

# The Ones To Watch

Thomson Scientific's review of phase changes  
in the pharmaceutical pipeline

July – September 2007

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 September 2007

Bookending our list this quarter are a total of three potential treatments for Alzheimer’s disease, two of which are just entering clinical trials. Approved this quarter in both the US and EU, Novartis’s transdermal version of Exelon® looks set to build on the success of its oral formulation, launched in June 2000 and reaching sales of \$525 million in 2006.

Our SWOT analysis of the oral drug in *Thomson Pharma*® lists its inconvenient twice-daily oral dosing regimen and gastrointestinal side effects as weaknesses. Both these drawbacks should be addressed by the new, more convenient dosing method. We look forward to following Exelon TDS’s progress in the market.

Meanwhile, as our tables show, pharmaceutical companies persevere in wrestling with the big issues — potential cancer treatments feature prominently once again, while *The Ones To Watch* continues to document a concern with diseases of our ageing, sedentary populations, particularly menopausal symptoms, osteoporosis and diabetes.

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 2007.

## The five most promising drugs receiving approval

Drug	Disease	Company
Exelon® TDS	Dementia	Novartis
AZOR™	Hypertension	Daiichi Sankyo
EvaMist™	Menopausal symptoms	KV Pharmaceutical
Yondelis®	Advanced soft tissue sarcoma	PharmaMar
Tasigna®	Leukemia	Novartis

**Exelon TDS**, a transdermal patch formulation of rivastigmine, looks like a sure winner for Novartis. In the seven years since its launch, the oral formulation of rivastigmine has enjoyed year-on-year US dollar growth as a treatment of Alzheimer’s disease- and Parkinson’s disease-associated dementia. While addressing its regimen and side-effect issues, the transdermal patch will also extend the life-span of rivastigmine beyond the drug’s expected patent expiry between 2011 and 2013.

The FDA approved Exelon TDS for mild-to-moderate dementia in July 2007. EU approval came two months later, while Novartis and Ono Pharmaceutical are developing the drug in Japan (for Alzheimer’s disease-associated dementia only). Japanese Phase III trials were initiated in January and are ongoing. Launch in the EU — the first patch formulation for Alzheimer’s disease to reach the market — took place shortly before the preparation of this report, while US launch is expected imminently.

**AZOR™** is the brand name of a combination of the angiotensin II receptor antagonist olmesartan and the calcium channel blocker amlodipine, developed by Daiichi Sankyo for the treatment of hypertension.

The two component drugs are established, efficacious treatments. Worldwide sales of Daiichi Sankyo's olmesartan, marketed as Benicar® and Olmetec®, were more than \$1.3 billion in the 15 months from January 2006 to March 2007 (recorded this way due to a change in accounting period), while amlodipine (marketed by Pfizer as Norvasc® in the US and Istin® in the UK) totaled \$4.9 billion in 2006. However, amlodipine lost patent protection in 2007 and a number of generic versions are available.

In Phase III trials, all doses of the combination produced greater mean reductions in blood pressure than either medication alone. This, along with its favorable side-effect profile, should make AZOR an attractive treatment option for patients whose blood pressure does not respond to either component drug in isolation. US approval was granted in September 2007.

The reason for menopause is unknown, since almost no other mammals experience it, but as our populations age it can no longer be viewed as signaling the onset of a woman's elderly years. Rather, it is simply the crossing from one stage in life to the next. For most women, the transition is without serious problems, but both physical and psychological symptoms can occur. A number of oral, gel and patch hormone replacement treatments are available, but KV Pharmaceutical believes **EvaMist™** may offer significant advantages.

The product, developed under license from VIVUS (which in turn licensed the drug from Acrux), is a spray formulation of the female hormone estradiol, incorporating ACROSS skin penetration enhancers. A small, easy-to-use hand-held applicator, it delivers a pre-set metered dose of the drug via the skin, releasing estradiol into the bloodstream over 24 hours. EvaMist gained FDA approval in July 2007.

