



## Clinical trial results: Validation of stimulated FGF19 for diagnosing bile acid diarrhoea Summary

EudraCT number	2016-002217-22
Trial protocol	DK
Global end of trial date	27 November 2017

### Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021
Summary attachment (see zip file)	journal paper (2020 AJG Borup et al. Biochemical_Diagnosis_of_Bile_Acid_Diarrhea.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	SJ-546
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03059537
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Lykkebaekvej 1, DK-Koege, Denmark, 4600
Public contact	Departement of internal medicine, Sjællands University Hospital, Køge, 0045 47322400, christianborup@hotmail.com
Scientific contact	Departement of internal medicine, Sjællands University Hospital, Køge, 0045 47322400, christianborup@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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	01 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 November 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

Validation of stimulated  $\Delta$ FGF19 for diagnosis of BAD in patients referred to SeHCAT

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

Notes:

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**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)	61
From 65 to 84 years	17
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruited from 22 March 2017 until 3 Nov 2017.

### Pre-assignment

Screening details:

Invited 209 patients, recruited 78 (n=131 declined invitation). 71 completed the protocol; n=7 dropped out (protocol violations: n=1 not fasting at visit 2, n=1 current treatment with colestyramine not paused, n= 2current treatment w oral budesonide; n=3 withdrew consent between study visit 1 and visit2)

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Meal+CDCA
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Arm description:

Meal+CDCA stimulation of bile acid homeostasis

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

Dosage and administration details:

5 capsules of 250 mg (in total 1,250 mg administered with a defined solid meal.

Number of subjects in period 1	Meal+CDCA
Started	78
Completed	71
Not completed	7
Consent withdrawn by subject	3
Protocol deviation	4

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
Reporting group description: -	

Reporting group values	overall trial	Total	
Number of subjects	78	78	
Age categorical			
Units: Subjects			
Adults (18-64 years)	61	61	
From 65-84 years	17	17	
Gender categorical			
Units: Subjects			
Female	50	50	
Male	28	28	

### Subject analysis sets

Subject analysis set title	SeHCAT retention <=10%
Subject analysis set type	Per protocol

Subject analysis set description:

Patients with bile acid diarrhea (defined by SeHCAT <= 10%)

Subject analysis set title	SeHCAT >10%
Subject analysis set type	Per protocol

Subject analysis set description:

PAntients with idiopathic (non-bile acid diarrhea) defined by SeHCAT retention > 10%

Subject analysis set title	SeHCAT <=5%
Subject analysis set type	Per protocol

Subject analysis set description:

PAntients with severe bile acid diarrhea

Subject analysis set title	SeHCAT >5%
Subject analysis set type	Per protocol

Subject analysis set description:

PAntients who do not have severe bile acid diarrhea

Reporting group values	SeHCAT retention <=10%	SeHCAT >10%	SeHCAT <=5%
Number of subjects	26	45	17
Age categorical			
Units: Subjects			
Adults (18-64 years)	23	36	
From 65-84 years	3	9	
Gender categorical			
Units: Subjects			
Female	17	27	
Male	9	18	

Reporting group values	SeHCAT >5%		
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Number of subjects	54		
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Gender categorical			
Units: Subjects			
Female			
Male			

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## End points

### End points reporting groups

Reporting group title	Meal+CDCA
Reporting group description: Meal+CDCA stimulation of bile acid homeostasis	
Subject analysis set title	SeHCAT retention <=10%
Subject analysis set type	Per protocol
Subject analysis set description: Patients with bile acid diarrhea (defined by SeHCAT <= 10%)	
Subject analysis set title	SeHCAT >10%
Subject analysis set type	Per protocol
Subject analysis set description: Patients with idiopathic (non-bile acid diarrhea) defined by SeHCAT retention > 10%	
Subject analysis set title	SeHCAT <=5%
Subject analysis set type	Per protocol
Subject analysis set description: Patients with severe bile acid diarrhea	
Subject analysis set title	SeHCAT >5%
Subject analysis set type	Per protocol
Subject analysis set description: Patients who do not have severe bile acid diarrhea	

### Primary: Negative predictive value (NPV) of stimulated delta FGF19 > 2.5 pg/mL for ruling out bile acid diarrhea

End point title	Negative predictive value (NPV) of stimulated delta FGF19 > 2.5 pg/mL for ruling out bile acid diarrhea
End point description:	
End point type	Primary
End point timeframe: visit 2	

End point values	SeHCAT retention <=10%	SeHCAT >10%		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	45		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	36 (-14 to 104)	10 (-28 to 51)		

### Statistical analyses

Statistical analysis title	ROC analysis w pred valuea
Statistical analysis description: "exact" Clopper-Pearson	

Comparison groups	SeHCAT retention ≤10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.17 <sup>[2]</sup>
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	NPV for stim d FGF19 vs SeHCAT 10%
Point estimate	68
Confidence interval	
level	95 %
sides	2-sided
lower limit	54
upper limit	80

