Clin. Invest. (2013) 3(2), 105–108

CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Positive Phase III trial results of pomalidomide in addition to low-dose dexamethasone suggest significant improvements for relapsed or refractory multiple myeloma patients

Data from MM-003, an open-label clinical trial, have been announced by Celgene International Sàrl (Boudry, Switzerland). A sample of 455 patients were enrolled on the multicenter, randomized trial. In the study, pomalidomide plus low-dose dexamethasone was compared with high-dose dexamethasone in participants diagnosed with refractory multiple myeloma who had previously failed therapy with both lenalidomide and bortezomib used either alone or in combination.

> "The analysis showed that the treatment of pomalidomide plus low-dose dexamethasone produced overall survival results that were deemed statistically significant and crossed the upper parameter for superiority."

Patients placed into the pomalidomide plus low-dose dexamethasone were given 4 mg of oral pomalidomide from days 1 to 21 of every 28-day cycle. Dexamthasone was administered orally at 40 mg every week. For those participants who were over the age of 75 years this dose was set to 20 mg a week.

The patients on the comparator arm in the study were in the high-dose dexamethasone treatment group and were given oral pomalidomide on days ranging from 1–4, 9–12 and 17–20 in an every 28-day cycle until disease progression. For those participants who were over the age of 75 years, this dose was set to 20 mg a week on the same schedule mentioned.

Common grade 3/4 hematologic toxicities for the pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone arms, respectively, included febrile neutopenia (7 vs 0%) and anemia (27 vs 29%) as examples. Progressive disease was the single largest contributing factor for discontinuation.

The primary end point was met in MM-003; an improvement in progression-free survival. This end point was shown to be significantly longer in those patients who had been administered with pomalidomide plus low-dose dexamethasone versus those who had been assigned to receive high-dose dexamethasone (a median of 3.6 vs 1.8 months, respectively).

In accordance to study design, analysis of overall survival was also carried out. The analysis showed that the treatment of pomalidomide plus low-dose dexamethasone produced overall survival results that were deemed statistically significant and crossed the upper parameter for superiority. As a consequence, the Data Monitoring Committee made a recommendation that patients on the comparator arm of high-dose dexamethasone who had not yet progressed should be placed onto the low-dose dexamethasone arm.

> "Recently, the FDA has accepted to review a new drug application and, earlier in 2012, a marketing authorization application for pomalidomide plus low-dose dexamethasone was sent to the European Medicines Agency."

An independent committee was able to adjudicate the results to conclude that pomalidomide plus low-dose dexamethasone was able to produce an overall response that was greater in comparison to the high-dose dexamethasone arm (21 vs 3%). Those participants that were randomized for a period of least 6 months demonstrated an overall response of 24 versus 3% and greater analysis of the response rates are currently underway.

Recently, the FDA has accepted to review a new drug application and, earlier in 2012, a marketing authorization application for pomalidomide plus low-dose dexamethasone was sent to the European Medicines Agency. A decision should be made by the European authorities by late 2013.

Written by Priti Nagda

Source: Celgene Press Release: http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-news&nyo=0

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ISSN 2041-6792 10.4155/CLI.13.4

Pharmaceutical companies to develop database on clinical trial sites

An 'Investigator Databank' of key clinical trial site information is being developed as part of the cross-pharmaceutical company TransCelerate initiative.

New Jersey-based Janssen R&D (a subsidiary of Johnson & Johnson) have recently announced the establishment of a novel clinical trial site database. The database will be 'cross-pharmaceutical', with Merck and Eli Lilly being the first pharmaceutical companies to join Janssen in this venture.

The aim of the Investigator Databank is to provide a common location where investigators can ascertain key information on clinical trial sites. Information such as infrastructure and GCP status, but not patient data, will be included.

This database is being developed as one of the five key projects of TransCelerate BioPharma Inc. and was founded by ten pharmaceutical companies, with the aim to "identify and overcome common drug development challenges in order to improve the quality of clinical studies and to bring new medicines to patients faster." Companies who are members of the TransCelerate initiative will automatically qualify for use of the databank.

