

# Key Events

## Anti-infectives

Last Updated: 29th May 2007

Date	Event	Status
24 – 28 <sup>th</sup> February 2007	14 <sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI), Los Angeles, USA	Reported
23 <sup>rd</sup> and 24 <sup>th</sup> April 2007	SMi's Superbugs and Superdrugs conference– a focus on antimicrobials, London, UK	Reported
18 <sup>th</sup> – 23 <sup>rd</sup> May 2007	American Thoracic Society (ATS) International Conference, San Francisco, USA	Reported
17 <sup>th</sup> – 21 <sup>st</sup> September 2007	47 <sup>th</sup> Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, USA	To be reported
4 <sup>th</sup> and 5 <sup>th</sup> October 2007	45 <sup>th</sup> Annual meeting of Infectious Disease Society of America (IDSA), San Diego, USA	To be reported

## American Thoracic Society 2007. Tuberculosis – a real and present danger

### Wood Mackenzie opinion

Although the main thrust of this year's ATC was asthma and chronic obstructive pulmonary disease (COPD), the respiratory infection tuberculosis (TB) received a significant amount of coverage. And justifiably so – TB is the 4<sup>th</sup> biggest killer world wide, with the World Health Organisation estimating that one third of the world's population is infected with *Mycobacterium tuberculosis*.

Historically, TB has been a low-interest area for big pharma. But it still remains an area of significant unmet clinical need. First-line therapies are long, complex and costly and as a consequence compliance is poor. This has been further complicated by the emergence of drug resistant forms of the disease. As a result, the drought in R&D activity appears to have been quenched, with a number of promising compounds in various phases of development, notably Tibotec's (J&J) TMC-207 – early clinical results suggest that this compound shows promise in fulfilling the criteria outlined by the TB Alliance for new TB drugs.

This surge of activity has been helped along by not-for-profit organisations such as the TB Alliance, who have been the driving force in developing pharma's involvement in this TB research. But overall, we believe that R&D activity in the area of TB is likely to remain relatively limited for the foreseeable future, with the primary focus on optimising existing therapy regimens. With the TB Alliance estimating the current global TB market to be worth some \$315m for first line drugs and \$54m for second line, we believe that there is little monetary reward for pharmaceutical companies in this area. Rather it represents an opportunity for companies to demonstrate their philanthropy in an increasingly commercial world.

### Introduction

According to the World Health Organisation's Global Tuberculosis Control 2007 report, tuberculosis is still a major cause of death worldwide, with an estimated 8.8 million new cases and some 1.6 million deaths globally in 2005. The vast majority of these cases are in Asia and Sub-Saharan Africa. But TB is still a real and present danger in the US and Europe, where it was previously believed to have been eradicated. In this key event, we will look at the some of the main areas of TB discussed at ATC 2007, including current treatment options; the challenges facing drug development; and promising R&D candidates.

### Current treatment options

The Tuberculosis Trials Consortium (TBTC) is part of the Centers for Disease Control and Prevention (CDC) and is a collaboration between North American and international clinical investigators. Their stated mission is to conduct relevant research concerning the diagnosis, clinical management, and prevention of TB infection and disease. Recognising that new TB therapies may still be some way from the market, the TBTC is keen to work with what they have got, optimising current regimens as much as possible. Standard TB treatments are rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin.

To this end, Susan Dorman, MD, Baltimore brought to our attention the urgent need for shorter and more effective treatment regimens for TB. Current treatment regimens require therapy to be continued for 6-9 months. Dorman discussed the rationale behind using higher doses of the rifamycins, rifampicin and rifapentine, for a shorter period of time.

Another potential way to reduce the length of TB therapy is to combine existing first-line agents with other anti-microbials. Dorman highlighted one of the TBTC's current trials – Study 29, a Phase II study evaluating rifampicin in combination with the quinolone antibiotic moxifloxacin (Bayer / Schering Plough's Avelox). Moxifloxacin is currently in Phase III development for the treatment of TB (see below for further details). Initial results of Study 29 suggest that the combination is potent and effective, with activity being shown during the first 8 weeks of therapy.

## Challenges in TB drug development

In addition to the challenge of developing shorter, more effective treatment regimens, the area of TB R&D faces a number of other significant hurdles. William Burman, MD, Denver highlighted that there were currently some 10,000 patients worldwide with **multi-drug resistant-TB** (MDR-TB). This is usually defined as resistance to the two most effective TB treatments (rifampicin and isoniazid). More worrying perhaps is the strain known as **extremely drug resistant TB** (XDR-TB), a form of TB that cannot be effectively treated with first or second line therapies. The scale of the XDR-TB problem is not yet fully understood.