The first of two potential treatments for cancer in our list of notable drugs gaining approval this quarter, the active ingredient in **Yondelis®** is the alkaloid trabectedin isolated from the Caribbean sea squirt *Ecteinascidia turbinata*. The drug has been developed by PharmaMar, a subsidiary of Zeltia, under license from the University of Illinois, and in collaboration with Johnson & Johnson Pharmaceutical Research & Development, for the treatment of soft tissue sarcoma.

Yondelis is the first approved product from PharmaMar, a Spanish biotech specializing in cancer drugs derived from marine organisms. Granted approval by the EU in September 2007, the drug should provide a new treatment option for patients who have not responded to previous regimens. It has Orphan Drug status in both the EU and US, securing PharmaMar extended protection against generic competition.

PharmaMar is also investigating trabectedin for a number of additional solid tumors, including ovarian cancer (a filing is anticipated in 2008), prostate cancer, osteosarcoma, non-small-cell lung cancer, endometrial adenocarcinoma and pediatric tumors.

A second approval win for Novartis this quarter, **Tasigna**<sup>®</sup> (nilotinib) is an orally available inhibitor of Bcr-Abl, c-Kit, PDGF-R and related receptor tyrosine kinases for the potential treatment of leukemias, including chronic myeloid leukemia, refractory gastrointestinal stromal tumor, systemic mastocytosis, relapsed/refractory acute Philadelphia chromosome-positive acute lymphoblastic leukemia, and hypereosinophilic syndrome.

Though the drug has so far been approved only in Switzerland for chronic myeloid leukemia, it is awaiting approval in the US and has been recommended for approval across the EU. Approval is also pending in Japan.

Novartis hopes Tasigna will prove effective for patients who are either intolerant or resistant to its imatinib treatment (marketed as Gleevec<sup>®</sup> in the US and Glivec<sup>®</sup> elsewhere), a hugely successful and generally effective drug that achieved worldwide sales of \$2.5 billion in 2006. The target population is therefore much smaller than imatinib, but analysts are upbeat, noting that Tasigna has a better side-effect profile than imatinib and is at least as efficacious as Bristol-Myers Squibb's Sprycel<sup>™</sup>, with significantly fewer side effects.

## The five most promising drugs entering Phase III trials

Drug	Disease	Company
bevasiranib sodium	Wet AMD	Opko
recombinant active glucocerebrosidase	Gaucher's disease	Protalix
odanacatib	Osteoporosis	Merck & Co
laquinimod	Multiple sclerosis	Active Biotech/Teva
elesclomol	Solid tumors	Synta

Turning our eye to the notable drugs changing phase this quarter, we find **bevasiranib sodium**, under development by Opko for the potential treatment of exudative age-related macular degeneration (wet AMD) and diabetic macular edema/diabetic retinopathy. We continue to see interest in this therapy area, having highlighted Pfizer's wet AMD treatment RTP-80li-14 in the April 2007 edition of *The Ones To Watch* and Athenagen's ATG-003 in October 2006. Further up the pipeline, we'll glance at another potential AMD treatment, TargeGen's TG-100801, later in this report.

There's no surprise at the interest. Macular degeneration is the leading cause of sight loss in the US and UK, and wet AMD is its most devastating form. The therapy market is currently dominated by Novartis's Visudyne®, achieving sales of \$354 million in 2006, and Lucentis®, which generated \$380 million in the second half of 2006 following its approval in June.

Opko's 104-week Phase III trials will compare bevasiranib sodium to Lucentis, hoping to show improved efficacy or safety. Both drugs target vascular endothelial growth factor (VEGF), a protein responsible for the growth of blood vessels, though their action is different. Lucentis is an antibody fragment that binds to the VEGF receptor, preventing it from binding, while bevasiranib sodium inhibits the gene encoding VEGF. In the trial, 330 patients will receive either bevasiranib sodium, administered every eight or 12 weeks, or injections of Lucentis every four weeks. The trial is expected to be completed in August 2010.

Protalix has begun Phase III trials for **recombinant active glucocerebrosidase**, a plant cell culture-derived enzyme replacement therapy for the potential treatment of Gaucher's disease. Most prevalent among certain ethnic groups (particularly specific Jewish, Swedish and African tribal populations and their descendents), the disease leads to an accumulation of glucocerebroside in the liver and spleen, kidneys, lungs and brain, enlarging the spleen and leading to anemia, neutropenia and thrombocytopenia. It also affects bone marrow, causing bone lesions and osteoporosis.

