REUTERS

THE ONES TO WATCH

A PHARMA MATTERS REPORT

Expert review from Thomson Reuters of the most promising drugs changing clinical phase, receiving approval and launched this quarter, based on the strategic data and insight of Thomson Reuters Cortellis™ for Competitive Intelligence, your advanced source for timely and accurate Life Sciences information.

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INTRODUCTION

With the number of diabetics increasing worldwide, largely as a result of the much-reported obesity epidemic, the diabetes market is big business. In 2012, the World Health Organization (WHO) estimated that 347 million people worldwide had diabetes, with deaths associated with the disease projected to double between 2005 and 2030. Diabetes is a major causative factor in blindness, kidney disease and amputation. Consensus data from Cortellis for Competitive Intelligence forecasts that the market for oral diabetic agents will be worth $22 billion in 2017 while the market for human insulin and analogs for diabetes will reach $26.5 billion in the same year, figures set to rise in line with increasing numbers of cases. As such, it is no surprise that new diabetes treatments feature heavily in this quarter's **The Ones to Watch** as companies prepare to meet this challenge.

There are many established targets for treating type 2 diabetes (T2D), for example, alpha glucosidase, glucagon-like peptide-1 (GLP-1), sodium glucose transporter-1 (SGLT-1) and dipeptidyl peptidase IV (DDP-IV). In the field of GLP-1 agonists for treating T2D, this quarter has seen development milestones achieved by Novo Nordisk's **semaglutide**, a once-weekly subcutaneous treatment for T2D, which entered phase III trials for T2D, and also Sanofi's **Lyxumia®**, a once-daily injectable treatment, which was registered in Europe. With several GLP-1 agonists already on the market these agents will face stiff competition, but the incentive is a share of the antidiabetic GLP-1 agonist market, projected by Cortellis for Competitive Intelligence to be worth $7 billion in 2017.

Another agent arising from Novo Nordisk's extensive diabetes program, **Tresiba®**, was approved this quarter in Japan and the European Union (EU), and subsequently launched in Denmark for the treatment of both type 1 (T1D) and type 2 diabetes. Tresiba® a once-daily basal insulin analog, was demonstrated in clinical trials to be non-inferior to Sanofi's Lantus®, which currently commands 32 percent of the human insulin and analogs diabetes market. Lantus® requires injection at the same time each day, providing 24-hour control of blood sugar levels, whereas the action of Tresiba® lasts up to 42 hours, potentially allowing greater flexibility.

Directly related to the diabetes market, and also set to increase in value with increasing incidence of diabetes, is the market for agents treating the long-term effects of the high blood sugar levels associated with the disease. This quarter, the topical agent **DSC-127** from Derma Sciences entered phase III clinical testing for the treatment of diabetic foot ulcers, which are estimated to occur in 15 percent of people suffering from the disease.

Let's take a closer look at the five most promising drugs launched or receiving approval, and moving through each of the clinical phases, between January and March 2013.

SECTION I

THE FIVE MOST PROMISING DRUGS LAUNCHED OR RECEIVING APPROVAL

DRUG	DISEASE	COMPANY
Acofide®	Functional dyspepsia	Zeria/Astellas
FluBlok®	Influenza virus infection	Protein Sciences Corp
Tresiba®	Types 1 and 2 diabetes	Novo Nordisk
Lyxumia®	Type 2 diabetes	Sanofi
Cometriq™	Medullary thyroid cancer	Exelixis

In this quarter, Zeria Pharmaceutical and development partner Astellas Pharma received approval from the Ministry of Health, Labor and Welfare in Japan for **Acofide®** (acotiamide), a thiazole-4-carboxamide muscarinic M1 and M2 receptor and adenosine A1 receptor antagonist, with prokinetic and antiacetylcholinerase activity, for the treatment of functional dyspepsia.

Functional dyspepsia, or indigestion, is one of the most common digestive complaints, with approximately 15 percent of the general US population estimated to experience it. The main symptom of dyspepsia is upper abdominal pain, which can be accompanied by bloating, feeling full, belching, nausea or heartburn. The condition is usually non-serious and treated with antacids, H2 receptor antagonists, proton-pump inhibitors and prokinetics. Acofide® may offer a useful alternative to proton-pump inhibitors and, unlike widely used prokinetic agents, it has low affinity for 5-HT and dopamine D2 receptors and reduced potential for induction of negative cardiovascular side effects.

