

The Ones To Watch

October 2006



Thomson Pharma's Review of Phase Changes in the Pharmaceutical Pipeline

Expert insight into the five most promising drugs:

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

during July to October 2006

The big story in last quarter's *The Ones To Watch* was the launch of Gardasil®, the first vaccine for preventing cervical cancer. In June 2006 the US Advisory Committee on Immunization Practices voted unanimously to recommend vaccinating all females from 11 to 26 years old with Gardasil, at a projected cost of up to \$200 dollars per therapy.

But what about this quarter? The headline-grabber has to be Atripla™, the product of a joint venture between Bristol-Myers Squibb and Gilead Sciences that is expected to become the new gold standard for first-line treatment of HIV.

Together, Gardasil and Atripla are proof that, despite a lingering gloom in the industry, there are still exciting potential blockbusters in the pipeline. 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 July and September 2006.

The Five Most Promising Drugs Receiving Approval

Drug	Disease	Company
Atripla™	HIV	Bristol-Myers Squibb & Gilead Sciences LLC
Elaprase™	Hunter syndrome	Shire
TheLin™	Pulmonary arterial hypertension	Encysive Pharmaceuticals
Chantix™	Smoking addiction	Pfizer
Sebivo®	Heptatitis B	Novartis/Indenix

Fast-tracked to approval in the US under the FDA's expedited review process for fixed-dose combination products for treating HIV, and eligible for launch in up to 15 African countries under the President's Emergency Plan for AIDS Relief, **Atripla** looks like this quarter's sure winner. Analysts expect the drug, developed through a joint venture between Bristol-Myers Squibb and Gilead Sciences, to be able to penetrate and ultimately expand the HIV market, becoming the new gold standard for first-line treatment. Approval in Europe is expected toward the end of 2007.

Atripla's selling point is its convenience — the world's first once-daily triple-cocktail pill for HIV, it combines the nucleoside and non-nucleoside reverse transcription inhibitors Truvada® (a combination of Viread® and Emtriva®, both developed by Gilead) and Sustiva® (from Bristol-Myers Squibb). This ease of administration is likely to attract patients away from drugs such as GlaxoSmithKline's Combivir®, though analysts model that about half its sales will come from those already on Truvada.

From a drug with a projected global market in the millions to one with a very small niche: the genetic disorder Hunter syndrome affects just 2,000 people worldwide. Targeting this market is Shire's **Elaprase™**, FDA-approved this quarter after highly encouraging Phase III trials. Patients will still have to confront a black-box warning of anaphylactoid reactions, but with a lack of other treatments this is not expected to affect sales.

It's this lack of options, too, that can ensure Shire recoups its investment: at between \$300,000 and \$400,000 per patient per year, Elaprase is likely to be one of the most expensive drugs ever launched. Worldwide sales could exceed \$240 million by 2010. Elaprase is currently pending approval in Europe, where launch is scheduled for early 2007.

Encysive Pharmaceuticals' **Thelin™** is set for a bumpier ride, going head-to-head against Actelion's Tracleer®, already established in the European market for the treatment of pulmonary arterial hypertension. Thelin's just gained EMEA licensing, with first launch in Germany toward the end of this year, and has received two approvable letters in the US, where it's expected to launch in 2007.

How Thelin plays against Tracleer remains to be seen, though as studies show significant improvements in the risk of clinical worsening events and liver function abnormalities, analysts give it the upper hand and pencil in sales of \$125 million by 2009.

Despite ever more prominent smoking awareness campaigns and anti-smoking legislation, research into new treatments for nicotine addiction has been moribund in recent years. Pfizer's **Chantix™** is the first new drug to hit the US market in nearly a decade.

An orally active partial agonist at the $\alpha 4\beta 2$ nicotinic receptor, the drug is designed to reduce the urge to smoke, diminish the sense of satisfaction derived from smoking, and alleviate withdrawal symptoms. In studies, Chantix enabled 44% of users to quit smoking within 12 weeks, a marked step-up from the 30% success rate of GlaxoSmithKline's Wellbutrin SR® and a placebo baseline of 18%. The drug has also been approved in Europe as Champix®.

Finally this quarter, Swissmedic has approved Novartis and Idenix's DNA synthesis inhibitor **Sebivo®** for treatment of compensated patients with evidence of hepatitis B virus (HBV) replication and acute liver inflammation. Shire's Epivir-HBV® currently dominates the European market, but Phase III data suggest Sebivo is more effective: after one year of treatment, 70% of patients on Sebivo had undetectable HBV levels, compared to Epivir-HBV's 43%. Should current EMEA and FDA review lead to wider approval, we can expect worldwide sales of \$300 million by 2011.

