



UCB announces start of C-EARLY™ study

- Phase III study to evaluate Cimzia® (certolizumab pegol) in adult patients with early, active, moderate to severe rheumatoid arthritis who have not been exposed to disease-modifying antirheumatic drugs

BRUSSELS, BELGIUM, 22nd February – UCB today announced the start of C- EARLY™ – a phase III study that will evaluate the efficacy and safety of Cimzia® (certolizumab pegol) in combination with methotrexate (MTX) for inducing and sustaining clinical response in adults with early, progressive, active, moderate to severe rheumatoid arthritis (RA), who have not previously been treated with disease-modifying antirheumatic drugs (DMARDs). The study also aims to assess whether the frequency of certolizumab pegol administration can be reduced after sustained low disease activity* has been achieved. C-EARLY™ will evaluate patients in the early stage of their disease, that is less than one year since diagnosis.

"We are pleased to announce the start of this study which focuses on treatment for people with early active RA and reflects our continuing commitment to improving the lives of patients at all stages of this severe, progressive disease," said Professor Dr. Iris Loew-Friedrich, Chief Medical Officer and Executive Vice President, UCB.

The European League Against Rheumatism (EULAR) recommends that DMARD treatment of RA should aim to achieve remission or low disease activity as soon as possible in every patient and that, once remission has been achieved, tapering of treatment can be considered¹. Research has shown that achieving early control of disease activity can improve long term outcomes for patients with RA^{2,3}.

"There is growing evidence to support the value of detecting and treating rheumatoid arthritis patients as soon as possible after the onset of disease in order to prevent disease progression. By rapidly achieving the target of sustained remission early in the course of RA, drug-free remission could become an achievable goal," said Professor Paul Emery, Professor of Rheumatology, University of Leeds, UK. "With C-EARLY™ we are starting an important study which should inform all stakeholders including patients, rheumatologists and payers how to optimize anti-TNF treatment in patients with early RA who have achieved sustained low disease activity."

C-EARLY™ is a phase III, multi-center, randomized, double-blind, placebo-controlled study which will randomize patients diagnosed with early, moderate to severe RA to certolizumab pegol plus methotrexate (MTX) or placebo plus MTX for 52 weeks. Patients who achieve sustained remission with certolizumab pegol at week 52 will be re-randomized to varying reduced doses of certolizumab or withdrawn from certolizumab for a further 52 weeks. The co-primary efficacy variables are the proportion of patients reaching sustained remission* at week 52, and the proportion of patients who maintain low disease activity between week 52 and week 104. The study aims to enroll approximately 800 adult patients in the U.S., Canada and Europe with early, progressive, active, moderate to severe RA who are naïve to DMARDs. Headline results for the study are expected in 2016.



Cimzia[®] is indicated for the treatment of adult patients with moderately to severely active RA. Serious and sometimes fatal side effects have been reported with Cimzia[®], including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens (such as Legionella or Listeria). Patients should be closely monitored for the signs and symptoms of infection during and after treatment with Cimzia[®]. Lymphoma and other malignancies also have been reported in children and adolescents. Cimzia[®] is not indicated for use in pediatric patients.

**Sustained low disease activity defined as Disease Activity Score 28[ESR] ≤ 3.2 at week 40 and week 52 visits*

***Sustained remission defined as Disease Activity Score 28[ESR] < 2.6 at week 40 and week 52 visits*

About CIMZIA[®]

Cimzia[®] is the only PEGylated anti-TNF (Tumor Necrosis Factor). Cimzia[®] has a high affinity for human TNF-alpha, selectively neutralizing the pathophysiological effects of TNF-alpha. Over the past decade, TNF-alpha has emerged as a major target of basic research and clinical investigation. This cytokine plays a key role in mediating pathological inflammation, and excess TNF-alpha production has been directly implicated in a wide variety of diseases. The U.S. Food and Drug Administration (FDA) has approved Cimzia[®] for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for the treatment of adults with moderately to severely active rheumatoid arthritis. Cimzia[®] in combination with MTX, is approved in the EU for the treatment of moderate to severe active RA in adult patients inadequately responsive to disease-modifying antirheumatic drugs (DMARDs) including MTX. Cimzia[®] can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. UCB is also developing Cimzia[®] in other autoimmune disease indications. Cimzia[®] is a registered trademark of UCB PHARMA S.A.

Cimzia[®] (certolizumab pegol) in the US important safety information

Risk of Serious Infections and Malignancy

Patients treated with CIMZIA are at an increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use.***
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients***



with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

- ***Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.***

The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.

Patients treated with CIMZIA are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. CIMZIA should be discontinued if a patient develops a serious infection or sepsis. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. Patients who develop a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for immunocompromised patients, and appropriate antimicrobial therapy should be initiated. Appropriate empiric antifungal therapy should also be considered while a diagnostic workup is performed for patients who develop a serious systemic illness and reside or travel in regions where mycoses are endemic.

