# Positive Phase III results of FTY720 (fingolimod) for multiple sclerosis

Preliminary results from the Efficacy and Safety of Fingolimod in Patients With Relapsing-Remitting Multiple Sclerosis (FREEDOMS) study, a 2-year, double-blind, placebo-controlled, Phase III clinical trial involving 1272 relapsing–remitting multiple sclerosis (MS) patients in 22 countries to assess the efficacy, safety and tolerability of oral FTY720 (fingolimod), have shown that the drug could reduce the MS relapse rates by 54–60% compared with placebo, and disability progression by 30–32%.

Multiple sclerosis is an autoimmune disease in which the immune system attacks the CNS. MS is one of the leading causes of neurological disability in young adults. The new drug FTY720 is a sphingosine 1-phosphate receptor modulator, and has the potential to be the first in this new drug class of MS therapies.

The FREEDOMS study is the second of three Phase III studies involving more than 4000 MS patients worldwide. Previous results from the 1-year Trial Assessing Injectable Interferon vs FTY720 Oral in RRMS (TRANSFORMS) study showed a significant reduction in relapse rates compared with IFN-$\beta_{1a}$, a standard of care for MS. The third study, FREEDOMS II, is currently ongoing.

> *"The positive results from the FREEDOMS study confirm the efficacy and safety of fingolimod, and provide important evidence of its effect on disability."*

"We are proud to have reached this critical milestone in the development of FTY720, a novel oral therapy that has the potential to transform the treatment of this ultimately disabling disease," said Trevor Mundel, Global Head of Development at Novartis Pharma AG (Basel, Switzerland). "FTY720 0.5-mg therapy offers compelling efficacy on all relevant end points compared with both placebo and a standard of care, complemented by extensive safety data."

The safety profile of FTY720 has been studied well, with more than 5300 patient-years of exposure, including patients now in their sixth year of treatment. In the FREEDOMS study, there were no cases of macular edema or melanoma at the 0.5-mg dose. Reversible and generally asymptomatic liver enzyme elevations were observed more frequently with FTY720 than placebo, and lung infections were also slightly more common. Mild elevation in blood pressure was observed with FTY720. Three patients died during the FREEDOMS study, one on a FTY720 higher dose (1.25 mg) and two on placebo. None of the deaths was related to the study drug.

> *"As an oral therapy, it is clear that fingolimod potentially represents a significant advance in the treatment of MS."*

"The positive results from the FREEDOMS study confirm the efficacy and safety of fingolimod, and provide important evidence of its effect on disability," said Ludwig Kappos, Chair of Neurology and Research Group Leader in the Department of Biomedicine at the University Hospital in Basel, Switzerland, and the principal investigator of the FREEDOMS study. "As an oral therapy, it is clear that fingolimod potentially represents a significant advance in the treatment of MS."

Future development of FTY720 in relapsing–remitting MS will focus on the 0.5-mg dose. Regulatory submissions of the drug are planned in the USA and EU at the end of 2009.

*Source: Novartis, Switzerland: www.novartis.com*

## in the news...



future medicine part of fsg

# Silent stroke risk could rise with hypertension

According to a new prospective population-based study, hypertension increases the risk of silent strokes, or lacunar infarct, by up to 60%.

The findings from the Prince of Wales Hospital in Sydney, Australia, have been published in *Neurology*, which also discusses the prevalence of other factors such as white matter hyperintense lesions on MRI and the ratio of anterior ventricle to brain volume.

The researchers noted that these so-called silent strokes "...are not truly silent, as they have been associated with cognitive deficits and their accumulation, or presence in strategic brain regions, has also been suggested as an important pathologic substrate of vascular dementia." The researchers hope that by finding a modifiable risk factor they could gain an insight into the prevention of cerebrovascular disease.

The group, led by Dr Sachdev, analyzed findings from the 60- to 64-year-old cohort of the larger prospective, longitudinal PATH Through Life Study.

A total of 477 participants in this cohort were recruited randomly from the compulsory electoral roll in two areas of Australia. Among other measurements, the study included two MRI brain scans carried out 4 years apart. Baseline results indicated that 7.8% had at least one lacunar infarct on MRI, at second MRI the prevalence rose to 8.8%.

Results indicated that those with lacunar infarcts were significantly more likely to have hypertension, as well as higher average systolic blood pressure and mean arterial pressure. However, the degree of hypertension did not appear to impact the volume of the lesions.