In the company press release, Andreas Koester, Head of Clinical Trial Innovation/External Alliances at Janssen, explained why the database should expedite drug development, "The current clinical trial environment is inefficient, costly and unsustainable. The Investigator Databank can help expedite the process to achieve our most important goal – to deliver high-quality, effective novel medicines to the patients who are waiting for them."

The database is anticipated to be operational by the end of 2012 and will be hosted by the independent company DrugDev.org.

Written by Alice O'Hare

Source: Johnson & Johnson Press Release: www.tinyurl.com/a79kn68

US FDA approves new treatment for schizophrenia or bipolar-related agitation

Alexza Pharmaceuticals, Inc. has announced that ADASUVE® (loxapine) Inhalation Powder 10 mg has been approved by the US FDA for the treatment of acute agitation experienced by adults with schizophrenia or bipolar I disorder.

Agitation, including irritability and hostility, is a severe symptom evident in both schizophrenia and bipolar disorder. It is thought that nine out of every ten of these patients experience agitation at some point throughout the disease course.

Described as a 'unique product', ADASUVE combines the antipsychotic drug, loxapine, with Alexza's Staccato® delivery system, which is a hand-held inhaler that is able to deliver the drug to the lung resulting in rapid systemic delivery and absorption.

"We believe that the ability to deliver medications rapidly and noninvasively will be important for patients and the professionals who care for them," said Thomas King, President and CEO of Alexza, before continuing, "We project that ADASUVE will be available for commercial launch early in the third quarter of 2013." This will be the first approved non-injectable therapy for agitation in these patients.

The results from Phase III trials of the inhalant in schizophrenia and bipolar I patients were described as "compelling" by a principal investigator in the ADASUVE clinical trials, Michael Lesem, Executive Medical Director of Claghorn-Lesem Research Clinic (TX, USA). "I believe that ADASUVE represents an important new and much needed therapeutic option in treating agitation patients who will benefit from a non-coercive therapeutic intervention that works quickly to relieve their symptoms," explained Lesem.

> "...ADASUVE combines the antipsychotic drug, loxapine, with Alexza's Staccato® delivery system..."

The FDA's decision was based on a clinical data package involving over 1600 subjects. In two Phase III trials, ADASUVE 10 mg was deemed efficacious following statistically significant reductions in agitation compared with placebo 2 h after administration (the primary endpoint). In some cases, agitation was reduced as quickly as 10 minutes following administration.

Alexza identified a risk of bronchospasm in certain asthma and chronic obstructive pulmonary disease patients following ADASUVE administration and is therefore only available in enrolled healthcare facilities under a restricted program.

Written by Sarah Freeston

Source: US FDA Approves Alexza's ADASUVE® (loxapine) Inhalation Powder for the Acute Treatment of Agitation Associated with Schizophrenia or Bipolar I Disorder in Adults: www.tinyurl.com/c4e6ybj

Fluarix® Quadrivalent vaccine garners approval from the US FDA

The US FDA has approved GlaxoSmithKline's Influenza Virus Vaccine for use in persons aged 3 years of age and older for the prevention of seasonal influenza.

It is estimated that seasonal influenza could cause approximately 500,000 deaths worldwide every year. Vaccination against the influenza virus strains most commonly responsible for causing seasonal influenza can be an effective method to prevent contraction of the virus, thereby reducing influenza-related mortality.

The virus responsible for seasonal influenza can be broadly classified as being either an A or a B strain. Most currently available vaccines are trivalent and are designed to protect against the two most common A virus strains and one B strain. The B strain found in these vaccines is usually chosen according to which strain is expected to be the most widespread for that particular year. As it can be difficult to predict the circulation of these strains in any given year, trivalent vaccines do not necessarily provide protection against the most predominant B strain of the season.

The tetravalent vaccine is designed to provide protection against four strains of influenza; two A strains and two B strains, thereby broadening the protection against seasonal influenza compared with trivalent vaccines. Leonard Freidland, vice president of GlaxoSmithKline's North America Vaccines Clinical Development and Medical Affairs, is hopeful that this will have the effect of lowering influenza-related morbidity.

"Trivalent influenza vaccines have helped protect millions of people against flu, but in six of the last 11 flu seasons, the predominant circulating influenza B strain was not the strain that public health authorities selected," commented Friedland. "Fluarix Quadrivalent will help protect individuals against both B strains and from a public-health standpoint, can help decrease the burden of disease."

Fluarix Quadrivalent is expected to be made available for the 2013–2014 flu season.

Written by Sophie Breeze

Sources: Jain V. Clinical Development of GSK's Fluarix Quadrivalent Influenza Vaccine. Presented at: *ACIP October 2012 Meeting*. Atlanta, GA, USA, 24–25 October 2012. Available at: www.cdc.gov/vaccines/acip/meetings/slides-oct-2012.html; GlaxoSmithKline Press Release: www.gsk.com/media/press-releases/2012/FDA-pproves-GlaxoSmithKline-four-strain-seasonal-influenza-vaccine-for-use-in-the-US.html

Quintiles and Clinical Research Advantage sign strategic alliance

Community-based trial management organization to collaborate with biopharmaceutical service provider.

Quintiles have recently selected Clinical Research Advantage (CRA) to collaborate on a 'strategic alliance' to improve the company's clinical trial services.

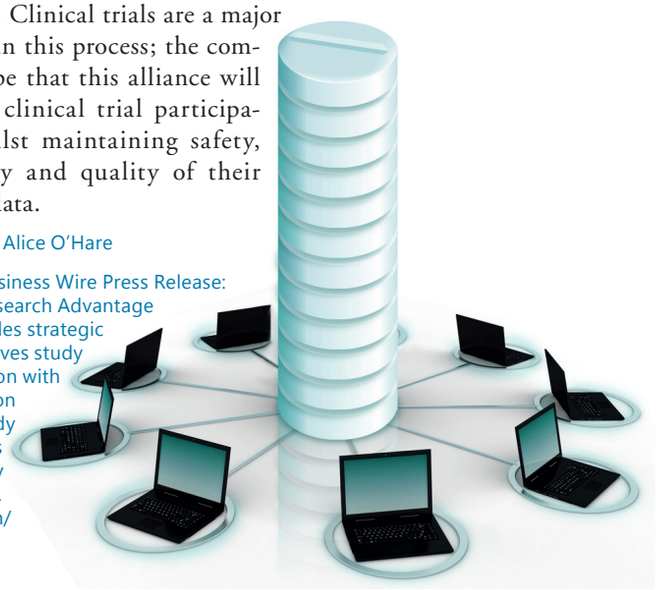
Quintiles selected CRA, a provider of research services focusing on clinical trial management, for this strategic alliance after being impressed by their high standards in patient enrollment, quality of data and starting up studies. Lindy Jones, Senior Vice President of Integrated Site Services at Quintiles, explained their hopes for the alliance, "Many chronic conditions such as diabetes and heart disease are now managed in the community. It is imperative that these patient populations have the opportunity to participate in studies and be a part of the quest to develop new and better medicines for conditions that have a significant impact on both individuals and society. We are pleased to enter into this relationship with CRA and anticipate that together we will ensure that studies start on the right path."

Mark Hanley, Chief Executive Officer of Clinical Research Alliance, said of their selection by Quintiles, "It is an honor to be chosen by Quintiles... The core value and principal purpose of CRA is to improve the lives of patients through the development of new medical therapies. Working with Quintiles will allow CRA to conduct an increased number of community-based trials with unparalleled accuracy and safety."

Quintiles help biopharmaceutical and health science customers develop and commercialize pharmaceuticals. Clinical trials are a major element in this process; the company hope that this alliance will improve clinical trial participation whilst maintaining safety, efficiency and quality of their clinical data.

Written by Alice O'Hare

Source: Business Wire Press Release: Clinical Research Advantage and Quintiles strategic alliance drives study participation with emphasis on safety, study efficiencies and quality data: www.tinyurl.com/cuunmv9



Rituximab could combat non-criteria manifestations of antiphospholipid syndrome

New research suggests that clinical problems that are unresponsive to anticoagulation therapy could be relieved by rituximab in patients with antiphospholipid antibodies (aPLs).

Antiphospholipid syndrome (APS), which can be associated with systemic lupus erythematosus, is a life-threatening condition that can cause venous thrombosis, arterial thrombosis and fetal loss. APS is quite common in aPL-positive individuals, as they have an increased production of proteins responsible for the formation of clots. Other symptoms of APS, including cognitive dysfunction, skin ulcers and kidney disease, are classified as non-criteria manifestations of APS.

Previous research had shown that aPLs are secreted by B cells, and that APS could be prevented from developing if B cells were eliminated. Rituximab, which has already been approved for the treatment of leukemia and rheumatoid arthritis, is able to destroy B-cells. "The idea is if you kill the inflammatory B-cells, they can not secrete antiphospholipid antibodies that cause problems," explained author of the study Doruk Erkan, rheumatologist at the Hospital for Special Surgery (NY, USA). Case reports have also supported the theory that APS may respond to rituximab.

Researchers at the Hospital for Special Surgery carried out a Phase II pilot trial in 19 aPL-positive patients with non-criteria manifestations of APS. Investigators measured aPL profiles and clinical outcomes monthly up to six months after treatment with rituximab. Improved outcomes were noted in several patents at completion of the study. Four out of five patients with cognitive dysfunction had at least partial response, similarly, three out of five patients with skin ulcers had complete responses and one patient has a partial response. However, none of the patients with cardiac valve disease had a response.

Interestingly, the aPL antibody profiles of the patients did not change during the study. The reason behind this may be due to the fact that B cells are active in many intricate ways in the immune system, including helping other inflammatory cells. Therefore, the B cells may be acting through other channels to dampen down the effect of aPLs.

Researchers are hopeful that rituximab will be a viable option to treat some if not all non-criteria APS manifestations. Their next step will be to predict the response and identify which patients will respond to rituximab.

Written by Sophie Breeze

Sources: Hospital for Special Surgery Press Release: www.hss.edu/newsroom_rituximab-shows-promise-antiphospholipid-antibodies.asp; Erkan D, Vega J, Ramon G, Kozora E, Lockshin MD. A pilot open label Phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum.* doi: 10.1002/art.37759 (2012) (Epub ahead of print).

Ibrutinib shows promising results in the treatment of Resistant Mantle Cell Lymphoma

Researchers at the University of Texas MD Anderson Cancer Center (TX, USA) have shown, in an international multicenter Phase II study, ibrutinib can be used to treat relapsed or refractory mantle cell lymphoma (MCL) with long lasting results and few side effects. These interim findings were presented at the 54th American Society of Hematology Annual Meeting and Exposition (8–11 December 2012, GA, USA).

MCL is an aggressive and rare B-cell subtype of non-Hodgkin lymphoma, and although patients have high response rates, they often relapse. Michael Wang, (University of Texas MD Anderson Cancer Center) lead investigator, explains the principle behind the study; "…the B-cell receptor pathway is critical in B-cell lymphoma. BTK is the driver molecule in this pathway, and ibrutinib targets the BTK molecule."

So far 115 patients have enrolled in the study, with a median age of 68 years. Wang goes on to summarize the findings; "In a heavily treated relapsed or refractory population, oral ibrutinib induced a response rate as high as 70 percent - better than any other single agent ever tested in MCL…the response is durable with a long progression-free survival."

Wang concludes; "I believe we are witnessing a breakthrough in mantle cell lymphoma. This is great news for patients … What impressed me the most is the high complete remission rate, which continues to improve with time, and yet it is the safest drug we have for mantle cell lymphoma … previously such a rate could be achieved only with combination cyto-reductive chemotherapy, which is bone marrow suppressive and toxic."

Written by Sophie Wraight

Source: The University of Texas MD Anderson Cancer Center Press Release: www.mdanderson.org/newsroom/news-releases/2012/ibrutinib-has-unprecedented-impact-on-mantle-cell-lymphoma.html