PROTOCOL SUMMARY

Study title: *A two-part study to investigate the effects in adults of two doses of a new drug called golexanolone in patients with primary biliary cholangitis with fatigue and cognitive dysfunction*

Study code: UCAB-CT-05

EU Trial Number: 2024-515907-20-00

Sponsor: Umecrine Cognition AB

Rationale: The clinical study named UCAB-CT-05 is a Phase 1b/2 trial evaluating a new drug called golexanolone in patients with primary biliary cholangitis with fatigue and cognitive dysfunction. Primary biliary cholangitis (PBC) is a serious chronic liver disease that harms the liver's ability to function. Patients with PBC can experience cognitive dysfunction: inability to think, learn and remember clearly. Also they experience significant fatigue (tiredness).

Golexanolone is a new drug that was developed for treatment of the spectrum of cognitive dysfunction associated with chronic liver disease. Up to date, golexanolone has been investigated in research studies in more than 100 people, including healthy adults, patients with cirrhosis, and patients with idiopathic hypersomnia, in single and multiple doses up to 200 mg daily. In all human studies to date, golexanolone has been well tolerated.

Objectives: The present study was designed to evaluate how safe and well tolerated golexanolone is, how golexanolone is absorbed, modified, and removed from the body, and evaluate the effects of golexanolone on your symptoms. The effects of golexanolone will be compared with placebo (inactive substance).

Main trial endpoints: The endpoints include tracking side effects, and changes in safety parameters, like physical examination, measurements of your blood pressure, pulse rate, and body temperature, and laboratory test results.

Secondary trials endpoints:

- the level of golexanolone in your blood
- the intensity of your symptoms, like sleepiness, cognitive function and quality of life

Trial design: The study consists of two separate parts:

- In Part A (completed) participants who qualified were randomly assigned in a 3:1 ratio to receive either golexanolone 40 mg or placebo orally twice daily for 5 days at the clinic (a full procedure) or at clinic and at home (a modified procedure).
- In Part B participants who qualify will be randomly assigned in a 1:1:1 ratio to receive either golexanolone 40 mg or golexanolone 80 mg or placebo orally twice daily for 28 days.

The total duration of Part A for a participant was maximum 5 weeks (± 3 days), with 8 days in clinic (hospitalisation) and one follow-up visit (the full procedure) or with visit to clinic at Day 1,

18-hour hospitalisation (6 hours on Day 1 and 12 hours on Day 5- Day 6), daily phone calls (Day 2 – Day 5) and one follow-up visit (the modified procedure).

The total duration of part B for a participant will be maximum 8 weeks (± 3 days), with 5 visits to a clinic and 2 phone calls.

The total duration of Part A and part B for a participant will be maximum of 17 weeks (5 + 8 weeks with a period of at least 1 month between completion of Part A and randomisation in Part B).

Previously prescribed PBC therapy will be allowed as long as it is stable during the study.

Trial population: Male and female participants aged 18 years or older, with confirmed PBC, with presence of fatigue and cognitive symptoms, and on stable treatment, without any other significant illnesses.

Interventions:

- Participants will take golexanolone or placebo capsules
- Participants will undergo several assessments:
  - blood sampling
  - urine collection
  - alcohol breath test
  - electrocardiogram (ECG, to measure the electrical activity of the heart);
  - vital signs measurements (blood pressure, heart rate and body temperature)
  - physical examination (including height, weight, and body mass index)
  - data collection about demographic data, past medical history, prior and concomitant medications, symptoms, or side effects observed during the study.

Ethical considerations: The study will be conducted according to consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, and applicable laws and regulations.

Based on research in animals and patients with cirrhosis, it is assumed that golexanolone may offer normalization of cognitive dysfunction and fatigue in patients with PBC.

Given the available nonclinical and clinical data to date about golexanolone, considering the potential improvement in participants, and the scientific value, the conduct of the study is considered justifiable.