UCB News

UCB announces approval of RYSTIGGO® (rozanolixizumab) and ZILBRYSQ® (zilucoplan) for the treatment of adult patients with generalized myasthenia gravis in Japan

- Japanese Ministry of Health, Labour and Welfare (MHLW) approves two UCB treatments, RYSTIGGO® (rozanolixizumab) and ZILBRYSQ® (zilucoplan), for the treatment of generalized myasthenia gravis (gMG) in adult patients (only for patients who inadequately respond to steroids or other immunosuppressants).[1,2]
- Approvals are based on pivotal phase 3 data for both medicines, showing statistical and clinically relevant improvements in gMG-specific outcomes[3,4]
- Zilucoplan is the first once-daily subcutaneous, targeted C5 complement inhibitor for gMG. It is the only gMG-targeted therapy to be self-administered by adult patients
- Rozanolixizumab is a humanized IgG4 monoclonal antibody that binds to the neonatal Fc receptor (FcRn), indicated for the the treatment of adult patients with gMG
- With zilucoplan and rozanolixizumab, the Japanese gMG community is first in the world to benefit from choice of two new targeted therapies from a single company
- UCB's two different medicines for gMG, each with a distinct mechanism of action, offer a unique portfolio of treatments that embody our commitment to addressing the gMG community's unmet needs

Brussels (Belgium), 25 September 2023, 1800: (CET) - UCB (Euronext Brussels: UCB), a global biopharmaceutical company, today announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has granted approval for RYSTIGGO® (rozanolixizumab)[1] and for ZILBRYSQ® (zilucoplan)[2], for the treatment of generalized myasthenia gravis (gMG) in adult patients (only for patients who inadequately respond to steroids or other immunosuppressants).

Japan is the first country in the world to approve both rozanolixizumab and zilucoplan simultaneously. This means Japanese physicians and their patients will be the first to have choice of two new targeted therapies to treat gMG from one company, delivering unique optionality and versatility.

Combined with UCB's highly regarded team of Japanese medical and scientific experts, and the company's long-established heritage in neurology, UCB has an opportunity to deliver individualized and transformational patient value for adult patients in Japan living with gMG.

"With the approval in Japan of zilucoplan and rozanolixizumab, we are very proud and excited to expand our support to the gMG community and to offer new and additional choices allowing treatment to be tailored according to patient needs.' said Iris Loew-Friedrich, Executive Vice-President and Chief Medical Officer at UCB. "*I am confident that UCB will be the only company able to deliver a portfolio of two targeted therapies with different mechanisms of action and the experience to provide truly individualized transformational patient value in managing this often-debilitating rare disease, both at home and in the healthcare setting."*

Today's announcement marks the first approval worldwide of zilucoplan, the first once-daily subcutaneous (SC), targeted peptide inhibitor of complement component 5 (C5 inhibitor) and the only gMG target therapy for self-administration by adult patients with AChR antibody-positive gMG.[4] In September 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending granting marketing authorization for zilucoplan in the European Union (EU) as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult patients who

are anti-acetylcholine receptor (AChR) antibody positive.[5] A final decision on approval in the EU is expected before the end of the year, in line with the EMA's standard review timeline.

As a C5 inhibitor, zilucoplan inhibits complement-mediated damage to the neuromuscular junction through its targeted dual mechanism of action.[4] Benefits of SC self-injection can include reduced traveling time to and from hospitals, decreased interference with work obligations, and increased independence. Unlike monoclonal antibody C5 inhibitors, as a peptide, zilucoplan can be used concomitantly with intravenous immunoglobulin and plasma exchange, without the need for supplemental dosing.[4]

The Japanese MHLW approval of rozanolixizumab, for treatment of adults with generalized Myasthenia Gravis (only for patients who inadequately respond to steroids or other immunosuppressants)[1] is the second approval worldwide for this medicine, following approval by the U.S. Food and Drug Administration (FDA) in June 2023 for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.[6] Rozanolixizumab injection by subcutaneous infusion is a humanized IgG4 monoclonal antibody that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG.[7]

"With the approval of these two new medicines, we are very happy to take an additional step forward in contributing to gMG community - a new area for UCB in Japan", explained Kanako Kikuchi, Head of Neurology and Country Operations, UCB Japan*. "Developing and providing solutions for rare diseases, for which treatment options are often limited, is a very important commitment for our UCB team in Japan. Zilucoplan and rozanolixizumab are an important addition to our portfolio. By providing these two medicines, each with their own mechanism of action, and way of administration, we are excited to support patients and physicians as they strive to manage the symptoms of gMG and to improve quality of life."*