Mary Reichler MD, CDC, discussed a number of other risk factors associated with TB. In areas of high HIV prevalence, **co-infection with TB and HIV** has become a serious problem, fuelling an increase in the number of TB cases. Immunosuppressed HIV patients are 40% more likely to get TB compared to non-HIV patients. Co-infection not only increases the proportion of the population who develop active TB, but it also presents treatment challenges owing to interactions between TB and HIV drugs. In addition, smoking and the abuse of alcohol have also been linked with an increased risk of TB infection.

## R&D candidates

Dr Tom Shinnik, CDC Division of Tuberculosis Elimination re-iterated Susan Dorman's call to exploit existing TB therapies as much as possible, as well as the need to develop entirely novel treatments. A number of ideal characteristics for new TB therapies have been identified by the TB Alliance. These include activity against drug-resistant TB strains, lack of interaction with anti-retroviral agents and the ability to shorten treatment duration.

The main R&D candidates discussed are summarised in the table below.

**Table 1: Lead TB R&D candidates**

Drug	Trial Sponsors	Drug class	Status	Comments
<b>moxifloxacin</b>	Bayer, TB Alliance, TBTC	fluoroquinolone	Phase II / III	May shorten current treatment from 6 to 4 months. Used in combination with existing therapies
<b>OPC-67683</b>	Otsuka, TB Alliance	nitroimidazole	Phase II	May shorten duration of therapy in active TB and MDR-TB
<b>TMC-207</b>	Tibotec (J&J)	ATP modulator / diarylquinoline derivative	Phase II	May allow once weekly dosing; high potency against drug resistant strains and low potential for drug interactions – good fit with TB Alliance's drug profile
<b>PA-824</b>	TB Alliance (ex. Chiron)	ATP modulator / nitroimidazole	Phase I	Combines the most effective features of rifampicin and isoniazid
<b>Sudoterb</b> (LL3858 + isoniazid, rifampicin and pyrazinamide)	Lupin Pharmaceuticals	Combination product (LL3858 is a pyrrole)	Phase I	May reduce treatment duration to 2-3 months
<b>SQ-109</b>	Sequella Pharmaceuticals, NIH	Diamine	Phase I	Could replace two current TB agents and reduce treatment time by 25%

Although there was little in the way of new clinical information on these candidates at ATC 2007, we expect to hear more at this year's ICAAC and IDSA conferences in September and October respectively.

Nevertheless, this recent flurry of R&D activity in TB is encouraging, with a several candidates e.g. TMC-207 offering significant advances in current therapy. But the majority of speakers at the TB symposia called for further research, and investment, in this area.

For the future, Neil Schluger MD, New York called for improved diagnostics, both for use in the active and latent forms of the disease. GlaxoSmithKline is funding a programme in partnership with Stellenbosch University, South Africa to help identify biomarkers in people who respond to specific treatments. Such biomarkers may be used to predict whether or not patients will respond quickly to treatment or if TB is likely to recur. In addition, Schluger highlighted the need for better vaccines.

**Jane Kidd, Therapy Area Analyst (+44 131 243 4531)**

## Superbugs and Superdrugs – a focus on antimicrobials

### Wood Mackenzie opinion

Anti-microbial research has become something of an outcast in recent years, as big pharma has focused its efforts on developing chronic therapies with maximum profit potential. But the growing problem of bacterial resistance has highlighted the real clinical need for novel antibiotic and anti-fungal therapies. We believe that, as public and government concerns grow, and regulatory and legislative processes change, anti-microbial research will once again be back on big pharma's agenda.

## Introduction

In July 2004, the Infectious Diseases Society of America (IDSA) published an alarming report entitled “Bad Bugs, No Drugs”. Not only did the report highlight the ever-growing problem of antibiotic resistance, but it also brought to our attention the fact that R&D activity by pharmaceutical and biotechnology companies for new antibiotics is drying up. At the time, IDSA put forward three initiatives to address this problem: potential legislative solutions to fuel innovation e.g. wild-card patent extensions; FDA recommendations e.g. accelerate the publication of up-dated guidelines for antibiotic clinical trials to provide needed clarity; and National Institute of Allergy and Infectious Diseases (NIAD) recommendations e.g. increase the number and size of grants.

Some three years on, has the IDSA paper had the desired effect on an industry reluctant to engage in antibiotic R&D? SMI's Superbugs and Superdrugs conference sought to address this issue, looking at a wide range of novel antibiotics and anti-fungals in a variety of stages in the development cycle. We will discuss some of the drug candidates which target the six most dangerous, drug resistant microbes (“superbugs”) as identified by IDSA as being the priority hit-list for R&D (see table below).

