

# The Ones To Watch

April – June 2007

Review of Phase Changes in the Pharmaceutical Pipeline from *Thomson Pharma*<sup>®</sup>

Expert insight into the five most promising drugs:

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

during April to June 2007

**THOMSON Pharma**<sup>®</sup>

For innovation-based companies, these are days of sobering statistics. New research from CMR, a Thomson company, shows that the revenue derived from new products (those launched within the last five years) dropped from 21% of total revenue in 2005 to just 16% in 2006. This is worrying indeed when so many of the products the industry relies on are coming toward the end of their patent protection.

Meanwhile, although the cost of research and development continues to rise, there's no sign of a sustained upturn in the number of new products reaching the market. If the blockbuster model is truly dead, then where are the revenues of the future to come from? Concentrating on niche therapy areas — where drugs are relatively quick and cheap to develop — cannot possibly be the answer.

Against this background, pipeline activity is always encouraging, and happily there's much to get excited about. 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 April and June 2007.

## The Five Most Promising Drugs Receiving Approval

Drug	Disease	Company
Optaflu®	Influenza infection	Novartis Vaccines & Diagnostics
Lybrel™	Female contraception	Wyeth
Staybla®	Urinary incontinence	Kyorin Pharmaceutical/Ono Pharmaceutical/LG Life Sciences
Inovelon™	Epilepsy	Eisai
Torisel™	Advanced renal cell carcinoma	Wyeth Research

Few diseases are as prevalent or hit the headlines as often as flu. Not only is seasonal influenza infection so commonplace among those of working age as to be a near annual event for many, costing countless lost days to business, but the virus can be fatal to children and the elderly, and epidemics of new strains can kill millions in their spread around the planet.

Vaccination is the answer, and for many this too is an annual event. Two new seasonal vaccines feature in our list this quarter, the first of which is **Optaflu®** from Novartis Vaccines & Diagnostics, formerly Chiron. This influenza vaccine, the first to be derived from cell culture, was approved for use in the EU in June 2007, and launch is expected in Germany and Australia in time for the 2007/2008 season. The rest of the EU should get the drug the following winter. Novartis also hopes to file for US approval in 2008.

Also featuring twice in our list this quarter are new female contraceptives, beginning with Wyeth's **Lybrel**<sup>™</sup> (formerly known as Librel<sup>®</sup>), a combination of levonorgestrel and ethinyl estradiol. A continuous-use, low dose, daily oral tablet, the drug eliminates the menstrual cycle and was approved for the US in May 2007.

Launch is imminent as this report goes to press. Wyeth is also trialing the drug as a potential treatment for severe premenstrual syndromes — Phase III studies are ongoing.

Urinary incontinence is almost always a symptom of another medical condition. It is particularly prevalent in men, where it is usually associated with aging. Where the problem is an overactive bladder, patients may benefit from the M<sub>1</sub> and M<sub>3</sub> muscarinic receptor imidafenacin, developed by Kyorin Pharmaceutical, Ono Pharmaceutical and LG Life Sciences. Administered in oral tablet form, the drug was launched in Japan for the treatment of incontinence and pollakiuria (frequent urination) in June 2007 under the name **Staybla**<sup>®</sup>.

According to the World Health Organization, at any one time approximately 50 million people worldwide suffer from epilepsy. One of its most severe forms is Lennox-Gastaut Syndrome (LGS), which affects approximately 5% of the children who have the disease. LGS typically appears in early childhood and is characterized by daily multiple seizures of a wider range than any other type of epilepsy, arrested psychomotor development and behavior disorders. There is no known uniform cause, and for as many as a third of sufferers no cause can be found at all.

LGS is often treatment-resistant, though some patients respond to drugs such as anticonvulsants, anesthetics and steroids. Eisai's rufinamide, licensed from Novartis, is the first drug approved in the EU specifically for LGS. An oral GABA B antagonist, it reduced total seizure frequency by 32.7% relative to baseline in a 183-patient, double-blind study over 28 days, compared with the 11.7% reduction experienced by subjects taking placebo.