The randomized, double-blind, dose-ranging trials will enroll 30 patients in the US, Israel and elsewhere, with the primary endpoint of reducing spleen volume. Protalix hopes the drug will continue the promise of Phase I trials, in which it showed superior activity to Genzyme's Cerezyme®, the current standard of care. Cerezyme recorded sales of \$1 billion in 2006, and is believed to be the most expensive biopharmaceutical product to date, with annual costs that may top \$500,000 per patient. The FDA has permitted Protalix to move straight from Phase I to Phase III trials, as its drug is expected to provide easier and less expensive scale-up and production.

Osteoporosis is also of concern to Merck & Co. The company's **odanacatib**, developed under license from Celera, is the most advanced example in clinical trials of cathepsin K inhibition, a potential new mechanistic approach to treatment of the disease, as well as arthritis and cancer.

The drug may prove an effective replacement to Merck's Fosamax®, which recorded sales of more than \$3 billion in 2006 (a 40% market share, according to *Thomson Pharma's* strategic drugs content), but which is expected to begin to lose market share to generic competition when it loses patent protection in February 2008.

In Phase II trials, elderly patients receiving odanacatib showed 3.4% increased lumbar spine bone mineral density, compared with a 0.1% decrease for patients on placebo. Bone turnover was also reduced, compared with no reduction in the placebo group. The Phase III trials, initiated in September 2007, will study the drug's efficacy and safety on post-menopausal women with osteoporosis. Merck anticipates filing with the FDA in 2011.

Meanwhile, a second cathepsin K inhibitor, Ono Pharmaceuticals' ONO-5334, entered Phase II trials this June.

Currently, all leading therapies for multiple sclerosis are administered by injection, with all its attendant problems (not least in a disease that affects children). Active Biotech and Teva are therefore hopeful of a blockbuster with their oral therapy **laquinimod**. It's certainly a huge market, with an estimated 2.5 million sufferers worldwide and no known cure. Existing therapies focus merely on slowing the rate of relapse.

The therapy area is a rocky path for new drugs. The dominant therapy, according to *Thomson Pharma*, is interferon beta 1a (marketed as, for example, Biogen Idec's Avonex® and Serono's Rebif®), with sales of over \$3 billion in 2006. We expected Elan/Biogen Idec's Tysabri® to eat into this, but concerns about its safety have limited its use so far.

A selective autoimmune suppressant, laquinimod utilizes Active Biotech's immune modulating-compound SAIK. Phase IIb trials, lasting 36 weeks, demonstrated decreased inflammatory disease activity and a substantial reduction in the number of clinical relapses compared to placebo. Phase III trials to examine the drug's efficacy and safety in patients of relapsing, remitting multiple sclerosis began in August 2007, and are likely to last 24 months.

Finally for this section, Synta is developing **elesclomol** (formerly STA-4783) for the potential treatment of solid tumors. The drug is an apoptosis stimulator that acts by inducing expression of heat shock protein 70 on tumor cell surfaces and disrupting the cytoskeletal network. It's a novel mechanism for cancer treatment, and elesclomol is the first such therapy to enter Phase III trials.

These trials, initiated in August 2007, will study how a combination of the drug and paclitaxel compares to paclitaxel alone in patients with metastatic melanoma, the cause of 8,000 deaths per year in the US alone. There are currently few treatment options, and none that can improve overall survival beyond the median 6 to 9 months. Phase II trials of elesclomol alongside paclitaxel doubled progression-free survival compared with paclitaxel alone, and the combination was well tolerated.

The FDA has granted the drug Fast Track status for metastatic melanoma. Phase II trials are also ongoing in non-small-cell lung cancer and sarcoma.

