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MATTERS

THE ONES TO WATCH

Thomson Scientific's expert review of the most promising drugs changing clinical phase, receiving approval and launched this quarter, based on the strategic data and insight of *Thomson Pharma*[®], the world's leading pharmaceutical competitive intelligence solution.



Section I: Introduction

The world markets have shouted recession for so long now, that recession itself seems inevitable (if it isn't already happening). Clearly, any economic downturn risks further stifling research and shifting yet more focus on established medicines and generic drugs.

Against this background, it's particularly gratifying to be able to begin this quarter's *The Ones To Watch* with a pair of remarkable technological success stories. **ATryn**[®] is a breakthrough in transgenic (inter-species genetic modification) research, a human blood product that doesn't require human blood but is expressed in the milk of goats. **OncoVAX**[®] uses the patient's own surgically-removed tumor to produce a vaccine that can manipulate the body's immune system into preventing return of the disease—effectively “turning cancer on itself”.

These might be headliners, but our report is also filled with pharmaceutical companies working equally hard, and with equal innovation, against some of the most prevalent diseases in society. Among them are promising new treatments for HIV infection, Alzheimer's disease, and hepatitis.

So let's take a look at the five most promising drugs either launched or receiving approval, and the five most promising drugs to enter each new phase of clinical development, between October and December 2007.

Section II: The five most promising drugs launched or receiving approval

Drug	Disease	Company
ATryn [®]	Hereditary antithrombin deficiency	GTC Biotherapeutics/ LEO Pharma
OncoVAX [®]	Colon cancer, melanoma, renal cell carcinoma	Vaccinogen
Ixempra [™]	Breast cancer	Bristol-Myers Squibb
Isentress [™]	HIV-1 infection	Merck & Co
Perforomist [™] Inhalation Solution	Chronic obstructive pulmonary disease	Dey

First of this quarter's list of notable drugs heading into the market is the aforementioned **ATryn**[®], the world's first approved drug produced in transgenic goats. Developed by GTC Biotherapeutics (formerly Genzyme Transgenics) and LEO Pharma, it was launched in the UK in late 2007 for the prevention of deep-vein thrombosis and thromboembolism in patients with hereditary antithrombin deficiency undergoing surgery.

The breakthrough rests on the fact that ATryn doesn't require donor blood. Human antithrombin is expressed in the milk of the goats and then processed into a safe, highly-purified product.

The target patient population may be small, but ATryn is the only recombinant human antithrombin product being developed to address the need. It has also been investigated for the potential treatment of acquired antithrombin deficiency as a result of various conditions including disseminated intravascular coagulation associated with severe sepsis, hemorrhagic diseases caused by Ebola and Marburg viruses, and severe burns.

Commanding Fast Track and Orphan status by the FDA, ATryn is expected to launch in the US in the first half of 2009.

Colon cancer is the fourth most prevalent malignancy in the world, according to the American Cancer Society, with approximately 210,000 new cases diagnosed each year in the US and Western Europe. There are currently no adjuvant therapies for Stage II colon cancer—the standard of care is surgery alone—which makes Vaccinogen's development of [OncoVax®](#) (under license from Intracel) extremely interesting. As a result, the FDA granted the drug Fast Track designation in July 2006.

OncoVAX has an equally fascinating mechanism of action. It is a sterile, metabolically-active, irradiated, non-tumorigenic multivalent vaccine produced from the patient's own surgically-removed tumor.

The therapy (dubbed "turning cancer on itself" by Vaccinogen) is based on attempts by scientists to manipulate the body's immune response and its long-term memory to prevent the return of disease months or years after surgery. The approach has already been successful in preventing a number of infectious diseases.

OncoVAX has been approved in a number of European countries for Stage II colon cancer, with the drug expected to become available to self-pay patients in Switzerland in early 2008. Meanwhile, Vaccinogen is progressing Phase III trials in Stage III colon cancer and Phase I and Phase II trials for melanoma and renal cell carcinoma.