Notes:

[1] - AREA under the ROC curve compared with true area = 0.5

[2] - p value for ROC curve

### Secondary: PPV for C4 > 5.5 ng/mL for SeHCAT <10%

End point title	PPV for C4 > 5.5 ng/mL for SeHCAT <10%
End point description:	
End point type	Secondary
End point timeframe:	
visit2	

End point values	Meal+CDCA	SeHCAT retention ≤10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: %				
number (confidence interval 95%)	44 (39 to 49)	0 (0 to 0)	0 (0 to 0)	

### Statistical analyses

Statistical analysis title	Diag 2x2 table w CI for predictive values
Statistical analysis description:	
"exact" Clopper-Pearson confidence intervals	
Comparison groups	SeHCAT retention ≤10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 <sup>[3]</sup>
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	PPV for C4 >5.5 for SeHCAT 10%
Point estimate	44

Confidence interval	
level	95 %
sides	2-sided
lower limit	39
upper limit	49

Notes:

[3] - for True ROC-AUC=0.5

### Secondary: ROC analysis accuracy for stim delta FGF19 > 2.5 pg/mL for detecting SeHCAT < 5%

End point title	ROC analysis accuracy for stim delta FGF19 > 2.5 pg/mL for detecting SeHCAT < 5%
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End point description:

End point type	Secondary
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End point timeframe:

Visit 2

End point values	Meal+CDCA	SeHCAT retention <=10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: %				
number (confidence interval 95%)	52 (39 to 63)	0 (0 to 0)	0 (0 to 0)	

### Statistical analyses

Statistical analysis title	Diag 2x2 table w CI for predictive values
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Statistical analysis description:

"exact" Clopper-Pearson confidence intervals

Comparison groups	SeHCAT retention <=10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.903 <sup>[4]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - value for true ROC-AUC=0.5

### Secondary: ROC analysis accuracy for C4 > 5.5 for detecting BAD compared with SeHCAT <5%

End point title	ROC analysis accuracy for C4 > 5.5 for detecting BAD compared with SeHCAT <5%
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End point description:

End point type	Secondary
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End point timeframe:  
visit2

End point values	SeHCAT ≤5%	SeHCAT >5%		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	54		
Units: %				
number (confidence interval 95%)	42.5 (28.2 to 63.9)	9.4 (7.3 to 12.2)		

### Statistical analyses

Statistical analysis title	Diag 2x2 table w CI for predictive values ie accur
Statistical analysis description: "exact" Clopper-Pearson confidence intervals	
Comparison groups	SeHCAT ≤5% v SeHCAT >5%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.00001 <sup>[5]</sup>
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Accuracy for C4>5.5 comp SeHCTA 10%
Point estimate	44
Confidence interval	
level	95 %
sides	2-sided
lower limit	32
upper limit	56

Notes:

[5] - p value for true ROC-AUC=0.5

### Secondary: correlation(spearman) between stim delta FGF19 and mean number of stools per day

End point title	correlation(spearman) between stim delta FGF19 and mean number of stools per day
End point description:	
End point type	Secondary
End point timeframe: vvisit2	

End point values	Meal+CDCA	SeHCAT retention ≤10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: none				
number (not applicable)	0.064	0	0	

### Statistical analyses

Statistical analysis title	Spearman correlation
Comparison groups	SeHCAT retention ≤10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.593
Method	spearman corr
Parameter estimate	spearman corr
Point estimate	0.593
Confidence interval	
level	Other: 1 %
sides	2-sided
lower limit	0.593
upper limit	0.593

### Secondary: correlation between SHS item general well being and SF36v2 general well being for patients with Hjortswang criteria pos diarrhea

End point title	correlation between SHS item general well being and SF36v2 general well being for patients with Hjortswang criteria pos diarrhea
End point description:	
End point type	Secondary
End point timeframe:	
vivist2	

End point values	Meal+CDCA	SeHCAT retention ≤10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: none				
number (not applicable)	-0.602	-0.766	-0.503	

## Statistical analyses

<b>Statistical analysis title</b>	Spearman corr
Comparison groups	SeHCAT retention <=10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.00001 <sup>[6]</sup>
Method	Spearman corr
Parameter estimate	spearman corr
Point estimate	-0.587
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.587
upper limit	-0.587

Notes:

[6] - p value for spearman corr

## Secondary: Median stimulated delta FGF19 in SeHCAT strata

End point title	Median stimulated delta FGF19 in SeHCAT strata
End point description:	
End point type	Secondary
End point timeframe:	
visit 2	

End point values	SeHCAT retention <=10%	SeHCAT >10%		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	45		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	36 (-14 to 104)	10 (-28 to 51)		

