

The Ones To Watch

January 2007

Review of Phase Changes in the Pharmaceutical Pipeline from *Thomson Pharma*[®]

Expert insight into the five most promising drugs:

- Receiving Approval
- Entering Phase III Trials
- Entering Phase II Trials
- Entering Phase I Trials

During October to December 2006

Last quarter we predicted a bumpy ride for Encysive Pharmaceuticals' Thelin™, partly because it looked set for a hard fight against the established treatment, Actelion's Tracleer®. How bumpy is now becoming clear, which is why we've placed it in our *The Ones To Watch* list for the second time. After a difficult approvals process, the drug has finally been accepted for FDA review.

As our tables show, pharmaceutical companies will continue to grapple with the big issues far into the future. So let's take a look at the five most promising drugs receiving approval, and the five most promising drugs to enter each new phase of clinical development, between October and December 2006.

The Five Most Promising Drugs Receiving Approval

Drug	Disease	Company
Januvia®	Type 2 diabetes	Merck & Co
Thelin™	Pulmonary arterial hypertension	Encysive Pharmaceuticals
Brovana™	Chronic obstructive pulmonary disease	Sepracor Inc
Invega™	Schizophrenia	Johnson & Johnson
Polyphenon® E	Genital warts	MediGene

This quarter's drug to watch must be **Januvia**® from Merck & Co, a once-daily tablet regime and the lead in a series of dipeptidyl peptidase IV inhibitors designed to treat type 2 diabetes. It's a timely launch, with the disease increasing rapidly in the western world and showing every sign of following suit in developing markets. Though there appears to be a considerable genetic risk, it is thought that the disease can also be a result of factors such as obesity and lack of exercise, practically assuring its growing prevalence.

Given all this, it is unsurprising that Merck & Co is splashing the drug across the world markets. The company launched Januvia in Mexico in October 2006, and is launching it in the US as this report goes to press. Launch in the UK is expected "in the near future". Merck's Japanese subsidiary Banyu and licensee Ono Pharmaceutical are developing the drug in Japan, where it is currently in Phase III trials.

Encysive Pharmaceuticals must be hoping things will get easier for **Thelin**™ now a fairly fraught US approvals process finally appears to be heading towards approval. The drug is the first selective endothelin A receptor antagonist targeted at pulmonary arterial hypertension, a therapy area that has already shown huge advances in the last two decades and where Actelion's Tracleer® is dominant, at least in Europe.

Thelin was approved by the European Medicines Agency in August 2006. It launched in the UK in November, and in Germany the following month.

In the US, Encysive first filed its NDA in May 2005. The FDA issued an approvable letter in March 2006, requesting further clinical trials. In May the company submitted a complete response, but in July the FDA issued a second approvable letter. Encysive submitted another complete response in November, but the FDA deemed this incomplete. The agency has now finally accepted the complete response, and set a Prescription Drug User Fee Act (PDUFA) review date in June 2007.

Respiratory disorders are also the target of **Brovana™**, a single isomer version of racemic formoterol developed by Sepracor Inc as a bronchodilator for the potential treatment of chronic obstructive pulmonary disease. The drug is the first long-acting beta-2 adrenergic to be approved as an inhalation solution, administered twice daily by nebulizer. The FDA approved Brovana in October 2006, and Sepracor plans to launch in the second quarter of 2007. The company is also looking at developing Brovana as a potential treatment for asthma.

Schizophrenia is vexing the minds of Johnson & Johnson. **Invega™**, developed with its subsidiary Janssen Korea, is the first new prescription treatment for the disorder to be approved by the FDA since 2003. The drug is a once-daily oral administration of paliperidone, a 5-HT antagonist and metabolite of risperidone.

Unlike Thelin, Invega had a fairly smooth run through the regulatory hurdles: Johnson & Johnson filed for US approval in November 2005, and the following July the FDA canceled a scheduled meeting to discuss the application as it had not identified any issues requiring its feedback. The drug was approved in December. Launch is taking place as this report goes to press, and Johnson & Johnson is expecting sales of more than \$1.6 billion in 2010.

