UCB News

New data published in the *Journal of Neurology* show clinically meaningful improvement of fatigue in generalized myasthenia gravis (gMG) with ZILBRYSQ®▼ (zilucoplan)

- Publication reports treatment with zilucoplan showed statistical and clinically meaningful improvements in fatigue scores and severity versus placebo at Week 12 during RAISE, which were sustained to Week 60 in RAISE-XT.
- With these findings, zilucoplan was the first C5 inhibitor to show a clinically meaningful reduction in fatigue including severe fatigue, which is especially debilitating for patients.
- Zilucoplan is the first once-daily subcutaneous (SC), targeted complement component 5 (C5) inhibitor for generalized myasthenia gravis (gMG), recently approved in the UK, Europe, the U.S., and Japan for adult patients with anti-acetylcholine receptor antibody positive (AChR-Ab+) gMG.[1,2,3,4]

Brussels (Belgium) 14 May 2024 – 07:00 AM (CET) – UCB, a global biopharmaceutical company, today announced that the *Journal of Neurology* has published data from a post hoc analysis of the pivotal Phase 3 RAISE study and the ongoing Phase 3 RAISE-XT open-label extension (OLE) study evaluating the long-term effect of zilucoplan on fatigue in adult patients with mild to severe anti-acetylcholine receptor antibody positive (AChR-Ab+) gMG.[5,6]

The results showed that patients with gMG treated with once daily subcutaneous injections of the complement C5 inhibitor zilucoplan experienced clinically meaningful improvements in fatigue sustained for more than a year.[5] Clinically meaningful improvement from baseline was defined as a change of − 3.5.

"For people living with gMG, fatigue can be debilitating and have a huge impact across daily life, reducing their ability to engage in physical, functional, social and mental activities. The unpredictable nature of these gMG symptoms can lead to feelings of vulnerability and lack of control," explained Donatello Crocetta, MD, Head of Global Rare Disease and Rare Medical at UCB. *"This post hoc analysis reveals ZILBRYSQ's role in helping manage an important yet understudied symptom of gMG. It follows the publication of the primary data in The Lancet Neurology last year which described clinically meaningful and statistically significant improvements in different MG-specific efficacy outcomes. UCB is committed to providing targeted treatment options that can help reduce the ongoing burden of gMG, giving patients flexible treatment options that work alongside their daily life."*

The post hoc analysis showed that mean Neuro-QoL Short Form Fatigue T-scores improved from double-blind baseline to Week 12 in the zilucoplan group (n=86) with a clinically meaningful difference versus placebo (n=88; least squares mean difference: −3.61 [nominal p-value=0.0060]), and these improvements were sustained up to Week 60 mean [SE] CFB −9.15 [1.80]. At Week 12, more patients on zilucoplan (n=34, 47.2%) experienced improvements in ≥1 fatigue severity level from baseline versus placebo (n=23, 28.4%; p=0.017).[5]

The improvements in fatigue observed in the zilucoplan group during the double-blind period of RAISE continued further into RAISE-XT, the ongoing OLE study, and were sustained up to Week 60 (mean [SE] CFB −10.71 [1.81]), indicating that zilucoplan improved fatigue in patients with MG up to 60 weeks. Among patients who transitioned from placebo to zilucoplan in the OLE (placebo-switch group), improvements were observed at the first week after switching to zilucoplan 0.3mg/kg (Week 13).[5]

Looking at fatigue severity scores, at double-blind baseline, the majority of patients had "severe" or "moderate" fatigue (n=66, 78.6%; N=84). Overall, by Week 60, most patients had seen an improvement to "mild" or no fatigue (n=55, 65.5%). These findings were consistent across the zilucoplan group and in the placebo-switch group (data not shown).

"The results showing improvements in fatigue scores and severity with zilucoplan treatment seen in the RAISE and RAISE-XT post hoc analysis are important as this is the first analysis of T-score transformation of Neuro-QoL Short Form Fatigue scores in patients with MG in a Phase 3 study, allowing us to assess the clinical meaningfulness of these data," said Michael Weiss, Professor of Neurology at University of Washington and lead author on the paper. *"Fatigue is one of the more debilitating symptoms in gMG and a major contributor to reductions in patients' health-related QoL. In addition to MG-specific outcome measures, it is important for clinicians to routinely measure fatigue as part of the overall assessment of MG symptoms in their patients."*

Overall, zilucoplan was well tolerated and had a favorable long-term safety profile. Out of 200 enrolled patients, 188 (94.0%) patients experienced a TEAE, and 64 (32.0%) patients experienced serious TEAEs. The most common TEAEs were (worsening of) MG (26.0%), COVID-19 (24.5%), headache (17.5%), diarrhoea (15.0%) and nasopharyngitis (15.0%). Seventeen (8.5%) patients had a TEAE resulting in permanent withdrawal from treatment.[5]

gMG is a rare, chronic, heterogeneous, unpredictable autoimmune disease characterized by dysfunction and damage at the neuromuscular junction (NMJ).[7,8,9] Several factors are understood to be drivers of gMG disease pathology, including the complement cascade, immune cells and pathogenic immunoglobulin G (IgG) autoantibodies.[7,8,9]

In AChR antibody positive gMG, pathogenic AChR autoantibodies (IgG1 and IgG3) initiate the classical complement pathway, which, together with the alternative and lectin complement pathways, converge at C5, leading to MAC (membrane attack complex) deposition, damage to the NMJ, loss of AChRs and subsequent impaired synaptic transmission.[9,10] Preventing MAC formation reduces damage to the post-synaptic membrane, reduces disruption of ionic channel conductance and helps to preserve neuromuscular transmission.