## Statistical analyses

<b>Statistical analysis title</b>	Comp of median stim delta FGF19 in SeHCAT groups
Comparison groups	SeHCAT retention <=10% v SeHCAT >10%

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.17
Method	Wilcoxon (Mann-Whitney)

### Secondary: Mean (lognorm + backtransf) C4 in SeHCAT groups

End point title	Mean (lognorm + backtransf) C4 in SeHCAT groups
End point description:	
End point type	Secondary
End point timeframe: visit 2	

End point values	SeHCAT retention ≤10%	SeHCAT >10%		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	45		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	30 (19 to 46)	8 (7 to 11)		

### Statistical analyses

<b>Statistical analysis title</b>	Comp of mean C4 in SeHCAT groups
Comparison groups	SeHCAT retention ≤10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.00001
Method	t-test, 2-sided

### Secondary: Median FGF19 values in SeHCAT groups

End point title	Median FGF19 values in SeHCAT groups
End point description:	
End point type	Secondary
End point timeframe: visit 2	

End point values	SeHCAT retention ≤10%	SeHCAT >10%		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	45		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	72 (53 to 146)	119 (84 to 240)		

## Statistical analyses

Statistical analysis title	Comp of fasting median FGF19
Comparison groups	SeHCAT retention ≤10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

## Post-hoc: Negative predictive value for C4 < 15ng/mL for SeHCAT >10%

End point title	Negative predictive value for C4 < 15ng/mL for SeHCAT >10%
End point description:	
End point type	Post-hoc
End point timeframe:	
visit 2	

End point values	Meal+CDCA	SeHCAT retention ≤10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: %				
number (confidence interval 95%)	85 (74 to 96)	0 (0 to 0)	0 (0 to 0)	

## Statistical analyses

Statistical analysis title	Diag 2x2 table w CI for predictive values
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Statistical analysis description:

"exact" Clopper-Pearson confidence intervals

Comparison groups	SeHCAT retention <=10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0001 [7]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	NPV for C4<15 comp SeHCAT10%
Point estimate	85
Confidence interval	
level	95 %
sides	2-sided
lower limit	74
upper limit	96

Notes:

[7] - p value for ROC curve real AUC = 0.5

### Post-hoc: positive predictive value of C4 > 48 ng/mL for SeHCAT < 10%

End point title	positive predictive value of C4 > 48 ng/mL for SeHCAT < 10%
End point description:	
End point type	Post-hoc
End point timeframe:	
vsisit2	

End point values	Meal+CDCA	SeHCAT retention <=10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: %				
number (confidence interval 95%)	82 (59 to 100)	0 (0 to 0)	0 (0 to 0)	

### Statistical analyses

Statistical analysis title	ROC analysis w pred valuea
Statistical analysis description:	
"exact" Clopper-Pearson confidence intervals	
Comparison groups	SeHCAT retention <=10% v SeHCAT >10%

Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.001 [8]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	PPV for C4 > 48ng/mL comp SeHCAT 10%
Point estimate	82
Confidence interval	
level	95 %
sides	2-sided
lower limit	59
upper limit	100

Notes:

[8] - p value for true ROC-AUC=0.5

### Post-hoc: Accuracy of C4 cutoff 30ng/ml for SeHCAT 10%

End point title	Accuracy of C4 cutoff 30ng/ml for SeHCAT 10%
End point description:	
End point type	Post-hoc
End point timeframe:	
visit2	

End point values	Meal+CDCA	SeHCAT retention <=10%	SeHCAT >10%	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	71	26	45	
Units: %				
number (confidence interval 95%)	78 (66 to 87)	30 (19 to 46)	8 (7 to 11)	

### Statistical analyses

Statistical analysis title	Diag 2x2 table w CI for predictive values
Statistical analysis description:	
"exact" Clopper-Pearson confidence intervals	
Comparison groups	SeHCAT retention <=10% v SeHCAT >10%
Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.01
Method	Fisher exact
Parameter estimate	Accuracy of C4>30ng/mL for SeHCAT 10%
Point estimate	78

Confidence interval	
level	95 %
sides	2-sided
lower limit	66
upper limit	87



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE reg strat at visit 2 with adm of IMP (CDCA) and for seven days

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	Meal+CDCA
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Reporting group description:

Meal+CDCA stimulation of bile acid homeostasis

Serious adverse events	Meal+CDCA		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 71 (2.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Gastroenteritis norovirus	Additional description: Acute norovirus gastroenteritis (pt age 78) with dehydration. Pt hospitalized for fluid therapy. Full recovery.		
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Meal+CDCA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 71 (52.11%)		
Gastrointestinal disorders			

Diarrhoea	Additional description: Acute diarrhoea		
subjects affected / exposed	20 / 71 (28.17%)		
occurrences (all)	20		
Abdominal pain			
subjects affected / exposed	17 / 71 (23.94%)		
occurrences (all)	17		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32740083>