Last on our list is **Polyphenon® E**, developed by MediGene under license from Epitome Pharmaceuticals. The treatment, a formulation of a green tea extract, is a topical ointment designed to deal with genital warts. The company also hopes Polyphenon E can target actinic keratosis (Phase II trials began in April 2004) and basal cell carcinoma.

Again this drug shows the complex nature of the approvals process in the US. MediGene submitted its NDA in September 2005, anticipating launch in 2007. However, the FDA extended its review by 90 days in June 2006 after requesting the company submit a major amendment to the NDA. Though this was expected to delay launch, the drug was approved in October 2006 and Polyphenon E is now back on track to reach patients in the second half of 2007. MediGene suggests annual peak sales of up to \$100 million in the US, and is planning to submit MAAs in a number of European countries before the end of the year.

The Five Most Promising Drugs Entering Phase III Trials

Drug	Disease	Company
Albuferon™	Hepatitis C	Human Genome Sciences/Novartis
LibiGel®	Female sexual dysfunction	BioSante Pharmaceuticals/Antares Pharma
isavuconazonium chloride (oral form)	Invasive fungal disease	Basilea Pharmaceutica
SinuNase™	Chronic rhinosinusitis	BioDelivery Sciences/Accentia
Zesteem	Wound healing	Renovo

A little further ahead, the contenders for headline drug of the future include **Albuferon™**, the first of two candidates we highlight this quarter targeting hepatitis C (HCV), an infectious, blood-borne viral disease that currently has no cure — the other is A-831 by Arrow Therapeutics, now entering Phase I.

Albuferon, developed by Human Genome Sciences and Novartis under license from ZLB Behring, is a long-acting albumin/human IFN-alpha-2b fusion protean that requires half as many injections as the current standard. Moreover, clinical results to date suggest that Albuferon has the potential for less impairment of health-related quality of life, with efficacy and safety at least comparable. A substantial percentage of HCV patients take only limited treatment with the current standard due to side effects. The first of two Phase III combination trials began in December 2006, with a second due to start in the first half of this year.

A tougher ride is expected for **LibiGel®**, a once-daily transdermal testosterone gel developed by BioSante Pharmaceuticals and Antares Pharma to treat female sexual dysfunction. The disorder is common among women as they approach menopause, meaning that a simple, effective treatment could command a huge market, but it is an area fraught with difficulty, not least a lack of awareness among physicians (many of whom do not yet accept the diagnosis) and the patients themselves. Education of the market will take significant resources. In addition, no therapy has yet received approval by the FDA, and there is not yet regulatory clarity on the FDA's safety data requirements for testosterone drugs of this type.

All this could delay development of LibiGel — seen by analysts as “a key driver” for BioSante — still further. Phase II trials began way back in June 2001 and were completed three years later. Phase III trials of 360 surgically menopausal women started in December 2006 and are likely to last six months. Once two Phase III trials and a year of safety data have been gathered, BioSante and Antares hope finally to achieve FDA approval. This

being the case, analysts predict that sales into the surgically menopause market alone could reach approximately of \$400 million by 2017.

Invasive fungal diseases such as candidiasis and aspergillosis are the target of an **oral formulation of isavuconazonium chloride**, the water-soluble prodrug of the triazole isavuconazole, currently in the Basilea Pharmaceutica pipeline. There is certainly a huge call for the treatment: reportedly, the currently available antifungal drugs fail in more than half the acute invasive aspergillosis patients that take them, and in up to 30% of patients with candidemia. Basilea's once-daily oral formulation should please both clinicians and patients, increasing dosing flexibility, diminishing side effects, and retarding the development of resistance.

Isavuconazonium chloride was granted FDA Fast Track status in May 2006 and began Phase III in December. The trials are designed to compare the safety and efficacy of the drug against voriconazole for the primary treatment of invasive fungal disease in 360 patients. A second trial will compare the drug to a candidin regimen for candida infections in 526 patients.

According to the Mayo Foundation, fungal inflammation may also be a cause of chronic rhinosinusitis, a respiratory disorder with no currently approved pharmaceutical on the market despite affecting more than 30 million patients worldwide — almost twice as many as those for the next largest respiratory disorder, asthma. The only recourse is surgery.