Zilucoplan: Supporting data

Approval of zilucoplan in Japan for the treatment of generalized myasthenia gravis (gMG) in adult patients (only for patients who inadequately respond to steroids or other immunosuppressants) is supported by safety and efficacy data from the Phase 3 RAISE study (NCT04115293), published in *The Lancet Neurology* in May 2023.[4]

The primary endpoint for the RAISE study was change from baseline to Week 12 in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.[4] MG-ADL is a measurement tool that assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. These include activities such as breathing, talking, swallowing, and being able to rise from a chair.[3] Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment.

A statistically significant and clinically meaningful difference favoring zilucoplan in comparison to placebo was observed in the MG-ADL total score change from baseline: least squares mean change −4.39 [95% CI −5.28 to −3.50] vs −2.30 [−3.17 to −1.43], least squares mean difference −2.09 [−3.24 to −0.95]; p=0.0004. Secondary endpoints included change from baseline to Week 12 in QMG, MGC and MG-QoL15r*.[4]

A statistically significant and clinically meaningful difference favoring zilucoplan compared to placebo was observed in the QMG total score change from baseline to Week 12 (p<0.0001), least squares mean change −6.19 [95% CI −7.29 to −5.08] vs −3.25 [−4.32 to −2.17].[4]

Change from baseline to Week 12 in MGC in comparison to placebo was clinically meaningful and statistically significant. MG-QoL 15r change from baseline to Week 12 compared to placebo was also statistically significant*.[4]

Additionally, improvements in fatigue were observed as an exploratory endpoint. Change from baseline to week 12 in the Neuro-QoL short-form fatigue scale was an exploratory end point, therefore, p value was nominal, not multiplicity controlled.[4]

The most common adverse events (reported in at least 10% of patients treated with zilucoplan within the RAISE study) were injection-site bruising, headache, diarrhea and MG worsening.[4]

**The threshold for clinical meaningfulness for MG-QoL 15r has not been established.*

Rozanolixizumab: Supporting data
Approval of Rozanolixizumab in Japan for the treatment of generalized myasthenia gravis (gMG) in adult patients (only for patients who inadequately respond to steroids or other immunosuppressants) is supported by safety and efficacy data from the pivotal Phase 3 MycarinG study (NCT03971422), also published in *The Lancet Neurology* in May 2023.[3]

The primary efficacy endpoint was the comparison of the change from baseline between treatment groups in the MG-ADL total score at Day 43.[3]

Reductions in MG-ADL score from baseline to day 43 were greater in the rozanolixizumab 7 mg/kg group (least-squares mean change –3.37 [SE 0·49]) and in the rozanolixizumab 10 mg/kg group (–3.40 [0.49]) than with placebo (–0.78 [0.49]; for 7 mg/kg, least-squares mean difference −2.59 [95% CI −4.09 to −1.25], p<0.0001; for 10 mg/kg, −2.62 [−3.99 to −1.16], p<0.0001).[3]

Secondary efficacy endpoints included change from baseline to day 43 in the QMG. The QMG is a 13-item categorical grading system that assesses muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment. A statistically significant difference favoring rozanolixizumab compared to placebo was observed in the QMG total score change from baseline to day 43 [least squares mean difference -3.48 (95% CI (−5.61 to −1.58), p<0.0001 for rozanolixizumab 7mg/kg; least-squares mean difference −4.76 (95% CI −6.82 to −2.86), p<0.0001 for rozanolixizumab 10mg/kg.

The most common adverse reactions (reported in at least 10% of patients treated with rozanolixizumab within the MycarinG study) were headache, infections, diarrhea, pyrexia, hypersensitivity reactions, and nausea.[3]

About generalized Myasthenia Gravis (gMG)
gMG is a rare autoimmune disease with a global prevalence of 100–350 cases per every 1 million people.[8] People living with gMG can experience a variety of symptoms, including severe muscular weakness that can result in double vision, drooping eyelids, difficulty with swallowing, chewing and talking, as well as life-threatening weakness of the muscles of respiration.[9,10]
In gMG, pathogenic autoantibodies can impair synaptic transmission at the neuromuscular junction (NMJ) by targeting specific proteins on the post-synaptic membrane.[11] This disrupts the ability of the nerves to stimulate the skeletal muscle and results in a weaker contraction. gMG can occur in any race, gender or age.[9,10]

About the MycarinG study[3]
The MycarinG study (NCT03971422) was a multi-center, Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of rozanolixizumab in adult patients with gMG, with an ongoing open-label extension.

