Clinical trial results:
Statins for prevention of disease progression and hospitalization in Liver Cirrhosis: A multi-center, randomized, double blind, placebo-controlled trial. The STATLiver Trial.

Summary

EudraCT number	2019-001806-40
Trial protocol	DK
Global end of trial date	04 April 2023

Results information

Result version number	v1 (current)
This version publication date	27 April 2023
First version publication date	27 April 2023

Trial information

Trial identification

Sponsor protocol code	STATLiver2019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04072601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hvidovre University Hospital
Sponsor organisation address	Gastro Unit, 360, Kettegaard alle 30, Hvidovre, Denmark, 2650
Public contact	Nina Kimer , Afsnit 360, Gastroenheden, 0045 38621968, thit.mynster.kronborg@regionh.dk
Scientific contact	Nina Kimer , Afsnit 360, Gastroenheden, 0045 38621968, thit.mynster.kronborg@regionh.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	04 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2023
Global end of trial reached?	Yes
Global end of trial date	04 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Add on treatment with atorvastatin 10-20 mg to standard treatment improves survival in patients with cirrhosis of any etiology.
The second primary endpoint was hospitalisation rate.

Protection of trial subjects:

All trial subjects were offered standard treatment following national guidelines. All trial subjects were monitored regarding safety end side effects to treatment. All patient data were anonymized.

Background therapy:

Standard treatment with diuretics, antihypertensive medication and symptomatic care in case of complications.

Evidence for comparator:

Placebo

Actual start date of recruitment	11 November 2019
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: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

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)	51
From 65 to 84 years	27

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between February 2020 and December 2021, 78 participants were enrolled in the trial. Recruitment was hindered by Covid19, and lack of funding resources.

Pre-assignment

Screening details:

Patients with cirrhosis attending outpatient clinics and medcial wards in the Hospitals Hvidovre, Aarhus and Herlev were screened for eligibility

Period 1

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

Blinding implementation details:

Randomisation lists were produced by an external partner at the regional Pharmacy in Capital Region of Denmark. Participants were allocated to study medication based on these randomisation lists. All trial participants, study personnel, investigators and monitors were blinded. Six months data assessment on both clinical (primary, secondary and safety) and exploratory outcomes were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Atorvastatin Group

Arm description:

Trial participants received 10 mg atorvastatin (1 capsule) in addition to standard treatment. If the trial medication was tolerated the dose was increased to 20 mg (two capsules)

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	C10AA05
Other name	Lipistad
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

10 mg (one capsule), increased to 20 mg (two capsules) daily, administered orally and taken at night time.
Medication was delivered to the patient at baseline and every 3 months. Excess capsules were returned be the trial participant at each study visit

Arm title	Placebo group

Arm description:

Trial participants received placebo capsules similar in colour, size and shape to the atorvastatin capsules

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

Dosage and administration details:

One capsule similar in shape, size and color to atorvastatin capsules, containing flavorless and colorless filler, were administered at night time. Dosage was regulated to two capsules if the trial medication was tolerated. Capsules were administered at baseline and every 3 months.
Excess capsules were returned at study visits

Number of subjects in period 1	Atorvastatin Group	Placebo group
Started	38	40
Completed	28	31
Not completed	10	9
Adverse event, serious fatal	3	2
Physician decision	3	3
Consent withdrawn by subject	4	4

Baseline characteristics

Reporting groups	
Reporting group title	Study

Reporting group description: -

Reporting group values	Study	Total	
Number of subjects	78	78	
Age categorical			
Inclusion criteria were age 18 to 80 years of age.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	47	47	
From 65-84 years	31	31	
85 years and over	0	0	
All study paticipants	0	0	
Age continuous			
Units: years			
median	60.5		
full range (min-max)	37 to 70	-	
Gender categorical			
Units: Subjects			
Female	33	33	
Male	45	45	

End points

End points reporting groups

Reporting group title	Atorvastatin Group
Reporting group description:	
Trial participants received 10 mg atorvastatin (1 capsule) in addition to standard treatment. If the trial medication was tolerated the dose was increased to 20 mg (two capsules)	
Reporting group title	Placebo group
Reporting group description:	
Trial participants received placebo capsules similar in colour, size and shape to the atorvastatin capsules	