## The five most promising drugs entering Phase II trials

Drug	Disease	Company
CPP-109	Addiction to cocaine and methamphetamine	Catalyst Pharmaceuticals
intranasal insulin formulation	Diabetes	Nastech
LCP-AtorFen	Cholesterol	LifeCycle
EC-145	Ovarian and lung cancer	Endocyte
TG-100801	AMD, diabetic macular edema, diabetic retinopathy	TargeGen

As the cost of research into new entities rises, with no guarantee of a return on the investment, we see innovators turn increasingly to finding new uses for established drugs. Among other benefits, this repurposing can mean that fewer trials are needed to secure approval.

A good example is Catalyst Pharmaceutical's **CPP-109**, currently in development (under license from Brookhaven National Laboratory) for treatment of addiction to cocaine and methamphetamine. The active ingredient vigabatrin, an orally-active, selective, irreversible, enzyme-activated GABA transaminase inhibitor, has been available in the UK for treating epilepsy since 2001, marketed by sanofi-aventis as Sabril®.

In early clinical trials in Mexico, vigabatrin was safe and reduced or completely eliminated cocaine use and cravings. Double-blind, randomized, placebo-controlled Phase II trials were initiated in July 2007, studying the drug's efficacy in treating 180 cocaine addicts at various centers in the US. The primary endpoint is freedom from cocaine use in the last two weeks of treatment. Data are expected in the third quarter of 2008.

Diabetes continues to be a therapy area of interest. In terms of insulin treatment alone, we've been following the progress of a series of candidates that aim to alleviate the burden of injection regimes, including Oramed's oral gel capsule formulation and Phosphagenic's transdermal gel, in previous issues of *The Ones To Watch*.

Now Nastech has commenced Phase II trials of its **intranasal insulin formulation** which the company believes will provide a more rapid onset of action than these alternatives. According to Dr Harold E. Lebovitz, Professor of Medicine in the Division of Endocrinology at the State University of New York Health Science Center at Brooklyn, nasal administration may have "a unique value proposition" for Type 2 patients who have adequate insulin stores but a slow post-meal insulin response.

It will be interesting to see how Natestch's candidate performs, given the voluntary withdrawal as we go to press of Pfizer's inhaled formula Exubera®, the first non-injectable insulin to reach the market. Doubts about Exubera's pulmonary safety, dosing errors, and its problems among smokers, children and patients with lung disease, dampened sales almost from the start. Moreover, although it is more convenient to administer insulin via inhalation, it is not as cost-effective, the reason given for the UK Government deciding not to recommend Exubera for the NHS. Given this background, Natestch may face a rocky road to approval and clinical acceptance.

Natestch's trials will compare various doses of intranasal insulin with Novo Nordisk's injected insulin aspart NovoLog® and placebo in 20 Type 2 diabetics. These will build on Phase I trials which showed that the candidate achieved peak plasma concentrations more rapidly than Exubera.

You can research more on the issues that led to Exubera's withdrawal with Thomson Scientific's unique *Thomson Message Mapping System*<sup>SM</sup>, which measures the impact of launched drugs on the prescribing habits of clinicians, or the Brand Management Module of *Thomson Pharma*.

The world's best-selling drug is Pfizer's cholesterol-lowering treatment Lipitor, which achieved sales of \$12.9 billion in 2006 (and which is, incidentally, due to come off-patent in 2011). Its active ingredient atorvastatin is also one of the components of **LCP-AtorFen**, developed by LifeCycle for the treatment of a number of disorders requiring lipid management, including atherosclerosis, coronary heart disease, diabetes, obesity and metabolic syndrome.

LifeCycle believes that the once-daily oral formulation, combining atorvastatin with the PPAR alpha agonist fenofibrate, will provide the lowest effective dose on the market. It uses the company's MeltDose technology to enhance the bioavailability of compounds, eliminating the problems of absorption of oral drugs with low water solubility.

With cholesterol imbalance arguably the disease of our age, as the success of Lipitor shows — more than 36 million American adults have high cholesterol levels, according to the American Heart Association — LifeCycle clearly hopes to maintain the momentum after Lipitor's loss of patent protection. Phase II trials studying 200 mixed dyslipidemia patients began in July 2007.

