GALAXY

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

DELIVERABLE NUMBER: D1.3
DELIVERABLE DUE DATE: 30 November 2021
(According to Periodic Report for 3rd Period)
COMPLETION DATE OF DELIVERABLE: 30 November 2021
DISSEMINATION LEVEL: PUBLIC

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1. AIMS

1. PATIENTS IDENTIFIED FROM GALA-ALD WITH ESTABLISHED LIVER DISEASE BASED ON LIVER HISTOLOGY (FIBROSIS DEGREE F0-3). THE STUDY WILL INCLUDE BOTH ONGOING ALCOHOL ABUSERS AND NON-DRINKERS TO ELUCIDATE THE IMPACT OF ALCOHOL ON THE MICROBIOME.

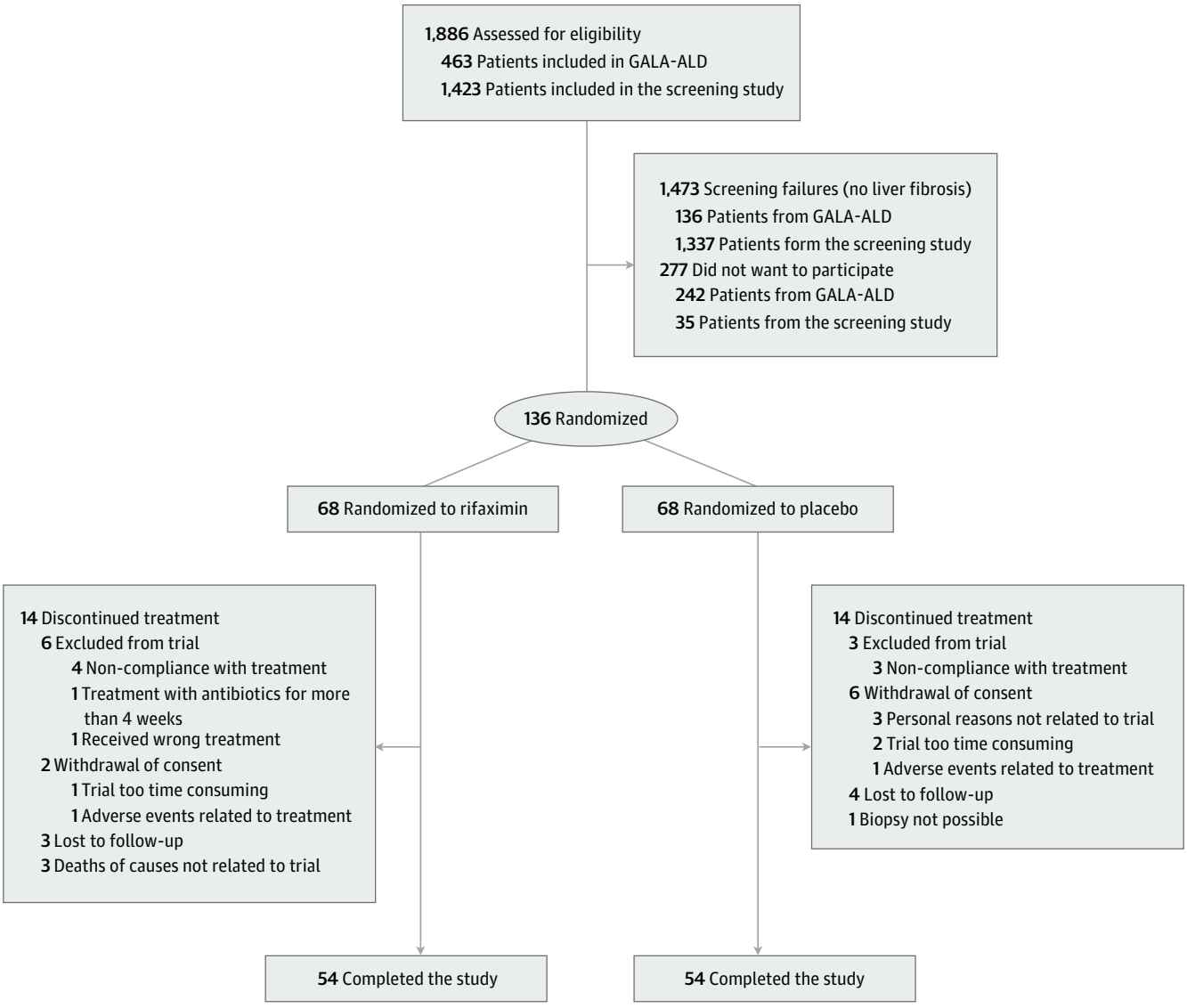
2. ONEHUNDRED-THIRTY SIX PATIENTS INCLUDED IN GAB-ALD:
   COLLECT INFORMED CONSENT. AFTER CONSENT, PATIENTS WILL BE RANDOMISED IN A DOUBLE-BLIND MANNER. RANDOMISATION STRATIFIES ACCORDING TO DRINKING STATUS AND DEGREE OF FIBROSIS. AFTER RANDOMISATION, ALL INVESTIGATIONS WILL BE PERFORMED AS DESCRIBED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