An NDA for Acofide® was filed in Japan in September 2010, following successful large-scale, multicenter, phase III trials, in which the drug was safe, alleviated functional dyspepsia symptoms, and improved global patient outcome assessment in 73.2 percent of patients. This drug is to be first launched in Japan, ahead of other countries. According to consensus data from Cortellis for Competitive Intelligence, Acofide® sales of $69.7 million are forecast for 2017.

An RNA virus of the family Orthomyxoviridae, influenza is a contagious disease that is rarely out of the news. Under normal circumstances, influenza is estimated to cause up to 500,000 deaths annually, but can kill millions, or in extreme cases tens of millions, when pandemics occur. Each year vaccines are produced against the strains that are considered likely by the WHO to be the most prevalent in that year.

In January 2013, the FDA approved Protein Sciences Corp's **FluBlok®**, a cell-culture-produced vaccine comprising three recombinant hemagglutinin proteins corresponding to the influenza virus strains recommended by the WHO each year, for the prevention of influenza virus infection.

The recombinant protein for the vaccine is produced using a baculovirus expression system in moth-derived insect cells. It contains no adjuvants, does not require live influenza virus, thimerosal or antibiotics, and is the first recombinant egg-free influenza vaccine. A BLA for approval of the vaccine was first filed with the FDA in 2007; however, further safety studies were requested which were completed in September 2011. The final approval was based on several large-scale, phase III trials in which FluBlok® was shown to be safe, immunogenic and non-inferior to a trivalent egg-derived vaccine. Protein Science Corp plans to launch the vaccine in time for the 2013/14 influenza season in the US, and has licensed the technology to Astellas and Il Dong (via UMN Pharma) for development in Asian markets.

Launched by Novo Nordisk in Japan and the EU this quarter, **Tresiba®** (insulin degludec) is a next-generation, ultra-long-acting, once-daily basal insulin analog for the treatment of T1D and T2D.

T1D, or insulin-dependent diabetes, results from the autoimmune system attacking and destroying insulin-producing beta cells in the pancreas, while T2D, or non-insulin-dependent diabetes, is caused by insulin resistance and/or insufficient insulin production. Both types lead to increased glucose levels in blood and urine, with long-term complications including blindness, kidney damage, nerve damage, heart disease and stroke. T2D is often linked with obesity, and is more common in individuals over 40 years of age, although there is a growing trend for diagnosis in younger people and children. Of the hundreds of millions of individuals worldwide who have diabetes, 90 percent have T2D. Current standard treatment for T1D is multiple daily insulin injection, while, for T2D, treatment generally involves diet and lifestyle changes, or oral medications which lower blood sugar levels.

Tresiba® is part of the Novo Nordisk diabetes program that also includes Ryzodeg® (Tresiba® plus insulin aspart) and IDegLira® (Tresiba® plus liraglutide), diabetes combination products which will be made available in the FlexTouch® prefilled auto-injector pen device. In January 2013, Tresiba® was approved in the EU, and the product was launched in Denmark in March 2013. Approval in Japan was obtained in September 2012. However, Tresiba® cannot be approved in the US until additional cardiovascular data from a dedicated trial are submitted to complete the NDA review.

Phase III trials had demonstrated Tresiba® to be non-inferior to insulin glargine, with a lower risk of confirmed nocturnal or severe hypoglycemia. Tresiba® has big potential for Novo Nordisk; consensus forecast data from Thomson Reuters Cortellis for Competitive Intelligence predict 2017 sales of $863 million, representing 3 percent of the human insulin and analogs market.

Also in the field of diabetes, Sanofi, under license from Zealand Pharma, this quarter launched **Lyxumia®** (lixisenatide), a subcutaneous GLP-1 and exendin-4 analog, for the treatment of T2D. Sanofi obtained development and worldwide commercialization rights to Lyxumia® from Zealand Pharma in June 2003. Zealand received an upfront payment of $10 million, and will receive further milestone payments and royalties on product sales.

GLP-1 is a hormone which stimulates glucose-dependent insulin secretion, improves beta-cell function and exhibits a cardiovascular protective effect. Native GLP-1 has a short half-life of only 1 or 2 min resulting from breakdown by DPP-IV, so GLP-1 analogs have been developed which circumvent this. Clinical trials with GLP-1 analogs have suggested that they can decrease body weight in T2D patients.