MG has a global prevalence of 100–350 cases per every 1 million people.[8]

Zilucoplan has been approved by the European Commission (EC), the US FDA, the Japanese Ministry of Health, Labour and Welfare (MHLW), and the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA), for the treatment of gMG.[1,2,3,4]

▼ *This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.*

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.[6]

In September 2023, the Japanese Ministry of Health, Labour and Welfare (MHLW) approved zilucoplan for the treatment of gMG in adult patients (only for patients who inadequately respond to steroids or other

immunosuppressants).[1] In October 2023, the U.S. Food and Drug Administration (FDA) approved zilucoplan for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.[3] In December 2023, the European Commission granted zilucoplan approval 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.[2] In January 2024, the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorization for Zilbrysq as an add-on to standard therapy for adult patients who are anti-acetylcholine receptor (AChR) antibody positive.[4]

Zilucoplan is currently under review by the Australian Therapeutic Goods Administration (TGA) and Health Canada for the treatment of adults with gMG. Responses from these regulatory bodies are expected during 2024.

About generalized myasthenia gravis (gMG)
gMG is a rare autoimmune disease with a global prevalence of 100–350 cases per every 1 million people.[5,8] 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.[7,11]

In MG, pathogenic autoantibodies can impair synaptic transmission at the neuromuscular junction (NMJ) by targeting specific proteins on the post-synaptic membrane.[12] This disrupts the ability of the nerves to stimulate the muscle and results in a weaker contraction.[9] gMG can occur in any race, gender or age. [7,11]

About the RAISE/RAISE-XT studies[5,6]
RAISE (NCT04115293) was a multi-centre, 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.[6]

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 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. Change from baseline to week 12 in Neuro-QoL short form fatigue scale was assessed as exploratory endpoint. The secondary safety endpoint was incidence of TEAEs.[6] A clinically meaningful improvement from baseline was defined as a change of – 3.5, and clinically meaningful worsening was defined as a change of + 3.2, in Neuro-OoL Short Form Fatigue T-score from double-blind baseline.[6]

Patients who completed the RAISE trial had the possibility to enter the open-label extension study, RAISE-XT (NCT04225871).[5,6] RAISE-XT is an ongoing, multicentre, open-label extension (OLE) study of zilucoplan where participants who completed the 12-week treatment period in either the Phase 2 double-blind study of zilucoplan or RAISE could opt to receive daily subcutaneous doses of 0.3mg/kg zilucoplan.[5,6]

For more information about the trials visit https://clinicaltrials.gov/ct2/show/NCT04115293 and https://clinicaltrials.gov/study/NCT04225871.

UCB News

About UCB

UCB, Brussels, Belgium 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).

▼ZILBRYSQ® (zilucoplan) EU/EEA* Important Safety Information

▼*This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions*. The most frequently reported adverse reactions were injection site reactions (injection site bruising (13.9%) and injection site pain (7.0%)) and upper respiratory tract infections (nasopharyngitis (5.2%), upper respiratory tract infection (3.5%) and sinusitis (3.5%)). The adverse reactions from the pooled placebo controlled (n=115) and open-label extension (n=213) studies in gMG are as follows: Very common adverse reactions: (≥ 1/10): Upper respiratory tract infections and Injection site reactions; Common adverse reactions (≥ 1/100 to < 1/10) Diarrhoea, Lipase increased, Amylase increased and Morphoea; Uncommon adverse reaction ((≥ 1/1000 to < 1/100) blood eosinophils increased. Zilucoplan is contra-indicated in patients with hypersensitivity to the active substance or to any of the excipients, in patients who are not currently vaccinated against *Neisseria meningitidis* and in patients with unresolved *Neisseria meningitidis* infection. Due to its mechanism of action, the use of zilucoplan may increase the patient's susceptibility to infections with *Neisseria meningitidis*. As a precautionary measure, all patients must be vaccinated against meningococcal infections, at least 2 weeks prior to the start of treatment. If treatment needs to start less than 2 weeks after vaccination against meningococcal infections, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose. Meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infections. Vaccines against serogroups A, C, Y, W, and where available, serogroup B, are recommended for preventing the commonly pathogenic meningococcal serogroups. Vaccination and prophylactic antibiotic treatment should occur according to most current relevant guidelines. During treatment, patients should be monitored for signs and symptoms of meningococcal infection and evaluated immediately if infection is suspected. In case of a suspected meningococcal infection, appropriate measures such as treatment with antibiotics and discontinuation of treatment, should be taken until the meningococcal infection can be ruled out. Patients should be instructed to seek immediate medical advice if signs or symptoms of meningococcal infections occur. Prescribers should be familiar with the educational materials for the management of meningococcal infections and provide a patient alert card and patient/carer guide to patients treated with zilucoplan. In addition to Neisseria meningitidis, patients treated with zilucoplan may also be susceptible to infections with other Neisseria species, such as gonococcal infections. Patients should be informed on the importance of gonorrhea prevention and treatment. Prior to initiating zilucoplan therapy, it is recommended that patients initiate immunizations according to current immunization guidelines. *Please consult the full prescribing information in relation to other side effects, full safety and prescribing information.* Zilbrysq, INN-zilucoplan (europa.eu)

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