Unsurprisingly, the Mayo Foundation's **SinuNase™** is causing a great deal of interest. A novel encochleated BioNasal formulation of the antifungal agent amphotericin B, it is the only drug of its type in Phase III trials and has been granted FDA Fast Track status. The drug's developers, BioDelivery Sciences in collaboration with Accentia, have to date initiated Phase III trials at 43 sites, 29 of which are cleared to enroll patients.

The prevention and reduction of scarring is a significant need in the treatment of trauma and injury, as well as in elective surgery such as cosmetic, plastic and reconstructive procedures. With no other pharmaceuticals on the market, and no foreseeable competition in the pipeline, Renovo sees a clear market for **Zesteem**, a formulation of 17beta-estradiol that can potentially accelerate re-epithelialization following surgery or wounding. This December, the company initiated Phase III trials in split-thickness skin graft donor sites in Europe.

Zesteem is only the first of a number of candidates in Renovo's pipeline, all aiming to reduce or prevent scarring. Juvista has just completed Phase II efficacy trials in the UK, while Juvindex and Prevascar are currently progressing through Phase II. Renovo aims to extend the significant market potential for its drug candidates to multiple other body sites and fibrotic disorders, such as pulmonary fibrosis.

The Five Most Promising Drugs Entering Phase II Trials

Drug	Disease	Company
FX-06	Reperfusion injury following myocardial infarction	Fibrex Medical R&D
Resten-CP™	Restenosis following coronary artery bypass graft	AVI BioPharma
DCVax®-Brain	Glioblastoma multiforme	Northwest Biotherapeutics
TC-2696	Post-operative pain	Targacept
Curaxin CBLC-102	Hormone refractory prostate cancer	Cleveland BioLabs

Of the drugs we highlight entering Phase II this quarter, two are concerned with matters of the heart. Acute myocardial infarction, commonly known as a “heart attack”, is the leading cause of human death in both sexes. Those who survive face further complications, ranging from blood clots to bypass surgery, while damage to the heart tissues during the period of ischemia (oxygen starvation) can lead to deteriorating health in later life.

A common problem is reperfusion injury, an inflammatory response where the heart tissues are damaged still further when the blood supply returns. Fibrex Medical R&D GmbH, the research subsidiary of Fibrex Medical Inc, is developing **FX-06** specifically to target this inflammation. The drug is a peptide that inhibits leukocyte transmigration by inhibiting the interactions between fibrin fragments and VE-cadherin. Phase II studies began in October. Fibrex Medical intends to administer FX-06 to 140 patients in seven European countries shortly after acute myocardial infarction, to study the effect on heart muscle preservation. Results are expected in May 2007.

Hopes for the drug are high. Its novel mechanism also lends itself to application in other diseases involving an acute inflammatory response, such as hemorrhagic and septic shock, where patients have very few treatment options and there is a great risk of mortality.

AVI BioPharma, meanwhile, has progressed **Resten-CP™** to a Phase II study of 110 patients undergoing coronary artery bypass graft. The drug is a potential treatment for coronary restenosis following bypass, a condition where the vein graft itself becomes blocked. The Phase II safety assessment is likely to last three months. After this AVI BioPharma plans to commence double-blind Phase III trials on 600 patients in the Ukraine and Poland to assess the benefit of administering the drug to the saphenous vein immediately before connecting it to the coronary artery circulation. Patients will be monitored for blockage of the graft over the course of a year. If these trials are successful, the company hopes to launch Resten-CP within five years.

From the heart to the head. Glioblastoma multiforme (GBM) is the most common type of brain tumor. Patients have a less than 3% chance of surviving the disease for five years. Existing treatments, using a combination of surgery, aggressive radiotherapy and chemotherapy, aim merely to increase survival time by a few months.

Northwest Biotherapeutics hopes its autologous dendritic cell-based immunotherapy **DCVax®-Brain** can make a positive difference. The FDA approved Phase II studies in May 2005, as we reported in the first edition of *The Ones To Watch* in August 2006. These trials have now begun at Henry Ford Hospital in Detroit, Michigan. The company intends to evaluate up to 290 subjects who had undergone surgical resection, radiation and Temodar® therapy.

