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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Linagliptin tablets first to receive US FDA approval at one dosage strength for Type 2 diabetes treatment

The US FDA has announced the approval of linagliptin tablets, developed by a collaboration between Boehringer Ingelheim an d Eli Lilly and Co., for the treatment of Type 2 diabetes either as a monotherapy or in combination with other medications. This approval follows clinical trial results, which demonstrated linagliptin tablets as significantly reducing hamoglobin A1c (HbA1c or A1c) levels, an indicator of blood sugar control, by an average of up to 0.7% when compared with placebo.

Linagliptin, an oral hypoglycemic that falls in the subclass of dipeptidyl peptidase-4 (DPP-4) inhibitors, is the first of this subclass of drugs to receive regulatory approval at one dosage strength, approved at 5 mg once daily. This means that no alteration of dose need occur in the treatment of patients with kidney or liver impairments. John Gerich, an expert in diabetes at the of the University of Rochester (NY, USA) comments exclusively to *Clinical Investigation* on the significance of the recent FDA decision: "The recent approval of linagliptin by the FDA is quite important for people with Type 2 diabetes because it gives them another therapeutic option". He continues, highlighting how the approval could impact on ease of treatment for sufferers, "monotherapy with linagliptin will aid compliance because of its ease of use. No titration is required; the medication is once daily and can be taken any time of day with or without meals. Finally, it is the only DPP-4 inhibitor for which no dose adjustment is recommended in patients with impaired renal function and no prior testing and subsequent monitoring of renal function is recommended".

The clinical studies that preceded approval consisted of three separate placebo-controlled studies involving approximately 4000 adult patients with Type 2 diabetes and assessed linagliptin as a monotherapy, as well as in combination with common antihyperglycamic therapies metformin and suphonylurea [1-3]. HbA1c levels in participants were meaused as an indicator of blood-sugar control in diabetes patients taking antihyperglycemic medication. As a monotherapy, linagliptin showed an average difference in HbA1c levels of up to 0.7%. In combination with metformin or metformin and sulfonylurea, linagliptin demonstrated a difference in blood levels of HbA1c 0.6% when compared with placebo. Following on from this, in a further study, the combination of linagliptin and pioglitazone, another hypoglycemic therapy, was compared with pioglitazone administered with placebo [4]. The average HbA1c observed in the linagliptin and pioglitazone arm was 0.5% lower than that observed in the and pioglitazone placebo arm.

Boehringer Ingelheim and Eli Lilly and Co., launched a diabetes alliance in January 2011, making this FDA approval the first regulatory milestone since its inception. Klaus Dugi of Boehringer Ingelheim comments: "Type 2 diabetes is increasing at an alarming rate and we are proud to offer people in the USA a new treatment option from our Boehringer Ingelheim research laboratories that could potentially help the millions of patients with Type 2 diabetes whose blood sugar is not adequately controlled". Enrique Conterno, of Lilly Diabetes, continues "Linagliptin is the first regulatory approval of what we hope will be many new treatment options this alliance brings to the millions of people living with Type 2 diabetes"

Sources: Del Prato S, Barnett AH, Huisman H *et al.* Effect of linagliptin monotherapy on glycemic control and markers of β-cell function in patients with inadequately controlled Type 2 diabetes: a randomized controlled trial. *Diabetes Obes. Metab.* 13(3), 258–267 (2011); Taskinen MR, Rosenstock J, Tamminen I *et al.* Safety and efficacy of linagliptin as add-on therapy to metformin in patients with Type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes. Metab.* 13(1), 65–74 (2011); Owens DR, Swallow R, Woerle HJ *et al.* Linagliptin improves glycemic control in Type 2 diabetes patients inadequately controlled by metformin and sulfonylurea without weight gain and low risk of hypoglycemia. Presented at: *The 70th American Diabetes Association Scientific Sessions.* Orlando, FL, USA, 25–29 June 2010; Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled Type 2 diabetes: a randomized, double-blind, placebo controlled study. *Diabetes Obes. Metab.* 13(7), 653–661 (2011); FDA approves linagliptin tablets for the treatment of Type 2 diabetes: www.boehringer-ingelheim.com/news/news_releases/press_releases/2011/03_may_2011_diabetes.html

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Clinical trials: (a)head in the clouds

A white paper has recently been published on the back of a 2010 pilot study, detailing how innovative technology such as digital signatures and 'cloud computing' could accelerate the start of the clinical trial process, as well as lowering its costs. The study, which highlights how modern digital technology could aid drug development by facilitating the clinical trial process, involves scientists from industry and regulatory bodies, such as the NCI Cancer Therapy Evaluation Program, Bristol-Myers Squibb and Sanofi.

