Positive Phase 1 top line data with GR3027 demonstrate safety, tolerability, and CNS target engagement

STOCKHOLM/UMEÅ. Umecrine Cognition AB, a Karolinska Development (Nasdaq Stockholm: KDEV) portfolio company today announced positive top-line results from its Phase 1 first in human clinical trial with GR3027, a novel orally active GABAA receptor modulating steroid antagonist, in development for treatment of hepatic encephalopathy (HE) in patients with liver cirrhosis.

"We are very encouraged by the pharmacodynamic effect of GR3027 in our Phase 1 trials, along with its favorable safety and tolerability profile," said Magnus Doverskog, CEO of Umecrine Cognition. "These findings show that oral GR3027 reaches the brain target with an expected mechanism of action and combined with our previous pre-clinical results [1] support our belief that GR3027 could be an attractive new therapy for patients with liver cirrhosis and hepatic encephalopathy."

Umecrine Cognition's lead candidate GR3027 is designed to reduce GABAA receptor mediated inhibition of brain function by antagonizing endogenous inhibitory neurosteroids such as allopregnanolone. Enhanced GABAA receptor mediated signaling is a key driver for the neurological symptoms associated with HE.

In the current trial, GR3027 was found to be well tolerated with no serious adverse events reported and with dose proportional pharmacokinetics. Assessment of Saccadic Eye Velocity and self-rated sedation after a challenge with allopregnanolone showed evidence that orally administered GR3027 antagonizes neurosteroid modulation of GABAA receptor function.

The primary objectives of the study were to evaluate the safety and tolerability of GR3027 after single dose administration in healthy volunteers and to identify the Maximum Tolerated Dose (MTD) or the Study Maximal Dose (SMD), if the MTD was not reached. The secondary objectives were to determine the single oral dose PK characteristics of GR3027 in healthy volunteers and to evaluate the capacity of GR3027 to antagonize allopregnanolone-induced activation of GABAA as determined by its pharmacodynamic effects on Saccadic Eye Velocity (SEV) and self-rated sedation.

In the first part, 48 subjects were randomized to receive either GR3027 or placebo (6:2) at doses ranging from 1 mg to 200 mg. None of the pre-specified dose escalation stopping criteria were obtained and GR3027 was found to be well tolerated throughout the dose range up to the SMD of 200 mg. The pharmacokinetic profile obtained displayed dose linearity over the dose range applied.

In the second part of the study, 18 subjects were randomized in a three-part cross-over design to receive either GR3027 at 3 mg (low dose) or 30 mg (high dose), or placebo. As expected, allopregnanolone administration decreased SEV in the placebo group. Prespecified statistical analysis of the difference between treatment groups with GR3027 and placebo showed a significant improvement with GR3027 in the high dose group (p=0.03; Wilcoxons Signed Rank Test). The results also provide evidence that the impaired self-rated sedation produced by allopregnanolone was also improved by GR3027.

The company plans to announce further details and data of the trial at the 9th International Meeting – Steroids and Nervous System in Torino, Italy (February 11-15, 2017).

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TO THE EDITORS

About Umecrine Cognition AB
Umecrine Cognition, a Karolinska Development (Nasdaq Stockholm: KDEV) portfolio company, is developing a potential therapy that represents a new target class relevant for several major CNS-related disorders. The primary focus is to develop a treatment for life-threatening overt Hepatic Encephalopathy and long-term treatment in minimal Hepatic Encephalopathy in patients with liver disease, a growing area with high unmet medical need. The current lack of therapeutics that directly addresses the neurocognitive signs and symptoms of Hepatic Encephalopathy makes a novel treatment likely to become a major contribution for the treatment of this disorder. For more information, please visit www.umecrinecognition.com.

About Hepatic Encephalopathy (HE)
HE is a frequent neurological complication and one of the most debilitating manifestations of liver disease affecting millions around the world. Caused by liver insufficiency, HE leads to a general depression of the central nervous system with clinical manifestations ranging from mild cognitive impairment to deep coma. This severely affects the lives of patients and their caregivers. The cognitive impairment associated with cirrhosis can also result in the utilization of more health care resources for adults than other manifestations of liver disease. There are no known treatments on the market that directly target the neurological cause of HE.

References
[1] Johansson M et al., GR3027 antagonizes GABAA receptor potentiating neurosteroids and restores spatial learning and motor coordination in rats with hepatic encephalopathy, Am J Physiol Gastrointest Liver Physiol. 2015 Sep 1;309(5):G400-9