[Ixempra™](#) is the name by which Bristol-Myers Squibb is marketing its lactam analog of epothilone B, ixabepilone, one of a series of epothilone tubulin inhibitors licensed from the German Research Centre for Biotechnology, in the US. The product is indicated in combination with capecitabine for the treatment of metastatic or locally-advanced breast cancer in patients after failure of an anthracycline and a taxane. It is also indicated as a monotherapy where both anthracycline, taxane and capecitabine have failed. Ixempra launched in the US in October 2007.

The size of these markets is approximately 32,000 patients, but promising additional indications may make that a conservative figure. Indeed, Bristol-Myers Squibb is also developing the compound for the potential treatment of other neoplasms, and has reported encouraging Phase II trials of renal cell carcinoma, lung, prostate and pancreas cancers, and lymphoma. It is currently recruiting for Phase II trials in pancreatic cancer.

Sales are expected to reach \$300 million in 2010.

Merck & Co joins the long list of innovators currently grappling with HIV, an area in which interest is always welcome. [Isentress™](#) is the trade name of raltegravir, an oral tablet-formulated HIV-1 integrase inhibitor and the lead from the company's series of integrase strand transfer inhibitors, a new class of antiretroviral drugs. It is administered as a single 400mg tablet, taken twice daily with other HIV medications.

Raltegravir works by inhibiting the insertion of HIV DNA into human DNA by the integrase enzyme, limiting the ability of the virus to replicate and infect new cells. Though there are already drugs on the market that inhibit two other enzymes critical to the HIV replication process (protease and reverse transcriptase), raltegravir is the only approved drug that inhibits integrase.

The product is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Interest among physicians and patients should be high, since it is effective, well-tolerated, does not require boosting with ritonavir, which can be associated with adverse side effects, and has few side effects of its own.

It is likely that sales of Isentress will overtake its indirect competitor Pfizer's maraviroc (brand names [Selzentry™](#) and [Celsentri](#)), which has a greater number of issues that would affect uptake. *Thomson Pharma* pencils in sales of \$725 million in 2011.

Isentress has been launched in Canada (in November 2007) and was approved in Europe in December 2007 (launch in the UK occurred during preparation of this review). Accelerated approval in the US was granted in October 2007, for use of the drug in combination with other antiretroviral agents, but at the time further trial data were required before traditional approval could be granted.

A year after we flagged Sepracor's [Brovana™](#) as a possible breakthrough in the treatment of chronic obstructive pulmonary disease, we're pleased to highlight two others. Dey, a subsidiary of Mylan Laboratories, launched [Perforomist™ Inhalation Solution](#) in the US in October 2007, just ahead of reporting positive long-term Phase III data. The drug is a nebulized formulation of formoterol fumarate, a long-acting beta 2 agonist.

In the 12-week, multicenter, randomized, double-blind study, patients were treated twice daily with either 2ml of Perforomist, the active comparator formoterol or placebo. Among other findings, the data showed the nebulized formulation to be significantly superior compared with placebo, providing rapid bronchodilation that persisted for 12 hours, enabled patients to use less rescue medication, and maintained lung function improvements with no evidence of tolerance.

This is excellent news: formoterol itself, packaged by Novartis under the trade name Foradil® Aerolizer®, administered by dry-powder capsule for oral inhalation with the Aerolize Inhaler, had sales outside the US of \$331 million in 2006. That drug is also available in a number of different doses and preparations under various trade names including AstraZeneca's Oxis® Turbuhaler®.

We look forward to following Perforomist's progress in the market. Meanwhile, the second of this edition's chronic obstructive pulmonary disease drugs of note is SVT-40776, just entering Phase II trials—see below for more.

