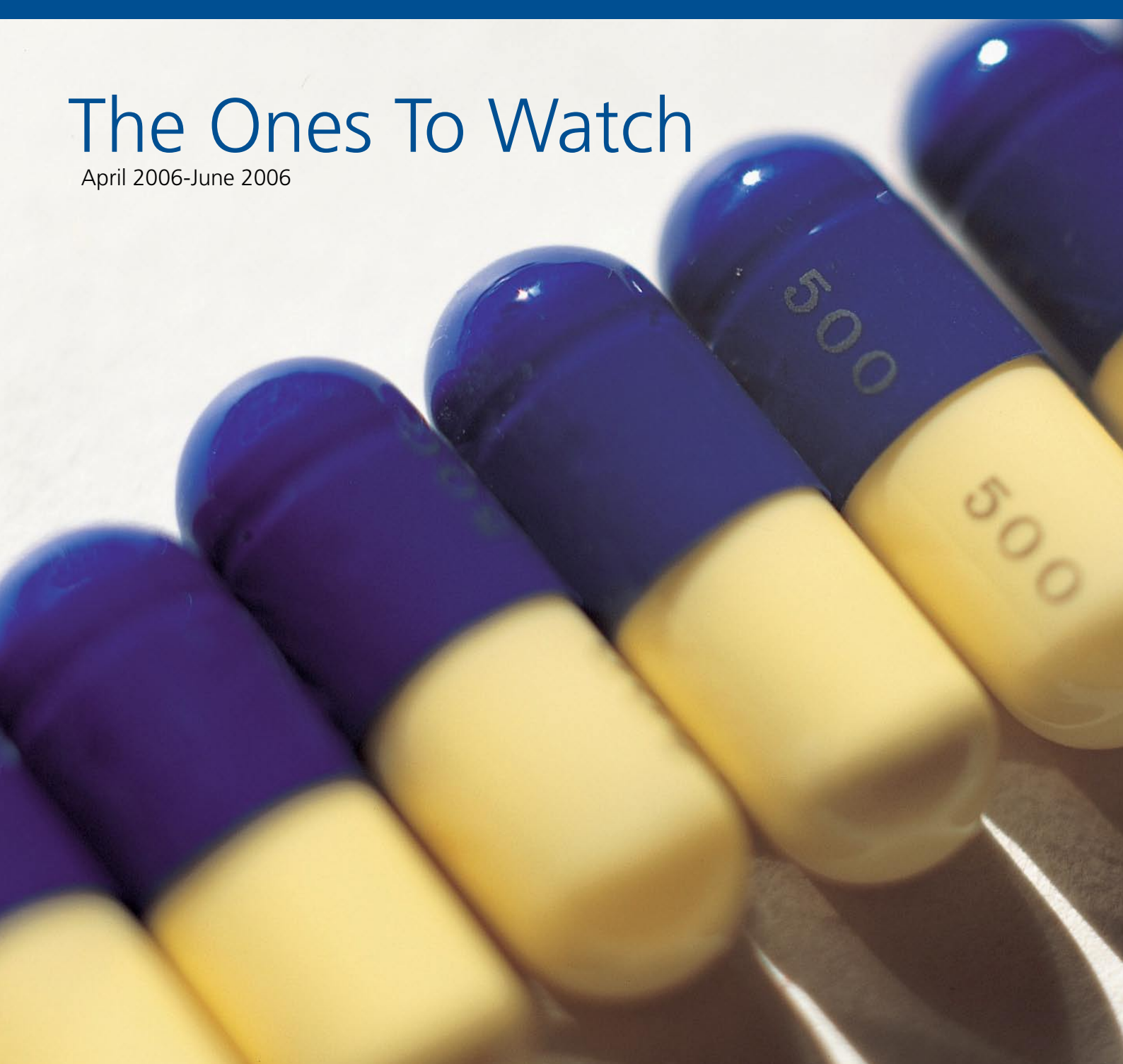


# The Ones To Watch

April 2006-June 2006



Thomson Pharma's Quarterly Review Of Phase Changes In The Pharmaceutical Pipeline

Expert insight into:

- The Five Most Promising Drugs Reaching the Market
- The Five Most Promising Drugs Entering Phase III Trials
- The Five Most Promising Drugs Entering Phase II Trials
- The Five Most Promising Drugs Entering Phase I Trials

US pharmaceutical giant Merck made headlines with the launch of Gardasil™, the first vaccine for preventing cervical cancer, this summer. But what else does the pharmaceutical industry have up its sleeve?