The researchers used interoperable digital identities, signatures and cloud computing, a form of secure, shared storage for digital data, to replace traditional hard copy paper versions of the forms and documents needed in the clinical trial process. The preliminary results demonstrated that a reduced reliance on these paper forms meant, not only time and cost saving from an administrative perspective, but that employing a 'paperless' strategy, as well as improving security and environmental impact, may also improve the delivery of therapies to patients.

> "The preliminary results demonstrated that a reduced reliance on these paper forms meant, not only time and cost saving ... but ... may also improve the delivery of therapies to patients."

The clinical trial process is typically delayed owing to physical documents, necessitating a signature and thus having to be sent through the post, by courier or fax. To counteract this, the researchers used 'interoperable digital identity credentials', a type of software that can run on devices such as computers and mobile phones, and acts to link the (proven) identity of the person using the device to the electronic document in question, allowing digital, legally binding signatures to be applied. These electronic documents were then placed in the 'cloud', allowing the researchers to gain access to them for further signatures or information.

The pilot study is to expand, aiming to include other researchers in industry and government bodies, as well as university-based academics, and could prove to alter the landscape of clinical trial administration.

Sources: Innovative paperless clinical trial study white paper now available: www.medicalnewstoday.com/articles/223622.php; White paper download: www.safe-biopharma.org/whitepaperform.htm

Results from the Phase III ORAL Standard and ORAL Step studies demonstrate promise for tofacitinib as a treatment of rheumatoid arthritis

Pfizer have announced top-line results from two pivotal Phase III studies of its investigational, novel oral JAK inhibitor, tofacitinib. Both the ORAL Standard and ORAL Step studies met their primary end points and demonstrated no new safety concerns regarding the use of tofacitinib in patients with active rheumatoid arthritis (RA). ORAL Standard and ORAL Step are the final two pivotal trials in a program designed by Pfizer to study tofacitinib for RA. The program consists of five pivotal trials and a sixth long-term treatment study, carried out at >350 locations in 35 countries worldwide.

The 12-month ORAL Standard trial enrolled 717 patients with moderate-to-severe active RA who had an inadequate response to methotrexate (MTX). Patients were randomized to receive tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously biweekly or placebo, each of which was added to stable background MTX. All primary end points of the study were met, demonstrating statistically significant changes versus placebo in reducing the signs and symptoms of RA, as measured by ACR20 response rates at 6 months, in improving physical function, as measured by mean change in HAQ DI at 3 months; and in reaching DAS28-4(ESR) <2.6 at 6 months.

The ORAL Step study was conducted over a 6-month period and enrolled 399 patients with moderate-to-severe active RA who had an inadequate response to a TNF inhibitor. Patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, which were added to stable background MTX. As with the ORAL Standard study, all primary end points of the ORAL Step were met, at both the 5 and 10 mg twice-daily doses. Tofacitinib demonstrated statistically significant changes versus placebo in reducing signs and symptoms of RA, as measured by ACR20 response rates; in improving physical function, as measured by mean change in HAQ DI; and in reaching DAS28-4(ESR) <2.6, all assessed at 3 months.

A more detailed analysis of the ORAL Standard and ORAL Step efficacy and safety data is likely to be presented at a scientific meeting in the near future.

