Clinical trial results:
Changes in bile acid homeostasis and stool habits after cholecystectomy

Summary

EudraCT number	2016-004692-53
Trial protocol	DK
Global end of trial date	15 May 2019

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	SJ-434

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03168555
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Lykkebaekvej 1, DK-Koege, Denmark, 4600
Public contact	Department of Medicine, Zealand University Hospital Køge, 0045 47322400, chrbo@regionsjaelland.dk
Scientific contact	Department of Medicine, Zealand University Hospital Køge, 0045 47322400, chrbo@regionsjaelland.dk

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	03 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2019
Global end of trial reached?	Yes
Global end of trial date	15 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate changes in hormonal regulation (particularly by FGF19 and 7α-hydroxy-4-cholesten-3-one) and composition of the bile acid pool before and after elective cholecystectomy to deem the role of the intact gall bladder.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2017
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	20
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	23
Intermediate milestone: Number of subjects	Completed study visit 1 (pre-op): 22
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Intercurrent disease, cholecystectomy cancelled: 1

Period 1

Period 1 title	Pre-operative study visit
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Meal with chenodeoxycholic acid

Arm description:

Solid study meal with 1,250 mg chenodeoxycholic acid

Arm type	Experimental
Investigational medicinal product name	chenodeoxycholic acid
Investigational medicinal product code	ATC: A05AA01
Other name	CDCA, 3 alpha- 7 alpha dihydroxycholic acid, Chendiol, Xenbilox
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1,250 mg single dose (5 capsules of 25g mg)

Number of subjects in period 1[1]	Meal with chenodeoxycholic acid
Started	22
Completed	18
Not completed	4
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Lost to follow-up	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 23 patients enrolled, one patient withdrew from the study before study visit one, and therefore did not start the baseline periode

Period 2

Period 2 title	Post-operative study visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Meal with chenodeoxycholic acid

Arm description:

Solid study meal with 1,250 mg chenodeoxycholic acid

Arm type	Experimental
Investigational medicinal product name	chenodeoxycholic acid
Investigational medicinal product code	ATC: A05AA01
Other name	CDCA, 3 alpha- 7 alpha dihydroxycholic acid, Chendiol, Xenbilox
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1,250 mg single dose (5 capsules of 25g mg)

Number of subjects in period 2	Meal with chenodeoxycholic acid
Started	18
Completed	18

Baseline characteristics

Reporting groups

Reporting group title	Pre-operative study visit

Reporting group description: -

Reporting group values	Pre-operative study visit	Total	
Number of subjects	22	22	
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	54		
inter-quartile range (Q1-Q3)	38 to 59	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	12	12	

End points

End points reporting groups

Reporting group title	Meal with chenodeoxycholic acid
Reporting group description: Solid study meal with 1,250 mg chenodeoxycholic acid	
Reporting group title	Meal with chenodeoxycholic acid
Reporting group description: Solid study meal with 1,250 mg chenodeoxycholic acid	

Primary: 150 minute increment in stimulated FGF19

End point title	150 minute increment in stimulated FGF19
End point description:	
End point type	Primary
End point timeframe: Comparison of visit 1 (pre-operative) with visit 2 (post-operative)	

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	81 (-20 to 274)	186 (111 to 382)		

Statistical analyses

Statistical analysis title	Wilcoxon signed rank test
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)

Secondary: Change in fasting C4

End point title	Change in fasting C4

End point description:

End point type	Secondary

End point timeframe:

Comparing visit 2 with visit 1

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	6.0 (4.1 to 8.7)	7.5 (5.5 to 10)		

Statistical analyses

Statistical analysis title	paired t-test (of lognormalized base values)

Statistical analysis description:

paired t-test (of lognormalized base values)

Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.63
Method	Paired t-test

Notes:

[1] - paired t-test (of lognormalized base values)

Secondary: Change in total area under the curve of stimulated C4

End point title	Change in total area under the curve of stimulated C4

End point description:

End point type	Secondary

End point timeframe:

comparing visit 1 with visit 2

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: ng/mL x minutes				
arithmetic mean (confidence interval 95%)	774 (524 to 1143)	1040 (765 to 1417)		

Statistical analyses

Statistical analysis title	paired t-test (of lognormalized base values)
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	Paired t-test

Secondary: Change in fasting FGF19

End point title	Change in fasting FGF19

End point description:

End point type	Secondary

End point timeframe:

comparing viist 1 with visit 2

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: pg/mL				
arithmetic mean (confidence interval 95%)	102 (74 to 141)	92 (67 to 125)		