Lyxumia® was launched in the UK in March 2013, following EU approval in February 2013. This was based on data from the 11-trial GETGOAL clinical program which enrolled over 5,000 patients whose blood glucose levels remained high despite treatment with basal insulin and common oral antidiabetic medications. Lyxumia® demonstrated comparable efficacy to Byetta®, and significantly reduced glycosylated hemoglobin (HbA1c) levels without increasing the risk of hypoglycemia. Further regulatory filings have been made in the US and Japan. Sanofi is also developing Lyxumia® in combination with Lantus® for treating T1D and T2D, currently in phase II trials, which would potentially compete with the IDegLira® combination product.

Lyxumia® is administered once-daily by pen injection, offering a key advantage over the first-to-market, twice-daily injected Byetta® from Amylin and AstraZeneca. There are other GLP-1 agonists on the market, which will also provide direct competition for Lyxumia®, such as market leader Victoza® from Novo Nordisk, Bydureon® from Amylin and potentially Syncria® from GlaxoSmithKline, compared to which it offers good tolerability with low incidence of nausea.

According to consensus data from Cortellis for Competitive Intelligence, Lyxumia®, Bydureon® and Victoza® are predicted to achieve sales of $791 million, $1.4 billion and $3.5 billion in 2017, respectively.

Exelixis has launched **Cometriq™** (cabozantinib), an oral inhibitor of multiple tyrosine kinases including MET, VEGFR2, RET, Kit and Flt3, in the US for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). Medullary tumors are the third most common of all thyroid cancers, accounting for between 3 and 8 percent of cases. In about a quarter of these, the disease is the result of an inherited faulty gene. There are few drug treatment options available for patients with MTC and patients are generally treated with surgery and radiotherapy. Another tyrosine kinase inhibitor, Caprelsa® was launched by AstraZeneca in the US in 2011, and in Europe in 2012, but this remains the only other approved pharmacological treatment.

Cometriq™ was approved in November 2012, following a fast-tracked, rolling NDA filing under Orphan Drug and Priority Review designations. In a pivotal phase III MTC trial, Cometriq™ significantly improved rates of progression-free survival, compared with placebo. The US prescribing information carries a boxed warning highlighting the risks of gastrointestinal perforations and fistulas, and severe and sometimes fatal hemorrhage.

Cometriq™ is also in late-stage clinical development for the treatment of other cancers, including metastatic castration-resistant prostate cancer, progressive glioblastoma multiforme, other solid tumors and multiple myeloma. US rights to Cometriq™ belong to Exelixis, while Swedish Orphan Biovitrum has obtained European commercialization rights; Cometriq™ is currently under EU regulatory review for MTC. According to consensus data from Cortellis for Competitive Intelligence, sales of Cometriq™ are expected to reach $9 million in 2013, rising to $150 million in 2017.

SECTION 2

THE FIVE MOST PROMISING DRUGS ENTERING PHASE III TRIALS

DRUG	DISEASE	COMPANY
BBI-608	Colorectal cancer	Boston Biomedical
latanoprostene bunod	Glaucoma/ocular hypertension	Bausch & Lomb
lumacaftor + Kalydeco™	Cystic fibrosis	Vertex /Cystic Fibrosis Foundation Therapeutics
DSC-127	Diabetic foot ulcer	Derma Sciences
Semaglutide	Type 2 diabetes	Novo Nordisk

Colorectal cancer is the third most common cancer overall and the second most common cancer in women. Over 1.2 million cases were diagnosed in 2008, and, according to WHO figures, 608,000 deaths were caused by colorectal cancer in that year.

Boston Biomedical, a company focused on the discovery and development of novel cancer therapeutics targeting cancer stem cells, has initiated this quarter a phase III trial of its most advanced candidate, BBI-608. While the molecular target of the compound has not been disclosed, it simultaneously inhibits multiple cancer stemness pathways and targets malignant cancer stem cells and other heterogeneous cancer cells. The drug reached the clinic in less than 24 months and is currently targeted for the treatment of colorectal cancer. **BBI-608** has demonstrated safety and clinical activity in phase I trials, and phase II trials are ongoing in colorectal cancer patients.

In April 2011, Dainippon Sumitomo Pharma signed an option to license BBI-608 for all cancer indications in Japan and negotiation rights for the US and Canada. Dainippon subsequently acquired Boston Biomedical for $200 million in February 2012, agreeing to pay up to $540 million in milestone payments related to the development of BBI-608 and BBI-503, a cancer stemness kinase inhibitor, plus $1890 million in milestones based on the achievement of certain sales targets. This deal is considerably more lucrative to Boston Biomedical than the previous option agreement which allowed for a maximum of $55 million as a portion of development costs and a maximum of approximately $100 million for milestone payments and running royalties for BBI-608.