Eisai launched rufinamide in Germany, Australia and Scandinavia in June 2007 under the name **Inovelon**<sup>™</sup>. US filing is in process. Meanwhile, Synosia Therapeutics is also investigating rufinamide, this time for the potential treatment of anxiety and bipolar mood disorders.

Finally for this section this quarter, **Torisel**<sup>™</sup> is the brand name of temsirolimus, an analog of the mTOR inhibitor sirolimus (rapamycin) developed by Wyeth Research for the oral treatment of advanced renal cell carcinoma (RCC). Having received FDA approval in May 2007, the drug should have launched in the US by the time you read this report, while approval is pending in the EU.

The treatment comes with encouraging study data. In Phase III trials, 626 patients were given temsirolimus or interferon-alpha. The temsirolimus subjects

demonstrated a 49% increase in median overall survival, with a significantly improved secondary endpoint of progression-free survival (5.5 months versus interferon-alpha's 3.1 months). According to Dr Gary Hudes, the trials' lead investigator, this makes Torisel the first drug to demonstrate a significant increase in overall survival in RCC patients. Analysts predict first year sales of \$25 million, rising to \$375 million in 2012.

Meanwhile, Wyeth Research continues post-marketing studies assessing the drug's QT prolongation and hepatic impairment, and it is also investigating Torisel's efficacy in treating other cancers (including breast cancer), rheumatoid arthritis and multiple sclerosis.

## The Five Most Promising Drugs Entering Phase III Trials

Drug	Disease	Company
trazodone (once-daily)	Depression	Labopharm
pimavanserin	Schizophrenia	ACADIA Pharmaceuticals
salmon calcitonin (tablet)	Osteoporosis/Paget's disease	Novartis/Nordic Bioscience
Generx™	Coronary artery disease	Cardium Therapeutics
Pravafen	Mixed dyslipidemia	Sciele Pharma/Galephar PR

At the top of our list of notable drugs changing phase this quarter, Labopharm's **once-daily formulation of trazodone** entered Phase III studies in June 2007. The drug is a dual serotonin agonist and serotonin reuptake inhibitor using Labopharm's Contramid controlled-release technology for the treatment of depression. Trials will compare the safety and efficacy of the drug against placebo in 350 patients with major unipolar depression in North America. Labopharm expects to submit a New Drug Application (NDA) for trazodone to the FDA under section 505(b)(2), whereby only one positive Phase III trial is required for approval.

Staying with the mind, ACADIA Pharmaceuticals has begun Phase III trials of its 5-HT 2a inverse agonist **pimavanserin**, the lead compound in a series of potential antipsychotics and antidyskinetic agents. The company is particularly hopeful that pimavanserin will prove itself an add-on treatment in schizophrenia and a remedy for treatment-induced dysfunctions in Parkinson's disease, suggesting that pimavanserin could provide a unique combination of antipsychotic efficacy, motoric tolerability and safety. Analysts agree, predicting sales of \$800 million in 2012.

In the Phase III trials, 240 patients will receive either 10 or 40 mg of pimavanserin or placebo once-daily for six weeks, alongside stable doses of their existing

dopamine replacement therapy. Those that may benefit from continued treatment with pimavanserin will be able to participate in an open-label safety extension study. This follows positive results from Phase II trials of pimavanserin as an adjunct to other antipsychotic drugs in schizophrenia patients.

Meanwhile, ACADIA is also planning Phase II trials for the drug as a treatment for insomnia, another therapy area we'll return to later in this report. Proof-of-concept trials for this were completed in April last year.

As the western population ages, doctors are bound to encounter diseases such as osteoporosis and Paget's disease of bone more often. Novartis hope to treat these diseases with an oral tablet formulation of the calcium-modulating, bone resorption inhibitor **salmon calcitonin** (SCT). Preclinical data have shown that the drug, developed with Nordic Bioscience and utilizing Emisphere's oral drug delivery technology, protects against cartilage breakdown in animal models.

Phase III trials began in February 2007 in both the US and EU, with an expected enrolment of more than 2000 patients. Novartis is also investigating SCT for the potential treatment of osteoarthritis. Phase III trials for this began in May . The company expects to file the compound in 2008.

