# 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:<br>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:<br>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