BBI-608 could potentially become the first anticancer drug targeting cancer stem cells; Dainippon anticipates commercialization in North America in 2015, followed by launch in Japan in 2016. Cortellis for Competitive Intelligence predicts global sales of $21 million in 2015, increasing to $374 million in 2017.

Nitric oxide-donating prostaglandin F2-alpha analog **latanoprostene bunod** is being developed by Bausch & Lomb under license from Nicox, for the reduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension. The drug entered a phase III program this quarter, consisting of two trials to be conducted in North America and Europe.

Increased fluid pressure in the eye, to above 21 mmHg, is often linked to glaucoma or ocular hypertension, both of which are more common in elderly populations. If left untreated, this increased pressure can lead to optic nerve damage and vision loss. Treatment to reduce IOP can prevent the progression of glaucoma.

In a phase II trial, patients with elevated IOP due to glaucoma and ocular hypertension were treated with latanoprostene bunod or prostanoid-selective prostaglandin F receptor agonist Xalatan® for 28 days. Latanoprostene bunod dose-dependently lowered IOP, with two out of four of the doses tested providing a greater reduction than with Xalatan®. The responder rate was 68.7 percent versus 47.5 percent for latanoprostene bunod and Xalatan®, respectively.

Xalatan® was developed by Pharmacia (now Pfizer) and was initially launched in the US and EU for elevated IOP in glaucoma and ocular hypertension patients in 1996. In 2012 the drug achieved world sales of $631 million.

Bausch & Lomb is developing latanoprostene bunod under a worldwide agreement with Nicox which resulted in an initial license payment of

$10 million. Following positive phase IIb trial data, Bausch & Lomb made a further $10 million milestone payment in April 2012. The company is committed to potential payments of up to $162.5 million if certain milestones are met and Nicox will also receive double-digit royalties on sales.

Cystic fibrosis (CF) is a genetic disease caused by mutations in the gene encoding the CF transmembrane regulator (CFTR) protein, which regulates chloride and water transport. Defects in this protein lead to a build-up of mucus in the lungs and other parts of the body, leading to respiratory, digestive and other problems. Worldwide, 70,000 people are affected by CF, with most cases occurring in individuals of European decent. Individuals with CF have an average life expectancy of 30 to 40 years, although this is increasing as more treatments become available. Current management strategies include treatment with antibiotics to control chronic lung infection, and lung transplantation.

In the first quarter of 2012, Vertex Pharmaceuticals and Cystic Fibrosis Foundation Therapeutics (CFFT), the commercial arm of the not-for-profit Cystic Fibrosis Foundation, launched Kalydeco™ (ivadactor), the first personalized medicine targeted to a genetically distinct patient subgroup: CF patients carrying the G551D mutation. Kalydeco™ is a CFTR potentiator which restores function of the defective protein. Vertex and CFFT are also developing lumacaftor (VX-809), which is considered to be a CFTR corrector as it helps the defective protein to the cell surface in patients with the F508del mutation, the most common CFTR gene mutation. The two companies are also developing an oral **lumacaftor + Kalydeco™** fixed-dose combination for treating CF.

In January 2013, the FDA granted the combination Breakthrough Therapy designation for CF based on data from a phase II trial. In the trial, CF patients with two copies of F508del were treated with lumacaftor alone for 28 days, followed by lumacaftor plus Kalydeco™. When treated with the combination therapy, a significant improvement in lung function was observed in each dose group compared with placebo; those receiving the highest dose experienced a mean absolute improvement in lung function of 8.5 percent. A mean absolute improvement in lung function was also observed in a subset of heterozygous patients with one copy of the F508del mutation and a second mutation that was not expected to respond to Kalydeco™ or lumacaftor monotherapies.

In February 2013, a phase III program consisting of two trials was initiated and Vertex reported that data from the trials would be used in submissions to the FDA and the EMA.

Derma Sciences is a US-based company focused on the development of specialty medical devices and pharmaceuticals in the area of wound care. In February 2013, the company initiated patient enrollment in the first of two planned phase III trials of its first-in-class, topical gel formulation of NorLeu3-A(1-7), an angiotensin analog. The drug, known as **DSC-127**, is indicated for the treatment of diabetic foot ulcer and works by recruiting mesenchymal stem cells to the sites of tissue injury.

