UCB News

Results published in *Neurology* highlight a 95% reduction in risk of death with pyrimidine nucleos(t)ide therapy in patients with thymidine kinase 2 deficiency (TK2d)

- First published data from a multicenter retrospective chart review study to explore the safety and efficacy of pyrimidine nucleoside and/or nucleotide therapy in patients with thymidine kinase 2 deficiency (TK2d).[1]
- *Neurology* published results from a multicenter retrospective chart review study of pyrimidine nucleoside and/or nucleotide therapy which showed a reduction in the risk of death by 95%.[1]
- UCB's pyrimidine nucleoside therapy is currently under regulatory review by US and EU regulatory authorities. If approved, it will become the first and only treatment for TK2d in patients with an age of symptom onset on or before 12 years.[2]

Brussels (Belgium) October 13, 2025 – 07:00 (CET) – UCB, a global biopharmaceutical company, today announced that *Neurology* has published results from a multicenter retrospective chart review study of investigational pyrimidine nucleoside and/or nucleotide therapy in people living with thymidine kinase 2 deficiency (TK2d). The results indicated that pyrimidine nucleoside and/or nucleotide therapy may reduce risk of death and can impact functional outcomes in patients with TK2d.[1]

TK2d is an ultra-rare, life-threatening, genetic mitochondrial disease characterized by progressive and severe muscle weakness (myopathy), which can impact the ability to walk, eat, and breathe independently.[3,4,5,6,7]

Key findings of the *Neurology* publication include:

- No deaths among treated patients (0/38), compared to 58% mortality in untreated patients (40/69).
- Estimated reductions in risk of death with treatment were between 85% and 93% (HR 0.067–0.147) for time from TK2d symptom onset and between 75% and 91% (HR 0.091–0.251) for time from treatment start. Treated patients showed a 95% reduction in risk of death by exact conditional logistic regression analysis.[1]
- Before treatment, around 71% (27/38) of patients lost ≥1 motor milestone and 29% (11/38) of patients lost ≥4 motor milestones. During treatment, no patients lost motor milestones, and after starting treatment, of those who had lost motor milestones, 65% (17/26) regained at least one motor milestone.[1]
- Over 50% (19/38) of the patients were using ventilatory support before treatment. Among those who received treatment, 29% (6/21) experienced a reduction in their need for ventilatory support.[1]

Safety information:

- Most treatment-emergent adverse events (TEAEs) were mild and did not lead to discontinuation.[1] The most common TEAEs were diarrhea (overall 26/38, 68% those treated with age of symptom onset of ≤12 years, 18/29, 62%), increased blood creatine kinase (CK; overall, 9/38, 23%; those treated with age of symptom onset of ≤12 years, 8/29, 28%), pyrexia (overall, 6/38, 16%; those treated with age of symptom onset of ≤12 years, 6/29, 21%), increased alanine aminotransferase (ALT; overall, 6/38, 16%; those treated with age of symptom onset of ≤12 years, 5/29, 17%), and increased aspartate aminotransferase (AST; overall, 5/38, 13%; those treated with age of symptom onset of ≤12 years, 4/29, 14%).[1]

Study limitations:

Date of preparation: September 2025 | GL-MT-2500022

- The study's limitations included potential selection bias due to differing eligibility criteria (mitigated, in part, by a patient matching algorithm), large confidence intervals from no deaths in the treated group complicating result precision, low patient numbers due to the rarity of the condition, and challenges in comparing treated and untreated groups due to variability in data collection and assessment protocols, as well as missing additional data on patient health metrics.[1]

"Publication of these results in *Neurology,* a leading medical journal, underscores the significance of these data for the TK2d community," said Cristina Domínguez-González, Neurology Specialist, University Hospital 12 de Octubre, Madrid, and lead author. "Our study showed positive results, with pyrimidine nucleoside and/or nucleotide therapy demonstrating improvement in survival. These findings highlight the potential of pyrimidine nucleoside and/or nucleotide therapy as a clinically important therapeutic option, offering hope for a new standard of care if approved by the regulatory authorities."

"TK2 deficiency is an ultra-rare, progressive mitochondrial disorder with no approved therapies or internationally recognized clinical guidelines, leaving patients and families with only supportive disease management," said Donatello Crocetta, Chief Medical Officer at UCB. "As part of our mission to address severe, underserved diseases, the publication of these findings marks an important milestone — reinforcing our commitment to advancing science into potential first-in-class medicines for this community."

