Clin. Invest. (2012) 2(11), 1057–1060

CLINICAL INVESTIGATION

NEWS

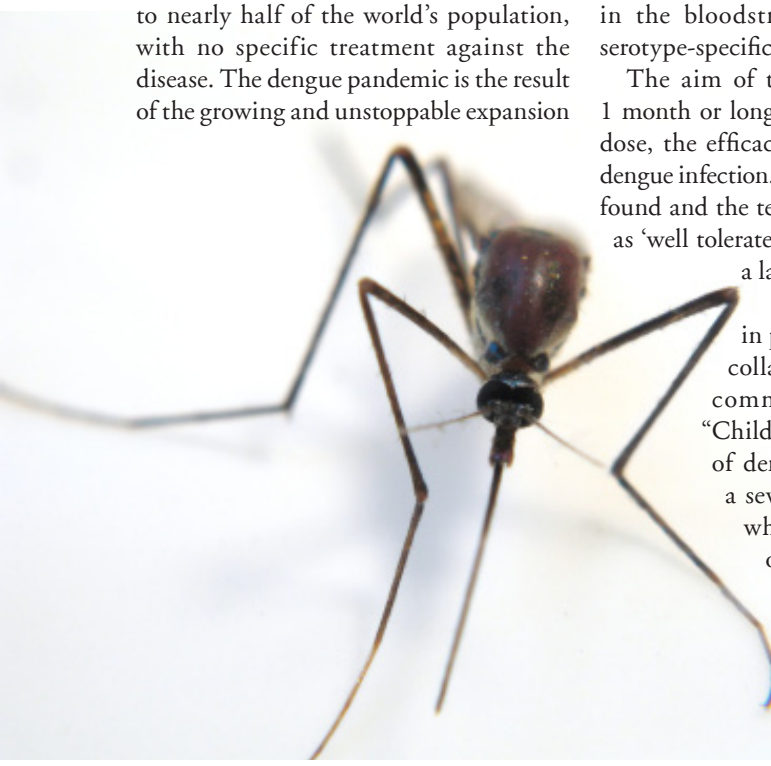
Highlights from the latest news and research in clinical investigation

Results published on Phase II clinical trial for dengue vaccine

A group of scientists has recently published results on a Phase II trial of a vaccine against dengue fever. Published in *The Lancet*, the results indicate for the first time the possibility of a vaccine against this prevalent disease.

Dengue fever is a viral infection prevalent in many tropical and subtropical regions of the world. The virus is transmitted by several species of the *Ades* mosquito, and causes a fever – ranging from mild to severe – that can lead to dengue hemorrhagic fever, a potentially lethal condition.

Speaking exclusively to *Clinical Investigation*, one of the authors of the study, Derek Wallace (Sanofi Pasteur, Singapore) explained the importance of finding such a vaccine: "Dengue is a threat to nearly half of the world's population, with no specific treatment against the disease. The dengue pandemic is the result of the growing and unstoppable expansion of dengue-transmitting mosquitoes (mainly *Aedes Aegypti* and *Aedes Albopictus*) worldwide due to urbanization and global warming and resistance to insecticides. The consensus by public health experts is that dengue vaccination is essential to effectively control the disease."



The vaccine candidate studied was a recombinant, live-attenuated vaccine – the 'CYD tetravalent dengue vaccine'. The vaccine was tested in a Phase II, observer-masked, randomized, controlled, monocenter, proof-of-concept trial. A total of 4002 healthy Thai schoolchildren aged 4–11 years were given either vaccine or placebo at 0, 6 and 12 months; and patients were followed until month 25. The presence of dengue vaccine in the bloodstream was measured by serotype-specific RT-PCR and ELISA.

The aim of the study was to assess, 1 month or longer after the final vaccine dose, the efficacy of the vaccine against dengue infection. An efficacy of 30.2% was found and the team describes the vaccine as 'well tolerated' with no indications of a lack of safety.

Wallace explained that in preparation for the study, collaboration with the local community was essential: "Children are especially at risk of dengue hemorrhagic fever, a severe form of the disease, which is a leading cause of hospitalization. The study was conducted in partnership with the Mahidol University, under the patronage of the Ministry of Public Health." He continued to explain that "Sanofi Pasteur has been collaborating with Thai Mahidol University for the development of a dengue vaccine since 1993."