Primary: Mortality

End point title	Mortality
End point description:	

End point type	Primary
End point timeframe:	
180 days	

End point values	Atorvastatin Group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: number	3	2		

Statistical analyses

Statistical analysis title	Comparison of mortality
Statistical analysis description:	
Comparison of mortality in the two groups	
Comparison groups	Atorvastatin Group v Placebo group
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.54
Method	t-test, 2-sided

Primary: Admissions

End point title	Admissions
End point description:	
Number of hospital admissions within 180 days	

End point type	Primary
End point timeframe: 180 days	

End point values	Atorvastatin Group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: Number				
All admissions	23	22		
Liver-related admissions	17	13		

Statistical analyses

Statistical analysis title	Comparision of admissions
Statistical analysis description: Comparison of the number of admissions in the two groups	
Comparison groups	Atorvastatin Group v Placebo group
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.97
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From 0 to 547 days	
Adverse event reporting additional description:	
Adverse events during trial period. Min. follow-up was 180 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Atorvastatin group
Reporting group description:	
Group exposed to Atorvastatin intervention	
Reporting group title	Placebo group
Reporting group description:	
Patients exposed to placebo intervention	

Serious adverse events	Atorvastatin group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 38 (39.47%)	17 / 40 (42.50%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	3	2	
Injury, poisoning and procedural complications			
Trauma, poisoning and procedures			
subjects affected / exposed	4 / 38 (10.53%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac related events	Additional description: Events due to cardiac events		
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cramps			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cancers	Additional description: Events related to complications of cancer disease (cancer diagnosis established after inclusion).		
subjects affected / exposed	1 / 38 (2.63%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Death	Additional description: Death outside of hospital, unknown causes and circumstances		
subjects affected / exposed	2 / 38 (5.26%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Changed general condition	Additional description: Exhaustion, in general need for help, also from communal providers		
subjects affected / exposed	2 / 38 (5.26%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GI-related	Additional description: Gastrointestinal events as nausea, vomiting, abdominal pain, intestinal and gastric lesions		
subjects affected / exposed	1 / 38 (2.63%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cirrhosis decompensations	Additional description: Events incuding hepatorenal syndrome, ascites, edema, spontaneous bacterial peritonitis, electrolyte disturbances, esophageal varices , hepatic encephalopathy and alcoholic hepatitis		
subjects affected / exposed	8 / 38 (21.05%)	10 / 40 (25.00%)	
occurrences causally related to treatment / all	0 / 27	0 / 22	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal and urinary disorders			
Kidney related	Additional description: Kidney related, hepatorenal syndrome excluded		
subjects affected / exposed	0 / 38 (0.00%)	3 / 40 (7.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Psychiatric and alcohol abuse related	Additional description: Admissions due to alcohol intoxication and/or psychiatric problems		
subjects affected / exposed	2 / 38 (5.26%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections	Additional description: Infections, not including spontaneous bacterial peritonitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atorvastatin group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)	15 / 40 (37.50%)	
Injury, poisoning and procedural complications			
Injuries	Additional description: Injuries in musculoskeletal system and joints including the scalp		
subjects affected / exposed	4 / 38 (10.53%)	4 / 40 (10.00%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Oropharyngeal symptoms	Additional description: Tongue disease, dysphagia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 38 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Tremor and vertigo			
subjects affected / exposed	2 / 38 (5.26%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Eye disorders			
Symptoms from eyes			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Gastrointestinal disorders			

Symptoms from GI tract	Additional description: Includes cholecystitis, abdominal pain, obstipation, ascites		
subjects affected / exposed	2 / 38 (5.26%)	4 / 40 (10.00%)	
occurrences (all)	3	5	
Respiratory, thoracic and mediastinal disorders			
Respiratory symptoms	Additional description: Symptoms of cough and/or dyspnoea, and/or Covid-19		
subjects affected / exposed	1 / 38 (2.63%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Psychiatric disorders			
Alcohol problem			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Calculus of kidney			
subjects affected / exposed	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Product issues			
Side effects	Additional description: Creatine kinase affection or subjective adverse effects		
subjects affected / exposed	2 / 38 (5.26%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
occurrences (all)	1	1	

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