intervention in Asthma and COPD

Standard therapy for both COPD and asthma continues to be inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABAs), or a combination of both. Although prophylactic use of ICS/LABA drugs has proven useful in controlling asthma, the disease continues to be a major cause of death, whilst ICS/LABA therapy has little effect on overall COPD mortality. The SMI conference was therefore dominated by novel targets and therapeutics for these disease states (see table, below). Whilst the majority of novel compounds came from small biotechnology companies, both Wyeth and J&J (companies with little or no presence in the asthma and COPD arenas) have early-stage programmes in progress.

Dr. Sandy Goldman, Director, Respiratory Disease and Inflammation, **Wyeth**, highlighted how the company was working on an anti-IL-13 antibody, whilst Dr. Chris Molloy, Senior Research Fellow, Inflammation and Pulmonary Diseases, **J&J**, presented data on **RWJ-355871**, an inhaled inhibitor of both Chymase and Cathepsin G, which is currently in early-stage clinical development. A number of smaller companies, such as **Topigen** and **Actimis** have compounds in clinical development, although both companies are unlikely to be able to continue development unless a partner with financial muscle is found.

Dr. Paolo Renzi, **Topigen**, presented data on **TPI ASM8**, which utilises RNA interference against two separate targets – CCR3 and the  $\beta$ c-subunit of interleukin receptors. TPI ASM8 is an inhaled compound which is currently in Phase II development for the treatment of asthma, although we understand that the company is actively seeking to out-licence the product. However, due to its novel mechanism of action, the drug may require extended clinical evaluation before regulatory approval. **Actimis** is developing **AP-761**, currently in Phase I for the treatment of asthma. The drug is a small molecule antagonist of CRTH2.

## TNF as a Target in Asthma and COPD?

Although neither Wyeth or J&J have a significant presence in the respiratory field, both companies currently market blockbuster products for other inflammatory diseases such as rheumatoid arthritis, psoriasis and ankylosing spondylitis. Wyeth's Enbrel and J&J's Remicade are monoclonal antibodies directed against TNF $\alpha$  – a molecule implicated in the inflammatory response. As such, researchers have hypothesised that the anti-TNF's (which also includes Abbott's Humira) may be effective in treating asthma and COPD.

Interestingly, Wyeth is now developing Enbrel for asthma (currently in Phase II), whilst J&J's Remicade is in clinical development for both asthma and COPD. If these drugs are shown to be effective in clinical trials, then J&J and Wyeth may be able to force themselves into the respiratory arena in the future. However, we would sound some caution, as results published in July 2006 reported that, although Remicade decreased the number of asthma exacerbations in a small trial, the drug had no significant effect on peak respiratory flow – the study's primary endpoint. However, we believe that drugs such as these, and those presented at SMI's Asthma and COPD conference, with novel targets within the inflammatory response, represent the next generation of therapeutics in asthma and COPD.

**Table 1 : Novel therapeutics presented at SMI's Asthma and COPD conference, London, 25<sup>th</sup> and 26<sup>th</sup> April 2007**

Compound (Phase)	Mechanism	Indication	Company	Wood Mackenzie's Opinion
AP-761 (Phase I)	CRTH2 antagonist	Asthma	Actimis	Small molecule which entered Phase I in July 2006. Unlikely to reach the market unless product is out-licensed to company with the financial muscle to take AP-761 through late-stage development.
TA-106 (Discovery)	Factor B Inhibitor	Asthma	Taligen	Monoclonal antibody targeting Factor B. Expected to enter clinical trials in 2008. Unlikely to ever reach the market unless Taligen seeks a partner to aid development of the product.
TPI ASM8 (Phase II)	Inhibitor of CCR3 / $\beta$ c-subunit of interleukin receptors	Asthma	Topigen	Inhaled formulation containing two RNA anti-sense oligonucleotides which target CCR3 and the $\beta$ c-subunit of interleukin receptors. Topigen is actively seeking to out-licence the product. We believe that, although it represents a novel approach to asthma therapy, regulatory authorities may be reluctant to approve such RNA technology unless extensive clinical trials are undertaken.
TPI 1100 (Discovery)	PDE4 / PDE7 Inhibitor	COPD	Topigen	Inhaled formulation containing an RNA anti-sense oligonucleotide which targets PDE4 and PDE7. Ultimately, should TPI 1100 progress to Phase II, we believe that Topigen will attempt to out-licence the product. However, like TPI ASM8 (see above), regulatory authorities may be reluctant to approve such RNA technology unless extensive clinical trials are undertaken.
RWJ-355871 (Clinical)	Chymase / Cathepsin G inhibitor	COPD / Asthma	J&J	Inhaled dual inhibitor of Chymase and Cathepsin G which, we believe, entered clinical trials in October 2005. J&J has no presence in the COPD or asthma fields but, with Remicade in development for both conditions, RWJ-355871 may prove a useful addition to the company's efforts to enter the COPD and asthma arenas.

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