A diabetic foot ulcer is a patch of broken skin on the lower leg or foot which is unable to repair itself properly due to a disruption of the normal healing process. Diabetic foot ulcers are a major complication of diabetes, often resulting in lower leg amputation. In 2011, approximately 25.8 million people in the US were living with diabetes, with 1.6 million new cases diagnosed each year, suggesting a substantial potential market for the drug. Current treatments for diabetic foot ulcer include special wound dressing, debridement, surgery to increase blood flow and antibiotics to control infection.

In a phase II trial, 65 percent of wounds treated with DSC-127 were healed after 24 weeks, compared with 38 percent in a placebo-treated control group. The phase III DSC-127 trials are intended to support an NDA filing in the US following the report of data, which is expected in early 2015. Derma Sciences estimates the drug could reach peak global sales of up to $900 million.

Another GLP-1 analog progressing this quarter is Novo Nordisk's **semaglutide**, a once-weekly, subcutaneous treatment for T2D.

In a phase II trial, 0.8- and 1.6-mg doses of semaglutide were more effective in treating T2D patients than daily subcutaneous injections of GLP-1 analog Victoza®, resulting in greater reductions in HbA1c levels over 12 weeks of treatment. A phase III trial of the once-weekly formulation began in February 2013 and is expected to complete in January 2016. Victoza®, also from Novo Nordisk is indicated in the US as an adjunct to diet and exercise to improve blood sugar control in adults with T2D. In Europe the drug is used to achieve glycemic control in combination with metformin. In 2011 the drug had a 61 percent share of the diabetes market and reported sales of over $1.1 billion. An ability to achieve similar or even better control of blood glucose levels with a weekly dosing regimen would represent a significant advantage to patients.

SECTION 3

THE FIVE MOST PROMISING DRUGS ENTERING PHASE II TRIALS

DRUG	DISEASE	COMPANY
AYX-1	Post-surgical pain	Adynxx/Cubist
menadione	Skin rash associated with anticancer EGFR inhibitors	Talon Therapeutics
ALD-403	Migraine	Alder Biopharmaceuticals
NNZ-2566	Rett syndrome	Neuren
GSK-2586184	Systemic lupus erythematosus / chronic plaque psoriasis	GlaxoSmithKline

Surgery results in local trauma to tissues and nerve endings, overloading pain receptors and leading to hypersensitivity of the central nervous system. Any stimulation may then be interpreted as pain, even movement or touch at locations other than the site of surgery. Over 70 percent of patients undergoing surgical procedures suffer from moderate or severe post-surgical pain and less than half of those experience adequate pain relief, with 10 to 50 percent of patients going on to develop chronic pain. Post-surgical pain may be constant in the form of aching or cramping, or may occur with movement or touch, as a sharp or shooting pain. Post-surgical pain delays discharge from hospital, increases medical care costs, increases the chances of post-surgical complications and hinders the patient's recovery and return to normal daily activities. Current analgesics may adequately relieve pain during rest, but often they have dose-limiting side effects which can interfere with the patient's recovery.

Adynxx's first-in-class platform of therapeutics utilizes oligonucleotides that bind to and inhibit transcription factors, which are responsible for the regulation of multiple pain-related proteins. They are intended to treat pain as a disease rather than a symptom. The company's lead candidate, **AYX-1**, is designed to reduce acute post-surgical pain and prevent transition into chronic pain with a single dose during surgery. AYX-1 is a double-stranded DNA decoy which binds to the EGR-1 transcription factor.

In January 2013, Adynxx began a phase II, proof-of-concept trial to evaluate the efficacy and safety of AYX-1 in 95 patients undergoing unilateral total knee arthroplasty in the US. Patients were to receive placebo or AYX-1 administered as a single intrathecal injection just before administration of an intrathecal spinal anesthetic. The trial is designed to assess the drug's ability to reduce acute pain and prevent chronic pain, with a primary endpoint of pain with walking and secondary endpoints including pain at rest, pain with knee movements, function recovery rate and extent of function recovery, use of opioids and safety. The first patient was dosed in February 2013, and the trial is expected to be completed in August 2013. AYX-1 has been evaluated in a phase I dose-escalation trial in 30 healthy volunteers. All doses of the drug were well tolerated with no serious adverse events. A single administration of AYX-1 demonstrated long-term efficacy in preclinical pain and functional assessment models.