Section III: The five most promising drugs entering Phase III trials

Drug	Disease	Company
SCH-530348	Ischemic complications in acute coronary syndromes	Schering-Plough
intranasal epinastine	Allergic rhinitis	Inspire
bapineuzumab	Alzheimer's disease	Elan/Wyeth
Lu-AA21004	Depression	H Lundbeck/Takeda
atacept	Autoimmune diseases	ZymoGenetics/ Merck Serono

Schering-Plough's SCH-530348 is the lead from a series of orally active thrombin receptor antagonists and protease-activated receptor-1 antagonists for the potential prevention of ischemic complications in acute coronary syndromes (ACS) such as unstable angina, acute myocardial infarction (MI) and arterial thrombosis. Its potentially unique mechanism of action inhibits platelet aggregation through a different pathway from other antiplatelet agents currently available.

If that seems dry, the figures speak for themselves—Schering-Plough estimates potential peak sales at over \$1 billion, and the drug has been granted FDA Fast Track status.

A Phase III trial was initiated in October 2007 to study the drug's efficacy in preventing heart attack and stroke in patients with ACS or atherosclerosis. The trial will be a multinational, randomized, double-blind, placebo-controlled study, expected to last one year and enroll

19,500 patients who will receive a 2.5mg maintenance dose of the compound. The primary endpoint is the composite of cardiovascular death, MI, urgent coronary revascularization or stroke.

Far from just a runny nose, rhinitis is a widespread, often serious disease that may affect more than 50 million people in the US alone, and may be associated with other problems such as sleeping disturbance. Seasonal allergic rhinitis, commonly known as 'hay fever', can lead to coughing, headache, conjunctivitis and fever. Commonly, patients receive intranasal steroids, but Inspire Pharmaceuticals hopes to offer an alternative with its [intranasal formulation of epinastine](#), a non-sedative histamine H1 antagonist.

Inspire began Phase III trials in the US in November 2007, comparing 0.1 and 0.15% concentrations of epinastine to placebo in 750 patients with a history of seasonal allergic rhinitis to mountain cedar pollen. The company expects to complete studies in March 2008, and to report top-line results in the second quarter of the year, projecting an NDA filing in 2009. With this timescale in mind, product sales of \$45 million are projected by 2011.

We continue to see interest in new treatments for Alzheimer's disease, this time the active immunization [bapineuzumab](#) under development by Elan and Wyeth. This is a humanized monoclonal antibody to amyloid beta which began US Phase III trials in December 2007. Enrollment in the rest of the world is expected as you read this report. Four pivotal trials will be run in total, evaluating the safety of bapineuzumab in patients (1,250 in the US trial) with mild-to-moderate Alzheimer's disease who are apolipoprotein E4 non-carriers.

Meanwhile, we await the arrival of pooled Phase II efficacy data, which are expected to form the basis for Wyeth to file the drug. Although there is little known about bapineuzumab, the decision to advance the drug into pivotal studies, and the fact that there are no existing treatments that alter the cause of the disease, are causes for significant excitement. Nevertheless, it will take another three years at least to bring the drug to market. When this happens, sales could reach \$250 million in the first year, doubling to \$500 the following year.

Clinical depression is extremely widespread, affecting millions of adults in the US alone, where it is the leading cause of disability. The World Health Organization expects that it will become the second leading cause of disability worldwide by 2020, after heart disease. Couple this with other central nervous system conditions such as substance abuse, and the potential market for an effective treatment is enormous.

Two of the drugs highlighted in this edition of *The Ones To Watch* have high potential in this market. The second, Sepracor's SEP-225289, is just entering Phase II trials. Ahead of it, Lundbeck and Takeda's [Lu-AA21004](#) began enrollment for Phase III trials in December 2007, one of several planned in a program that is expected to involve up to 2,000 patients.

Lu-AA21004 belongs to a new chemical class. As a bis-aryl-sulfanyl amine that inhibits serotonin reuptake, its mode of action is markedly different from the antidepressants currently on the market. Its in vitro pharmacological profile shows that the compound combines potent effect on several serotonin receptors and serotonin transporter proteins, thus modulating relevant parts of the neurochemical architecture in the brain in a beneficial way.

426-patient Phase II trials demonstrated that the drug was significantly more effective than placebo at both 5mg and 10mg dose levels, with an attractive safety profile.