Cancer is a terrible enough disease without having to face the side effects of treatment, which in some cases are perceived to be still worse and can prevent patients from successfully following a therapy regime. Many side effects are due to the toxicity of cancer therapies on non-cancerous cells. A treatment that doesn't harm normal cells can enable higher doses to be used safely, or lower doses to be concentrated in the tumor, increasing efficacy.

In August 2007, Endocyte initiated Phase II trials of **EC-145**, its lead in a series of folate-targeted cancer therapies for the potential treatment of ovarian and lung cancer, among others. The drug uses a folate molecule that selectively binds the chemotherapeutic to the tumor, since the folate receptor is highly expressed on many cancer cells. Studies on patients with ovarian and endometrial cancer should be completed in August 2008, with those on progressive adenocarcinoma of the lung following in May 2010.

Lastly we return to diseases of the eye and TargeGen's **TG-100801**, which entered Phase II trials for wet AMD in July 2007. The drug's notable feature is its application by eye-drop, a potential huge improvement over current AMD therapies which are administered by injection directly into the eye.

TG-100801 is the lead in a series of multitarget kinase inhibitors of Src/Yes, FGFR and Ephrin B4 under development by TargeGen. The company hopes these drugs, which inhibit VEGF-mediated vascular permeability, angiogenesis and inflammation, will prove effective for the treatment of a number of eye diseases, including diabetic macular edema and diabetic retinopathy.

Readers will remember Pfizer's RTP-801i-14 in the April 2007 edition of *The Ones To Watch*, another candidate for treatment of these diseases and currently in Phase I trials.

## The five most promising drugs entering Phase I trials

Drug	Disease	Company
Affitope AD-01	Alzheimer's disease	AFFiRiS
MEM-63908	Alzheimer's disease, CNS disorders	Memory/Roche
TC-5619	Schizophrenia, depression	Targacept
RDEA-806	HIV infection	Ardea Biosciences
APD-791	Arterial thrombosis	Arena Pharmaceuticals

Four of our notable drugs coming into trials this quarter act on targets associated with the central nervous system, and two are potential treatments for Alzheimer's disease (AD). The interest is certainly welcome, since the disease is a huge potential market but commands less investment in research than other therapy areas — the UK Alzheimer's Research Trust claims that in the UK researchers spend only £11 per patient on the disease, compared to £289 for cancer.

The first candidate we highlight is **Affitope AD-01**, which entered Phase I trials for mild-to-moderate AD in July 2007. The drug is a novel approach to therapy, since it is a peptide-based vaccine based on AFFiRiS's proprietary Affitope technology

designed to induce the body's immune response. It's also a landmark for AFFiRiS, as their first program to reach clinical trials.

Preclinical studies showed that the vaccine induces antibodies which attacked AD plaques, leading to a reduction in beta-amyloid fragments. Normal cerebral cells were not affected. The Phase I trials, conducted in Austria, will enroll a total of 24 patients aged 50 years and above with the primary outcome measure of tolerability over a one-year period and the secondary outcome measure of the vaccine's immunological and clinical efficacy. We look forward to analyzing the results next year.

Memory and Roche are developing **MEM-63908**, a partial nicotinic alpha-7 agonist, for the potential treatment of AD and other central nervous system disorders. Randomized, double-blind, placebo-controlled, single-ascending dose trials began in Canada in August 2007 to assess the drug's safety, tolerability and pharmacokinetics in male volunteers. The companies expect to complete this study in the first quarter of 2008, and to follow it with a food interaction study in male volunteers and a randomized, placebo-controlled, single-dose study in elderly subjects.

Aside from Alzheimer's disease, but still with disorders of the brain, Targacept's **TC-5619** has a similar target to MEM-63908, but is in development for schizophrenia and depression. Both indications have quite established therapies, so the candidate will need to show significant benefit in efficacy or safety if it's to make it to market. Assuming that it does, TC-5619 represents a huge opportunity for Targacept, which specializes in drugs selective for the nicotinic acetylcholine receptors for the treatment of cognitive impairment disorders, including AD.