Infarcts present at both MRI scans grew significantly over the intervening 4 years, with a nonsignificant trend for correlation with age.

The group added, "although this was only demonstrated in a limited number of subjects … it may indicate a progressive process of atrophy in surrounding tissue of the lesion."

The authors concluded that "nonetheless, this study provides invaluable information on the healthy population in their 60s, which is the main target of primary prevention in vascular disease."

*Source: Chen X, Wen W, Anstey KJ, Sachdev PS: Prevalence, incidence, and risk factors of lacunar infarcts in a community sample.* Neurology *73, 266–272 (2009).*

# Benefits with sirolimus-eluting stents found to continue in MISSION! Intervention study

Researchers from Leiden University Medical Center (the Netherlands) have presented the 3-year outcomes of the MISSION! Intervention study at the recent European Society of Cardiology (ESC) Congress. They found that patients with ST-elevation myocardial infarction (STEMI) treated with sirolimus-eluting stents (SES) continued to experience benefits in terms of requiring significantly fewer target vessel revascularization procedures compared with those treated with bare-metal stents (BMS). However, this was at the cost of a higher incidence of very late stent thrombosis.

The MISSION! Intervention study was a single-blind, single-center, randomized study to compare the use of drug-eluting stents with BMS in the treatment of acute STEMI in terms of efficacy and safety. The study included 310 consecutive patients (age: 59 ± 11 years, 78% male), who were followed for a median of 38 months. A total of 158 patients received SES, with 152 receiving BMS. The clinical end points of the trial included: death, myocardial infarction, target vessel/lesion revascularization, target vessel failure (composite of all end points related to the target vessel) and stent thrombosis. The patients were treated with life-long aspirin and clopidogrel for 1 year after the stent was implanted.

After 3 years the researchers found that the cumulative incidence of cardiac death and myocardial infarction were similar between the SES- and BMS-treated patients. There was a slightly lower cumulative incidence of target vessel revascularization, target lesion revascularization and target vessel failure in the SES group. However, this advantage mainly occurred within the first year of treatment. Jael Z Atary, who presented the results at the ESC Congress said: "The SES benefit in STEMI patients occurred entirely within the first year". Rates of target vessel revascularization, death and nonfatal recurrent myocardial infarction were similar in the second and third years.

However, the cumulative incidence of definite stent thrombosis was higher in the SES group compared with the BMS group (4 vs 0.7%; p = 0.11), and was statistically significant for very late stent thrombosis (3.3 vs 0%; p = 0.05).

The researchers concluded that at 3 years the SES-treated patients continued to show a trend towards a favorable clinical outcome compared with the BMS-treated group.

*Source: Atary JZ, Van Der Hoeven BL, Liem SS* et al.*: Drug-eluting vs bare-metal stents for the treatment of ST-elevation myocardial infarction: three-year clinical outcome of the MISSION-Intervention study.* Eur. Heart J. *30(Abstract Suppl.), 676 (2009).*

# New biodegradable polymer stent found to be 'noninferior'

According to the results of the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST4) trial, a new type of stent coated with a rapamycin-eluting biodegradable polymer is noninferior to the two leading permanent polymer-based drug-eluting stent (DES) platforms. The trial represents the largest randomized study to date investigating the use of biodegradable polymer-based DES.

The primary end point of the trial was a composite of cardiac death, myocardial infarction related to the target vessel or revascularization related to the target lesion. This end point was met in 13.8% of patients treated with the biodegrable stent, compared with 14.4% for those treated with a permanent polymer stent.

The results were presented by Julinda Mehilli from the Technische University in Munich (Germany), who said: "This study shows the noninferiority of the biodegradable polymer compared with the permanent polymer DES, but the follow-up of 1 year is probably too short to reveal safety differences."

In an accompanying editorial in the *European Heart Journal*, Aron Kugelmass commented: "Despite the theoretical advantages of a biodegrable polymer, this report must be viewed only as an initial encouragement for this technology. It is naive to believe that a novel technologic breakthrough will be free of a yet to be determined new limitation". Mehilli commented that a further 2-year analysis is planned to investigate this technology further.