In its first quarterly review of phase changes in the pharmaceutical pipeline, Thomson Pharma has singled out the five most promising drugs to reach the market, and the five most promising drugs entering each new phase of clinical development, between April and June 2006.

## The Five Most Promising Drugs Reaching The Market

Drug	Disease	Company
Gardasil	Cervical cancer	Merck & Co.
Neupro	Parkinson's disease	Schwarz Pharma (under licence from Aderis Pharmaceuticals)
Vaprisol	Hyponatraemia	Astellas Pharma
Emsam	Major depressive disorder	Bristol-Myers Squibb and Somerset Pharmaceuticals
Dacogen	Myelodysplastic syndrome	MGI Pharma and SuperGen (under licence from Pharmachemie)

**Gardasil** must be one of the hottest contenders for drug of the year. It is effective against the two types of human papillomavirus (HPV), 16 and 18, believed to be responsible for about 70% of cervical cancer cases. It also protects against low-grade lesions and genital warts caused by HPV types 6, 11, 16 and 18. All four types are sexually transmitted.

Merck is currently conducting further studies to establish whether Gardasil is suitable for use in women who have already been infected with HPV, since there is some evidence that such patients may experience abnormal tissue growth after being vaccinated. If this proves true, it would substantially reduce the size of the market; 30% of women are infected with HPV within a year of becoming sexually active. But the vaccine can be administered to girls as young as nine – and Merck has at least a year's head start on GlaxoSmithKline, which is currently developing a rival vaccine – so it is still likely to bring in big money. Analysts at Bear Stearns have pencilled in US sales of \$2.10 billion for Gardasil by 2010.

High hopes also exist for **Neupro**<sup>®</sup>, a once-daily rotigotine patch for the treatment of Parkinson's disease. Patients with Parkinson's disease cannot produce enough dopamine to control their motor function, but most of the existing therapies only come in oral formulations, so the amount of medication in the bloodstream rises and falls, reducing their efficacy. Schwarz Pharma has designed Neupro to overcome this problem by delivering a continuous level of medication on a 24-hour basis. It is also developing a formulation for the treatment of restless legs syndrome.

Meanwhile, Astellas Pharma has launched **Vaprisol**<sup>®</sup> – the first arginine vasopressin (AVP) receptor antagonist approved for the management of euvoletic hyponatraemia, a potentially life-threatening condition that occurs when the blood sodium level falls too low. Vaprisol blocks the activity of the AVP hormone and enables patients to urinate without losing valuable electrolytes like sodium and potassium.

Bristol-Myers Squibb and Somerset Pharmaceuticals (a joint venture between Mylan Laboratories and Watson Pharmaceuticals) have also launched **Emsam**<sup>®</sup>, the first skin patch for the treatment of major depressive disorder in adults. Emsam is a monoamine oxidase inhibitor, but oral formulations of the drug pass through the digestive tract and reduce the production of intestinal monoamine oxidase A, which is needed to break down a substance found in some foods. Transdermal delivery minimises the amount of medication to which the digestive tract is exposed, while ensuring that enough reaches the brain to produce an anti-depressant effect.

Last on our list of the most promising drugs to reach the market in the past quarter is **Dacogen**<sup>™</sup>, a cytosine analogue DNA methyltransferase inhibitor for the intravenous treatment of patients with myelodysplastic syndromes (MDS), a group of diseases of the bone marrow. Patients with MDS often suffer from anaemia, bleeding, infection and fatigue. In clinical trials, Dacogen produced a positive response in 21% of patients – a higher response rate than its main competitor. It also shows potential as a treatment for various forms of leukaemia, solid tumours, melanomas and sickle cell disease.