Turning to the heart, **Generx**<sup>TM</sup> is the trade name of alferminogene tadenovec, an angiogenic gene therapy developed by Schering AG (previously Collateral Therapeutics) and acquired by Cardium Therapeutics (also known as Aries Ventures). The drug consists of a replication-deficient E1-deleted type 5 adenovirus vector encoding human FGF-4 that is delivered non-surgically to the heart for the potential treatment of patients with coronary artery disease.

Phase III trials began in May 2007. An expected 300 myocardial ischemia patients in the US will be studied to see how Generx affects myocardial blood flow. The primary endpoint is improvement in myocardial ischemia measured by time to onset of electrocardiogram changes during treadmill exercise testing at six months following treatment.

Dyslipidemia, a disruption of the amount of fatty acids or cholesterol in the blood (in the western world, generally an elevation due to diet), is the target of **Pravafen**, an oral controlled-release combination of fenofibrate and pravastatin under development from Sciele Pharma and Galephar PR. The companies began enrollment in a pivotal Phase III trial in April 2007, during which they intend to compare the combination with fenofibrate and pravastatin alone in 500 patients in the US.

The primary endpoint in the trials, which will take more than a year, is improvement in non-HDL cholesterol, but the drug's safety will also be assessed.

## The Five Most Promising Drugs Entering Phase II Trials

Drug	Disease	Company
VSF-173	Excessive sleepiness	Vanda Pharmaceuticals
APD-125	Insomnia	Arena
Neugranin™	Chemotherapy-induced neutropenia	CoGenesys
Hepaconda®	Hepatitis C virus infection	Giaconda
GRC-6211	Pain	Glenmark

Sleep — too much, and too little — is the subject of the first two of our headline drugs entering Phase II this quarter. **VSF-173** is an orally-administered stimulant that Vanda Pharmaceuticals (developed under license from Novartis) hopes will treat excessive daytime sleepiness. In preclinical studies, the drug demonstrated effects on animal sleep/wake patterns and gene expression suggestive of a stimulant.

Vanda's randomized, double-blind, placebo-controlled studies began in April 2007 to assess the safety and efficacy of three oral doses of VSF-173 in 60 healthy volunteers. Vanda hopes to show a difference from placebo on the maintenance of a wakefulness test.

Chronic insomnia, meanwhile, is the focus of a multicenter, randomized, double-blind study of **APD-125**, an oral 5-HT 2a inverse agonist developed by Arena Pharmaceuticals. In the Phase II trials, a hundred patients will receive 10 and 40 mg night-time doses of the drug, or placebo, for a week, followed by at least a one-week 'wash-out' period, to evaluate APD-125's affect on wake-after-sleep onset, number of awakenings, total sleep time and latency to persistent sleep.

CoGenesys has commenced Phase I/IIa trials of its long-acting form of granulocyte colony stimulating factor (G-CSF) **Neugranin™** (albugranin). The drug is a potential treatment for neutropenia, a type of leukopenia characterized by abnormally low numbers of neutrophil granulocytes in the blood. Neutrophil granulocytes usually make up slightly more than half of the white blood cells that are the body's primary defense against bacteria — those with neutrophil are therefore more susceptible to severe infections. Unfortunately, treatment for more life-threatening diseases such as chemotherapy can also destroy neutrophil granulocytes leading to neutropenia in already weakened patients.

G-CSF drugs can be effective. The market leader is Amgen's Neulasta®, but CoGenesys is confident that Neugranin will exhibit a comparable therapeutic

profile. In the first of the Phase I/IIa trials, 60 breast cancer patients will receive a subcutaneous dose of Neugranin prior to beginning chemotherapy in order to assess the drug's safety, tolerability and efficacy. In the second phase, patients will begin chemotherapy prior to receiving the drug, and a positive control group will receive Neulasta.

Hepatitis C continues to be a therapy area of note, with another drug in the pipeline, Giaconda's **Hepaconda**<sup>®</sup>, entering Phase IIa trials in June this year. The drug is an oral dual therapy containing the lipase stimulator and antihypercholesterolemic agent bezafibrate, and the bile acid sequestrant chenodeoxycholic acid.