*Source: Mehilli J: Randomized trial of 3-limus agent-eluting stents with biodegradable or permanent polymer coating. ISAR-TEST-4 study. Presented at:* ESC Congress 2009. *29 August–2 September 2009, Barcelona, Spain (Prog. no.: 1852).*

# US FDA approves pitavastatin for combined dyslipidemia

The US FDA has recently approved the use of Livalo® (pitavastatin) for patients with hypercholesterolemia and combined dyslipidemia. The HMG-CoA reductase inhibitor (statin), developed by Kowa Pharmaceuticals (AL, USA), is expected to be launched in the USA during spring 2010.

Dyslipidemia is accepted to be one of the principal independent predictors of cardiovascular complications. Although several management possibilities exist, mainly dietary changes, physical exercise and lipid-lowering drugs, there is still a need for better control and treatment for dyslipidemia.

Kowa Pharmaceuticals America claim that the statin will "fill an unmet need for clinically complex patient populations". Antonio M Gotto Jr of Cornell University (NY, USA) comments, "Livalo has a robust safety, efficacy and tolerability profile, and offers an attractive alternative for patients with primary hypercholesterolemia or combined dyslipidemia." He continues, "Livalo has very positive attributes that will help continue to fill current unmet needs in the statin market for clinically complex patient populations, such as the elderly, patients with diabetes or patients who take multiple medications for comorbid conditions."

> *"Livalo has a robust safety, efficacy and tolerability profile, and offers an attractive alternative for patients with primary hypercholesterolemia or combined dyslipidemia."*

Livalo belongs to the family of statins, but differs in its unique cyclopropyl group on the base structure. The cyclopropyl group is suggested to allow more effective inhibition of the HMG-CoA reductase enzyme, as well as greater low-density lipoprotein cholesterol clearance. The drug's property of only being minimally metabolized through the cytochrome P4590 pathway by the liver makes it ideal for patients who take other medications.

Livalo is only just being launched in the USA, but is already being used in Japan, South Korea, Thailand and China, accruing many patient-years of exposure. Kowa Pharmaceuticals state that pitavastatin is frequently prescribed as first-line therapy for patients whose disease status is made more complex by concurrent illnesses and medication. In the Phase III trials that led to the FDA approval of Livalo, the statin successfully reduced low-density lipoprotein cholesterol and improved other lipid parameters in special patient populations. These included patients with diabetes, those at increased cardiovascular risk and the elderly. The trials demonstrated a similar safety and tolerability profile to other commonly prescribed statins.

Ben Stakely, CEO and President of Kowa Pharmaceuticals America, is very positive about the launch of pitavastatin in the USA. He states, "Kowa Pharmaceuticals America is very pleased with the approval of Livalo and is excited about the opportunity to introduce this new therapeutic option to physicians and patients."

*Source: www.kowapharma.com/PressReleases/news080209.htm*

**Drug approvals August to October 2009.**

| Trade name | Generic name | Indication | Region | Manufacturer | Date approved |
|---|---|---|---|---|---|
| ***Cardiology*** | | | | | |
| Fibricor™ | Fenofibric acid | To reduce triglyceride levels in patients with severe hypertriglyceridemia (> 500 mg/dl) and for the reduction of total cholesterol, low-density-lipoprotein cholesterol, triglyceride and apolipoprotein B and to increase high-density lipoprotein cholesterol in patients with primary hyperlipidemia or mixed dyslipidemia | USA | Mutual Pharmaceutical Company | August 2009 |
| Valturna® | Aliskiren and valsartan | For the treatment of high blood pressure in patients not adequately controlled on aliskiren or angiotensin receptor blocker monotherapy, and as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals | USA | Novartis | September 2009 |
| ***Dermatology*** | | | | | |
| Azzalure® | Botulinum toxin type A | For the temporary improvement in the appearance of moderate to severe glabellar lines seen at the frown (vertical lines between the eyebrows), in adult men and women aged 65 years and under, when the severity of these lines has an important psychological impact on the patient | Spain | Ipsen | September 2009 |
| Stelara™ | Ustekinumab | For adult patients 18 years or older with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy | USA | Centocor Ortho Biotech | September 2009 |
| Toctino® | Alitretinoin | For adults with severe chronic hand eczema unresponsive to potent topical corticosteroids | Switzerland | Basilea Pharmaceutica Ltd | October 2009 |
| Veregen® | Sinecatechins | For the treatment of genital warts | Germany | MediGene | September 2009 |
| ***Endocrinology & metabolism*** | | | | | |
| Januvia® | Sitagliptin | Type 2 diabetes | EU | Merck & Co | September 2009 |
| Oral-lyn™ | Oral insulin | Patients with serious or life-threatening Type 1 or 2 diabetes who have no satisfactory alternative therapy options for the condition, and who are not eligible to participate in the company's ongoing Phase III trial for the drug | USA | Generex | September 2009 |
| Zenpep™ | Pancrelipase | Exocrine pancreatic insufficiency due to cystic fibrosis or other conditions | USA | Eurand Pharmaceuticals | August 2009 |
| Onglyza™ | Saxagliptin | For adult patients with Type 2 diabetes mellitus to improve glycemic control | EU | Bristol-Myers-Squibb Company and AstraZeneca | October 2009 |
| Glucagen® | Recombinant glucagon for injection | For the treatment of severe hypoglycemia in diabetic patients being treated with insulin | Canada | Paladin Labs Inc. | September 2009 |
| Glucophage® | Metformin | An adjunct to diet and exercise to improve glycemic control in adults and children with Type 2 diabetes mellitus. | Switzerland | Aurobindo Pharma | September 2009 |