The Five Most Promising Drugs Entering Phase III Trials

Drug	Disease	Company
Prochymal™	Graft-versus-host disease	Osiris Therapeutics
denufosal tetrasodium (inhaled form)	Cystic fibrosis	Inspire Pharmaceuticals
Lipsovir®	Labial herpes	Medivir
lorcaserin	Obesity	Arena Pharmaceuticals
methylnaltrexone (intravenous form)	Post-operative ileus	Wyeth/Progenics Pharmaceuticals

Moving on to the pipeline, the most prominent new drug to enter Phase III trials this quarter may well be Osiris Therapeutics' **Prochymal™**, not just for its boast as the most advanced mesenchymal stem cell therapy ever developed, but because the debate over stem cell research continues to hit the headlines. Prochymal avoids many of the ethical and political pitfalls that have held up development of other stem cell therapies by being derived from adults, rather than embryos.

Targeting graft-versus-host disease, Prochymal has Fast Track status in the US, where there are currently no approved treatments for the disease. If licensed, analysts forecast annual revenues of \$200 million. Results are expected in the second half of 2008.

Elsewhere, Inspire Pharmaceuticals' **nebulized formulation of denufosal tetrasodium** for the treatment of cystic fibrosis has also progressed to Phase III. Although Phase II trials were not powered to demonstrate superiority to placebo, the drug showed a trend toward improving lung function and reducing expectoration, so hopes are high, reflected by Orphan Drug status from both the FDA and EMEA and Fast Track status in the US. Analysts project that within a year of expected launch in 2009, the drug could achieve sales of \$40 million. However, Inspire hopes to outlicense the drug and may only see a percentage of this.

Medivir is pinning its hopes on its labial herpes treatment **Lipsovir®**, a novel combination of an antiviral and an anti-inflammatory that could reduce the incidence of cold sores. This would make it unique among existing treatments and has encouraged the company's CEO Lars Adlersson to declare the treatment a potential "half-blockbuster". ABN AMRO analysts aren't quite as optimistic, but still suggest revenues of around \$200 million.

Obesity weighs heavy on the minds of Arena Pharmaceuticals. The company has started the first of two 3,000 patient trials of **lorcaserin**, the first drug candidate selective for the 5HT-2c receptor to enter Phase III. This receptor selectivity is expected to limit its side effects after encouraging Phase II trials in which patients enjoyed an average weight reduction of 7.9 lb (3.6 kg) with no dose-dependent adverse effects. The Phase III BLOOM study will evaluate the same dosing regimen for one year in subjects with a body mass index of 27 to 30. Arena plans to review 6-month data in mid-2007.

Wyeth and Progenics Pharmaceuticals have shifted their **intravenous form of the opioid antagonist methylnaltrexone** into Phase III trials for post-operative ileus. The condition refers to a lack of passage due to paralysis of the bowel and currently has no effective pharmaceutical treatment — further surgery is the only option. The study, approved under an FDA Special Protocol Assessment and granted Fast Track status this quarter, will involve 500 patients undergoing segmental colectomy. If the outcome is promising, analysts suggest sales of \$220 million by 2012.

The Five Most Promising Drugs Entering Phase II Trials

Drug	Disease	Company
AT-1001	Celiac disease	Alba Therapeutics
rexomun™	Breast cancer	Fresenius Biotech (inlicensed from TRION Pharma)
XL-647	Lung cancer	Exelixis
ICX-PRO	Diabetic foot ulcers	Intercytex
dihydroergotamine (inhaled form)	Migraine	MAP Pharmaceuticals

As methylnaltrexone moves out of Phase II trials, a treatment for another disorder of the bowel is just entering. Celiac disease (commonly called “gluten intolerance”) is a genetically-predisposed autoimmune disorder against the gluten protein in wheat that affects approximately 1% of the Caucasian population. However, with only general symptoms such as diarrhea and fatigue, it is significantly underdiagnosed.

Alba Therapeutics hopes to offer a breakthrough with its zonulin receptor antagonist **AT-1001**. Zonulin is an endogenous signaling protein discovered by the company’s founder Dr Alessio Fasano. Preclinical studies of ex-vivo human intestinal mucosa from patients with celiac disease showed that the drug prevented gluten-induced intestinal permeability. Alba’s Phase II trials will evaluate the drug’s efficacy, tolerability and safety in 79 patients.

Two interesting potential cancer treatments have entered Phase II this quarter. The first, **rexomun™**, is a ‘Triomab®’ antibody inlicensed by Fresenius Biotech from TRION Pharma that belongs to a new class of bispecific, trifunctional monoclonal antibodies. In development for hormone-refractory metastatic breast cancer, rexomun binds to cancer cells, T-cells and macrophages. The drug is expected to eradicate tumor cells more efficiently than existing antibody therapeutics, particularly those cancerous cells that persist after surgical resection, thereby preventing relapse and metastasis.