According to Dr Nicole Onetto, Senior VP and CMO of ZymoGenetics, there is a need for better treatment options for patients of lupus nephritis, an inflammation of the kidney caused by a disease of the immune system, helping them to maintain kidney function and avoid kidney failure.

To fill the gap, ZymoGenetics and Merck Serono (formerly Serono) are developing **atacept**, a fusion protein of the extracellular portion of the TACI receptor and the Fc portion of human immunoglobulin G, that inhibits the binding of BLyS and APRIL to B-lymphocytes.

ZymoGenetics believes that atacept has the potential to reduce lupus nephritis disease symptoms and may help patients improve kidney function. It is also under investigation for the potential treatment of a number of autoimmune diseases, including rheumatoid arthritis and hematological malignancies such as multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia and Waldenstrom's macroglobulemia, as well as multiple sclerosis.

A one-year, randomized, double-blind, placebo-controlled Phase II/III clinical trial for lupus nephritis began in December 2007. It will enroll 200 patients at 80 sites in North America, Europe, Latin America and Asia. Concurrently, Phase I and II trials for the other diseases mentioned above are also in progress. The companies plan to evaluate their B-cell cancer program after completing ongoing CLL trials.

Section IV: The five most promising drugs entering Phase II trials

Drug	Disease	Company
ChronVac-C®	Hepatitis C virus	Tripep/Inovio
hepatitis B prophylactic vaccine	Hepatitis B virus	Vaxine
SEP-225289	Depression	Sepracor
SVT-40776	Chronic obstructive pulmonary disease, overactive bladder	Laboratorios SALVAT
DG-051	Heart attack	deCode

One of the recurring therapy areas of interest to *The Ones To Watch* is hepatitis virus infection. Unsurprising, given the area's huge potential market—expected to rise to more than \$8 billion against hepatitis C alone by 2015. We've flagged a number of potential vaccines in past issues, and now we're turning our attention to two more.

[ChronVac-C®](#) is a therapeutic DNA vaccine developed by Tripep and Inovia against the stable components of hepatitis C virus, incorporating Inovia's MedPulser® electroporation delivery system. Tripep's CEO Jan Nilsson is optimistic, claiming that current therapies for chronic hepatitis C virus infections have limited efficacy, are costly and are associated with significant side effects. ChronVac-C promises results with a lower number of treatments, lower cost and fewer side effects—a potential first-line therapy in the making.

Phase I/II trials began in November 2007, assessing the vaccine's safety and its effect on virus replication and host immune response in 48 treatment-naïve Swedish patients with chronic hepatitis C virus genotype 1 infections and a low viral load.

In what is claimed to be the first human study in the world in which a DNA vaccine against an infectious disease is being administered by in vivo electroporation, the patients will receive monthly vaccinations in one of the four doses of the drug for four months. They will then be monitored for a further six months. Three of the four groups of 12 patients will receive escalating doses of the vaccine, and the fourth will receive the most effective dose.

Australian researcher Vaxine's concern is hepatitis B, which itself currently commands a vaccine market greater than \$2 billion per year worldwide. Since there is currently no native producer of the vaccine, Vaxine hopes its [hepatitis B prophylactic vaccine](#) will enable Australia to become self-sufficient in vaccine production, as well as having the potential to create significant export income.

The drug comprises a proven hepatitis B virus antigen in combination with the ADVAX Super D adjuvant developed by Vaxine as a "vaccine booster". ADVAX is a plant sugar derived from dahlia bulbs, which demonstrated in Phase I trials that it was tolerated well by the body, causing less discomfort than existing vaccines—perhaps because it is a natural product.

Indeed, Vaxine's combination was found to be safe, with no side effects, and pain similar to the levels occurring in patients treated with antigen or saline. Levels of seroprotection were shown to be similar to those of commercial vaccines, with excellent T-cell stimulation. Phase II trials began in October 2007.

