Clinical trial results:
PBC induced fatigue treated with thiamine
- The effect of oral thiamine supplement in 4 weeks to patients with primary biliary cholangitis (PBC) and chronic fatigue.
A randomised, double-blinded, placebo-controlled, crossover study

Summary

EudraCT number	2020-004935-26
Trial protocol	DK
Global end of trial date	30 August 2022

Results information

Result version number	v1 (current)
This version publication date	08 October 2023
First version publication date	08 October 2023

Trial information

Trial identification

Sponsor protocol code	PIFT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04893993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Henning Grønbæk, Aarhus University Hospital, +45 21679281, henngroe@rm.dk
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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	01 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2022
Global end of trial reached?	Yes
Global end of trial date	30 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if the levels of fatigue can be reduced after 4 weeks treatment with Thiamine, among patients with primary biliary cholangitis and chronic fatigue

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and the GCP principles and was monitored by the GCP unit at Aarhus and Aalborg University Hospitals

Background therapy:

All patients received standard therapy for PBC i.e. UDCA and in some cases also bezafibrate.

Evidence for comparator: -

Actual start date of recruitment	03 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	28
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with PBC were recruited at the outpatient clinic at the department of hepatology and gastroenterology, Aarhus University Hospital, Denmark
Patients with PBC for more than 3 months, age ≥ 18 years, a total fatigue score on the PBC-40 questionnaire > 32 and a fatigue duration > 6 months were eligible for study inclusion

Pre-assignment

Screening details:

PBC patients complaining about fatigue were screened with the PBC-40 questionnaire, and if they scored above 32 on the fatigue subscale, they were informed about the study, signed informed consent and where screened with biochemistry before final inclusion.

Period 1

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

Blinding implementation details:

At the baseline visit, all participants received tablets for the two treatment periods in two separate anonymised containers, labelled E1 and E2, each containing 200 tables. The pharmacy made sealed envelopes with codes for the blinding. These envelopes remained sealed until the trial was completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Thiamine

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

Dosage and administration details:

The daily dose depended on gender (female/male) and body weight (BW) according to the scheme: BW < 60 kg: 600/900 mg (2/3 tablets), BW 60-70 kg: 900/1200 mg (3/4 tablets), BW 71-80 kg: 1200/1500 mg (4/5 tablets), and BW > 80 kg: 1500/1800 mg (5/6 tablets)

Arm title	Group 2

Arm description:

Placebo

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:

The daily dose depended on gender (female/male) and body weight (BW) according to the scheme: BW < 60 kg: 600/900 mg (2/3 tablets), BW 60-70 kg: 900/1200 mg (3/4 tablets), BW 71-80 kg: 1200/1500 mg (4/5 tablets), and BW > 80 kg: 1500/1800 mg (5/6 tablets)

Number of subjects in period 1	Group 1	Group 2
Started	18	18
Completed	18	18

Period 2	
Period 2 title	Wash out
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

At the baseline visit, all participants received tablets for the two treatment periods in two separate anonymised containers, labelled E1 and E2, each containing 200 tables.
Period 2 occured 4 weeks after the ending of period 1 (=4-week wash out)

Arms	
Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Wash out

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group 2

Arm description:

Wash out

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Group 1	Group 2
Started	18	18
Completed	17	17
Not completed	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Period 3

Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

At the baseline visit, all participants received tablets for the two treatment periods in two separate anonymised containers, labelled E1 and E2, each containing 200 tables.
Period 2 occured 4 weeks after the ending of period 1 (=4-week wash out)

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Placebo

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:

The daily dose depended on gender (female/male) and body weight (BW) according to the scheme: BW < 60 kg: 600/900 mg (2/3 tablets), BW 60-70 kg: 900/1200 mg (3/4 tablets), BW 71-80 kg: 1200/1500 mg (4/5 tablets), and BW > 80 kg: 1500/1800 mg (5/6 tablets)

Arm title	Group 2

Arm description:

Thiamine

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

Dosage and administration details:

The daily dose depended on gender (female/male) and body weight (BW) according to the scheme: BW < 60 kg: 600/900 mg (2/3 tablets), BW 60-70 kg: 900/1200 mg (3/4 tablets), BW 71-80 kg: 1200/1500 mg (4/5 tablets), and BW > 80 kg: 1500/1800 mg (5/6 tablets)

