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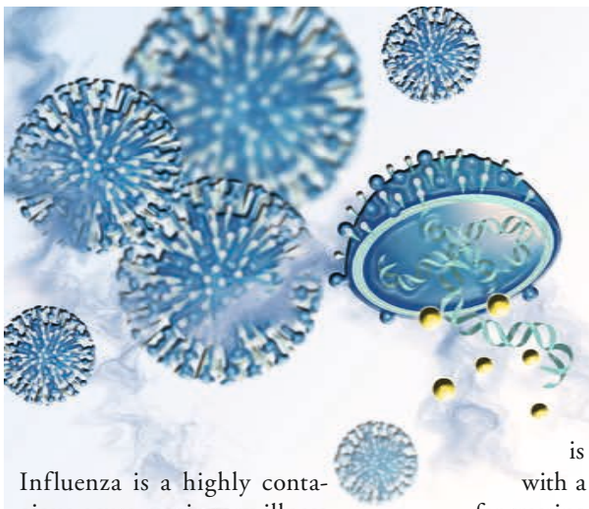
CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation



Promising results for new influenza drug presented at the Infectious Diseases Society of America Annual Meeting

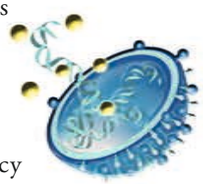
Romark Laboratories, a pharmaceutical company based in Tampa (FL, USA), have announced positive trial results of its new flu drug NT-300 (nitazoxanide), showing that it can significantly reduce the time from treatment to the alleviation of flu symptoms.

Influenza is a highly contagious acute respiratory illness, caused by viruses such as the new H1N1 influenza. The illness affects all age groups and can lead to several complications, including sinusitis, otitis, bronchitis, pneumonia and CNS disease. In the USA alone, influenza is responsible for approximately 36,000 deaths and 216,000 hospitalizations per year.

In 1999, two classes of drugs for treating flu have were by the US FDA: the neuraminidase inhibitors, oral Tamiflu® (oseltamivir) and inhaled Relenza® (zanamivir) and the older M2 inhibitors, amantadine and rimantadine, which are now showing resistence. There has not been a new class of drugs approved for treating influenza since.

NT-300 is a new investigational drug. It is an oral controlled-release tablet containing 300 mg of nitazoxanide (NTZ) as the active ingredient, a new class of small-molecule immunomodulatory drug called thiazolides. Now, several communications presented at the 49th Annual Meeting of the Infectious Diseases Society of America (MA, USA), have announced promising results in the clinical development of NT-300. Jean-Francois Rossignol, Chairman and Chief Science Officer of Romark, explained the significance of the work, "there is an urgent need for a new drug with a different mechanism of action for treating influenza."

One communication presented results of a Phase II trial, which enrolled 624 patients, between 12 and 65 years of age, at 74 outpatient primary care centers throughout the USA during the 2010–2011 flu season. Approximately half of the influenza-infected patients enrolled were infected with influenza A subtype H1N1 ('swine flu') the remaining 30% and 20% of patients were infected with influenza B and influenza A subtype H3N2, respectively.



The primary efficacy end point of the study was time from first dose to alleviation of symptoms (all symptoms absent or mild and remain so for 24 h). The trial achieved its primary end point, with results showing that influenza-infected patients treated with NT-300 administered 600 mg twice daily for 5 days, compared with influenza-infected patients receiving the placebo, experienced a statistically significant reduction in time from beginning treated to the alleviation of flu symptoms ($p = 0.008$). Median time to alleviation of symptoms was 95.5 h, 109.1 h and 116.7 h for the 600 mg, 300 mg and placebo dose group, respectively.

Two other communications also presented data from Phase II clinical trials conducted at a single center in Cajamarca (Peru). This included results from a pediatric trial, enrolling 100 children aged 1–11 years, and an adults and adolescents trial, enrolling 86 patients age 12–65 years. Patients in the pediatric trial received NTZ 100 mg (age 12–47 months), NTZ 200 mg (age 4–11 years) or placebo twice daily, for 5 days as an oral suspension. Patients enrolled in the adults and adolescents trial received NTZ 500 mg or placebo twice daily, for 5 days as an oral tablet.