The primary endpoint for the MycarinG study was change in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score at day 43, an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities. Additional endpoints include changes in the Myasthenia Gravis composite (MGC) score, the Quantitative MG (QMG) score, patient-reported outcomes at Day 43 and adverse events (AEs).

The majority of patients taking part in the MycarinG study opted to enroll in any future extensions to this clinical trial. As a result, UCB is exploring the potential for further extension studies into this treatment.

For more information about the trial, visit https://clinicaltrials.gov/ct2/show/NCT03971422.

About the RAISE study[4]
The RAISE study (NCT04115293) was a multi-center, Phase 3, randomized, double-blind, placebo-controlled study to confirm the efficacy, safety profile, and tolerability of zilucoplan in adult patients with anti-acetylcholine receptor (AChR) antibody-positive gMG. Patients were randomized in a 1:1 ratio to receive daily subcutaneous (SC) injections of 0.3 mg/kg zilucoplan or placebo for 12 Weeks.

The primary endpoint for the RAISE study was change from baseline to Week 12 in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.

Secondary endpoints included change from baseline in the Quantitative Myasthenia Gravis (QMG) score, the Myasthenia Gravis Composite (MGC) and the Myasthenia Gravis Quality of Life 15 revised (MG-QoL15r) score from baseline to Week 12, time to first rescue therapy, the proportion of patients with minimal symptom expression (MSE) (defined as MG-ADL of 0 or 1 without rescue therapy), the proportion with a ≥3-point reduction in MG-ADL without rescue therapy and the proportion with a ≥5-point reduction in QMG without rescue therapy, all measured at Week 12. Safety was assessed by the incidence of treatment emergent adverse events (TEAEs). Patients who completed the RAISE trial had the possibility to enter the open-label extension study, RAISE-XT (NCT04225871).[4]

For more information about the trial visit https://clinicaltrials.gov/ct2/show/NCT04115293.

About rozanolixizumab
Rozanolixizumab is a subcutaneous administered, humanized monoclonal antibody that specifically binds, with high affinity, to human neonatal Fc receptor (FcRn). It has been designed to block the interaction of FcRn and Immunoglobulin G (IgG), accelerating the catabolism of antibodies and reducing the concentration of pathogenic IgG autoantibodies.[7]

*Rozanolixizumab-noli*** was approved by the FDA in June, for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive,[12] having been granted Priority Review for its Biologic License Application (BLA). Rozanolixizumab is also under review by the European Medicines Agency (EMA), the Australian Therapeutic Goods Administration (TGA) and Health

Canada for the treatment of adults with gMG. Responses from regulatory agencies to these submissions are expected during H2 2023 and H1 2024.

***In the U.S., the International Nonproprietary Name (INN) for rozanolixizumab is 'rozanolixizumab-noli' following the FDA's 'Non-proprietary Naming of Biological Products Guidance'. This guidance advises that the nonproprietary name designated for originator biological products should be a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters. This nomenclature only applies in the U.S.*

About zilucoplan
Zilucoplan is a once-daily SC, self-administered peptide inhibitor of complement component 5 (C5 inhibitor). As a C5 inhibitor, zilucoplan inhibits complement-mediated damage to the neuromuscular junction through its targeted dual mechanism of action.[4]

In September 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending granting marketing authorization for zilucoplan in the European Union (EU) as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.[5] Zilucoplan is also currently under review by the U.S. FDA, the Australian Therapeutic Goods Administration (TGA) and Health Canada for the treatment of adults with gMG. Responses from regulatory agencies to these submissions are expected during H2 2023 and H1 2024.

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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 approximately 8,600 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: the global spread and impact of COVID-19, 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 the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement activities and outcomes. Finally, a breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of UCB's data and systems.

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otherwise. UCB is following the worldwide developments diligently to assess the financial significance of this pandemic to UCB. UCB expressly disclaims any duty to update any information contained in this press release, either to confirm the actual results or to report or reflect any change in its forward-looking statements with regard thereto or any change in events, conditions or circumstances on which any such statement is based, unless such statement is required pursuant to applicable laws and regulations.

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