Post hoc analysis showed meaningful efficacy of certolizumab pegol for RA patients with high Rheumatoid Factor (RF) levels

- A post hoc analysis from the EXXELERATE trial shows that 65.7 percent of certolizumab pegol-treated patients, and 48.3 percent of adalimumab-treated patients, with rheumatoid arthritis (RA) and high rheumatoid factor (RF) levels achieved low disease activity at Week 104[1]
- Certolizumab pegol maintained drug concentrations and achieved Low Disease Activity regardless of RF levels in patients with established RA until the end of the study period (w104)[1]
- The results are in line with previous analyses from independent studies that demonstrate the consistent efficacy of certolizumab pegol across the entire RA population, while TNFis with an Fc fragment showed a decline in efficacy in high RF patients.
- In patients with RA and high RF levels, who are at increased risk of disease progression, certolizumab pegol has the potential to deliver meaningful outcomes[1]

Brussels (Belgium), 11 November 2023 – 07:00 (CEST) – UCB, a global biopharmaceutical company, will present a post hoc analysis of the EXXELERATE trial examining the efficacy of certolizumab pegol and adalimumab in patients with rheumatoid arthritis (RA) with high rheumatoid factor (RF) levels. The data are being presented at the American College of Rheumatology (ACR) Convergence 2023 in San Diego, U.S., November 10–15.[1]

In the initial EXXELERATE trial comparing the efficacy of certolizumab pegol and adalimumab, the primary endpoints of superiority were not met. The post hoc analysis assessed the efficacy of certolizumab pegol, a PEGylated fragment crystalized (Fc)-free tumor necrosis factor inhibitor (TNFi) and adalimumab, an Fc-containing TNFi in patients with RA across RF subgroups.[1] Patients were randomized 1:1 to certolizumab pegol 200 mg every 2 weeks plus methotrexate (MTX) or adalimumab 40 mg every 2 weeks plus MTX. At Week 12, patients were classified as responders or non-responders, non-responders were switched to the other TNFi with possible follow-up to Week 104. The results of this post hoc analysis showed that for patients in the higher RF quartile (≤Q3: ≤203 IU/mL; >Q3: >203 IU/mL; measured by Roche Tina-quant®), 65.7 percent of 453 patients treated with certolizumab pegol achieved low disease activity at Week 104 and 48.3 percent of 454 patients treated with adalimumab achieved low disease activity.[1]

"It is well known that high rheumatoid factor (RF) levels are associated with a poor prognosis[2]. In addition, high pre-treatment RF levels may lead to decreased drug concentrations of monoclonal antibodies and potentially lower response to TNFis in

patients with rheumatoid arthritis (RA)[1,3]. The results of this analysis highlight how certolizumab pegol maintained constant blood concentrations and therapeutic responses regardless of RF levels," said Professor Josef Smolen, Emeritus Professor of Internal Medicine, Medical University of Vienna, Division of Rheumatology, Vienna, Austria. "These data may be of clinical relevance in the context of using a personalized medicine approach for patients with RA and high RF levels[1]."

RA is a chronic disease that causes inflammation throughout the body and commonly presents as joint pain, swelling and deformity, which results in a decline in physical function and quality of life.[4,5] It is estimated that, as of 2019, more than 18 million people worldwide live with this disease.[6] High RF is associated with a more aggressive and destructive disease course, which is often more difficult to treat.[7] One reason for this is the high levels of RF autoantibodies binding with the Fc parts of TNFis to form large immune complexes that are then degraded by macrophages, resulting in lower bioavailability of the biologic drugs.[8,9]

To treat RA when high RF levels are present, American College of Rheumatology 2021 guidelines recommend biologic disease-modifying anti-rheumatic drugs (bDMARDS), if there is no observed improvement with MTX treatment.[10] However, many bDMARDs such as TNFis contain an Fc region that RF antibodies bind to, which can result in a lower clinical efficacy and the need for additional interventions.[11,12,13] The distinctive, FC-free structure of certolizumab pegol could mean RF may not bind to the drug, which may allow its concentration to remain stable over time.[14]

"At UCB, we aspire to achieve long-lasting remission for as many patients living with rheumatoid arthritis (RA) as possible," said Emmanuel Caeymaex, Executive Vice President, Immunology Solutions & Head of U.S., UCB. "The data presented at this year's ACR Convergence demonstrate the benefits of certolizumab pegol, as it continues to deliver value for those with high unmet need late into its lifecycle and beyond. We are excited to continue exploring its scientific potential as a personalized solution for RA patients with high levels of rheumatoid factor (RF)[1]."

Abbreviations: ACR: American College of Rheumatology, Fc: fragment crystalized, MTX: methotrexate, RA: rheumatoid arthritis, RF: rheumatoid factor, TNFis: tumor necrosis factor-α inhibitors.

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Abbreviations: bDMARDS: biologic disease-modifying anti-rheumatic drugs, Fc: fragment crystalized, MTX: methotrexate, RA: rheumatoid arthritis, RF: rheumatoid factor, TNFis: tumor necrosis factor-α inhibitors.