Also achieving the milestone of phase II this quarter is **menadione topical lotion**, a first-in-class topical formulation of menadione (vitamin K3) being developed by Talon Therapeutics for the treatment of skin rash associated with the use of epidermal growth factor receptor (EGFR) inhibitors. EGFR inhibitors are used to treat patients with lung, colon, breast, pancreas and head and neck cancers. One of the side effects of these drugs is a painful skin rash which may limit dosage and lead to a lack of compliance, reducing the effectiveness of the cancer treatment. Early onset skin rash affecting the face, neck and upper torso develops in up to 90 percent of patients treated with EGFR inhibitors and up to 30 percent of those stop treatment because of skin toxicity. With no currently approved therapeutics for cancer-treatment-related toxicity, and over-the-counter topical products generally considered to be ineffective, there remains an unmet medical need to treat this condition.

Talon aims to meet this need with a topical lotion formulation of menadione, a small-molecule phosphatase inhibitor and EGFR signaling activator, which is designed to target the underlying cause of the rash. The lack of systemic uptake means it should not interfere with the effect of the EGFR therapy on the tumor itself. The phase II trial follows results from a phase I program in which the drug was well tolerated, with a favorable pharmacokinetic profile and no appreciable systemic absorption.

Preclinical data demonstrated that menadione does not interfere with the anti-tumor activity of EGFR inhibitors and indicated that the drug may be able to prevent skin toxicities resulting from inhibition of protein kinases involved in tumor growth signaling pathways. Talon licensed worldwide, exclusive development and commercialization rights for the use of topical menadione in skin rash from the Albert Einstein College of Medicine in October 2006.

Migraines are a common condition, estimated to affect 15 percent of the world's population, most frequently experienced as a severe headache. Migraines usually start in young adults and are more common in women than men, suggesting possible hormonal involvement. Approximately one third of patients experience a warning sign, or aura, which may take the form of visual problems, such as flashing lights, or stiffness in the limbs. Some people experience several migraines a week, whereas others may only suffer with them occasionally and may even go years between attacks. The underlying cause of migraine is unknown, although it is believed to be a combination of genetic and environmental factors. Possible triggers include stress, fatigue, diet, low blood sugar, bright lights and hormonal influences, such as the contraceptive pill and menstruation. If a patient suffers a severe migraine attack they may be bed-bound for days at a time, severely impacting on their quality of life.

In March 2013, Alder Biopharmaceuticals dosed the first patient in a phase II, proof-of-concept trial to assess **ALD-403** for preventing frequent, episodic migraine. ALD-403 is a potent humanized monoclonal antibody that inhibits calcitonin-gene-related peptide (CGRP). The company is able to produce high quantities of antibodies using its Mab Xpress technology.

ALD-403 has the potential to prevent a migraine before it begins. Whereas most currently available preventative treatments need to be taken daily, ALD-403 is designed to be administered as a once-a-month subcutaneous injection. Current treatments reduce migraine frequency by about 50 percent in approximately half of patients and often come with significant adverse events. ALD-403 has the potential to offer a preventative treatment with increased efficacy and fewer side effects. It targets CGRP, which is believed to play a role in migraine with increased concentrations being observed during attacks.

The 6-month phase II trial is designed to evaluate the safety and efficacy of monthly administered ALD-403 in 160 patients who have experienced 4 to 14 migraines per month for at least 3 months and who receive treatment for acute migraine. The trial follows a phase I trial which assessed the safety, immunogenicity and pharmacokinetics of ALD-403 in healthy volunteers in Australia.

Rett syndrome is a developmental disorder caused by a mutation in the MECP2 gene, found on the X chromosome. The gene codes for MeCP2 protein, which is vital for brain development. The condition almost exclusively affects females because they have another normal copy of the MECP2 gene, so are able to produce some MeCP2 protein, unlike males who are unable to produce any of the protein and therefore cannot survive. Development in children with Rett syndrome may appear normal for the first few months, but then slows and regresses. Children have problems with communication, language, coordination and learning. Patients tend to be prone to gastrointestinal disorders and up to 80 percent suffer with seizures. Although many sufferers survive into adulthood, they will have a shortened lifespan and will need 24 hour care throughout their lives. Available treatments for Rett syndrome are targeted at alleviating symptoms.

Neuren Pharmaceuticals is developing **NNZ-2566**, a small-molecule analog of the naturally occurring neuroprotectant and N-terminus IGF-1 tripeptide, Glypromate®, which demonstrated multi-faceted actions in preclinical studies, significantly reducing inflammation and apoptosis, protecting neurons and inhibiting seizures. In March 2013, a phase II trial was initiated in the US to assess the safety of NNZ-2566 in 60 adolescent and adult female patients with Rett syndrome. NNZ-2566 was safe and well tolerated in a phase I trial in healthy volunteers. Neuren is also developing the drug for mild traumatic brain injury and fragile X syndrome and has an intravenous formulation in development for similar neurological indications.

