Clinical trial results:
Treatment effect of colesevelam for bile acid diarrhoea

Summary

EudraCT number	2016-001452-22
Trial protocol	DK
Global end of trial date	14 February 2022

Results information

Result version number	v1 (current)
This version publication date	07 October 2023
First version publication date	07 October 2023

Trial information

Trial identification

Sponsor protocol code	SJ-641

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Lykkebaekvej 1, Koege, Denmark, 4600
Public contact	Department of Medicine, Zealand University Hosipital, 0045 47322400, chrbo@regionsjaelland.dk
Scientific contact	Department of Medicine, Zealand University Hosipital, 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	14 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2022
Global end of trial reached?	Yes
Global end of trial date	14 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of treating bile acid diarrhoea with colesevelam.

Protection of trial subjects:

No SAEs in the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2018
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: 168
Worldwide total number of subjects	168
EEA total number of subjects	168

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)	139
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients referred for clinical routine SeHCAT scintigraphy were identified and patient charts prescreened for eligibility data. At the first of two hospital visits needed for the SeHCAT test, eligible patients were recruited baseline assessment (pre-screening/pre-assignment)

Pre-assignment

Screening details:

6 day diary of stool habits. Only patients fulfilling at least one criterion (A or B) for diarrhea were eligible for randomization.
the criteria were on mean number of bowel movements; means over the baseline period
A. Mean total bowel movements of3 or more per day
B. Mean number sum of watery (Bristol stool type 6 and 7) of 1 or more per day

Pre-assignment period milestones

Number of subjects started	168
Intermediate milestone: Number of subjects	Bile acid diarrhea or not: 41
Number of subjects completed	41

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not bile acid diarrhea: 127

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Tablets of 625mg; starting dose 2 tablets twice daily. Titrated to effect (taper or increase dose). three doses allowed: 1 tablet twice daily (bid), 2 tablets bid. 3 tablets bid.

Arm title	Colesevelam

Arm description:

Active treatment

Arm type	Experimental

Investigational medicinal product name	Colesevelamhydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets of 625mg; starting dose 2 tablets twice daily. Titrated to effect (taper or increase dose). three doses allowed: 1 tablet twice daily (bid), 2 tablets bid. 3 tablets bid.

Number of subjects in period 1[1]	Placebo	Colesevelam
Started	19	22
Completed	17	22
Not completed	2	0
Consent withdrawn by subject	1	-
Lack of efficacy	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: We enrolled all patients attending the nuclear medicine SeHCAT test for suspected bile acid diarrhea (BAD). All patients were tested with an alternative biochemical test called C4. Only patients with a positive C4 test (n=41) were eligible in the primary outcome population. Several diagnostic ROC analyses were done comparing C4 and SeHCAT positive vs negative ; however, these secondary and tertiary analyses were not the primary focus of the RCT

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Colesevelam
Reporting group description:	
Active treatment	

Reporting group values	Placebo	Colesevelam	Total
Number of subjects	19	22	41
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	64	45	
inter-quartile range (Q1-Q3)	53 to 69	37 to 59	-
Gender categorical			
Units: Subjects			
Female	14	16	30
Male	5	6	11

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Colesevelam
Reporting group description:	
Active treatment	

Primary: Remission of C4-defined bile acid diarrhea	
End point title	Remission of C4-defined bile acid diarrhea
End point description:	
Remission of both Hjortswang diarrhea criteria (A and B) of daily bowel habit means over the seven treatment days (6-12)	
End point type	Primary
End point timeframe:	
Treatment days 6-12	

End point values	Placebo	Colesevelam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[1]	22		
Units: Adjusted remission rate				
arithmetic mean (confidence interval 95%)	17 (5 to 44)	65 (41 to 83)		

Notes:

[1] - 2 missing values were defined as treatment failure (in a sensitivity analysis we imputed missing val

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Placebo v Colesevelam
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	62.8

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From treatment start (randomization) until 72 hours after treatment end	
Assessment type	Systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	2022MAR31
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Colesevelam
Reporting group description: Active treatment	

Serious adverse events	Placebo	Colesevelam	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 22 (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: 1 %

Non-serious adverse events	Placebo	Colesevelam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 19 (57.89%)	14 / 22 (63.64%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)	2 / 22 (9.09%)	
occurrences (all)	3	3	
Migraine			
subjects affected / exposed	0 / 19 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Malaise			

subjects affected / exposed	0 / 19 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 22 (0.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Bloated abdomen			
subjects affected / exposed	4 / 19 (21.05%)	5 / 22 (22.73%)	
occurrences (all)	9	9	
Abdominal pain			
subjects affected / exposed	4 / 19 (21.05%)	5 / 22 (22.73%)	
occurrences (all)	9	9	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	4 / 22 (18.18%)	
occurrences (all)	5	5	
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Flatulence			
subjects affected / exposed	1 / 19 (5.26%)	1 / 22 (4.55%)	
occurrences (all)	2	2	
heartburn			
subjects affected / exposed	1 / 19 (5.26%)	2 / 22 (9.09%)	
occurrences (all)	3	3	
Increased intestinal sounds			
subjects affected / exposed	1 / 19 (5.26%)	1 / 22 (4.55%)	
occurrences (all)	2	2	
Appetite disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Belching			
subjects affected / exposed	0 / 19 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Epigastric discomfort			
subjects affected / exposed	1 / 19 (5.26%)	0 / 22 (0.00%)	
occurrences (all)	1	1	

Hepatobiliary disorders Alanine aminotransferase increased subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 1	 1 / 22 (4.55%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2019	Exclusion Criteria: added 1) Acute suspected or proven viral gastroenteritis within the recent 4 weeks 2) Acute non-viral gastroenteritis within the recent 8 weeks
25 November 2020	Changed the C4 cut-off defining the primary endpoint from 15.4 to > 30 ng/mL. (Note all blood samples till in freezer biobank)
10 February 2022	Changed the cut-off value of 30 to 46 ng/mL. Other analyses had shown an analytical error in determining the C4 threshold in the previous reference lab (Paris). Measuring the samples originally used to determine the threshold again at two new labs (Copenhagen and Stockholm) showed agreement between these two new measurements. The trial reference lab was changed to Copenhagen

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2020	Due to COVID-19 lockdown and termination of research activities at affected hospitals	05 May 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36758570