Like Lundbeck and Takeda's Lu-AA21004, Sepracor hopes to provide a breakthrough against clinical depression with its novel combination of norepinephrine, dopamine and serotonin uptake inhibitors [SEP-22589](#), which began proof-of-concept Phase II trials in October 2007.

The company believes a triple reuptake inhibitor will exhibit greater efficacy and faster onset of action than the antidepressants currently on the market, as well as providing a broader spectrum of therapy.

The second of our notable drugs targeting chronic obstructive pulmonary disease, [SVT-40776](#) is one of a number of muscarinic M₃ antagonists under development by Laboratorios SALVAT.

Phase I trials demonstrated that SVT-40776 has a unique profile, exhibiting a reduced dry-mouth potential, a whole absence of cardiac effects, a long elimination half-life (more than 30 hours), and a low metabolic rate causing minimal inter-individual plasma-level variations in both young and elderly volunteers. It was also shown to be a selective M₃ antagonist for overactive bladder (OAB), a highly prevalent condition characterized by an increased urinary frequency, urgency and urge incontinence.

Enrollment for Phase II trials for OAB was completed in October 2007. The study will treat 332 patients from the US, Germany, Spain, The Netherlands, Hungary, Poland, Russia, South Africa, New Zealand and Australia. They will receive one of three doses of SVT-40776, 4mg of the existing standard treatment tolterodine (marketed by Pfizer as Detrol®), or placebo once daily, with the primary endpoint the mean change in the number of urinations per day.

Currently, the most widely used therapeutic agents for OAB are muscarinic receptors, but side effects such as dry mouth and tachycardia have limited their clinical use. This raises high hopes for SVT-40776 in the treatment of this disorder, potentially opening the floodgates for a new generation of OAB drugs.

Phase IIa trials also began in October 2007 for [DG-051](#), deCode's orally-available leukotriene A₄ hydrolase inhibitor, which also inhibits LTB₄. This drug is designed to form a back-up to deCode's problematic veliflapon for the potential prevention of heart attacks. Veliflapon, developed under license from Bayer, had its Phase III trials suspended for more than a year in October 2006 due to problems with tablet formulation.

The Icelandic company is nevertheless optimistic for the back-up compound, reporting that it effectively reins in the activity of a branch of the leukotriene pathway that has been linked to risk of heart attack, and demonstrates a solid safety and pharmacokinetic profile.

The randomized, double-blind, placebo-controlled Phase IIa study will investigate the effect of DG-051 on the production of LTB₄ in patients with a history of heart attack or coronary artery disease, and assess the drug's pharmacokinetics, safety and tolerability. Larger Phase IIb trials will follow. Initial results, published as this edition of *The Ones To Watch* went to press, were highly promising, showing a favorable profile with significant, dose-dependent reductions of LTB₄.

Section V: The five most promising drugs entering Phase I trials

Drug	Disease	Company
Lu-AA47070	Parkinson's disease	H Lundbeck
LCP-Siro	Transplant rejection	LifeCycle Pharma
STA-9090	Cancer	Synta Pharmaceuticals
AR-9281	Angiotensin-II-dependent hypertension	Arete Therapeutics
R-zileuton	Asthma	Critical Therapeutics

Heading our list of drugs entering trials this quarter, H Lundbeck's [Lu-AA47070](#) continues considerable interest in Parkinson's disease. It's the fourth potential treatment we've featured in less than two years. Lu-AA47070 shows promise as the first compound within the neurology area from Lundbeck's internal research, boasting a unique profile—unlike the antiparkinsonian dopamine agonists, it targets the adenosine A2a receptor.

After demonstrating efficacy in preclinical studies, in which it was shown to have Ki values of 28 nM for the human A2a receptor and 200 nM for the human A1 receptor, the drug commenced Phase I trials in November 2007 to evaluate its safety, tolerability and pharmacokinetics.