**Table 2: Top six most dangerous, drug-resistant microbes, as identified by IDSA (March 2006)**

Microbe	Classification	Problem
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Gram positive	Majority of health-care associated infections. Several treatment options are available for MRSA but resistance is growing in each of them. Most drugs in development are injectable – real need for oral.
Vancomycin-resistant <i>Enterococcus faecium</i> (VRE)	Gram positive	Cause of bloodstream infections, infections of the heart, meningitis and intra-abdominal infections. Current drugs do not rapidly kill VRE and only one is available orally.
<i>Escherichia coli</i> and <i>Klebsiella</i> species	Gram negative	Causes of urinary tract, gastro-intestinal and wound infections. Becoming resistant to a growing number of antibiotic classes. Both microbes tend to rapidly evolve resistance to new drugs.
<i>Acinetobacter baumannii</i>	Gram negative	Growing cause of hospital-acquired pneumonia. Mortality rates range from 20 to 50%.
<i>Pseudomonas aeruginosa</i>	Gram negative	Causes severe infection that can be life-threatening in immunocompromised patients. Increasing rates of <i>P. aeruginosa</i> hospital-acquired pneumonia, infections following surgery, and urinary tract infections. Particular threat to children with cystic fibrosis. Very little R&D activity.
Aspergillus	Fungus	Growing problem among immunocompromised patients e.g. cancer patients, organ transplant recipients and people with HIV. Even with new anti-fungals, death from Aspergillus infection are 50-60%.

## Gram positive bacteria

The bulk of R&D candidates discussed at the Superbugs and Superdrugs conference target gram-positive bacteria, perhaps unsurprisingly as these organisms cause the vast majority of nosocomial infections. There are a wide range of compounds in late-stage development with varying degrees of effectiveness against MRSA and VRE. These include the glycopeptides - Pfizer's dalbavancin (pre-registration), Astellas' telavancin (pre-registration) and Targanta's oritavancin (Phase III), as well as the cephalosporin's Basilea / J&J's ceftobiprole and Forest's ceftaroline (both in Phase III). But all of these candidates fall short of IDSA's cry for novel oral antibiotics – they are all in development as IV formulations.

So what of the early stage candidates? Of the compounds discussed with novel mechanisms of action, we would highlight

- Affinium Pharmaceuticals' **API-1252**. Obtained through a licensing deal with GlaxoSmithKline, API-1252 is a novel fatty acid synthesis inhibitor for Staphylococcal infections. Dr Nachum Kaplan, Vice President of Microbiology at Affinium noted that the compound is highly potent against *S. aureus*, including MRSA and MSSA (methicillin-sensitive *S. aureus*), with low to non-detectable frequencies of resistance in preclinical studies. Importantly, API-1252 was orally efficacious in the mouse thigh model – as a result, Affinium are developing it both as an oral and an IV formulation.
- Prolysis' **CDI-936**. Dr Lloyd Czaplewski, Director of Research at Prolysis presented data on CDI-936, a series of drugs that target the taxol-binding site on the FtsZ protein which causes disruption of cell division and lysis. The drugs are in preclinical development for the potential treatment of Staphylococcal infections, with Phase I slated to start in January 2009. Prolysis is hopeful that the lead candidate will have oral and IV activity
- Novozymes' **NZ2114** is a plectasin anti-microbial peptide. Data presented by Soren Kjaerulff, Director of Antimicrobial Peptides at Novozymes, showed that this novel antibiotic has shown good activity in vivo and in vitro against Staphylococcus (and Streptococcus) and compares to marketed antibiotics. First in man studies are scheduled to start in 2008 / 2009. More data will be presented on this compound at the 47<sup>th</sup> ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy) in September 2007.

- Rib-X Pharmaceuticals pipeline consists of three lead products. Dr Joyce Sutcliffe, Chief Research Scientist at Rib-X presented data on all three. **RX-01** is a family of oxazolidones targeting the bacterial ribosome – the most advanced of these will enter Phase II by Q3 2007, both as an oral and as an iv formulation. **RX-02** is a new class of orally active macrolides for the treatment of community acquired MRSA infections. Several candidate molecules are being progressed through advanced preclinical development, and at least one will be selected for progression to Phase I by Q4 2007. **RX-301** was obtained from Abbott (formerly known as ABT492). This IV antibiotic is currently in Phase II development and has been shown to have activity against Gram positive bacteria, including quinolone resistant MRSA. Phase III trials are due to start in July 2007.