## The Five Most Promising Drugs Entering Phase III Trials

Drug	Disease	Company
DG-031	Myocardial infarction	deCODE (under licence from Bayer)
darusentan	Uncontrolled hypertension	Myogen (under licence from Abbott)
Contrave	Obesity	Orexigen Therapeutics
metaglidasen	Diabetes	Metabolex
Puricase	Gout	Savient Pharmaceuticals (under licence from Duke University)

So much for the drugs that have been launched, but there are some exciting products in the pipeline, too, and several started life in a rather different guise. One such example is **DG-031**, which Bayer originally developed for the treatment of asthma. Icelandic genetics company deCODE subsequently established that DG-031 inhibits 5-lipoxygenase activating protein (FLAP) in patients with certain genetic variants that increase their risk of experiencing a heart attack, and is now conducting Phase III trials for its use in the treatment of myocardial infarction.

A second example is the oral endothelin receptor antagonist **darusentan**, which US biopharmaceutical company Myogen in-licensed from Abbott in 2003. Originally slated as a potential therapy for congestive heart failure, darusentan is now being developed for the treatment of uncontrolled hypertension, after evidence that it significantly reduces both systolic and diastolic blood pressure in patients who have failed to respond to other drugs.

Whereas deCODE and Myogen are focusing on hearts, clinical neuroscience company Orexigen Therapeutics is focusing on hips. Orexigen is looking at the role of the central nervous system (CNS) in regulating appetite. Its lead product, **Contrave™**, is novel in using a cocktail of CNS drugs that target specific pathways to release alpha melanocyte stimulating hormone (MSH), a hormone which binds to the body's melanocortin-4 receptors to reduce the craving for food and increase energy consumption.

Meanwhile, US biotechnology company Metabolex has just started Phase II/III trials of **metaglidasen**, an oral insulin sensitizer for the treatment of Type 2 diabetes. Metaglidasen is a selective peroxisome proliferator activated receptor (PPAR)-gamma modulator and has a different chemical structure and method of action from other insulin sensitizers on the market, which the company hopes will give it a better side-effect profile. Thus far, the signs are encouraging; metaglidasen appears to lower blood glucose levels without causing weight gain and fluid retention.

In May 2006, speciality pharmaceuticals firm Savient Pharmaceuticals also began Phase III trials of **Puricase®**, an intravenous treatment for gout, which is caused by deposits of needle-like crystals of uric acid in connective tissue and joints. Puricase is a polyethylene glycol (PEG) conjugate of urate oxidase. Earlier tests have shown that it lowers plasma urate levels and reduces uric acid deposits. Savient hopes to file a new drug application in 2007, and some analysts estimate that Puricase could generate peak sales of \$250 million a year.

## The Five Most Promising Drugs Entering Phase II Trials

Drug	Disease	Company
ostarine	Bone loss and muscle-wasting	GTx
NTx-265	Stroke	Stem Cell Therapeutics
mitoquinone	Parkinson's disease	Antipodean Pharmaceuticals
DCVax-Brain	Glioblastoma multiforme	Northwest Biotherapeutics
LAB-CGRP	Asthma	Lab International

Several interesting drugs – primarily for age-related diseases – have also just crossed the threshold from Phase I to Phase II. **Ostarine** is a potential treatment for bone loss and muscle wasting in elderly men and postmenopausal women, and the first selective androgen receptor modulator to reach this stage of testing. In preclinical studies, ostarine distinguished itself from other osteoporosis drugs, which only treat bone loss, by increasing both bone and muscle. Greater muscle mass helps patients maintain their balance, so they are less likely to fall and fracture their bones.

**NTx-265** is a combination of two currently marketed large molecules designed to stimulate the growth and differentiation of neural stem cells in adults who have suffered a stroke – the second leading cause of death worldwide. In May 2006, biotechnology company Stem Cell Therapeutics started a Phase IIa study of NTx-265. It is also investigating use of the compound for neurodegenerative disorders, such as Huntington's disease and Alzheimer's disease.