There's no shortage of preclinical efficacy data to raise hopes. The drug, an anti-inflammatory oral neuroprotectant discovered using the company's Pentad technology, demonstrates high binding affinity for alpha4-beta2 and alpha7 and is a full agonist for these receptors. It reduces locomotor hyperactivity induced by apomorphine in rats, is easily absorbed, and has positive effects over a wide dose range.

In July 2007, double-blind, placebo-controlled Phase I trials began to evaluate the drug's safety, tolerability and pharmacokinetics in healthy volunteers receiving single escalating doses.

Potential treatments for HIV infection continue to feature in our lists. Passing through Phase I trials this quarter, **RDEA-806** is one of a series of non-nucleoside reverse transcriptase inhibitors (NNRTIs) under examination by Ardea Biosciences. In trials announced in August 2007 and completed the following month, the once-daily oral treatment, developed under license from Valeant Pharmaceuticals, was profiled against 22 mutant viruses arising from treatment failures of Bristol-Myer Squibb's Sustiva® and 94 NNRTI-resistant clinical isolates.

---

The results are encouraging. The drug is highly active, has a high genetic barrier to resistance, a low potential for drug-drug interactions, and a good safety profile and pharmacokinetics. Ardea plan to commence Phase II trials later this year, with data anticipated in the first quarter of 2008.

We finish this edition of *The Ones To Watch* with a look at [APD-791](#), the lead oral small-molecule selective 5-HT 2a inverse agonist under development by Arena Pharmaceuticals for the potential treatment of arterial thrombosis and conditions such as acute coronary syndrome, myocardial infarction and cerebral ischemia. The link is that the 5-HT 2a receptor is more commonly associated with central nervous system disorders — APD-791 is the only inverse agonist of this receptor in development for thrombotic conditions.

Arena began Phase I trials in July 2007, studying the safety, tolerability and pharmacokinetics of single ascending doses of the compound in 72 volunteers. Pharmacodynamics will be evaluated by measuring ex vivo inhibition of platelet aggregation.

## About the Thomson Corporation

The Thomson Corporation ([thomson.com](http://thomson.com)) is a global leader in providing essential electronic workflow solutions to business and professional customers. With operational headquarters in Stamford, Conn., Thomson provides value-added information, software tools and applications to more than 20 million users in the fields of law, tax, accounting, financial services, scientific research and healthcare. The Corporation's common shares are listed on the New York and Toronto stock exchanges (NYSE: TOC; TSX: TOC).

## About Thomson Scientific

Thomson Scientific is a business of The Thomson Corporation. Its information solutions assist professionals at every stage of research and development—from discovery to analysis to product development and distribution. Thomson Scientific information solutions can be found at **[scientific.thomson.com](http://scientific.thomson.com)**

### Note to press

To request further information or permission to reproduce content from this review, please contact:

Eoin Bedford  
Phone +44 20 7433 4691  
[eoin.bedford@thomson.com](mailto:eoin.bedford@thomson.com)

To sign up to *The Ones to Watch* visit  
**[thomsonpharma.com/quarterlyreview](http://thomsonpharma.com/quarterlyreview)**

**For further information  
please contact your regional  
Thomson Scientific Head Office**

#### Americas

Phone: +1 800 336 4474  
+1 215 386 0100

#### Europe, Middle East and Africa

Phone: +44 20 7433 4000

#### Japan

Phone: +81 3 5218 6500

#### Asia Pacific

Phone: +65 6879 4118

#### Thomson Scientific Offices around the World

Sydney, Australia  
Rio de Janeiro, Brazil  
Paris, France  
Munich, Germany  
Hong Kong  
Bangalore, India  
Tokyo, Japan  
Mexico City, Mexico  
Beijing, People's Republic of China  
Seoul, Republic of Korea  
Singapore  
Taipei, Taiwan  
London, United Kingdom  
USA  
Alexandria, Virginia  
Ann Arbor, Michigan  
Carlsbad, California  
East Haven, Connecticut  
Horsham, Pennsylvania  
Philadelphia, Pennsylvania  
Lisle, Illinois  
Portland, Maine  
San Jose, California

For complete contact information, visit:  
**[scientific.thomson.com/contact](http://scientific.thomson.com/contact)**