The work studying this vaccine continues, with Phase III trials ongoing in ten countries in Asia and South America. Wallace explained that over 31,000 volunteers are involved in these studies, and that "they will be important to document efficacy of the dengue vaccine candidate in a broader population and different epidemiological environments. Upon successful completion of these studies the vaccine could be available in 2015 in countries where dengue is a public health priority."

Wallace described how the team aims to support the control group in these studies: "Sanofi Pasteur, the Mahidol and the Minister of Public Health are committed to offering dengue vaccination free of charge to the control group as soon as the vaccine is licensed in Thailand."

In addition to a safe and effective vaccine against the disease, other measures will need to be put in place to combat the spread of the disease. Wallace describes that following introduction of the vaccine into common use: "Dengue vaccination and vector-control measures will cohabit for maximum efficiency."

– Written by Alice O'Hare

Sources: WHO health topics; Dengue: www.who.int/topics/dengue/en/; Sabchareon A, Wallace D, Sirivichayakul C *et al.* Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled Phase 2b trial. *Lancet* doi:10.1016/S0140–6736(12)61428–7 (2012) (Epub ahead of print).

ISSN 2041-6792 10.4155/CLI.12.118

Chlorthalidone found to be more effective than hydrochlorothiazide when used in combination with azilsartan medoxomil to combat hypertension

Researchers in the USA, lead by a team from the University of Chicago Medicine (IL, USA) have compared the antihypertensives chlorthalidone and hydrochlorothiazide when used in combination with azilsartan medoxomil in a study published in *The American Journal of Medicine*. Chlorthalidone has been well documented as an effective method of blood pressure reduction but remains infrequently used in practice.

The researchers carried out a randomized, double-blind, titrate-to-target blood pressure trial comparing blood pressure reductions. The study consisted of 609 patients with stage 2 primary hypertension receiving either a single-pill combination of azilsartan medoxomil-chlorthalidone or azilsartan medoxomil coadministered with hydrochlorothiazide. For the first 2 weeks of the trial, patients received 40 mg azilsartan medoxomil alone. A 12.5 mg dose of either chlorthalidone or hydrochlorothiazide was added for the following 4 weeks. Any patients failing to reach their target blood pressure (defined as clinical blood pressure <140/90 mmHg for patients with diabetes or chronic kidney disease and <130/80 mmHg for those without such conditions) were titrated up to 25 mg until the end of the trial at week 10.

Evaluation of primary end-point data showed a statistically significant reduction in measured systolic blood pressure at week 6 in patients taking the chlorthalidone in combination with azilsartan medoxomil compared with those treated with hydrochlorothiazide combined with azilsartan medoxomil. Furthermore, patients undergoing treatment including chlorthalidone instead of hydrochlorothiazide were found to maintain a greater reduction in blood pressure through to week 10.

George Bakris (University of Chicago Medicine) has outlined the significance of his group's work stating, "this is the first head-to-head study to demonstrate a single-pill combination of an angiotensin receptor blocker (ARB) with chlorthalidone showing superiority over the same ARB combined with hydroclorothiazide. It demonstrates that using a diuretic coupled with an ARB, such as azilsartan, is the best diuretic combination that is available for blood pressure lowering."

Chlorthalidone combined with azilsartan medoxomil was found to achieve superior blood pressure reduction and an increased chance of achieving target blood pressure at no observable safety risk. Bakris has described the impact this study could have on favored treatment choices for those with hypertension; "Clinicians who have patients not at their goal blood pressure should substitute chlorthalidone for hydrochlorothiazide first, and if hypertension remains, should stop the ARB inhibitor being used and change to azilsartan. The likelihood of achieving target blood pressure (with such a treatment regime) is much better than with conventional diuretic combinations."

– Written by Hannah Wilson

Source: Bakris GL, Sica D, White WB *et al.* Antihypertensive efficacy of hydrochlorothiazide versus chlorthalidone combined with azilsartan medoxomil. *Am. J. Med.* doi:10.1016/j.amjmed.2012.05.023 (2012) (Epub ahead of print).

Aubagio® approved by US FDA

In a recent press release, the US FDA has announced its decision to approve Aubagio® (Teriflunomide) for the treatment of relapsing multiple sclerosis.