Systemic lupus erythematosus (SLE) is an autoimmune disease that occurs when the immune system attacks healthy cells leading to tissue damage. Symptoms include joint pain, muscle pain, fever, malaise and fatigue. The disease is much more common in women than in men, and estimates suggest that 130 in 100,000 of the US population have SLE, with a higher prevalence in individuals of non-European descent. Psoriasis is also an immune-mediated disease, affecting the skin. While the cause is not well understood, psoriasis occurs when the immune system is triggered and new skin cells are overproduced. Plaque psoriasis is the most common form of the disease manifesting as a silvery white scale on the top layer of skin. Men and women are affected equally by psoriasis, onset can occur at any age and the estimate worldwide prevalence is up to 3 percent. As with Rett syndrome, there is currently no cure for either SLE or psoriasis, and treatments are aimed at reducing symptoms.

This quarter, GlaxoSmithKline initiated two phase II trials of **GSK-2586184** (formerly known as GLPG-0778), a selective JAK1 inhibitor. JAK1 is believed to be a promising target for the treatment of inflammatory diseases as it plays an essential role in cytokine signaling. GSK-2586184 was discovered by researchers at Galapagos as part of a collaborative program with GlaxoSmithKline to identify and develop osteoarthritis treatments. In February 2012, GlaxoSmithKline exercised its option to exclusively license the drug.

One of the phase II trials is designed to assess the efficacy, pharmacodynamics, safety and tolerability of GSK-2586184 in 250 patients with mild to moderate SLE and the other is intended to evaluate the safety and efficacy of the drug in 64 patients with chronic plaque psoriasis. In phase I trials in healthy volunteers, GSK-2586184 demonstrated acceptable safety and pharmacokinetic profiles and significantly and dose-dependently suppressed an induced inflammatory response.

SECTION 4

THE FIVE MOST PROMISING DRUGS ENTERING PHASE I TRIALS

DRUG	DISEASE	COMPANY
ARGX-110	Cancer	arGEN-X
ALN-TTRsc	Transthyretin amyloidosis	Alnylam
BCX-4161	Hereditary angioedema	BioCryst
PRX-112	Gaucher's disease	Protalix
UE-2343	Age-related cognitive disorders	University of Edinburgh/Argenta

CD70 is a member of the tumor necrosis factor superfamily, and is transiently expressed on activated T- and B-cells and mature dendritic cells. CD70 has been identified in various human cancers, including B- and T-cell lymphomas (eg, non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Waldenström's macroglobulinemia) and in solid tumors (eg, glioblastomas, astrocytomas, ovarian cancers, renal cell carcinoma and nasopharyngeal carcinoma).

arGEN-X is developing the anti- CD70 human monoclonal antibody **ARGX-110** for the treatment of CD70-related cancers. The antibody was discovered using the company's SIMPLE (superior immunodiversity with minimal protein lead engineering) antibody platform and is a first-in-class therapy against this target.

In January 2013, a European phase Ib trial began in patients with CD70-positive malignancies. The trial is intended to investigate clinical and pharmacokinetic parameters, and also biomarkers relating to CD70 activity. Preclinical studies with ARGX-110 demonstrated picomolar binding to human and non-human primate CD70, dose-dependent inhibition of CD70/CD27-induced signaling, and depletion of CD70-overexpressing cell populations. ARGX-110 has demonstrated activity against CD70+ lymphomas and lymphocytic leukemias, and solid tumors, including those caused by oncogenic viruses (eg, nasopharyngeal, cervical and hepatocellular carcinomas).

Transthyretin (TTR) amyloidosis is a rare inherited condition resulting from mutations in the TTR gene, in which amyloid proteins accumulate in tissues, such as the peripheral nervous system (familial amyloid polyneuropathy; FAP) or the heart (familial amyloid cardiomyopathy; FAC).

FAP is a fatal disease, with a life expectancy of 5 to 15 years from diagnosis, but estimated to affect only 10,000 individuals worldwide. Symptoms include loss of pain and temperature response, loss of feeling in the extremities, foot lesions and high levels of pre-albumin in the blood. FAC is estimated to affect 40,000 individuals worldwide, and can result in heart failure and arrhythmias. Because the vast majority of TTR production occurs in the liver, early liver transplant is a well-established treatment. Currently, the only available pharmacological treatment is Vyndaqel®, a small-molecule TTR stabilizer, which is launched in Europe.