**Drug approvals August to October 2009 (cont.).**

| Trade name | Generic name | Indication | Region | Manufacturer | Date approved |
|---|---|---|---|---|---|
| ***Gastroenterology & hepatology*** | | | | | |
| Metozolv™ ODT | Metoclopramide hydrochloride | For relieving symptoms in adults with acute and recurrent diabetic gastroparesis and for short-term therapy (4–12 weeks) in adults with symptomatic, documented gastroesophageal reflux disease that fails to respond to conventional therapy | USA | Wilmington Pharmaceuticals | September 2009 |
| Welchol™ | Colesevelam hydrochloride | An adjunct to diet and exercise for the reduction of elevated low-density lipoprotein cholesterol in boys and postmenarchal girls, 10–17 years of age, with heterozygous familial hypercholesterolemia alone or in combination with a statin after failing an adequate trial of diet therapy | USA | Daiichi Sankyo | October 2009 |
| ***Immunology*** | | | | | |
| Astepro® | Azelastine HCl | For the symptoms of seasonal and perennial allergic rhinitis | USA | Meda Pharmaceuticals | September 2009 |
| Xyzal® | Levocetirizine dihydrochloride | For children aged 6 months and older for the relief of symptoms of perennial allergic rhinitis and chronic idiopathic urticaria (chronic hives) and for children aged 2 years and older for symptoms of seasonal allergic rhinitis | USA | UCB Pharma | August 2009 |
| Xolair® | Omalizumab | An add-on therapy for severe persistent allergic asthma in children aged 6–11 years | EU | Novartis | August 2009 |
| ***Infectious disease*** | | | | | |
| Hiberix vaccine | | For children aged 15 months through 4 years to prevent invasive disease caused by *Haemophilus influenzae* type B | USA | GlaxoSmithKline | August 2009 |
| Influenza A (H1N1) 2009 monovalent vaccine | | For active immunization of persons 6 months of age and older against influenza disease caused by pandemic (H1N1) 2009 virus | USA | Sanofi Pasteur | September 2009 |
| Valcyte® | Valganciclovir hydrochloride | Prevention of cytomegalovirus disease in pediatric kidney and heart transplant patients ≥4 months of age at high risk of developing cytomegalovirus | USA | Roche | August 2009 |
| Vibativ™ | Telavancin | For the treatment of complicated skin and skin-structure infections caused by susceptible Gram-positive bacteria | USA | Theravance | September 2009 |
| Kaletra™ | Lopinavir/ritonavir | For once-daily as well as twice-daily use in treatment-naïve patients in combination with other antiretroviral agents | EU | Abbott Laboratories | September 2009 |
| Isentress® | Raltegravir | For use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in adult patients, including adult patients starting HIV-1 therapy for the first time (treatment-naïve), as well as treatment-experienced adult patients. | EU | Merck Sharp & Dohme | September 2009 |