Multiple sclerosis is a chronic condition of the CNS that causes disrupted communication between the brain and other parts of the body. The disease is caused by inflammation within the CNS, believed to be caused by an autoimmune response. Aubagio is thought to work by blocking this autoimmune response, through blocking T and B lymphocytes.

The approval was based on efficacy data from the Phase III TEMSO trial; where Aubagio was compared with a placebo and shown to "significantly reduce annualized relapse rate and the time to disability progression" over 2 years.

Mark Freeman, *Clinical Investigation* editorial board member and director of the multiple sclerosis research unit at the Ottawa Hospital Research Institute (Ottawa, Canada), spoke about the impact this would have on future treatment for this condition, explaining that it "adds a new safe and effective oral medication to the 'tool chest' – one that can be chosen first line as an alternative to today's injectable therapies." He explained that the approval of the drug "offers an oral alternative to the injectables with comparable efficacy but clearly added convenience of a once-daily medication that has few to any symptomatic side effects."

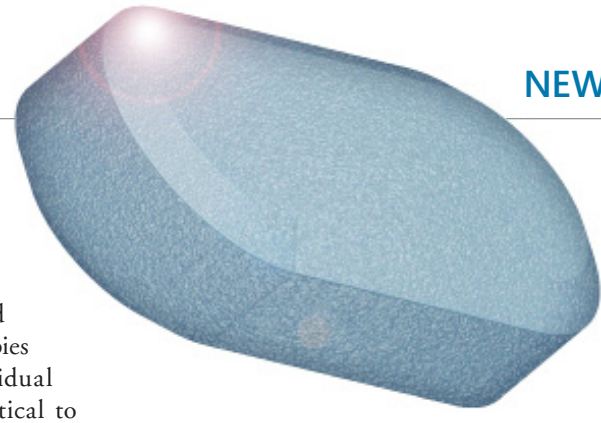
Freeman went on to explain that although "there is no real long-term safety data beyond clinical trial MS patients, if you add the very long-term data of its parent drug leflunomide used for rheumatoid arthritis, it reinforces the safety of the drug."

Aubagio is marketed by Sanofi-Aventis, and will be dispensed with a boxed warning of the potential side effects of the drug; including a risk of liver problems and a risk of birth defects. The therapeutic is labeled as 'Pregnancy Category X', meaning that prior to treatment, all women of child-bearing age must not be pregnant and in addition, be using effective birth control.

– Written by Alice O'Hare

Sources: Genzyme Press Release: http://en.sanofi.com/Images/31109_20120912_AUBAGIO-FDA-Approval_en.pdf; US FDA Press Release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm319277.htm

Novel HIV-1 treatment Stribild™ gains regulatory approval



Gilead Sciences, Inc. (CA, USA) have announced that the US FDA has approved Stribild™, a once-daily, single-tablet regimen for treatment-naive adults with HIV-1 infection.

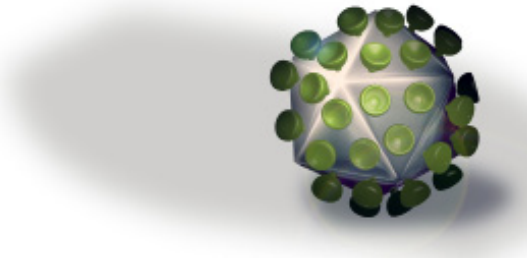
A novel comprehensive treatment has recently been approved by the FDA for patients with HIV who have not previously been treated for the infection. Stribild, previously known as 'Quad' prior to FDA approval, combines four compounds in a single daily tablet (elvitegravir 150 mg, an integrase inhibitor; cobicistat 150 mg, a pharmacoenhancing agent; emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) to form a comprehensive treatment regimen for HIV-infected individuals.

The single tablet regimen met its primary objectives of noninferiority compared with Atripla® (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) and ritonavir-boosted atazanavir plus Truvada® (emtricitabine/tenofovir disoproxil fumarate) in Gilead studies 102 and 103, respectively. At the end of the studies, 88–90% of individuals in the groups dosed with Stribild had an undetectable level of HIV in their blood. The data from these two pivotal, double-blind, 48-week, Phase III studies were crucial in the decision for the FDA approval of Stribild.