TC-2696 is a neuronal nicotinic receptor (NMR) modulator developed by Targacept as a potential oral treatment for acute post-operative pain. It entered double-blind proof-of-concept trials in December, where it was administered to 150 patients having undergone molar extraction. Targacept is bullish about the drug's chances, calling it one of several NMR-selective product candidates in its product pipeline with potential to be a first-in-class therapeutic. Phase I multiple ascending dose trials are ongoing.

Finally for this section, Cleveland BioLabs is contributing **Curaxin CBLC-102** to the list of potential cancer treatments currently moving through the pharmaceutical pipeline (another of which, EpiCept's EPC-2407, we highlight below). It shows promise: curaxins have a unique mechanism of action, stimulating p53 and inhibiting NF-κB, which research indicates would prove effective in the majority of cancers. Cleveland started Phase II trials in December, focusing on sufferers of advanced, hormone-refractory prostate cancer. The two-year study will treat 31 patients with the aim of demonstrating prostate specific antigen (PSA) reduction, decrease in tumor size and disease-free survival. Simultaneous Phase II trials in renal cell carcinoma are scheduled to begin this year.

The Five Most Promising Drugs Entering Phase I Trials

Drug	Disease	Company
A-831	Hepatitis C	Arrow Therapeutics
monoclonal antibody therapy	Rabies	Crucell/Vaxin
EPC-2407	Cancer	EpiCept
BIW-8405	Asthma	Kyowa Hakko Kogyo/BioWa/MedImmune
NXL-104	Gram-negative nosocomial infections	Novoxel

A number of potential headline-grabbing drugs have shifted into trials again this quarter. Not least of these is **A-831**, the lead in a program of non-nucleoside small-molecule NS5a inhibitors in development by Arrow Therapeutics (now part of AstraZeneca) for the treatment of hepatitis C. A-831's novel mechanism of action and distinction as the first NS5a inhibitor to reach trials indicate it is definitely one to watch. In November 2006 Arrow started clinical studies in the UK to evaluate the drug's safety, tolerability and pharmacokinetics. As we go to press, promising preclinical results are already coming in from A-689, a second compound from the same series.

Rabies is another viral disease with no cure, killing more than 30,000 people each year in India alone. Instead, treatment focuses on vaccination. In the US, where bats, skunks and raccoons all carry the disease, several thousand courses of treatment are administered annually, at a cost of as much as \$1500 per patient. Crucell and Vaxin hope their **combination of two human monoclonal** antibodies, CR-57 and CR-4098, can go some way to replace rabies immune globulin (RIG) derived from human or horse blood, traditional products that are in short supply and can be of variable quality. Phase I trials began in the US in December, with further studies in the Philippines expected in the first quarter of 2007.

Also in December, EpiCept (formerly Maxim Pharmaceuticals) began Phase I trials of **EPC-2407** at two cancer centers in the US. This drug (formerly MX-116407, MX-2407) is the first of a novel class of vascular-targeting tubulin inhibitors discovered by EpiCept. These compounds induce caspase activation, leading to apoptosis and disruption of cancer tumors. After highly encouraging preclinical studies, EpiCept will administer increasing doses of EPC-2407 to approximately 30 patients with advanced stages of solid tumors. The trials, which are expected to last a year, should identify early signs of anti-tumor response and determine safe doses.

Asthma affects up to a quarter of all urban children in the developed world, and is again a potentially huge therapy area in developing markets like India, where WHO estimates there are as many as 20 million sufferers. **BIW-8405**, a monoclonal antibody specific for the IL-5 receptor jointly developed by Kyowa Hakko Kogyo, its wholly-owned subsidiary BioWa, and MedImmune, could potentially gross over \$500 million worldwide. BIW-8405 began Phase I trials in asthma patients in the US in October.

Finally, Novexel, spun out from Aventis Pharma (now sanofi aventis) in December 2004, has focused its attention on nosocomial infection, particularly gram-negative bacteria such as *Pseudomonas aeruginosa* that are responsible for about one tenth of all hospital-acquired infections. The company believes that its intravenous administration **NXL-104** is the only beta-lactamase inhibitor in clinical trials that could potentially respond to the emerging resistance in gram-negative bacteria mediated by class C beta-lactamases. Studies began in December.

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