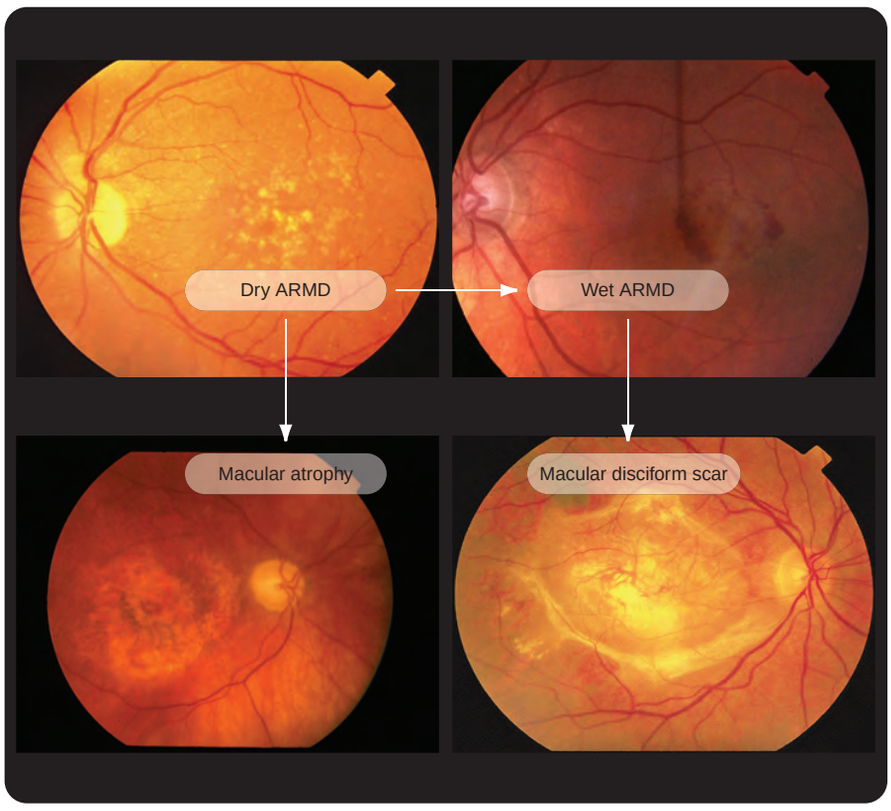
Source: Pfizer announces top-line results of final two pivotal Phase III trials of tofacitinib (CP-690550) in patients with active rheumatoid arthritis: www.pfizer.com/news/press_releases/pfizer_press_releases.jsp#guid=20110428005895en&source=RSS_2011&page=1

Comparison trial reveals bevacizumab to be as effective as ranibizumab for treating age-related macular degeneration

A recent study, published in the *New England Journal of Medicine*, has been hailed as wonderful news by scientists at the University of Wisconsin School of Medicine (WI, USA) researching age-related macular degeneration (ARMD). The study, part of the Comparison of ARMD Treatments Trials (CATT), compared ranibizumab (Lucentis®), an FDA-approved therapy for ARMD, with bevacizumab (Avastin®), a common therapy for colorectal cancer that is used off-label to treat ARMD, and demonstrated both drugs to have equivalent effectiveness when administered in the same way. The news is being greeted with much enthusiasm as, while the drugs demonstrate similar efficacy, they have very different prices. The cancer therapy bevacizumab costs approximately US$50 per dose, in comparison to ranibizumab, which comes in at roughly four-times the price.

Suresh Chandra, leader of the University of Wisconsin School of Medicine-Madison Center of Clinical Trials, comments "this is wonderful, it could result in billions of savings for the Medicare program". He continues, highlighting how the reduction in financial burden of ARMD treatment could help healthcare in less developed countries, "it also has important implications for patients in developing countries where they just can't afford Lucentis."

Bevacizumab, which was approved by the FDA for the treatment of metastatic colon cancer in 2004, was developed as a cancer therapy by Genentech to arrest the growth of blood vessels supplying tumors. Genentech also developed ranibizumab, which has been shown to be effective for the treatment of ARMD, from a protein with similarities to bevacizumab. Prior to ranibizumab being available commercially, bevacizumab was used off-label by ophthalmologists in the treatment of ARMD patients, despite the absence of supporting data.



The CATT were launched in 2008 by the National Eye Institute in order to compare the effectiveness of bevacizumab and ranibizumab. A total of 1208 patients with neovascular ARMD were enrolled in the multicenter, single-blind, noninferiority trial and randomized to receive intravitreal injections of either ranibizumab or bevacizumab. Injections were on a monthly basis, or as needed following monthly evaluation. The primary end point was the average change in visual acuity after 1 year, measured by letters gained on an eye-chart test. The results so far demonstrate that improvements in visual acuity are virtually equivalent for either drug for monthly and as-needed doses, with the improvements being within one letter on the eye chart. The study did, however, highlight a difference in the rate of severe adverse events – bevacizumab treatment having a greater risk of an event compared with ranibizumab. These events were observed in disease categories that had not been highlighted as potential risk factors in previous studies

The researchers will follow the participants for another year to elucidate long-term effects of both therapies, as well as studying the difference in the rates of serious adverse events.

Sources: The CATT Research Group, Martin DF, Maguire MG *et al.* Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* 364(20), 1897–1908 (2011); Avastin works well against age-related macular degeneration: www.med.wisc.edu/news-events/news/avastin-works-well-against-age-related-macular-degeneration/31287

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact: Joanne Walker, Commissioning Editor, *Clinical Investigation* Tel.: +44 (0)20 8371 6080; j.walker@future-science.com