   PATIENTS TREATED, FOLLOWED AND EVALUATED AT END-OF-TREATMENT:
   TREAT WITH RIFAXIMIN OR PLACEBO. THE TABLETS ARE PROVIDED BY NORGINE. PATIENTS ARE INVESTIGATED AT DAY 0 AND SEEN AGAIN AT MONTH 1, 2, 4, 6, 8, 10, 12, 14, 16 AND 18. A PROJECT NURSE REGISTERS COMPLIANCE, SIDE-EFFECTS, ALCOHOL USE AND ADVERSE EVENTS. UNDERTAKE END-OF-TREATMENT INVESTIGATIONS. ALL INVESTIGATIONS WILL BE PERFORMED AS DESCRIBED IN 1.2 INCLUDING A LIVER BIOPSY.

2. RESULTS

Identification of potential participants

From the GALA-ALD study, we identified 327 eligible individuals with liver fibrosis of which 85 consented to participate in the intervention study GAB-ALD. To reach the planned sample size of 136 participants, we expanded the screening of at-risk individuals, which included non-invasive testing of 1423 individuals with a history of excessive alcohol use. Here we identified 86 individuals eligible for the study of which 51 consented to participated (Study flow chart).



From 2015 to 2020, we included 136 participants in the GAB-ALD study. All participants had a liver biopsy verifying the presence of alcohol-related liver fibrosis. After providing informed consent, we conducted the following baseline investigations: collection of venous fasting blood, faeces, urine and saliva, physical examinations including anthropometric data, heart rate and blood pressure, non-invasive

assessment of liver fibrosis using serum markers and questionnaires evaluating alcohol use, alcohol dependency, demographic data, medicine use, comorbidity and health-related quality of life. Afterwards, the participants were randomly allocated 1:1 to either receive 550 mg of rifaximin twice daily or matching placebo for 18 months. In each treatment arm 68 participants were included.

Follow up during the intervention

During the intervention, each participant was seen after 1, 2, 4, 6, 8, 10, 12, 14 and 16 months. At these visits, study drugs were provided and a project nurse registered compliance, side-effects, alcohol use and adverse events.

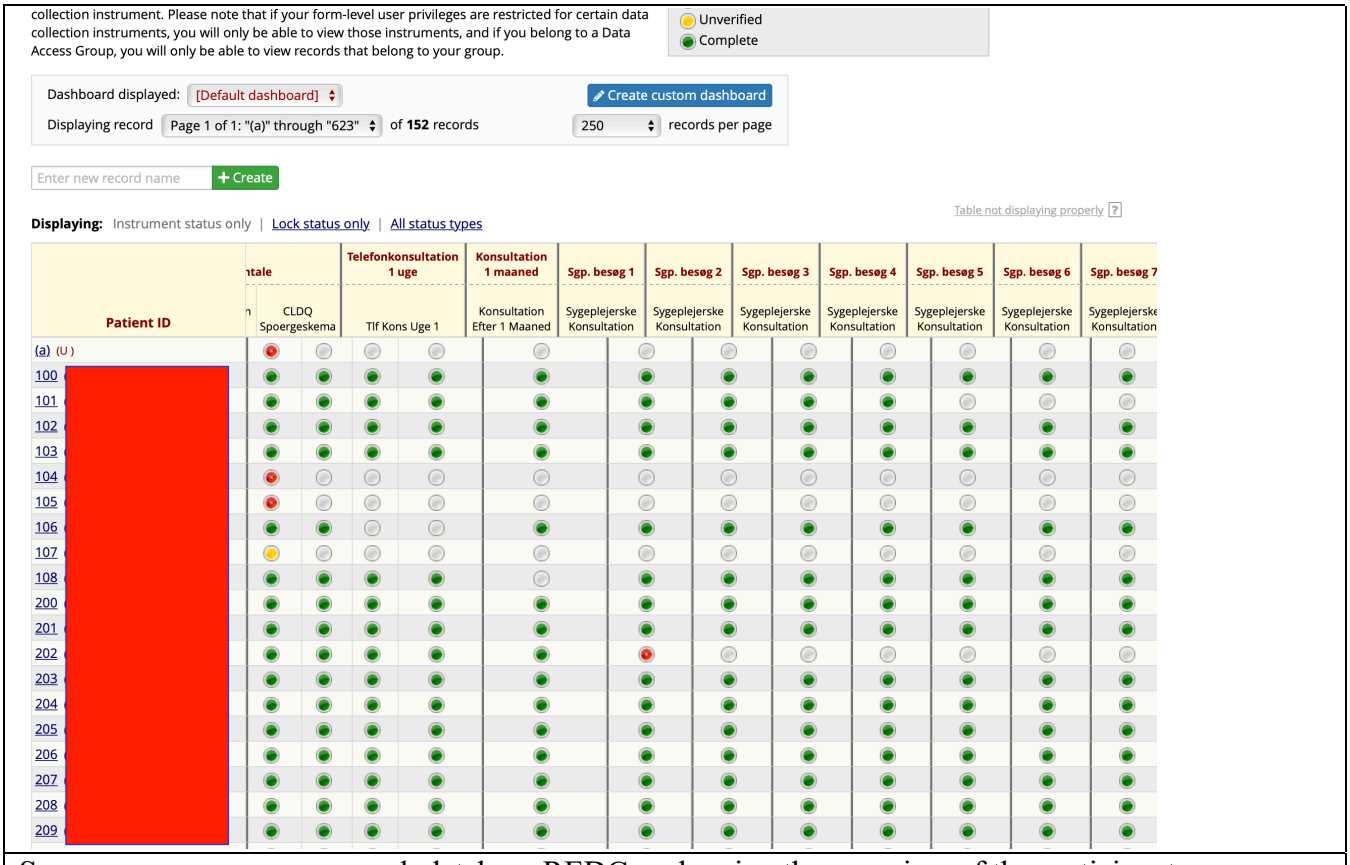
At end-of-treatment after 18 months, we performed the same investigations as performed at baseline including a liver biopsy to allow for evaluation of treatment effect.

END OF STUDY

In November 2021, the last participant finished the study. In total, 111 have completed the study of which 108 had adequate biopsies to compare treatment response. In total, 28 did not complete the study, 14 from each group. Lack of compliance was the main reason for leaving the study.

DATABASE AND BIOBANK

All data from the participants are stored on a secure server on Odense University Hospital using the research database REDCap (Screen shot figure) and Sharepoint Secure drives. All biobank tissues are logged and stored at Department of Clinical Biochemistry and Pharmacology, with Odense Patient Data Exploratory Network holding the overall responsibility for safe storage of both electronic data and tissue.



SCREEN SHOT OF THE research database REDCap showing the overview of the participants

Patient ID [redacted]

Table not displaying properly

Data Collection Instrument	Inklusionssamtale	Telefonkonsultation 1 uge	Konsultation 1 maaned	Sgp. besøg 1	Sgp. besøg 2	Sgp. besøg 3	Sgp. besøg 4	Sgp. besøg 5	Sgp. besøg 6	Sgp. besøg 7
Inklusion	●									
Baseline	●									
Sf36 Version 2	●									
CLDQ Spoergeskema	●									
Tlf Kons Uge 1		●								
Konsultation Efter 1 Maaned			●							
Sygeplejerske Konsultation				●	●	●	●	●	●	●
Afsluttende konsultation										
Hndelsesskema										
Dataark										
Medicinskema										
Ekstra besøg										
End of study										

SCREEN SHOT OF THE research database showing the data collection instrument for the individual participants

ANALYSIS OF EFFECTS, SAFETY AND MODE OF ACTION

Data analysis is currently conducted according to the statistical analysis plan. The primary endpoint is an improvement of at least one fibrosis stage. Secondary outcomes include progression in fibrosis stage, lobular inflammation, ballooning, steatosis, and transient elastography (TE). We assessed liver biopsies and have performed the initial statistical analyses blinded. In addition, serological biomarkers are being measured including PRO-C3 and PRO-C4, determining the formation of type III collagen and formation of type IV collagen respectively, with the intent of assessing ECM remodeling, the main constitute of fibrosis.

Statistical Analysis Plan

Version	2.3, dated 23/10/2022
Study title	Anti-fibrotic and molecular aspects of rifaximin in alcohol-related liver disease: A randomized placebo controlled clinical trial
Short title	The Rifaxmin study
Trial number	EudraCT: 2014-001856-51
Study protocol version	2.5.2, dated September 2019
Sponsors	Professor, PhD, Aleksander Krag Department of Medical Gastroenterology Odense University Hospital Sdr. Boulevard 29 5000 Odense C Tlf: +4521409915 Mail: aleksander.krag@rsyd.dk
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Data manager responsible	M. Sc. Eng. Peter Andersen
SAP writer / contact person	MD, PhD, Mads Israelsen

Front page of the Statistical analysis plan

PUBLICATION AND DISSEMINATION

We have submitted an abstract of the primary outcome for the International Liver Congress 2022. Currently, all outcome analyses are treated as confidential due to undergoing intellectual property review. Therefore, only data from the inclusion and adverse events are reported below. In the 108 participants who completed the study, the distribution of fibrosis stages at inclusion (F0/F1/F2/F3/F4) were 5/31/49/17/6, 84% were male, median TE 8.7 kPa (IQR=6.5-11.8) and mean age was 59±6 years. In total, 13 serious adverse events were reported, and the most frequent reported adverse event (n=20) was diarrhea with no difference between the groups.

Baseline characteristics of the participants are:

Variable	**GAB-ALD-patients n = 136**
Age, *years*	59 (53-65)
Males, *n*	114 (83.8%)
BMI, kg/m^2	30 (26-33)
Fibrosis stage (F1/F2/F3-4)	65/45/26
Diabetes, *n*	25 (18.4%)
Abstinence, *n*	43 (31.6%)
Liver parameters	

ALAT, *U/L*	37 (25-58)
Albumin, *g/L*	45 (42-47)
Alkaline phosphatase, *U/L*	81 (68-98)
Bilirubin, *µmol/L*	10 (8-14)
GGT, *U/L*	89 (45-202)
INR	1 (0.9-1.1)

We expect the first outcome data to be presented at the International Liver Congress 2022, 6th-10th of April in London. Furthermore, we plan to report our findings in an international peer-reviewed journal.