Antipodean Pharmaceuticals simultaneously started Phase II trials on **mitoquinone**, an oral compound that blocks mitochondrial oxidative damage, one of the key underlying mechanisms of Parkinson's disease. It is also exploring the drug's potential for treating retinal degeneration, Alzheimer's disease, Friedreich's ataxia (a progressive disorder of the nervous system and muscles) and cardiac ischemia.

Meanwhile, Northwest Biotherapeutics is wrestling with the big C in the form of glioblastoma multiforme (GBM), the most lethal type of brain cancer. **DCVax<sup>®</sup>-Brain** is a personalised vaccine made from a patient's dendritic cells, which mobilises his or her immune system to attack the disease. Many patients with GBM die within 15 months of being diagnosed, whereas patients in earlier trials of DCVax-Brain have survived, on average, for more than 26 months.

Integrated drug development company Lab International has also just initiated a Phase IIa trial of **LAB-CGRP**, one of several drugs in its pipeline of products for asthma and chronic obstructive pulmonary disease, a market that could be worth over \$17 billion by 2009, with more than 100 million sufferers worldwide. Preclinical trials showed that LAB-CGRP is effective in treating bronchial responses to allergic stimuli. It also has bronchodilatory, bronchoprotective and anti-inflammatory properties.

## The Five Most Promising Drugs Entering Phase I Trials

Drug	Disease	Company
H9N2 vaccine	Avian influenza	Crucell and University of Leicester
TD-1792	Bacterial infections	Theravance
AZD-103	Alzheimer's disease	Transition Therapeutics
RTA-402	Cancer	Reata Pharmaceuticals (under licence from Dartmouth College and the University of Texas)
SRT-501	Diabetes and obesity	Sirtris Pharmaceuticals

From breathing problems to bird flu: one of the most promising compounds to enter Phase I in the past three months is an **H9N2-based avian influenza vaccine**. Conventional vaccines against H5 and H9 avian influenza subtypes only work at much higher doses than those used in seasonal vaccines. So, if a pandemic occurred, it would currently be impossible to meet the world's vaccine requirements. Dutch biotechnology company Crucell has developed three types of H9 vaccine designed to enhance the immune response while minimising the dosage that is required, and is now testing all three in conjunction with a team of scientists at the University of Leicester.

While Crucell is concentrating on viral infections, Californian biopharmaceutical company Theravance is working on bacterial infections. It recently joined forces with Astellas Pharma to develop and commercialise **TD-1792**, a heterodimer antibiotic compound that combines the antibacterial properties of glycopeptides and beta-lactams. Theravance is already conducting Phase III trials on another very exciting product; telavancin is a novel lipoglycopeptide injectable antibiotic that targets serious Gram-positive infections like the MRSA superbug.

The three remaining compounds on our list cover diseases for which there are several potentially useful drugs further downstream, but they represent totally new ways of addressing these illnesses. **AZD-103** is an orally available small molecule that inhibits amyloid beta peptide aggregation. It is one of an emerging class of disease-modifying drugs that have the potential both to improve the symptoms of Alzheimer's disease and to reverse or slow down its progression.

**RTA-402** is a cancer therapy with a unique mechanism of action. It exploits fundamental physiological differences between cancerous and non-cancerous cells by modulating oxidative stress response pathways. As a result, RTA-402 is toxic to cancer cells but induces protective antioxidant and anti-inflammatory responses in normal cells.

Lastly, **SRT-501** is a small molecule that targets the SIRT1 sirtuin, one of a recently discovered family of enzymes, and increases mitochondrial activity. Biopharmaceutical firm Sirtris Pharmaceuticals completed its first clinical trial of SRT-501 in June 2006. It is now subjecting the molecule to further testing as a treatment for diabetes and obesity, and investigating its potential as a treatment for Huntington's disease.

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