About thymidine kinase 2 deficiency (TK2d)
Mitochondrial diseases, like TK2d, affect energy-demanding parts of the body such as muscles, heart, and brain.[4,5,8] TK2d is generally categorized as: age of symptom onset ≤12 years and >12 years.[3,4,5] TK2d presents with varying severity depending on the age of onset, with cases in the population with age of symptom onset ≤12 years typically being the most rapidly progressing and cases in the population with age of symptom onset >12 years slower progressing.[3,4,5] The estimated worldwide prevalence of TK2d is 1.64 [0.5, 3.1] cases per 1,000,000 people.[9]

TK2d profoundly affects multiple health, physical, quality-of-life, and psychosocial domains, as children struggle to achieve developmental milestones or lose them, and adults lose functional independence with challenges in breathing, eating, and walking.[10,11]

About doxecitine and doxribtimine
Administration of doxecitine and doxribtimine is intended to incorporate the pyrimidine nucleosides, deoxycytidine and deoxythymidine, into skeletal muscle mitochondrial deoxyribonucleic acid (DNA). This action restores mitochondrial DNA copy number in TK2d mutant mice, as suggested by preclinical data.[12,13,14]

The safety and efficacy of doxecitine and doxribtimine combination therapy has not been established and is not currently approved for use by any regulatory authority worldwide. It is currently under regulatory review by US and EU regulatory authorities.

For further information, contact UCB:

Global Communications
Nick Francis
T: +44 7769 307745
nick.francis@ucb.com

Date of preparation: September 2025 | GL-MT-2500022

UCB News

Corporate Communications, Media Relations
Laurent Schots
T +32.2.559.92.64
Laurent.schots@ucb.com

Investor Relations
Antje Witte
T +32.2.559.94.14
antje.witte@ucb.com

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 9000 people in approximately 40 countries, the company generated revenue of € 6.1 billion in 2024. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

Forward looking statements
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

Date of preparation: September 2025 | GL-MT-2500022

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.

Given these uncertainties, you should not place undue reliance on any of such forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labelling in any market, or at any particular time, nor can there be any guarantee that such products will be or will continue to be commercially successful in the future.

UCB is providing this information, including forward-looking statements, only as of the date of this press release and it does not reflect any potential impact from the evolving COVID-19 pandemic, unless indicated 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.

Additionally, information contained in this document shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any offer, solicitation or sale of securities in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to the registration or qualification under the securities laws of such jurisdiction.

References:

1. Domínguez-González C, et al. Pyrimidine Nucleos(t)ide Therapy in Patients With Thymidine Kinase 2 Deficiency. Neurology. 2025;105(6):e213908.
2. Thymidine kinase 2 deficiency. National Organization for Rare Disorders. Updated April 3, 2025. https://rarediseases.org/rare-diseases/thymidine-kinase-2-deficiency/. Accessed September 2025.
3. Berardo A, et al. Advances in Thymidine Kinase 2 Deficiency: Clinical Aspects, Translational Progress, and Emerging Therapies. J Neuromuscul Dis. 2022;9(2):225-35.
4. Wang J, et al. TK2-Related Mitochondrial DNA Maintenance Defect, Myopathic Form. 2018. In: Adam MP, et al. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025.
5. Garone C, et al. Retrospective natural history of thymidine kinase 2 deficiency. J Med Genet. 2018;55(8):515-21.
6. Domínguez-González C, et al. Late-onset thymidine kinase 2 deficiency: a review of 18 cases. Orphanet J Rare Dis. 2019;14(1):100.
7. National Institutes of Health. TK2-related mitochondrial DNA depletion syndrome, myopathic form. https://medlineplus.gov/genetics/condition/tk2-related-mitochondrial-dna-depletion-syndrome-myopathic-form/#genes. Accessed September 2025.
8. Cleveland Clinic. Mitochondrial Diseases. https://my.clevelandclinic.org/health/diseases/15612-mitochondrial-diseases. Accessed September 2025.

Date of preparation: September 2025 | GL-MT-2500022

9. Ma Y. 2023. ISPOR Europe. EPH140.
10. Amtmann D, et al. The impact of TK2 deficiency syndrome and its treatment by nucleoside therapy on quality of life. Mitochondrion. 2023;68:1-9.
11. United Mitochondrial Disease Foundation. TK2d Patient Listening Session. https://www.umdf.org/tk2d-patient-listening-session-january-2022. Accessed September 2025.
12. Lopez-Gomez C, et al. Deoxycytidine and Deoxythymidine Treatment for Thymidine Kinase 2 Deficiency. Ann Neurol. 2017;81(5):641-52.
13. Lopez-Gomez C, et al. Bioavailability and cytosolic kinases modulate response to deoxynucleoside therapy in TK2 deficiency. EBioMedicine. 2019;46:356-67.
14. ClinicalTrials.gov. NCT04581733. https://clinicaltrials.gov/study/NCT04581733#contacts-and-locations. Accessed September 2025.

Date of preparation: September 2025 | GL-MT-2500022