Hepaconda has already proved itself up to 75% effective against hepatitis C virus-1 infection (HCV-1) with reduced side effects in comparison to the current therapy. The Phase IIa trials will assess the drug's safety and efficacy in HCV-1-infected patients that have failed standard therapy. The primary endpoint is a virological response and a reduction in viral load at three and six months, with secondary objectives including significant improvements in elevated liver function tests at these time points. These trials are expected to complete at the end of the year, with data available in 2008.

Finally for this section, Glenmark is developing **GRC-6211**, the lead in a series of orally-available, potent and selective vanilloid receptor 1 antagonists for the potential treatment of pain. The company initiated Phase IIa proof-of-concept trials in December 2006, testing the drug on patients with dental pain. Phase II trials began in May and should end at the end of the year, after which Glenmark will begin Phase IIb trials in the first quarter of 2008.

The company hopes that GRC-6211 will prove beneficial in treating a range of different pain types, including osteoarthritic, migraine and urinary incontinence-associated pain, and will also treat asthma. Launch is penciled in for 2011.

## The Five Most Promising Drugs Entering Phase I Trials

Drug	Disease	Company
Ad35 HIV-ENvA vaccine	HIV infection	GenVec/NIAID Vaccine
nestorone and estradiol (transdermal gel)	Female contraception	Antares/Population Council
FluVacc	Influenza	Avir Green Hills Biotechnology
insulin oral capsule	Diabetes	Oramed
Trobusquemine	Obesity	Ganaera

The first of our notable drugs shifting into trials this quarter is an HIV-1 vaccine **Ad35 HIV-ENvA** developed by GenVec and the NIAID's Vaccine Research Center. Initially, this adenovector-based intramuscular vaccine will be given at three different doses to establish its safety, tolerability and immunogenicity. A second stage of the study will test prime-boost combinations of Ad35 HIV-ENvA and Ad5-based vaccines.

Earlier in this list we highlighted Wyeth's combination of levonorgestrel and ethinyl estradiol. Further up the pipeline, Antares and the Population Council are studying another potential female contraceptive, this time a **transdermal gel containing nesterone and estradiol**. This innovative low-dose contraceptive is the result of the union of Antares and the Population Council in July 2006, seeking to develop nesterone formulations based on Antares' Advanced Transdermal Delivery (ATD) technology.

In the Phase I trials, begun in May 2007, a total of 12 healthy, post-menopausal women will receive two different doses of the gel. The most effective dose will then be administered once-daily for ten days with the primary objectives of the pharmacokinetics of the combination and the determination of the most effective nesterone dose. Secondary objectives include establishing the estradiol dose needed to reach estrogen replacement levels and maintain regular bleeding patterns, and local skin irritation and tolerability.

We also highlighted seasonal influenza vaccine Optaflu from Novartis Vaccines & Diagnostics. As Optaflu gains approval, Avir Green Hills Biotechnology's **FluVacc** is beginning clinical trials. The drug is a replication-inhibiting, live-attenuated vaccine created by deleting the NS1 gene with delNS technology, but its main advantage may well be its method of administration — intranasally by nebulizer.

Preclinical studies indicated that FluVacc is safe, immunogenic and provides protection in animals against experimental challenge with wild type virus. The first human study will investigate its tolerance and immune response in 24 subjects.

Insulin is another drug typically administered by injection but now increasingly moving to other forms of delivery. Oramed, under license from Hadasit, is developing an **oral gel capsule formulation of insulin** for the potential treatment of type 1 and type 2 diabetes. Trials began in May 2007 among healthy volunteers in Israel, and are expected to last from eight to twelve months.

Lastly this quarter, Genaera (formerly Magainin) hopes that **trodusquemine** will become an effective treatment for obesity, acting as an appetite suppressant while normalizing glucose metabolism and insulin sensitivity.

Isolated from dogfish liver and developed in collaboration with the National Institute of Health, the drug is an aminosterol that inhibits the protein tyrosine

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phosphatase, dopamine and norepinephrine reuptake, an ion transport modulator and a down-regulator of Agouti-related protein and neuropeptide Y expression. Trials began in May.

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