John Martin, Chairman and Chief Executive Officer of Gilead Sciences, commented "For much of the company's 25-year history, Gilead has focused on the development of improved treatments and simplified regimens for HIV. Therapies that address the individual needs of patients are critical to enhancing adherence and increasing the potential for treatment success, and we are proud to introduce a new single-tablet regimen for the healthcare and patient communities."

The approval of Stribild means that Gilead now has another single-tablet HIV regimens to have gained FDA approval to add to its two existing drugs; Atripla, approved in 2006, and Complera® (combining Truvada and rilpivirine), approved in 2011. Stribild is their first single-tablet regimen to contain an integrase inhibitor, elvitegravir, which interferes with HIV replication. Elvitegravir blocks the ability of the virus to integrate into the genetic material of human cells, therefore preventing the spread of the virus. The tablet also contains cobicistat, a pharmacoenhancing agent that facilitates once-daily dosing of elvitegravir by inhibiting cytochrome P450 3A, an enzyme responsible for metabolizing elvitegravir in the body.

While not a cure, Stribild is seen as a much-anticipated alternative treatment for HIV-1 infection compared with some current treatments owing to its limited side-effect profile, with most adverse events in the studies recorded as mild-to-moderate. The main side effects noted are; lactic acidosis, severe hepatomegaly with steatosis and post-treatment acute exacerbation of hepatitis B.



Paul Sax, Professor of Medicine at Harvard Medical School (MA, USA) and principal investigator of one of the Stribild studies, concluded "Over the past decade, coformulated HIV medicines have simplified therapy for many patients and have become standard of care. Today's approval of Stribild will provide physicians and their patients an effective new single-tablet treatment option for individuals starting HIV therapy for the first time."

– Written by Sophie Breeze

Source: Gilead Press Release: www.gilead.com/pr_1728981

Phase III trial commences in frontotemporal dementia

TauRx Therapeutics (Aberdeen, UK) has announced that a global, double-blind, placebo-controlled Phase III trial is due to start imminently to investigate the safety and efficacy of LMTX® in an early-onset type of frontotemporal dementia (FTD) known as Pick's Disease. The frontal and temporal lobes are the first to be affected in FTD, causing changes in emotion and behavior, and the disease eventually results in a global dementia as it progresses and affects other areas of the brain. Neurodegenerative diseases such as dementia are a growing concern globally, as there are currently very few effective treatments.

The type of dementia to be studied in the trial is known as behavioral-variant FTD, which causes changes in personality such as emotional blunting and loss of empathy, and is most often characterized by abnormal aggregations of tau protein. LMTX, a second-generation tau-aggregation inhibitor, is believed to act by halting the self-perpetuating formation of tau-protein aggregates, which are responsible for nerve cell death, and releasing trapped tau protein so that it can be cleared safely. The development of LMTX was based on a new approach targeting abnormal tau-protein aggregates inside nerve cells in the brain.

LMTX has arrested the progression of the disease in previous pilot cases and has also shown promising results against Alzheimer's disease in Phase II

trials. Claude Wischik, CEO of TauRx Therapeutics and Professor of Old Age Psychiatry at the University of Aberdeen, commented on the trial's commencement, "We are building on over 30 years of research, and the encouraging results from our previous Phase II clinical trial in Alzheimer's Disease, which is also correlated with abnormal tau aggregates in the brain. This is an important step forward in our quest to find an effective treatment, with a goal to actually arrest the progression of the disease."

The research team at TauRx Therapeutics has also discovered that LMTX seems to be able to prevent abnormal aggregations of other proteins forming in the brain, such as TDP-43, another protein implicated in FTD, and synuclein, which is implicated in the progression of Parkinson's disease. If this trial is successful, LMTX will be the first investigational drug that has demonstrated the ability to halt the progression of FTD.

– Written by Sophie Breeze

Source: TauRx Press Release: www.taurx.com/pdfs/FINAL%20TauRx%20FTD%20Press%20Release%20Updated%2010Sep2012.pdf

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:
Isaac Bruce,
Managing Commissioning Editor, *Clinical Investigation*
Tel.: +44 (0)20 8371 6090
E-mail: i.bruce@future-science.com