Number of subjects in period 3	Group 1	Group 2
Started	17	17
Completed	17	17

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description: Thiamine	
Reporting group title	Group 2
Reporting group description: Placebo	

Reporting group values	Group 1	Group 2	Total
Number of subjects	18	18	36
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			
Age, years (SD)			
Units: years			
arithmetic mean	56	61	
standard deviation	± 10	± 9	-
Gender categorical Units: Subjects			
Female	16	17	33
Male	2	1	3
BMI			
BMI (SD)			
Units: 36			
arithmetic mean	29	27	
standard deviation	± 7	± 6	-
ALP			
ALP U/I (IQR)			
Units: 36			
median	134	128	
inter-quartile range (Q1-Q3)	73 to 195	54 to 202	-

End points

End points reporting groups	
Reporting group title	Group 1
Reporting group description: Thiamine	
Reporting group title	Group 2
Reporting group description: Placebo	
Reporting group title	Group 1
Reporting group description: Wash out	
Reporting group title	Group 2
Reporting group description: Wash out	
Reporting group title	Group 1
Reporting group description: Placebo	
Reporting group title	Group 2
Reporting group description: Thiamine	

Primary: Fatigue reduction	
End point title	Fatigue reduction
End point description: Crossover analysis for fatigue scores and HRQoL scores averaged the between-treatment difference for each patient within each treatment period and then across both treatment periods, providing an estimate of treatment effect . In our primary analytical approach per the crossover analysis, group 1 was considered to be in the thiamine treatment group at week 4 and in the control group at week 12, whereas group 2 was considered to be in the control group at week 4 and in the thiamine treatment group at week 12. Differences in fatigue between week 4 and week 12 were compared between groups, using an unpaired t-test	
End point type	Primary
End point timeframe: Week 4 to week 12	

End point values	Group 1	Group 2	Group 1	Group 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: Fatigue score				
arithmetic mean (standard deviation)	34.7 (± 7.1)	35.5 (± 7.2)	33.2 (± 7.5)	35.8 (± 5.3)

Statistical analyses

Statistical analysis title	Delayed treatment model

Statistical analysis description:

In our primary analytical approach per the crossover analysis, group 1 was considered to be in the thiamine treatment group at week 4 and in the control group at week 12, whereas group 2 was considered to be in the control group at week 4 and in the thiamine treatment group at week 12. Differences in fatigue between week 4 and week 12 were compared between groups, using an unpaired t-test.

Comparison groups	Group 1 v Group 2 v Group 1 v Group 2
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Secondary: HrQOL

End point title	HrQOL

End point description:

Crossover analysis for fatigue scores and HRQoL scores averaged the between-treatment difference for each patient within each treatment period and then across both treatment periods, providing an estimate of treatment effect. In our primary analytical approach per the crossover analysis, group 1 was considered to be in the thiamine treatment group at week 4 and in the control group at week 12, whereas group 2 was considered to be in the control group at week 4 and in the thiamine treatment group at week 12. Differences in fatigue between week 4 and week 12 were compared between groups, using an unpaired t-test.

End point type	Secondary

End point timeframe:

Week 4 to Week 12

End point values	Group 1	Group 2	Group 1	Group 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: HrQOL				
arithmetic mean (standard deviation)	68.3 (± 13.0)	69.1 (± 15.4)	69.5 (± 18.7)	70.2 (± 13.2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Within the 12 week study period

Adverse event reporting additional description:

Patients were told to report SAE/AE to the study personel. Patients where asked about SAE/AE at the end of the study. If patients reported SAE/AE's during the study period they were followed and monitored until the event resolved

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Group 1

Reporting group description:

Thiamine first

Reporting group title	Group 2

Reporting group description:

Placebo first

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were recorded for more than 5% of the cohort.

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
hemoptysis	Additional description: Hemoptysis with onset 3 days after period one finished. Was hospitalized but bleeding source was not located. Resolved quickly and stayed in the study.		
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Hospitalized with fever and abdominal pain. No site of infection identified but recovered on antibiotic treatment.		
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: Severe dyspnea due to Covid-19 infection. The patient has common variable immunodeficiency, which is judged as the reason for hospitalization and severe oxygen requiring dyspnea.		

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	

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

None reported