The primary efficacy end point in these trials was also that of time from first dose to alleviation of symptoms. In each of the two trials, treatment with NTZ was associated with a statistically significant reduction in duration of symptoms compared with the placebo; in the pediatric study median time from first dose to alleviation of symptoms was 4 days for the NTZ treatment group, compared with >7 days for the placebo treatment group ($p < 0.0001$); in the adults and adolescents study, median time from first dose to alleviation of symptoms was 4 days, compared with 7 days for the placebo treatment group ($p = 0.037$).

In light of the positive results, Romark announced plans to initiate a Phase III

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clinical trial of NT-300 during the coming flu season, with the aim to seek FDA approval to market NT-300 for treatment of acute uncomplicated influenza.

News story written by Ruth Williamson, Assistant Commissioning Editor. Sources: Lopez-Chegne N, Julcamoro L, Carrion M, Rossignol J-F, Bardin M. Randomized, double-blind, pilot study of nitazoxanide (NTZ) versus placebo (PCB) for the treatment of symptoms associated with viral respiratory infection (VRI) in adults and adolescents. Presentation at: *Infectious Diseases Society of America*. Boston, MA, USA, 20–23 October 2011; Lopez-Chegne N, Julcamoro L, Carrion M, Rossignol J-F, Bardin M. Randomized, double-blind, pilot study of nitazoxanide (NTZ) versus placebo (PCB) for the treatment of symptoms associated with viral respiratory infection (VRI) in Children. Presentation at: *Infectious Diseases Society of America*. Boston, MA, USA, 20–23 October 2011; Rossignol J-F, Samudrala S, Hoppers M et al. A randomized, double-blind, placebo (PCB) controlled study of nitazoxanide (NTZ) in adults and adolescents with acute uncomplicated influenza. Presentation at: *Infectious Diseases Society of America*. Boston, MA, USA, 20–23 October 2011; Romark announces clinical trial results for new influenza drug presented at IDSA meeting 2011: www.romark.com/news/46-romark-announces-clinical-trial-results-for-new-influenza-drug-presented-at-idsa-meeting-2011

Fixed dose combination treatment Juvisync® approved by the US FDA

Juvisync®, a fixed dose combination medication combining sitagliptin and simvastin, has recently been approved by the US FDA for the treatment of Type 2 diabetes and high cholesterol.

Individuals suffering from Type 2 diabetes often also suffer from high cholesterol, and the combination of these two conditions can lead to severe health risks, including increased risk of heart disease and stroke.

Sitagliptin is a previously approved medicine prescribed for the treatment of Type 2 diabetes. The drug is a dipeptidyle peptidase 4 inhibitor approved for treatment regimens combined with improved diet and exercise, and enhances the body's ability to reduce an elevated blood sugar level. Simvastatin is a statin designed to reduce the amount of low density lipoprotein cholesterol in the blood, when combined with a diet and exercise regime.

Juvisync represents the first product to combine treatments for these commonly co-existing medical problems. The newly approved medication allows patients to receive effective treatment in just one tablet, rather than taking two separate ones.

The director of the Division of Metabolism and Endocrinology Products at the FDA Centre for Drug Evaluation and Research, Mary H Parks, is enthusiastic about the new product, commenting, "this is the first product to combine a Type 2 diabetes drug with a cholesterol lowering drug in one tablet. However, to ensure safe and effective use of this product, tablets containing different doses of sitagliptin and simvastatin in fixed-dose combination have been developed to meet the different needs of individual patients. Dose selection should factor in what other drugs the patient is taking."

Juvisync, which is marketed by Merck, has been approved in dosage strengths of sitagliptin:simvastatin of 100 mg:10 mg, 100 mg:20 mg and 100 mg:40mg.

News story written by Cara Sutton, Managing Commissioning Editor. Source: FDA approves combination therapy Juvisync®: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm274748.htm

Boceprevir-based therapy clears hepatitis C virus in 70% of patients co-infected with hepatitis C and HIV-1

Merck Canada, a healthcare professional company based in Kirkland (Quebec, Canada), have announced results from a 24-week interim analysis of an ongoing 48-week Phase IIb clinical study, evaluating the investigational use of boceprevir in combination with pegIFN-α and ribavirin (R), for the treatment of chronic hepatitis C virus (HCV) genotype 1 infection in adult patients co-infected with HIV-1.