Entering the clinic this month is **ALN-TTRsc**, a small-interfering RNA (siRNA) therapy targeting the TTR gene. The agent is under development by Alnylam Pharmaceuticals and is delivered subcutaneously using GalNAc-conjugate delivery technology, representing the first siRNA therapy to be delivered in this way.

Alnylam filed a clinical trial authorization application with the UK Medicines and Healthcare products regulatory agency in January 2013 for a phase I safety and tolerability trial in healthy volunteers, which was initiated in March 2013. Phase II and III trials are planned to begin in late 2013 and 2014, respectively, in patients with FAC.

In preclinical studies, an 80 percent reduction in TTR was achieved with once-weekly dosing at a low dose for 4 weeks, following an initial loading period of once-daily treatment for 5 days. The drug was safe and well tolerated in rodents and non-human primates at doses up to 300 mg/kg, with a >100-fold therapeutic index. Robust and sustained silencing of TTR was achieved in preclinical models with once-weekly dosing.

Another inherited disorder, hereditary angioedema (HAE) is a blood condition in which patients experience episodes of swelling in various parts of the body, such as the face, genitals, hands and feet, or in the gastrointestinal tract, which can cause nausea and vomiting, or in the airways, which can lead to asphyxiation. Estimates suggest that between 10,000 and 50,000 individuals in the US alone have HAE, which has an associated 15 to 33 percent mortality rate. Current treatment/prophylactic agents for HAE include C1 inhibitors, such as Cinryze® or Berinert®, or the kallikrein inhibitor Kalbitor® (currently only available in the US). Each of these agents requires intravenous administration.

BCX-4161, an oral plasma kallikrein inhibitor, is under development by BioCryst Pharmaceuticals for the potential prevention and treatment of HAE. Kallikrein generates bradykinin in the body, which is believed to mediate the swelling associated with HAE. If successful, this agent could represent the first oral treatment for attacks of HAE.

In March 2013, a phase I pharmacokinetic and pharmacodynamic trial was initiated in healthy volunteers. In preclinical studies, plasma kallikrein activity was inhibited dose-dependently in rats and monkeys following oral administration. Intraperitoneal administration increased bleeding time 2-fold in a tail transection bleeding time test in rats and mice.

The lipid storage disorder Gaucher's disease is the most common genetic disease affecting Ashkenazi Jews in North America, carried by up to 10 percent of individuals, but can affect individuals from any ethnic background. Patients with this disease are deficient in the enzyme glucocerebrosidase (GCD), which plays a role in the breakdown of glucocerebroside. Thus, in individuals with Gaucher's disease glucocerebroside accumulates in tissues, such as the liver, spleen, lungs, kidneys and lymph nodes. Symptoms include an enlarged liver and spleen, anemia, bone thinning and respiratory problems. Current treatments are limited, but include splenectomy, bone marrow transplant and enzyme replacement therapy with recombinant GCD (eg, Vpriv® and Elelyso™) or a recombinant GCD analog (eg, Cerezyme®) every two weeks. Pharmacological treatments include Zavesca®, an oral glucosylceramide transferase inhibitor.

Protalix is developing **PRX-112**, an oral plant-cell-expressed recombinant GCD encapsulated within carrot cells, for the potential treatment of Gaucher's disease.

A phase I trial for PRX-112 began in Israel in March 2013, and is expected to enroll 12 patients with Gaucher's disease. Preclinical studies demonstrated accumulation of GCD in the spleen and liver of pigs and rats fed with PRX-112. The enzyme demonstrated good stability, remaining in the blood stream of rats for over 12 h. In an in vitro model of the gastrointestinal tract, the cellulose wall prevented enzyme degradation.

As a normal part of the aging process, individuals often experience a decline in memory, particularly short-term memory and what is termed 'episodic' memory (long-term memory related to events and experiences). This memory loss has been associated with excessive glucocorticoid activity, which increases during aging. 11β-HSD1 regulates glucocorticoid activity, suggesting it as a target for treating age-related memory decline.

UE-2343, an 11β-HSD1 inhibitor under development by the University of Edinburgh in collaboration with Argenta Discovery, entered phase I development this quarter for the potential oral treatment of age-related cognitive disorders, such as memory loss.

In January 2013, a phase I safety, efficacy, pharmacokinetics and pharmacodynamics trial of UE-2343 was initiated in healthy volunteers in the UK. Results from preclinical studies have demonstrated that treatment with UE-2343 for one month enhanced cognitive function in aged transgenic Tg2576 mice, as measured using a passive avoidance test and a Y maze memory test; amyloid plaque was also reduced.

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