**Drug approvals August to October 2009 (cont.).**

| Trade name | Generic name | Indication | Region | Manufacturer | Date approved |
|---|---|---|---|---|---|
| ***Infectious disease (cont.)*** | | | | | |
| Vibativ™ | Telavancin | For the treatment of adult patients with complicated skin and skin-structure infections caused by susceptible Gram-positive bacteria | Canada | Theravance | October 2009 |
| Loramyc® | Miconazole | For the treatment of oropharyngeal candidiasis in immunocompromised patients (mainly cancer and AIDS patients) | Switzerland | BioAlliance Pharma | September 2009 |
| Pruri-Ex® | Pentamycin | For the treatment of all types of infectious vaginitis | Switzerland | Lumavita | August 2009 |
| ***Neurology*** | | | | | |
| DuraSeal™ | | Suturing for intra-operative dural sealing in spine procedures | USA | Covidien | September 2009 |
| Embeda™ | Morphine/naltrexone | For the management of moderate-to-severe chronic pain | USA | King | August 2009 |
| Extavia® | Interferon β-1b | Relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations | USA | Novartis | August 2009 |
| Intuniv™ | Guanfacine | Attention-deficit hyperactivity disorder in children and adolescents aged 6–17 years | USA | Shire | September 2009 |
| Sabril® | Vigabatrin | Monotherapy to treat infantile spasms in children aged 1 month to 2 years. | USA | Lundbeck | August 2009 |
| Saphris® | Asenapine | Acute treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults | USA | Schering-Plough | August 2009 |
| Seroquel® | Quetiapine fumarate | For the prevention of recurrence of bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment | EU | AstraZeneca | September 2009 |
| Seroquel XR® | Quetiapine fumarate extended-release tablets | For the prevention of recurrence of bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment | EU | AstraZeneca | September 2009 |
| ***Oncology*** | | | | | |
| Folotyn™ | Pralatrexate injection | For use as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma | USA | Allos Therapeutics | September 2009 |
| Zevalin® | Ibritumomab | For patients with previously untreated follicular non-Hodgkin's lymphoma who achieve a partial or complete response to first-line chemotherapy | USA | Spectrum | September 2009 |
| MabThera® | Rituximab | For use in patients with relapsed or refractory chronic lymphocytic leukemia | EU | Roche | September 2009 |
| Torisel® | Temsirolimus | For the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma. Also indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors | EU | Wyeth Europa | August 2009 |
| Mabthera® | Rituximab | For relapsed and difficult-to-treat (refractory) patients with chronic lymphocytic leukemia | UK | Roche | October 2009 |

**Drug approvals August to October 2009 (cont.).**

| Trade name | Generic name | Indication | Region | Manufacturer | Date approved |
|---|---|---|---|---|---|
| ***Rheumatology*** | | | | | |
| Monovisc™ | Sodium hyaluronate | For the treatment of osteoarthritis of the knee | USA | Anika Therapeutics | August 2009 |
| Xiaflex™ | Collagenase clostridium histolyticum | For the treatment of Dupuytren's disease | USA | BioSpecifics Technologies | September 2009 |
| Cimzia® | Certolizumab pegol | For the treatment of adult patients with moderately to severely active rheumatoid arthritis | EU | Enzon Pharmaceuticals/ UCB | October 2009 |
| Simponi™ | Golimumab | For use in combination with methotrexate, for the treatment of moderate-to-severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate. Also for use alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. For the treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy | EU | Centocor Ortho Biotech and Schering-Plough | October 2009 |
| ***Opthalmology*** | | | | | |
| Bepreve™ | Bepotastine besilate ophthalmic solution | For ocular itching associated with allergic conjunctivitis in patients 2 years of age and older | USA | Ista Pharmaceuticals | September 2009 |
| Zirgan™ | Ganciclovir ophthalmic gel 0.15% | Acute herpetic keratitis | USA | Sirion Therapeutics | September 2009 |
| ***Other*** | | | | | |
| Berinert® | C1-esterase inhibitor | For adults and adolescents with hereditary angioedema, which can occur spontaneously or during stress, surgery or infection in patients diagnosed with hereditary angioedema | USA | CSL Behring | October 2009 |
| Helixate® FS | Antihemophilic factor (recombinant) | For routine prophylaxis in children with hemophilia A who are 16 years old or younger and do not have pre-existing joint damage | USA | CSL Behring | August 2009 |
| Mirena® | Levonorgestrel-releasing intrauterine system | For the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception | USA | Bayer HealthCare | October 2009 |
| Renvela® | Sevelamer carbonate | For the control of serum phosphorus in patients with chronic kidney disease on dialysis | USA | Genzyme | August 2009 |