Exelixis’ new chemical entity **XL-647** also has multiple targets — the tyrosine kinase receptors HER2, EGF, VEGF and EphB4. Although none of these are new targets for the treatment of cancer, the company hopes that efficacy will be increased by targeting all four simultaneously. Phase II trials are now underway in chemotherapy-naive advanced non-small-cell lung cancer, focusing on female non-smokers.

Meanwhile, Intercytex is investigating the novel strategy of using a topical fibrin-based gel containing allogeneic, human dermal fibroblasts to stimulate active repair of wounds. **ICX-PRO** has entered Phase II development for the new indication of diabetic foot ulcers, a potentially lucrative market since over half a million diabetics develop foot ulcers every year in the US alone. ICX-PRO is already in Phase II trials for treatment of chronic venous leg ulcers.

Finally for this section, there are few more frustrating or widespread chronic illnesses than migraine, affecting as it does as much as 15% of the population. MAP Pharmaceuticals hopes to bring a more convenient effective treatment to this large potential customer base with an **inhaled formulation of dihydroergotamine**. The drug has been highly efficacious in intravenous formulation for 60 years, but MAP's inhaled form doesn't require administration by a healthcare professional. The company has formulated the drug with its Tempo™ breath-synchronized plume-controlled inhaler.

The Five Most Promising Drugs Entering Phase I Trials

Drug	Disease	Company
trastuzumab-DM1	Breast cancer	Genentech
H7N1 vaccine	Avian influenza	sanofi pasteur
ATG-003	Age-related macular degeneration	Athenagen
TZP-101	Gastroparesis	Tranzyme Pharma
transdermal insulin gel	Diabetes	Phosphagenics

Looking further ahead, one potential headline drug of the future has to be Genentech's super-Herceptin®, **trastuzumab-DM1**, entering the clinic this quarter for treatment of HER2-positive breast cancer. Sales of Herceptin reached \$1.28 billion in 2005 and the drug is patent-protected until 2013. Trastuzumab-DM1 uses the Herceptin antibody to target ImmunoGen's maytansinoid cell-killing agent DM1 to breast tumors, causing complete tumor regression in all mouse trials, whereas Herceptin by itself only slowed growth. The modified antibody was even active in Herceptin-resistant tumors.

In last quarter's report, we flagged an H9N2-based avian influenza vaccine developed by Dutch biotechnology company Crucell as a potential high flyer. Hot on its heels, sanofi pasteur has added a split, inactivated pandemic **H7N1 vaccine** to the many potential bird flu vaccines under development. Although most of these vaccines focus on the H5N1 strains, H7 viruses are also a significant pandemic threat, particularly in Europe. Crucell is partnering with sanofi pasteur to produce the vaccine, which will initially trial in 60 volunteers in Norway.

Existing treatments for age-related macular degeneration (AMD), the biggest cause of sight loss in the UK, are invasive and expensive, generally requiring repeated injections directly into the eye. Athenagen's **ATG-003** may be cheaper, easier to administer, and more effective at catching the disease in its early stages. ATG-003 is an eye-drop formulation of the antiangiogenic nicotinic acetylcholine receptor inhibitor mecamylamine. Athenagen has begun a Phase I study to assess its tolerability and safety over a 14-day dosing schedule. Results are expected by the end of the year, and Phase II trials projected for early 2007.

Tranzyme Pharma has started trials of **TZP-101** in diabetics with gastroparesis. This first-in-class drug is a small-molecule ghrelin agonist, which is also being evaluated for post-operative ileus — see the report on methylnaltrexone on page 4 for another drug in this area changing phase this quarter. Tranzyme hopes to start Phase II trials of TZP-101 in early 2007, and an oral form, TZP-102, should enter the clinic in the second half of 2007. Until now, the most potent treatment for gastroparesis was Propulsid, which achieved \$1 billion in global sales but was withdrawn in 2000 due to adverse events. Tranzyme's drugs are expected to have fewer side effects.

Lastly, we highlight a promising treatment for diabetes sufferers. Phosphagenics' **transdermal insulin gel** has entered clinical trials in Australia. Interim data show that a single dose after overnight fasting penetrated the skin and the drug's activity was maintained for at least six hours, significantly lowering blood glucose levels. A final analysis of data is expected to be available on *Thomson Pharma* by the time you read this report.

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The Ones To Watch

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

Thomson Scientific takes the pulse of the industry with this lively **free** review of the latest phase changes in the pharmaceutical pipeline.

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- receiving approval
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- entering Phase II trials
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