### Gram-negative bacteria

Over the years, there has been a major increase in multi-drug resistant Gram-negative bacteria - three of the top six most dangerous, drug resistant microbes are Gram negative. But R&D activity has not kept up with this ever increasing problem. As a result, there are no new drugs in late stage development that have good overall coverage of the Gram-negative bacteria that cause life-threatening hospital infections. Clearly, this is a major gap in the market, which is crying out to be exploited by big pharma and biotechs. But with anti-microbial research still being viewed by many as an unattractive option, the near term prospects in this market look bleak.

Of the early stage programmes discussed at Superbugs and Superdrugs, we would highlight

- Basilea's novel approach to  $\beta$ -lactam resistance in Gram negative bacteria. Professor Malcolm G. P. Page, Head of Biology at Basilea Pharmaceutica presented data on the lead candidate **BAL30376**, which combines a  $\beta$ -lactamase stable antibiotic with a new mechanism-based  $\beta$ -lactamase inhibitor. BAL30376 is in preclinical development.

### Aspergillus

Aspergillus fungal infections are commonly treated with azoles, which target C-14 demethylase, an essential enzyme in ergosterol synthesis. Azoles are attractive clinically because of their broad spectrum of activity, relatively low toxicity and ease of administration – they are available as oral and iv formulations. However, the emergence of resistance to azoles presents a significant problem.

Dr Nafsika Georgopapadakou, former Vice President of Infectious Diseases, Methygene, presented data on their histone deacetylase (HDAC) inhibitor programme. The lead candidate – **MG3290** – is in preclinical development as an adjunct to azole therapy. Data so far have indicated that MG3290 has a synergistic effect with azoles, decreasing the frequency of resistance and increasing fungicidal effect. In addition, early data suggest that it has potential activity against azole-resistant fungi.

**Jane Kidd, Therapy Area Analyst (+44 131 243 4531)**

## 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, USA

### Wood Mackenzie opinion

HIV/AIDS is a highly emotive disease, with new treatment advances followed closely by physicians and patients alike. So the release of positive clinical trial results for two entirely new classes of HIV drugs – integrase inhibitors and CCR5 antagonists - at this year's Conference on Retroviruses and Opportunistic Infections (CROI) in Los Angeles generated an enormous amount of excitement within the medical and HIV communities. Both these drug classes are initially targeting a particularly vulnerable group of HIV patients; those who are resistant to standard anti-retroviral treatment (ART) regimens.

The companies involved – Merck & Co. and Gilead, with integrase inhibitors Isentress and GS-9137 respectively, and Pfizer with CCR5 antagonist maraviroc – see huge potential in their respective products. From our analysis of the most recent clinical data, we believe that Merck's Isentress will be the winner in terms of overall sales, with Wood Mackenzie forecasts tipped to reach some \$1bn by 2013. But the clear winners from the launch of these new products will be the HIV patients, whose range of treatment options is about to receive a boost on par with the advent of the protease inhibitors in the 1990s.

### Integrase inhibitors

Integrase inhibitors work by inhibiting the action of the integrase enzyme. Produced by the HIV virus, this enzyme incorporates the virus' genetic material into the DNA of a patient's immune cell. The viral DNA then hijacks the cell to make more copies of the virus. Clinical data for the two integrase inhibitors closest to market were presented at CROI 2007; these are Merck's Isentress (raltegravir, MK0518), and Gilead's GS-9137.

**Isentress.** Merck presented results from its Phase III BENCHMARK (Blocking integrase in treatment experienced patients with novel compound against HIV: Merck-0518) studies – BENCHMARK 1 and BENCHMARK 2. These ongoing trials are evaluating 699 patients, over 156 weeks, who are highly treatment experienced (i.e. resistant to one or more of the three oral classes of ARTs – NRTIs, NNRTIs and protease inhibitors). Twice daily Isentress in combination with optimised background therapy (OBT) is being compared to placebo plus OBT. Data was collected at the 16 week primary analysis time point, evaluating reduction in HIV viral load, change from baseline in CD4 counts and safety and tolerability.

In both studies, more than 75% of patients receiving Isentress plus OBT achieved viral load reductions to less than 400 copies / ml compared to 40% of placebo plus OBT patients. Between 61 and 62% of patients receiving Isentress plus OBT achieved viral load reduction to below 50 copies / ml – the target level of HIV suppression – compared to 33-36% for placebo plus OBT. The increase in CD4 cell count was 83-86 cells / mm<sup>3</sup> for Isentress patients, which was 2-3 times the increase in patients receiving placebo. Isentress was well-tolerated, while liver enzyme abnormalities seen in earlier Phase II trials were not seen in the BENCHMARK studies.

