Umecrine Cognition to present preclinical results showing beneficial effects of golexanolone on neuroinflammation and movement dysfunction

STOCKHOLM – February 21, 2022. Umecrine Cognition AB today announces that the company will present positive data from a recently concluded nonclinical study at the 11th International Meeting on Steroids and Nervous System. Novel findings reveal that treatment with the company's most advanced drug candidate golexanolone is linked to reduction in neuroinflammation and improvements in motor impairment, symptoms that arise as a result of chronic liver disorders and other similar pathologies. The data will be presented at the international meeting on February 19–22, 2022.

Umecrine Cognition is developing golexanolone, a novel GABAA receptor modulating steroid, which is currently in clinical development for impairments in the brain that arise due to the chronic liver diseases primary biliary cholangitis (PBC) and hepatic encephalopathy (HE). Based on its novel mode of action, golexanolone shows potential also for development in other indications related to neuroinflammation.

Neuroinflammation plays a key role in the induction of neurological impairment in a number of disease states, including toxic accumulation of ammonia (HA), HE, and PBC. This is a complex process involving activation of brain immune cells, such as microglia and astrocytes, and an increased production of pro-inflammatory factors. Current treatments of neuroinflammation have been found to reverse cognitive symptoms and motor impairment in research models of several diseases, suggesting that reduced neuroinflammation could improve the neurological status also in patients. For this reason, it is desirable to develop new treatments to safely and effectively reduce neuroinflammation.

The principal objective of the study performed in collaboration with Dr Vicente Felipo, at the Laboratory of Neurobiology, Centro de Investigación Principe Felipe, Valencia, was to evaluate whether oral treatment with golexanolone, at a clinically relevant dosage for human use, could reduce neuroinflammation in cerebellum in a disease model of chronic hyperammonemia (HA). To detect potential activation of microglia and astrocytes, the researchers used immunohistochemistry. As neuroinflammation in the cerebellum is associated with impaired motor coordination, the study investigated whether treatment with golexanolone could reverse movement dysfunction in HA. Motor coordination and locomotor gait were analyzed using the Motorater and CatWalk systems.

The study results revealed three key insights.

- Firstly, activation of astrocytes, as measured by the neuroinflammation marker Glial Fibrillary Acidic Protein (GFAP), was increased in the cerebellum of HA rats (129±5 % of control group; p<0.01). Treatment with golexanolone reversed the activation in this population of immune cells in HA rats, reflected by a reduction in GFAP levels (101±7 % of control rats; p<0.01)
- Secondly, in activated microglial cells, which is reflected in a reduced area, the area of the cells was reduced in the molecular layer of cerebellum in HA rats (127±6 µm2 versus 172±5 µm2 in the control group; p<0.05). Treatment with golexanolone reversed this effect, increasing the area of microglia in HA rats to 196±15 µm2, p<0.001. Similar effects were observed in the white matter.
- Thirdly, the number of errors in motor coordination was significantly higher in HA rats (1.40±0.16 slips, p<0.01) than in the control group (0.67±0.12), as measured with the Motorater. Treatment with golexanolone restored motor coordination, reflected by a reduction in the number of errors (0.70±0.14, p<0.05). In addition, analyses of locomotor gait in the CatWalk showed that HA rats experienced altered stand index, print area, swing, stride length, step cycle as well as dual stance. Treatment with golexanolone reversed all these alterations, returning the parameters to control values.

While the processes that lead to neuroinflammation, and which brain areas that are affected, may vary between neurological indications, the basic mechanisms are similar. Activation of brain immune cells and production of pro-inflammatory factors that alter neuronal function, are key mechanisms involved in all types of neuroinflammation associated to cognitive and motor impairment. It has been proposed that there is an interplay between neuroinflammation and GABAergic neurotransmission by which each one impact the other [1,2] and that, as a consequence of this interplay, neuroinflammation may be reduced by modulating GABAergic neurotransmission.

Umecrine Cognition's novel findings, to be presented at the meeting, have extended this finding, and demonstrates that by reducing the activation of GABAA receptors through treatment with golexanolone, activation of key immune cells resulting from hyperammonemia in the cerebellum may be reversed. The data further indicate that reversal of neuroinflammation is associated with reversal of motor dysfunction [3].

"Immunotherapy is a current research hotspot in neurodegenerative diseases and we are excited to, for the first time, present that by reducing the activation of GABAA receptors through treatment with our neurosteroid-based candidate drug golexanolone we may tackle neuroinflammation. Based on these and other supportive non-clinical and clinical results, we will continue our scientific collaborations and activities to explore golexanolone's therapeutic potential in full", said Magnus Doverskog, CEO of Umecrine Cognition.

The study results have been selected for an oral communication and will be presented by Dr Vicente Felipo at the 11th International Meeting on Steroids and Nervous System, on Monday, February 21, at 09.15-10.30 CET. A pdf copy of the abstract book will be put on the meeting web site before the beginning of the meeting (https://sites.google.com/view/neurosteroids2022/history).

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About Umecrine Cognition AB

Umecrine Cognition's golexanolone (aka GR3027) represents a first-in-class orally active product designed to normalize GABA-ergic transmission, of which allosteric activation by neurosteroids is implicated in several major CNS-related disorders, including HE, a potentially life-threatening disorder with high and growing unmet medical need, and cognitive dysfunction associated with PBC. Golexanolone was shown to inhibit allosteric activation by neurosteroids and normalize GABA-ergic transmission in humans. For more information, please visit www.umecrinecognition.com and see the references below.

[1] Groh J, Martini R. Neuroinflammation as modifier of genetically caused neurological disorders of the central nervous system: Understanding pathogenesis and chances for treatment. *Glia*. 2017;65 (9):1407-1422.

[2] Cabrera-Pastor A, et al. Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic encephalopathy: Underlying mechanisms and therapeutic implications. *Acta Physiol* (Oxf). 2019;226(2):e13270.

[3] Mincheva G. et al., 2022. GR3027, a GABAA receptor modulating steroid antagonist, reverses neuroinflammation in cerebellum and restores motor coordination in hyperammonemic rats. Abstract accepted for oral presentation at the 11th Steroids & Nervous systems Meeting, February 19-22, 2022.

Attachments

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