About the EXXELERATE trial methodology and patient population

In patients with RA, high RF levels are considered a poor prognostic factor and are associated with higher disease activity, risk of radiographic progression, and decreased response to TNF inhibitors (TNFis).[7] Recent data suggest that patients with RA and high RF levels may achieve and maintain greater clinical improvement with TNFis without a crystallizable fragment (Fc) compared to TNFis with an Fc.[12] In this post hoc analysis of the EXXELERATE trial, we assessed efficacy outcomes of certolizumab pegol, a PEGylated Fc-free TNFi, versus adalimumab (Fc-containing TNFi) in patients with RA and high RF levels.[1]

About CIMZIA® (certolizumab pegol) in the EU/EEA[15]

In the EU, CIMZIA® (certolizumab pegol) in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs), including MTX, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Certolizumab pegol in combination with MTX is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. Certolizumab pegol has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Certolizumab pegol, in combination with MTX, is also indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.

Certolizumab pegol is also indicated in the EU for the treatment of adult patients with severe active axial spondyloarthritis (axSpA), comprising:

- Ankylosing spondylitis (AS) – adults with severe active AS who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs (NSAIDs).
- Axial spondyloarthritis (axSpA) without radiographic evidence of AS – adults with severe active axSpA without radiographic evidence of AS but with objective signs

of inflammation by elevated C-reactive protein (CRP) and/or Magnetic Resonance Imaging (MRI) who have had an inadequate response to, or are intolerant to, NSAIDs.

Certolizumab pegol is also indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

CIMZIA® (certolizumab pegol) EU/EEA Important Safety Information[15]

Cimzia® was studied in 4,049 patients with rheumatoid arthritis (RA) in controlled and open label trials for up to 92 months. In the placebo-controlled studies, patients receiving Cimzia had an approximately 4 times greater duration of exposure compared with the placebo group. This difference in exposure is primarily due to patients on placebo being more likely to withdraw early. In addition, Studies RA-I and RA-II had a mandatory withdrawal for non-responders at Week 16, the majority of whom were on placebo.

The commonly reported adverse reactions (≥1/100 to <1/10) in clinical trials with certolizumab pegol and post-marketing were viral infections (includes herpes zoster, papillomavirus, influenza), bacterial infections (including abscess), rash, headache (including migraine), asthenia, leukopenia (including lymphopenia, neutropenia), eosinophilic disorder, pain (any sites), pyrexia, sensory abnormalities, hypertension, pruritus (any sites), hepatitis (including hepatic enzyme increase), injection site reactions, and nausea.

Certolizumab pegol was initially studied in 325 patients with active axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in the AS001 clinical study for up to 4 years, which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 156-week open-label treatment period. Certolizumab pegol was subsequently studied in 317 patients with non-radiographic axial spondyloarthritis in a placebo-controlled study for 52 weeks (AS0006).

Certolizumab pegol was also studied in patients with axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in a clinical study for up to 96 weeks, which included a 48-week open-label run-in phase (N=736) followed by a 48-week placebo-controlled phase (N=313) for patients in sustained remission (C-OPTIMISE). Certolizumab pegol was also studied in a 96-week open-label study in 89 axSpA patients with a history of documented anterior uveitis flares. In all 4 studies, the safety profile for these patients was consistent with the safety profile in rheumatoid arthritis and previous experience with certolizumab pegol.

Certolizumab pegol was studied in 409 patients with psoriatic arthritis (PsA) in the PsA001 clinical study for up to 4 years which included a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 168-week open-label treatment period. The safety profile for PsA patients treated with certolizumab pegol was consistent with the safety profile in RA and previous experience with certolizumab pegol.

Abbreviations: AS: Ankylosing spondylitis, axSpA: Axial spondyloarthritis, CRP: C-reactive protein, DMARDs: disease-modifying antirheumatic drugs, EEA: European Economic Area, EU: European Union, MRI: Magnetic Resonance Imaging, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, RA: rheumatoid arthritis, RF: Rheumatoid factor. TNFis: tumor necrosis factor-α inhibitors.

Certolizumab pegol was studied in 1112 patients with psoriasis in controlled and open-label studies for up to 3 years. In the Phase III program, the initial and maintenance periods were followed by a 96-week open-label treatment period. The long-term safety profile of certolizumab pegol 400 mg every 2 weeks and certolizumab pegol 200 mg every 2 weeks was generally similar and consistent with previous experience with certolizumab pegol.

Serious adverse reactions, defined as an adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect, include sepsis, opportunistic infections, tuberculosis (including miliary, disseminated and extrapulmonary), herpes zoster, lymphoma, leukemia, solid organ tumors, angioneurotic oedema, cardiomyopathies (includes heart failure), ischemic coronary artery disorders, pancytopenia, hypercoagulation (including thrombophlebitis, pulmonary embolism), cerebrovascular accident, vasculitis, hepatitis/hepatopathy (includes cirrhosis), and renal impairment/nephropathy (includes nephritis). In RA controlled clinical trials, 4.4% of patients discontinued taking certolizumab pegol due to adverse events vs. 2.7% for placebo.