Malignancies

During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate of 0.5 per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 per 100 patient-years among 1,319 placebo-treated patients. In studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients. In CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with



highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF blocker therapy in the development of malignancies is not known. Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which CIMZIA is a member. Approximately half of the cases were lymphoma (including Hodgkin's and non-Hodgkin's lymphoma, while the other cases represented a variety of different malignancies and included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants. Cases of acute and chronic leukemia have been reported with TNF-blocker use. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for developing leukemia.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. CIMZIA has not been formally studied in patients with CHF. Exercise caution when using CIMZIA in patients who have heart failure and monitor them carefully.

Hypersensitivity

Symptoms compatible with hypersensitivity reactions, including angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria, have been reported rarely following CIMZIA administration. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy.

Hepatitis B Reactivation

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. Some cases have been fatal. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating CIMZIA therapy. Exercise caution in prescribing CIMZIA for patients identified as carriers of HBV, with careful evaluation and monitoring prior to and during treatment. In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment.

Neurologic Reactions

Use of TNF blockers, including CIMZIA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barre syndrome. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA. Exercise caution in considering the use of CIMZIA in patients with these disorders.

Hematologic Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) has been infrequently reported with CIMZIA. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA.



Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

Drug Interactions

An increased risk of serious infections has been seen in clinical trials of other TNF blocking agents used in combination with anakinra or abatacept. Formal drug interaction studies have not been performed with rituximab or natalizumab; however because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA in these combinations. Therefore, the combination of CIMZIA with anakinra, abatacept, rituximab, or natalizumab is not recommended. Interference with certain coagulation assays has been detected in patients treated with CIMZIA. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation. CIMZIA may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities.

Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. Discontinue treatment if symptoms of lupus-like syndrome develop.

Immunizations

Do not administer live vaccines or attenuated vaccines concurrently with CIMZIA.

Adverse Reactions

In controlled Crohn's clinical trials, the most common adverse events that occurred in $\geq 5\%$ of CIMZIA patients ($n=620$) and more frequently than with placebo ($n=614$) were upper respiratory infection (20% CIMZIA, 13% placebo), urinary tract infection (7% CIMZIA, 6% placebo), and arthralgia (6% CIMZIA, 4% placebo). The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo.

In controlled RA clinical trials, the most common adverse events that occurred in $\geq 3\%$ of patients taking CIMZIA 200 mg every other week with concomitant methotrexate ($n=640$) and more frequently than with placebo with concomitant methotrexate ($n=324$) were upper respiratory tract infection (6% CIMZIA, 2% placebo), headache (5% CIMZIA, 4% placebo), hypertension (5% CIMZIA, 2% placebo), nasopharyngitis (5% CIMZIA, 1% placebo), back pain (4% CIMZIA, 1% placebo), pyrexia (3% CIMZIA, 2% placebo), pharyngitis (3% CIMZIA, 1% placebo), rash (3% CIMZIA, 1% placebo), acute bronchitis (3% CIMZIA, 1% placebo), fatigue (3% CIMZIA, 2% placebo). Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs. Patients receiving CIMZIA 400mg as monotherapy every 4 weeks in RA controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200mg every other week. The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA and 2.5% for placebo. Please consult the full prescribing information in relation to other side effects, full safety and prescribing information: www.cimzia.com



References

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3. Van der Heijde D, Schiff M, Keystone E, et al. Time to and level of initial DAS28 change with certolizumab pegol predicts the likelihood of having low disease activity at years 1 and 2 in patient with rheumatoid arthritis. *Ann Rheum Dis* (2010);69(Suppl3):505.

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About UCB

UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With more than 8 500 people in about 40 countries, the company generated revenue of EUR 3.2 billion in 2010. UCB is listed on Euronext Brussels (symbol: UCB).

Forward looking statements

This press release contains forward-looking statements based on current plans, estimates and beliefs of management. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, political, regulatory or clinical results and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and assumptions which could cause actual results to differ materially from those that may be implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms, costs associated with research and development, changes in the prospects for products in the pipeline or under development by UCB, effects of future judicial decisions or governmental investigations, product liability claims, challenges to patent protection for products or product candidates, changes in laws or regulations, exchange rate fluctuations, changes or uncertainties in tax laws or the administration of such laws and hiring and retention of its employees. UCB is providing this information as of the date of this press release and expressly disclaims any duty to update any information contained in this press release, either to confirm the actual results or to report a change in its expectations.

There is no guarantee that new product candidates in the pipeline will progress to product approval or that new indications for existing products will be developed and approved. Products or potential products which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences between the partners. Also, UCB or others could discover safety, side effects or manufacturing problems with its products after they are marketed.

Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement.