Clinical trial results:
Anti-fibrotic and molecular aspects of rifaximin in alcoholic liver disease: A randomized placebo controlled clinical trial

Summary

EudraCT number	2014-001856-51
Trial protocol	DK
Global end of trial date	27 January 2023

Results information

Result version number	v1 (current)
This version publication date	11 June 2023
First version publication date	11 June 2023
Summary attachment (see zip file)	Israelsen 2023, Lancet Gas Hep (Israelsen 2023, Lancet Gas Hep.pdf)

Trial information

Trial identification

Sponsor protocol code	12.007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	Kløvervænget 12, Odense, Denmark, 5000
Public contact	Mads Israelsen, Dept of Gastroenterology Odense Universityhospital, 0045 20681060, mads_israelsen@hotmail.com
Scientific contact	Mads Israelsen, Dept of Gastroenterology Odense Universityhospital, 20681060 20681060, mads_israelsen@hotmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2023
Global end of trial reached?	Yes
Global end of trial date	27 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We hypothesise that the gut microbiota is a major contributor to progression of fibrosis in alcoholic liver disease and that modulating gut flora by rifaximn halter disease progression.

Protection of trial subjects:

A full version of the protocol is available in the Appendix 2 (Israelsen 2023, Lancet Gas Hep) and a protocol paper has been published. The regional ethical committee approved the study (S-20140078) and all patients provided written informed consent. The trial was conducted according to the principles of the International Conference on Harmonization Good Clinical Practice guidelines and externally monitored by the Good Clinical Practice Unit at Odense University Hospital.

Background therapy:

The mechanism of rifaximin-α has been associated with modulating the gut microbiome and promoting gut barrier repair in decompensated cirrhosis. However, the efficacy in the attenuation of fibrogenesis and its safety in patients with ALD remain unknown.

Evidence for comparator: -

Actual start date of recruitment	01 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 136
Worldwide total number of subjects	136
EEA total number of subjects	136

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	38

From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial commenced March 23, 2015 and ended November 10, 2021.

Pre-assignment

Screening details:

During this period, we screened 1,886 consecutive patients with a history of excessive alcohol consumption and identified 413 eligible for inclusion

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The participants as well as sponsor, investigators, and nurses involved in the study were blinded to the outcome of the randomization and the randomization key was only available to designated personnel at the hospital pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rifaximin

Arm description:

tablet rifaximin-α 550 mg twice daily

Arm type	Experimental
Investigational medicinal product name	Rifaximin-α
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

tablet rifaximin-α 550 mg twice daily

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Number of subjects in period 1	Rifaximin	Placebo
Started	68	68
Completed	54	54
Not completed	14	14
Physician decision	14	14

Baseline characteristics

Reporting groups	
Reporting group title	Rifaximin
Reporting group description: tablet rifaximin-α 550 mg twice daily	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Rifaximin	Placebo	Total
Number of subjects	68	68	136
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	60	60	
inter-quartile range (Q1-Q3)	53 to 64	54 to 67	-
Gender categorical Units: Subjects			
Female	13	9	22
Male	55	59	114
Fibrosis stage			
Fibrosis stage according to Kleiner fibrosis score			
Units: Subjects			
Stage 0	3	4	7
Stage 1	17	20	37
Stage 2	33	30	63
Stage 3	11	12	23
Stage 4	4	2	6

End points

End points reporting groups

Reporting group title	Rifaximin
Reporting group description: tablet rifaximin-α 550 mg twice daily	
Reporting group title	Placebo
Reporting group description: -	

Primary: Regression of fibrosis

End point title	Regression of fibrosis
End point description: The primary outcome was regression of liver fibrosis. This was defined as a between-treatment group comparison of the proportion who had a decrease of at least one fibrosis stage according to the Kleiner histological scoring system.	
End point type	Primary
End point timeframe: 18 month	

End point values	Rifaximin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[1]	54[2]		
Units: Fibrosis score				
Regression	14	15		
no regression	40	39		

Notes:

[1] - Per protocol analysis
(Modified-intention-to-treat analysis can be found in the full paper)
[2] - Per protocol analysis
(Modified-intention-to-treat analysis can be found in the full paper)

Statistical analyses

Statistical analysis title	Fibrosis regression
Statistical analysis description: Comparison of binary outcome data are reported as odds ratio (OR) with 95% confidence intervals (CI), and continuous outcome data are reported as estimated mean difference from baseline to 18 months with 95% CI. Unless noted otherwise, results are reported after adjustment for stratification factors (abstinence six months prior to inclusion and baseline fibrosis stage) using logistic and linear regression analysis accordingly.	
Comparison groups	Rifaximin v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	2.68
Variability estimate	Standard deviation
Dispersion value	0

Secondary: Fibrosis progression

End point title	Fibrosis progression

End point description:

Comparison of binary outcome data are reported as odds ratio (OR) with 95% confidence intervals (CI), and continuous outcome data are reported as estimated mean difference from baseline to 18 months with 95% CI. Unless noted otherwise, results are reported after adjustment for stratification factors (abstinence six months prior to inclusion and baseline fibrosis stage) using logistic and linear regression analysis accordingly

End point type	Secondary

End point timeframe:

18 months

End point values	Rifaximin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[3]	54[4]		
Units: Liver fibrosis				
Progression	13	23		
no progression	31	21		

Notes:

[3] - Per protocol
(Modified intention to treat analysis can be found in full paper)
[4] - Per protocol
(Modified intention to treat analysis can be found in full paper)

Statistical analyses

Statistical analysis title	Fibrosis progression
Comparison groups	Rifaximin v Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.98

Variability estimate	Standard deviation
Dispersion value	0

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 18 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Rifaximin
Reporting group description: -	

Serious adverse events	Placebo	Rifaximin	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 68 (17.65%)	14 / 68 (20.59%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Serology normal			
subjects affected / exposed	12 / 68 (17.65%)	14 / 68 (20.59%)	
occurrences causally related to treatment / all	0 / 12	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Placebo	Rifaximin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 68 (77.94%)	48 / 68 (70.59%)	
Gastrointestinal disorders			
Pain			
subjects affected / exposed	53 / 68 (77.94%)	48 / 68 (70.59%)	
occurrences (all)	53	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation is that the primary endpoint, decrease of liver fibrosis, was not met. Preferably, the beneficial effect of rifaximin-α on haltering fibrosis progression should be validated in a multicentre phase III confirmatory efficacy trial.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36893774