GALAXY

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

DELIVERABLE NUMBER: D1.8
DELIVERABLE DUE DATE: 31 July 2021
(According to 3rd Periodic Reporting)
COMPLETION DATE OF DELIVERABLE: 12 July 2021
DISSEMINATION LEVEL: PUBLIC

DOCUMENT MAIN AUTHOR: WP1, Maja Thiele, OUH
DOCUMENT SIGNED OFF BY: Project Manager Louise Skovborg Just (University of Southern Denmark)

1. Aims

Treated and evaluated patients in SYN-ALD

1. Profermin and matching placebo produced and labelled for central randomisation. Due to the perishable nature of the intervention, active drug and placebo will be produced continuously.

2. Fourty patients treated, followed and evaluated at end-of-treatment: Treat with Profermin or placebo. The mixtures are provided by Nordic Rebalance. Patients are investigated at day 0 and seen again at four visits until month 6. A project nurse registers compliance, side-effects, alcohol use and adverse events. NR will gather clinical data during treatment in parallel with the participating hospital. Undertake end-of-treatment investigations. All investigations will be performed as described in 1.2 including a liver biopsy.

2. Results

Profermin and matching control (Fresubin Original) have been delivered by Nordic Rebalance (BEN 8). Both products have a shelf life of 9-10 months. According to the schedule of the clinical study, it was calculated that two batches of test product and two batches of control product should be used. Nordic Rebalance was to produce two batches of Profermin and purchase control product, Fresubin Original, twice each from different batches. Due to the schedule for the clinical study was extended, Nordic Rebalance had to produce another batch of Profermin and purchase Fresubin from another new batch. In summary, three batches of Profermin have been produced and Fresubin purchased from three batches during the clinical study.
The responsible conductor of the clinical study from OUH regularly contacted Nordic Rebalance for more product when needed. New product were delivered within a few days.

As described in deliverable 1.7 we included 56 participants in SYN-ALD. There were 28 participants randomised to both the Fresubin and Profermin group. As previously described in deliverable 1.6 and 1.7, 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 16 extra patients, due to a dropout rate which exceeded our expected estimate, and examples of biopsies which did not meet quality criteria for reliable histological reading. We consequently included and randomized 56 patients to ensure an adequate number of participants with valid liver biopsy data for assessment of the primary endpoint.

The last participant completed the 24 week intervention period on the 5th of July 2021, resulting in 41 participants with successful and valid liver biopsies at both baseline and end-of-treatment. This is essential for assessing the primary endpoint. In total 14 participants have dropped out of the study, seven in the Profermin group (5 withdrawals due to personal issues, and two withdrawals due to adverse effects of the study intervention), and seven patients randomised to Fresubin (6 due to personal issues, and 1 due to an inconclusive biopsy at inclusion and end of trial). 39 participants have completed the last visit “end

of study" 4-8 weeks after the intervention was completed (figure 1). The last two visits are scheduled in the beginning of August 2021.
During the clinical trial Nordic Rebalance was informed of the progress in recruiting of participants, dropout rate and clinical data.

The inclusion visit (week 0) consisted of collection of signed informed consent, same-day extensive phenotyping with demographical data, quality of life questionnaires, medical history, hand-grip-strength, liver routine blood samples, abdominal ultrasonography, and liver elastography to assess liver stiffness and a liver biopsy for both pathological purposes and for the biobank. Collected tissue samples for the biobank: full blood, plasma, serum, liver tissue, stool, saliva, urine and hair. After the investigations were completed, the participants were randomized into either the Profermin or the Fresubin group. A dietician introduced participants to the assigned product. We instructed the participants to contact a study employee if they noticed any side effects or adverse events between visits.
A dietitian conducted compliance visits after 4, 8 and 16 weeks of the intervention period. A compliance questionnaire was filled out. The participants collected lids from product ingested between visits. The lids were counted and the dietitian noted if any lids were missing. Furthermore, registrations of changes in drinking habits, lifestyle in general, or medication were reported. Abstinence from alcohol was always advised. If participants were in need of more study product, it was provided. Blood tests for immediate analysis was performed. Furthermore, at V1 biological samples were collected for the biobank: blood, urine, stool, saliva and hair.
To further secure compliance, the participants were contacted by telephone at least 9 times during the intervention. The telephone calls consisted of the same questions as the compliance visits.
After 24 weeks the participants came for investigations after intervention. A few participants had extended their intervention period with a few weeks due to practical reasons related to COVID-19. The visit corresponded to inclusion visit and consisted of same-day extensive phenotyping with demographical data, quality of life questionnaires, medical history, hand-grip-strength, liver routine blood samples, abdominal ultrasonography, and liver elastography to assess liver stiffness and performed a liver biopsy for both pathological purposes and for the biobank. Additionally we sampled tissue for biobank: blood, faeces, saliva, urine and hair. After the investigations, the participants were instructed not to ingest more study product.
4-8 weeks after intervention period the participants were invited for a follow-up visit. It was noted if there had been any change in drinking habits, lifestyle or medicine. Collection of material for the biobank were made.

Investigations and measurements	0 Week	4 Weeks	8 Weeks	16 Weeks	24 Weeks	End of study (4-8 weeks after last visit)
Time consumption	Whole day + 1 hour another day	30 minutes	30 minutes	30 minutes	Whole day + 1 hour another day	30 minutes
Follow up on compliance, adverse events and alcohol consumption	X	X	X	X	X	
Transjugular liver biopsy, portal pressure and liver vein blood sample	X				X	
Standard blood test	X	X	X	X	X	X
Venous fasting blood	X	X			X	X
Faeces	X	X			X	X
Urine	X	X			X	X
Saliva	X	X			X	X
Hair	X	X			X	X
Non-invasive assessments of liver fibrosis (Fibroscan, Aixplorer elastography)	X				X	
Nutritional status	X				X	
Questionnaires	X				X	
Preparation from participants	Meet fasting Overnight stay at the hospital*	Meet fasting	None	None	Meet fasting Overnight stay at the hospital*	Meet fasting

Figure 1. Overview of visits and investigations