Statistical analyses

Statistical analysis title	paired t-test (of lognormalized base values)
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.29
Method	Paired t-test

Secondary: Change in total area under the curve of stimulated chenodeoxycholic acid

End point title	Change in total area under the curve of stimulated chenodeoxycholic acid

End point description:

End point type	Secondary

End point timeframe:

comparing viist 1 with visit 2

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: µM x minutes				
median (inter-quartile range (Q1-Q3))	1554 (1084 to 2231)	1847 (1310 to 2193)		

Statistical analyses

Statistical analysis title	Wilcoxon paired signed rank test
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.22
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in mean stools per day

End point title	Change in mean stools per day

End point description:

End point type	Secondary

End point timeframe:

comparing viist 1 with visit 2

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Mean stool number				
median (inter-quartile range (Q1-Q3))	1.6 (1.1 to 2.0)	1.6 (1.3 to 1.7)		

Statistical analyses

Statistical analysis title	Wilcoxon paired signed rank test
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.73
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in stool consistency

End point title	Change in stool consistency

End point description:

End point type	Secondary

End point timeframe:

comparing viist 1 with visit 2

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Mean Bristol stool type				
median (inter-quartile range (Q1-Q3))	4.2 (3.7 to 4.8)	4.0 (3.6 to 4.5)		

Statistical analyses

Statistical analysis title	Wilcoxon paired signed rank test
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic

	acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in plasma triglycerides

End point title	Change in plasma triglycerides
End point description:	
End point type	Secondary
End point timeframe: comparing viist 1 with visit 2	

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	1.4 (1.1 to 2.1)	1.5 (1.1 to 1.9)		

Statistical analyses

Statistical analysis title	Wilcoxon paired signed rank test
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Post-hoc: Change in total area under the curve of stimulated FGF19

End point title	Change in total area under the curve of stimulated FGF19
End point description:	
End point type	Post-hoc
End point timeframe: comparing viist 1 with visit 2	

End point values	Meal with chenodeoxycholic acid	Meal with chenodeoxycholic acid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: pg/mL x minutes				
arithmetic mean (confidence interval 95%)	22323 (16658 to 29915)	27582 (20478 to 37149)		

Statistical analyses

Statistical analysis title	paired t-test (of lognormalized base values)
Comparison groups	Meal with chenodeoxycholic acid v Meal with chenodeoxycholic acid
Number of subjects included in analysis	36
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.07
Method	Paired t-test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collecter per study visit. One visit (visit 1) was before cholecystectomy and one visit (visit 2) was after cholecystectomy. At both visits a solid study meal with 1,250 mg chenodeoxycholic acid (IMP) was admisitered

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	2021-03-31

Reporting groups

Reporting group title	Visit 1 (pre-operative visit)
Reporting group description: -	
Reporting group title	Visit2 (post-operative visit)

Reporting group description: -

Serious adverse events	Visit 1 (pre-operative visit)	Visit2 (post-operative visit)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Visit 1 (pre-operative visit)	Visit2 (post-operative visit)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	15 / 18 (83.33%)	
Nervous system disorders			
Headache	Additional description: SNOMED 25064002		
subjects affected / exposed	1 / 22 (4.55%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dizzyness	Additional description: SNOMED 404640003		
subjects affected / exposed	1 / 22 (4.55%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Migraine	Additional description: SNOMED 37796009		

subjects affected / exposed	1 / 22 (4.55%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Tiredness	Additional description: SNOMED 224960004		
subjects affected / exposed	2 / 22 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal bloating	Additional description: SNOMED 116289008		
subjects affected / exposed	1 / 22 (4.55%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Nausea	Additional description: SNOMED 422587007		
subjects affected / exposed	3 / 22 (13.64%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Diarrhoea	Additional description: SNOMED 62315008		
subjects affected / exposed	14 / 22 (63.64%)	14 / 18 (77.78%)	
occurrences (all)	14	14	
Burping	Additional description: SNOMED 271834000		
subjects affected / exposed	1 / 22 (4.55%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Abdominal pain	Additional description: SNOMED 21522001		
subjects affected / exposed	3 / 22 (13.64%)	5 / 18 (27.78%)	
occurrences (all)	3	5	
Heartburn	Additional description: SNOMED 16331000		
subjects affected / exposed	1 / 22 (4.55%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Malaise	Additional description: SNOMED 367391008		
subjects affected / exposed	1 / 22 (4.55%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Abdominal sounds/growling	Additional description: SNOMED 249503000		
subjects affected / exposed	5 / 22 (22.73%)	2 / 18 (11.11%)	
occurrences (all)	5	2	

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