



## Clinical trial results:

**Estudio multicéntrico, aleatorizado, doble-ciego, controlado con placebo, sobre la eficacia de la asociación de simvastatina al tratamiento estándar en la prevención de la recidiva hemorrágica en pacientes con cirrosis hepática y hemorragia por varices.**

### Summary

EudraCT number	2009-016500-24
Trial protocol	ES
Global end of trial date	23 December 2013

### Results information

Result version number	v1 (current)
This version publication date	23 May 2022
First version publication date	23 May 2022
Summary attachment (see zip file)	BLEPS Results (.BLEPS paper.docx) BLEPS Results (.Bleps paper final revision JB 1_1_16.docx)

### Trial information

#### Trial identification

Sponsor protocol code	BLEPS
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01095185
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Hopsital Clinic, University of Barcelona
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Scientific contact	Dr Jaime Bosch, Hepatic Hemodynamic Laboratory, Liver Unit, +34 608110193, jbosch@clinic.cat

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
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Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2013
Global end of trial reached?	Yes
Global end of trial date	23 December 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Determinar si la asociación de simvastatina al tratamiento convencional para prevenir la recurrencia de la hemorragia por varices esofágicas ( $\beta$ -bloqueantes no selectivos más ligadura endoscópica con bandas elásticas) mejora la supervivencia libre de recidiva hemorrágica en pacientes cirróticos.

Protection of trial subjects:

Patients were closely monitored to detect potential adverse events related to the trial medication. Two cases of CPK elevation accompanied by muscle pain were identified and totally resolved uneventfully soon after withdrawal of the trial medication.

Background therapy:

All patients received best standard of care medical therapy for their condition. This involved repeat sessions of endoscopic band ligation of esophago-gastric varices and the administration of non-selective beta-blockers at near maximal tolerated doses (as determined by progressive titration and thereafter adjusted against clinical tolerance and follow-up visits). Patients were further subject to cross-sectional liver imaging and full biochemistry and hematological exams every 6 months.

Evidence for comparator:

The rationale for the use of the study drug (Simvastatin) was provide by previous pre-clinical and clinical studies from our lab, demonstrating that simvastatin ameliorates liver endothelial dysfunction, reduces portal pressure by decreasing liver vascular resistance through increased availability of nitric oxide at the liver microcirculation, improves liver function and decreases fibrogenesis. The evidence is summarized in the study protocol and in the trial report.

Actual start date of recruitment	07 April 2010
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	Spain: 158
Worldwide total number of subjects	158
EEA total number of subjects	158

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)	121
From 65 to 84 years	37
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment took place from 2010 to 2013

### Pre-assignment

Screening details:

The study included patients with cirrhosis who recovered from a variceal bleeding. 287 pts were screened and 158 were randomized.

### Period 1

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

Blinding implementation details:

Blinding was guaranteed by providing the active and placebo medications under capsules of an identical aspect prepared at the hospital pharmacy and labelled with the patient code. The medication received is difficult to uncover since patients with cirrhosis have low cholesterol levels (a decrease in cholesterol is the most characteristic biochemical effect in patients with hyperlipidemia treated with simvastatin, but the decrease in cholesterol in subjects without hyperlipidemia is mild)

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Active treatment arm
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Arm description:

Active treatment arm refers patients receiving simvastatin as per randomization. Randomization to the two study arms was 1:1

Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	D.3.9.2
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage was ff 20 mg per day in a single tablet to be taken per os. This was increased up to 40 mg per day if well tolerated and with no increase in CPK, AST and ALT after two-weeks of continued administration

<b>Arm title</b>	Placebo
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Arm description:

Patients randomized to placebo

Arm type	placebo group
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule per day first two weeks of follow-up period, then increased to 2 capsules per day if tolerated

Number of subjects in period 1	Active treatment arm	Placebo
Started	75	83
Completed	69	78
Not completed	6	5
Consent withdrawn by subject	4	2
Study drug not available	1	-
terminated before end of baseline	-	2
Protocol deviation	1	1

## Period 2

Period 2 title	follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:  
same as described in baseline period

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Active treatment arm

Arm description:

Active treatment arm refers patients receiving simvastatin as per randomization. Randomization to the two study arms was 1:1

Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	D.3.9.2
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage was ff 20 mg per day in a single tablet to be taken per os. This was increased up to 40 mg per day if well tolerated and with no increase in CPK, AST and ALT after two-weeks of continued administration

<b>Arm title</b>	Placebo Arm
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Arm description:

patients randomized to placebo (n=78)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	D.3.9.2
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dosage was of 1 capsule per day to be taken per os. This was increased up to 2 capsules per day if well

tolerated and with no increase in CPK, AST and ALT after two-weeks of continued administration

<b>Number of subjects in period 2</b>	Active treatment arm	Placebo Arm
Started	69	78
Completed	69	78

## Baseline characteristics

### Reporting groups

Reporting group title	baseline
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Reporting group description: -

Reporting group values	baseline	Total	
Number of subjects	158	158	
Age categorical			
Mean age was 57.5 years, with and standard deviation of 10.5 years. No patient was over 80 year old, and no patient was less than 35 year-old. 98 patients were male and 60 female.			
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			
All 158 included patients were adult. None was under 35 year-old and none over 80 year-old			
Units: years			
arithmetic mean	57.5		
standard deviation	± 10.5	-	
Gender categorical			
Units: Subjects			
Female	60	60	
Male	98	98	

### Subject analysis sets

Subject analysis set title	Simvastatin group
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:  
patients in the Simvastatin Group

Subject analysis set title	Placebo Group
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:  
patients randomized to receive placebo, receiving placebo and completing the study