Certolizumab pegol is contraindicated in patients with hypersensitivity to the active substance or any of the excipients, active tuberculosis or other severe infections such as sepsis or opportunistic infections, and moderate to severe heart failure.

Serious infections including sepsis, tuberculosis and opportunistic infections (e.g., histoplasmosis, nocardia, candidiasis) have been reported in patients receiving certolizumab pegol. Some of these events have been fatal. Before initiation of therapy with certolizumab pegol, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. If active tuberculosis is diagnosed prior to or during treatment, certolizumab pegol therapy must not be initiated and must be discontinued. If latent tuberculosis is diagnosed, appropriate anti-tuberculosis therapy must be started before initiating treatment with certolizumab pegol.

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including certolizumab pegol who are chronic carriers of the virus (i.e., surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with certolizumab pegol. Carriers of HBV who require treatment with certolizumab pegol should be closely monitored and in the case of HBV reactivation Certolizumab pegol should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

TNF antagonists including certolizumab pegol may increase the risk of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease

including multiple sclerosis; of formation of antinuclear antibodies and uncommonly of the development of a lupus-like syndrome; of severe hypersensitivity reactions. If a patient develops any of these adverse reactions, certolizumab pegol should be discontinued and appropriate therapy instituted.

With the current knowledge, a possible risk for the development of lymphomas, leukemia or other malignancies in patients treated with a TNF antagonist cannot be excluded. Rare cases of neurological disorders, including seizure disorder, neuritis and peripheral neuropathy, have been reported in patients treated with certolizumab pegol.

Adverse reactions of the hematologic system, including medically significant cytopenia, have been reported with certolizumab pegol. 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 certolizumab pegol. Consider discontinuation of certolizumab pegol therapy in patients with confirmed significant hematological abnormalities.

Severe infections and neutropaenia were reported in clinical trials with concurrent use of anakinra (an interleukin-1 antagonist) or abatacept (a CD28 modulator) and another TNF-antagonist, etanercept, with no added benefit compared to TNF-antagonist therapy alone. Because of the nature of the adverse events seen with the combination of another TNF-antagonist with either abatacept or anakinra therapy, similar toxicities may also result from the combination of anakinra or abatacept and other TNF-antagonists. Therefore the use of certolizumab pegol in combination with anakinra or abatacept is not recommended.

There is limited safety experience with surgical procedures in patients treated with Cimzia. The 14-day half-life of certolizumab pegol should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Cimzia should be closely monitored for infections, and appropriate actions should be taken. Please consult the full prescribing information in relation to other side effects, full safety and prescribing information.

European SmPC date of revision April 2023. https://www.ema.europa.eu/en/documents/product-information/cimzia-epar-product-information_en.pdf. Last accessed: October 2023.

Abbreviations: HBV: hepatitis B, RA: rheumatoid arthritis, RF: rheumatoid factor, TNF: tumor necrosis factor.

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 approximately 8,700 people in approximately 40 countries, the company generated revenue of €5.5 billion in 2022 UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news.

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This press release may contain forward-looking statements including, without limitation, statements containing the words “believes”, “anticipates”, “expects”, “intends”, “plans”, “seeks”, “estimates”, “may”, “will”, “continue” and similar expressions. These forward-looking statements are based on current plans, estimates and beliefs of management. All statements, other than statements of historical facts, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, arbitration, political, regulatory or clinical results or practices and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to known and unknown risks, uncertainties and assumptions which might cause the actual results, financial condition, performance or achievements of UCB, or industry results, to differ materially from those that may be expressed or 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 or within expected timing, 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, safety, quality, data integrity or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, product liability claims, challenges to patent protection for products or product candidates, competition from other products including biosimilars, 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. There is no guarantee that new product candidates will be discovered or identified in the pipeline, will progress to product approval or that new indications for existing products will be developed and approved. Movement from concept to commercial product is uncertain; preclinical results do not guarantee safety and efficacy of product candidates in humans. So far, the complexity of the human body cannot be reproduced in computer models, cell culture systems or animal models. The length of the timing to complete clinical trials and to get regulatory approval for product marketing has varied in the past and UCB expects similar unpredictability going forward. Products or potential products, which are the subject of partnerships, joint ventures or licensing collaborations may be subject to differences disputes between the partners or may prove to be not as safe, effective or commercially successful as UCB may have believed at the start of such partnership. UCB’s efforts to acquire other products or companies and to integrate the operations of such acquired companies may not be as successful as UCB may have believed at the moment of acquisition. Also, UCB or others could discover safety, side effects or manufacturing problems with its products and/or devices after they are marketed. The discovery of significant problems with a product similar to one of UCB’s products that implicate an entire class of products may have a material adverse effect on sales of the entire class of affected products. Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment, including pricing pressure, political and public scrutiny, customer and prescriber patterns or practices, and

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