Boceprevir, an oral HCV protease inhibitor, was approved for use in Canada in July 2011 for the treatment of chronic HCV genotype 1 infection; however, it is not currently indicated for the treatment of chronic HCV in patients co-infected with HCV and HIV-1. "There are thousands of Canadians living with chronic hepatitis C and HIV," explained Josée Brisebois, Director of Medical Affairs at Merck Canada, "helping patients who are dealing with both chronic hepatitis C and HIV is a critical issue in infectious diseases today."

This randomized, multicenter, double-blinded for boceprevir, Phase IIb trial enrolled 100 adult patients with previously untreated HCV genotype 1 infection and stable HIV-1 disease (HIV RNA <50 copies/ml; CD4 cell counts ≥200 cells/mm^3). The interim analyses is based on 98 patients who received at least one dose of study drug, due to two patients

randomized to the treatment arm receiving boceprevir in combination with pegIFN-α-2b (P) and R not receiving boceprevirl. In total, 64 patients were in the arm receiving boceprevir plus P/R, and 34 patients were in the control arm receiving P/R alone. All patients treated in the study received a 4-week lead-in with P/R alone followed by boceprevir plus P/R or placebo plus P/R for 44 weeks, for a total treatment duration of 48 weeks.

"...helping patients who are dealing with both chronic hepatitis C and HIV is a critical issue in infectious diseases today."

The primary objective of the ongoing study is to compare the efficacy of boceprevir 800 mg three times daily in combination with P 1.5 µg/kg weekly plus R 600–1400 mg daily with therapy with P/R alone, in adult patients co-infected with chronic HCV genotype 1 and HIV-1. Patients were randomized in a 2:1 ratio to the treatment arm with boceprevir plus P/R or the P/R control arm, respectively.

The interim results, presented for the first time in a late-breaker oral presentation at the Infectious Diseases Society of America Annual Meeting (MA, USA) showed that at week 24 of treatment, twice as many patients receiving boceprevir had undetectable HCV RNA. 70.5% (95% CI: 59.0, 81.9) of patients receiving boceprevir in combination with pegIFN-α-2b and R had HCV RNA, compared with 34.4% (95% CI: 17.9, 50.8) of patients receiving pegIFN α-2b and R alone, which made a treatment difference of 36.1% (95% CI: 16.1, 56.2).

Curtis Cooper, study investigator and Associate Professor of Medicine at the University of Ottawa Division of Infectious Diseases, commented on the results, "people living with chronic hepatitis C and HIV can be more challenging to treat and less likely to respond to HCV treatment." He continued, "these interim results are very promising because they demonstrate that the addition of boceprevir to standard treatment may increase the likelihood of permanently clearing their hepatitis C infection. We are eagerly awaiting the final results of this trial." Final results from the study are expected in 2012.

News story written by Ruth Williamson, Assistant Commissioning Editor. Source: Boceprevir based therapy cleared the hepatitis C virus in 70 percent of patients co-infected with hepatitis C and HIV-1: www.merck.ca/assets/en/pdf/press/product_infovictrelispress_releases/VICTRELIS_IDSA_Coinfection_Data_release_Oct_20_2011_EN.pdf

Why do patients participate in trials?

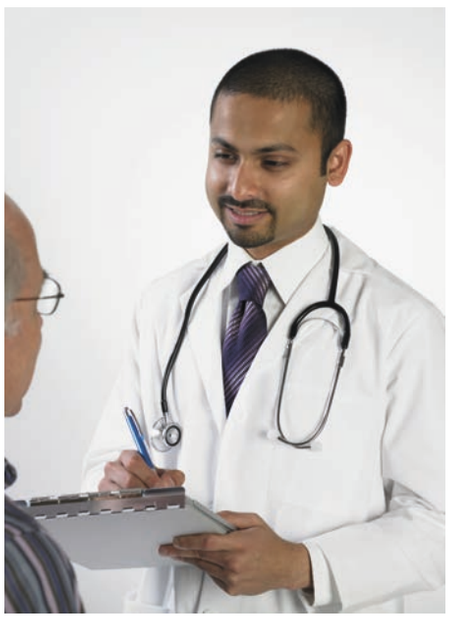
Collaborative researchers based at the Dana-Faber Cancer Institute (MA, USA), the Harvard School of Public Health (MA, USA), the Children's Hospital (MA, USA) and the University of Toronto (ON, Canada) have conducted research to understand the factors that influence patients' decisions to enroll in clinical trials.