Reporting group values	Simvastatin group	Placebo Group	
Number of subjects	69	78	
Age categorical			
Mean age was 57.5 years, with and standard deviation of 10.5 years. No patient was over 80 year old, and no patient was less than 35 year-old. 98 patients were male and 60 female.			
Units: Subjects			

In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
All 158 included patients were adult. None was under 35 year-old and none over 80 year-old			
Units: years			
arithmetic mean	57.4	57.6	
standard deviation	± 10.6	± 11.3	
Gender categorical			
Units: Subjects			
Female	24	25	
Male	45	53	



## End points

### End points reporting groups

Reporting group title	Active treatment arm
Reporting group description: Active treatment arm refers patients receiving simvastatin as per randomization. Randomization to the two study arms was 1:1	
Reporting group title	Placebo
Reporting group description: Patients randomized to placebo	
Reporting group title	Active treatment arm
Reporting group description: Active treatment arm refers patients receiving simvastatin as per randomization. Randomization to the two study arms was 1:1	
Reporting group title	Placebo Arm
Reporting group description: patients randomized to placebo (n=78)	
Subject analysis set title	Simvastatin group
Subject analysis set type	Intention-to-treat
Subject analysis set description: patients in the Simvastatin Group	
Subject analysis set title	Placebo Group
Subject analysis set type	Intention-to-treat
Subject analysis set description: patients randomized to receive placebo, receiving placebo and completing the study	

### Primary: Composite of Rebleeding and Death

End point title	Composite of Rebleeding and Death
End point description: Number of patients with variceal rebleeding or dying during the follow-up	
End point type	Primary
End point timeframe: 3 years	

End point values	Active treatment arm	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	78		
Units: number of events	22	30		

### Statistical analyses

Statistical analysis title	Main results combined end point
Statistical analysis description: There were no statistically significant differences between the number of patients with a primary combined end point in the Simvastatin group, 22 of 69 (32%) Vs the Placebo group, 30 of 78 (39%) (HR for simvastatin = 0.822; 95% CI: 0.473–1.427; stratified log-rank P = .423). Therefore, the	

addition of simvastatin to standard therapy was not statistically superior to placebo in preventing rebleeding or death after a variceal bleeding episode.

Comparison groups	Active treatment arm v Placebo Arm
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	< 0.05 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	30
Confidence interval	
level	95 %
sides	2-sided
lower limit	20
upper limit	41
Variability estimate	Standard deviation
Dispersion value	7

Notes:

[1] - comparison between Simvastatin Group and Placebo group

[2] - The HR for simvastatin was 0.822; 95% CI: 0.473–1.427; stratified log-rank P =0.423). Therefore, addition of simvastatin to standard therapy was not superior to placebo in preventing rebleeding or death after a variceal bleeding episode

## Secondary: Survival

End point title	Survival
End point description:	
Patients dying on follow-up from any cause. These were 6 in the active treatment arm (9%) and 17 in the placebo arm (22%) (HR: 0.387; 95% CI: 0.152 to 0.986; stratified log-rank p-value: 0.030). This indicates a 61% reduction in mortality.	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Active treatment arm			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: number of deaths during follow-up	6			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rebleeding

End point title	Rebleeding
End point description:	
Patients rebleeding from varices during the follow-up.	
These were 17 patients in the simvastatin group and 22 patients in the placebo group. The rebleeding	

rate was not significantly decreased by the addition of simvastatin to the standard therapy (HR: 0.858; 95% CI: 0.455 to 1.620; stratified log-rank p-value: 0.583)

End point type	Secondary
End point timeframe:	
3 years	

End point values	Active treatment arm	Active treatment arm	Placebo Arm	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	69	78	78
Units: Number of pts with variceal rebleeding	17	17	22	22

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Three years

Adverse event reporting additional description:

117 of the 149 patients included in the safety population reported adverse events (60 patients on placebo vs. 57 on simvastatin;  $p=0.718$ ). These were possibly or probably related to drug treatment occurred in 14 patients on placebo and in 16 patients on simvastatin. 2 patients on Simvastatin had CPK elevation & muscle pain, needing dose reduction

Assessment type	Systematic
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	1
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### Reporting groups

Reporting group title	Simvastatin
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Reporting group description:

patients receiving simvastatin

Reporting group title	Placebo group
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Reporting group description:

Patients receiving placebo

Serious adverse events	Simvastatin	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 69 (2.90%)	0 / 78 (0.00%)	
number of deaths (all causes)	6	17	
number of deaths resulting from adverse events	0	0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis	Additional description: 2 patients under simvastatin, both in Child-Pugh class C and receiving 40 mg of simvastatin, developed muscle pain and CPK elevation that subsided upon dose reduction		
subjects affected / exposed	2 / 69 (2.90%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 6	0 / 17	

Frequency threshold for reporting non-serious adverse events: 0.02 %

Non-serious adverse events	Simvastatin	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 69 (17.39%)	11 / 78 (14.10%)	
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	3 / 78 (3.85%) 3	
Gynecomastia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	0 / 78 (0.00%) 0	
Blood and lymphatic system disorders Iron-deficiency anemia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	0 / 78 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0	3 / 78 (3.85%) 3	
Gastrointestinal bleeding subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1	2 / 78 (2.56%) 2	
Hepatobiliary disorders Ascites subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2	2 / 78 (2.56%) 2	
Hepatic encephalopathy subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3	1 / 78 (1.28%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2010	Prolongation of trial duration (to 3 years) and of maximal interval between index bleeding and randomization (from 7 to 10 days)

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was sized for assessing changes in rebleeding and mortality (combined end-point). The results shown a significant reduction in mortality, but the reduction in rebleeding was not statistically significant.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26774179>