LifeCycle Pharma's [LCP-Siro](#) aims to make a difference to patients suffering acute transplant rejection. Because the recipient's lymphocytes recognize proteins in the donor organ as differing from those in its own body, they can attack and destroy the transplanted tissue. Episodes of acute transplant rejection occur in the majority of kidney and liver transplants, and rejection to some degree is likely in all transplants (except those between identical twins), though prompt treatment can usually prevent the donated organ failing altogether.

Traditional means of treatment involve immunosuppressant drugs administered during the first three months, when the risk is greatest. One of these, Wyeth's oral formulation of sirolimus (marketed under the name Rapamune®) was approved for organ rejection in patients receiving renal transplants in the US in August 2000 and in Europe the following March. Rapamune commanded worldwide sales of \$336.9 million in 2006.

Sirolimus is also the active ingredient in LCP-Siro. This is also administered orally, but LifeCycle Pharma believes its controlled-release formulation will improve bioavailability and lower dosing frequency, improving cost. If this is the case, the drug's sales could eventually overtake Rapamune's. Results of the Phase I trial are expected later this year.

Hopes are also high for [STA-9090](#), a potential new strategy for treating cancer under investigation by Synta Pharmaceuticals. This synthetic, small-molecule, intravenous Hsp90 inhibitor has a novel chemical structure that is unrelated to the Hsp90 inhibitor geldanamycin or its family of related compounds, such as 17-AAG.

The company believes STA-9090 is differentiated in important ways from the other Hsp90 inhibitors, offering superior potency, including activity against highly resistant cancers, among them cancers resistant to imatinib, erlotinib and sunitinib. In preclinical studies, the drug also demonstrated less toxicity than geldanamycin-based compounds.

Open-label Phase I trials began in November 2007 to determine the drug's safety, efficacy and maximum tolerated dose. Patients with solid tumors will receive STA-9090 intravenously every two weeks. A further Phase I trial with weekly dosing is also being planned.

Meanwhile, Arete Therapeutics is developing [AR-9281](#), the lead in a series of orally-available soluble epoxide hydrolase inhibitors, as a regulator of arterial pressure for the potential treatment of angiotension-II-dependent hypertension. The enzyme epoxide hydrolase plays a key role in arachidonic acid metabolism. Arete Therapeutics is also investigating other compounds from the series for inflammatory disease and sepsis.

According to the company, AR-9281's novel mechanism of action means it has the potential to be a first-in-class antihypertensive agent with end organ protection of the heart and kidney and anti-inflammatory properties—an "antihypertensive-plus" as President and CEO Dr Dinesh V Patel terms it.

Single-ascending dose, placebo-controlled trials began in November 2007 to evaluate the drug's safety, tolerability, pharmacokinetics and pharmacodynamics in up to 32 healthy subjects. Further multiple-dose Phase I studies, a food effect study, and studies in special populations are also expected.

Finally this quarter, [R-zileuton](#) is under development by Critical Therapeutics for the potential treatment of asthma and other inflammatory diseases. Beginning in October 2007, a randomized, open-label, single-center, two-period, crossover Phase I trial is evaluating the drug's safety, tolerability and profile among volunteers receiving 100 or 300mg doses. The trial hopes to confirm that R-zileuton has prolonged pharmacokinetic and potent pharmacodynamic properties when dosed alone for the first time.

R-zileuton is the oral R(+) isomer of the 5-lipoxygenase inhibitor zileuton, marketed by the company as Zylflo®. According to Critical Therapeutics, preclinical data suggests that the R-isomer might be a more potent leukotriene synthesis inhibitor than the S(-) isomer, with a more prolonged pharmacokinetic profile.

If this is true, then R-zileuton would offer a reduced dosing or smaller tablet size compared with Zylflo. It may also expand its treatment opportunities beyond asthma to chronic obstructive pulmonary disease, atherosclerosis, nasal polyps and more.

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THE ONES TO WATCH

Focuses on the latest phase changes in the pharmaceutical pipeline.

MOVERS AND SHAKERS

Unravels the most significant game-play in the US generics market.

WHO IS MAKING THE BIGGEST SPLASH

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