GALAXY

GUT-AND-LIVER AXIS IN ALCOHOLIC LIVER FIBROSIS
GRANT NUMBER 668031

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1. AIMS

IDENTIFIED AND INCLUDED 40 PATIENTS IN SYN-ALD

1. PATIENTS IDENTIFIED WITH CURRENT OR PRIOR ALCOHOL OVERUSE AND ALCOHOLIC LIVER FIBROSIS BASED ON THE CURRENT AVAILABLE STATE-OF-THE-ART NON-INVASIVE BIOMARKERS. INCLUSION CRITERIA ALSO INCLUDES A DYSBIOTIC MICROBIOME AS DEFINED BY WP4. ELIGIBLE PATIENTS ARE RECRUITED FROM ALCOHOL ABUSE CENTRES, OUTPATIENT LIVER CLINICS, EMERGENCY ROOMS AND FAMILY PHYSICIANS IN REGION OF SOUTHERN DENMARK AND VIA NATIONAL WEB ADVERTS.

2. FORTY PATIENTS INCLUDED:
COLLECT INFORMED CONSENT. AFTER CONSENT, PATIENTS WILL BE RANDOMISED IN A 1:1, DOUBLE-BLIND MANNER. RANDOMISATION STRATIFIES ACCORDING TO DRINKING STATUS AND DEGREE OF FIBROSIS. AFTER RANDOMISATION, ALL INVESTIGATIONS WILL BE PERFORMED AS DESCRIBED IN 1.2 EXCEPT LIVER BIOPSY.

2. RESULTS

We included the final patient in the SYN-ALD study on January 15th. At this time, we had included and randomised a total of 55 patients; 27 randomised to Fresubin and 28 to Profermin. As described in deliverable 1.6, the revised protocol estimated that 40 patients with compensated advanced chronic alcohol-related liver disease needed to be randomised to detect ≥10% attenuation in biopsy-verified hepatic expression of α-smooth muscle actin (αSMA), for 15% of participants in the Fresubin group versus 60% of participants in the Profermin group, in an intention-to-treat analysis. However, we decided to include 15 extra patients, due to a dropout rate which exceeded our expected estimate. We consequently included and randomized 55 patients to ensure an adequate number of participants with valid liver biopsy data for assessment of the primary endpoint. Eleven patients have dropped out of the study until now; six patients randomised to Profermin (4 withdrawals due to personal issues, and 2 withdrawals due to adverse effects of the study intervention), and five patients randomised to Fresubin (4 due to personal issues, and 1 due to an inconclusive biopsy at inclusion and end of trial). We have experienced technical challenges the baseline liver biopsy in four included patients were not of sufficiently good quality to assess the primary outcome. We therefore temporarily withdrew three of these patients from the trial. After a wash out period of at least 3 months we performed a new baseline liver biopsy and biobank sampling, before restarting them in study intervention according to their original randomisation number.
Originally, we planned for performing a transjugular liver biopsy in included patients, to allow for simultaneous liver vein catherisation with liver venous blood sampling and portal pressure measurement. However, shortage in specialised staff, and the COVID-19 pandemic, caused a substantial decrease in liver vein catherisations. We therefore instead obtained a percutanous liver biopsy in the majority of

patients at start- and end-of-treatment. Due to the reasons described above, we only obtained liver venous blood samples and transjugular biopsies in 12 participants.
As described in AMD-668031-20, the patients are not selected based on a dysbiotic profile, as originally planned, but rather on having compensated advanced chronic alcohol-related liver disease, defined by liver stiffness ≥15 kPa and/or F3-F4 cirrhosis on liver biopsy, and stable disease (no Child-Pugh class C, MELD score >15, or recent decompensation). Therefore, we recruit patients from hospital outpatient liver clinics, rather than from primary care. We were also able to recruit some patients from our own screening study to assess liver stiffness measurement as a method for liver fibrosis detection (H2020 grant number 847989, LiverScreen consortium; and Novo Nordisk Foundation grant number NNF20OC0059393)

Currently, 20 patients have finished the 6-month treatment period, 24 patients are active in the study, and 11 have dropped out of the study. The 55 randomised patients are mostly male (46/55, 84%), the mean age is 61 years (range 43-72y), mean MELD-Na score is 9 (range 7-14) and mean liver stiffness is 26.9 kPa (range 5.7-64.3).
The research database at Odense University Hospital contains baseline plasma and serum from periphery vein from all 55 randomised patients and lever vein plasma and serum in 12 patients. Faecal, urine and saliva sample is missing in approximately 5% of patients due to patient non-compliance. Biobank also contains liver samples from approximately half of included patients since biobanking is not always possible for the liver tissue due to small samples specimen.