The team surveyed 205 adults and 48 parents of children enrolled in Phase I, II or III cancer clinical trials to evaluate what motivated individuals to participate in the trial. The researchers chose the area of altruism to focus on throughout all phases of trials.

The respondents were questioned about their motivation to enroll and the scientists examined the correlates of altruistic motivation using univariate and multivariate analyses. Among the individuals surveyed, almost half reported altruistic motivations as being very important to their enrolment decision. Multivariate analysis of Phase II trial participants was shown to reveal altruism least often as a very important motivation. 33 respondents, 13%, reported altruism as being their primary motivation. The researchers found that altruistic motivation did not differ between adult patient respondents and parents of pediatric participants.

The researchers concluded that although participants commonly report altruism as contributing to their decision to enroll, it is rarely the primary motivation for participation in a study. Those participating in early phase trials, or those with poor prognoses, were found to be least motivated by altruism.

News story written by Cara Sutton, Managing Commissioning Editor. Source: Truong TH, Weeks JC, Cook EF, Joffe S. Altruism among participants in cancer clinical trials. *Clin. Trials* 8(5), 616–623 (2011).



"...respondents were questioned about their motivation to enroll."

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 6090; E-mail: j.walker@future-science.com

Ferriprox® for treatment in patients with thalassemia approved by the US FDA

"Results from the studies showed that half of the patients experienced at least a 20% decrease in ferritin levels, thereby receiving successful treatment."

Patients with thalassemia, a genetic blood disorder that causes anemia, have excess iron in the body due to frequent blood transfusions (transfusional iron overload). It is a serious condition that can be fatal, leaving patients at risk of developing liver disease, diabetes, arthritis, heart failure or an abnormal heart rhythm. The standard of care to treat transfusional iron overload is the use of chemical agents that remove heavy metals from the body, known as chelation therapy. Ferriprox® (deferiprone) is intended for use when chelation therapy is inadequate.

The safety and effectiveness of Ferriprox was based on an analysis of data from 12 clinical studies in 236 patients, who did not respond to prior iron chelation therapy. Ferriprox was considered a successful treatment for patients who experienced at least a 20% decrease in serum ferritin, a protein that stores iron in the body for later use.

Results from the studies showed that half of the patients experienced at least a 20% decrease in ferritin levels, thereby receiving successful treatment.

Richard Pazdur, Director of the Office of Hematology and Oncology Products in the US FDA's Center for Drug Evaluation and Research, commented on the significance the drug's approval, "Ferriprox represents the first new FDA-approved treatment for this disorder since 2005."

The most common side-effects seen in patients who received Ferriprox included nausea, vomiting, abdominal and joint pain, urine discoloration, a decrease in the number of white blood cells and an increase in the level of a liver enzyme that may be indicative of tissue or liver damage at unsafe amounts. The most serious side-effect, seen in approximately 2% of patients treated with Ferriprox, was the development of agranulocytosis, a serious and potentially life-threatening reduction in the number of granulocytes.

"However, concern was raised for the safety of Ferriprox if it were to be used in myelodysplastic syndromes (MDS) patients."

The advisory committee voted 10 to 2 to recommend that the FDA approve Ferriprox. However, concern was raised for the safety of Ferriprox if it were to be used in myelodysplastic syndromes (MDS) patients. It was noted that not many MDS patients were included in Ferriprox's clinical trials, and that the FDA explicitly recommends against the use of Exjade® (deferasirox), a drug similar to Ferriprox, in high-risk MDS patients, as Exjade may cause potentially life-threatening side-effects.

The therapy is being approved under the FDA's accelerated approval program and ApoPharma has agreed to several postmarketing requirements and commitments, one such commitment being further study of the use of Ferriprox in patients with sickle cell disease who have transfusional iron overload.

News story written by Ruth Williamson, Assistant Commissioning Editor. Sources: FDA approves Ferriprox® to treat patients with excess iron in the body: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm275814.html; FDA approves Ferriprox ... but not for myelodysplastic syndromes patients: www.mdsbeacon.com/news/2011/10/17/fda-approves-ferriprox-deferiprone-but-not-for-myelodysplastic-syndromes-patients