When we consider that the virologic responses seen in the placebo arms of the BENCHMARK studies are respectable in terms of current standards of care, the fact that the addition of Isentress doubled these responses is extremely positive. Assuming that full study results are similarly strong, we believe that Isentress has the potential to reach blockbuster status. Merck intends to file its NDA in H2 2007 – we expect launch in the US and Europe in early 2008.

**GS-9137.** Gilead presented 16 week data from a 278 patient Phase IIb study, comparing once daily GS-9137, boosted with ritonavir in combination with an OBT (protease-inhibitor based) with a boosted comparator protease inhibitor regimen in highly treatment experienced HIV infected patients. Between 38 and 40% of patients on GS-9137 reached 50 copies/ml at 16 weeks, compared to 30% of patients in the comparator arm. The increase in CD4 cell count was 52-61 cells / mm<sup>3</sup> for GS-9137 versus 28 cells / mm<sup>3</sup> for placebo. GS-9137 was well tolerated with no new or unexpected adverse events.

While GS-9137 looks like it has a good clinical profile, these early data suggest that it may not be as effective as Merck's Isentress. Coupled with Merck's development lead – Isentress is some 18 months ahead of GS-9137 in terms of development – GS-9137 is currently at a competitive disadvantage. But it is still early days. Given Gilead's experience in the HIV market, and its success in developing combination HIV products, we would expect the company to differentiate its product by developing fixed dose combinations with its own NRTIs e.g. Truvada in order to secure GS-9137's place in this new market.

### CCR5 antagonists

CCR5 antagonists work by blocking a protein on human immune cells that HIV uses as a portal to enter and infect cells. Theoretically, because CCR5 antagonists do not attack the virus itself (like other HIV treatments), HIV may be less likely to develop ways of resisting their effects.

Over the years, there has been a great deal of interest in CCR5 antagonists. But the road to market for this new class of HIV treatments has been far from smooth. GlaxoSmithKline terminated the development of its CCR5 inhibitor, aplaviroc in October 2005, following concerns of liver toxicity, while development of Schering Plough's vicriviroc has stalled due to links with an increased risk of haematological malignancies. So it came as a breath of fresh air to this much thwarted class, when Pfizer presented positive clinical trial data for its CCR5 antagonist maraviroc at this year's CROI.

**Maraviroc.** Pfizer reported results from its two Phase IIb / III studies MOTIVATE 1 and MOTIVATE 2. These ongoing studies are evaluating a total of 1076 treatment experienced patients with CCR5-tropic HIV virus. 24 week results showed that approximately twice as many patients treated with maraviroc plus OBT, either once or twice a day, achieved undetectable viral loads (less than 50 copies / ml) compared to those receiving placebo plus OBT – MOTIVATE 1 (42.2% once daily and 48.5% twice daily versus 24.6%) and MOTIVATE 2 (40.8% once daily and 45.6% twice daily versus 20.9%). Increases in CD4 cell count were 107-112 cells / mm<sup>3</sup> for once daily and 102-111 cells / mm<sup>3</sup> for twice daily maraviroc compared to 52-64 cells / mm<sup>3</sup> for placebo. Both trials showed that maraviroc had a good side effect profile, and that there was no evidence of hepatotoxicity, lymphoma or other malignancies associated with the drug.

We believe that these clinical trial results help vindicate the use of the CCR5 antagonists as a viable treatment option in HIV-resistant patients and will pave the way for Pfizer to launch maraviroc as first in class. An FDA advisory committee is scheduled to meet on 24<sup>th</sup> April 2007 to discuss Pfizer's NDA, which was filed in December 2006.

But we believe that maraviroc's commercial potential will be restricted by the fact that its use is limited to the CCR5-tropic virus. Only 85% of newly infected patients and 50% of highly drug resistant patients (Pfizer's initial target group) are infected with the virus that uses the CCR5 portal – the remainder are infected with CXCR4-tropic virus. Therefore, patients will have to be tested to see whether they are eligible for treatment with maraviroc – this could cost up to \$1000 and take approximately two weeks to receive results.

In addition, there are concerns that CCR5 antagonist therapy may drive HIV to switch co-receptor preference from CCR5 to CXCR4 – research links CXCR4 tropism with advancing HIV disease. Results from MOTIVATE 1 and 2 showed that substantially more people with treatment failure in the maraviroc arm, versus the placebo arm, had such a tropism switch.

With these points in mind, we believe that maraviroc will provide a useful weapon in the fight against HIV, with sales benefiting from first-to-market status. But unlike the integrase inhibitors, we believe that the CCR5 antagonists will gain a relatively small share of the HIV market.

**Jane Kidd, Therapy Area Analyst (+44 131 243 4531)**