



Clinical trial results:

Randomized study on the hemodynamic effect of the association of simvastatin with non-cardioselective beta-blockers in patients with liver cirrhosis and clinically significant portal hypertension.

Summary

EudraCT number	2010-022516-39
Trial protocol	ES
Global end of trial date	04 March 2016

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	SIMBETA
-----------------------	---------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau – IIB Sant Pau
Sponsor organisation address	c/ Sant Quintí, 77-79 , BARCELONA, Spain, 08041
Public contact	UICEC Sant Pau, Institut de Recerca Hospital de la Santa Creu i Sant Pau, 0034 935537636, uicec@santpau.cat
Scientific contact	UICEC Sant Pau, Institut de Recerca Hospital de la Santa Creu i Sant Pau, 0034 935537636, uicec@santpau.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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2015
Global end of trial reached?	Yes
Global end of trial date	04 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective will be to assess whether, in patients with compensated cirrhosis, portal hypertension greater than 10mmHg and esophageal varices at risk, the association of a selective hepatic vasodilator such as simvastatin together with non-cardioselective beta-blockers may have any long-term hemodynamic effect.

Protection of trial subjects:

The study will be conducted in strict accordance with international ethical recommendations for research and clinical trials in humans. Likewise, the standards contained in the Declaration of Helsinki will be guaranteed and will be developed in accordance with the protocol and with the standard work procedures (SOPs) that ensure compliance with the standards of Good Clinical Practice (PCB). The investigator should explain to the patient (when possible) or his authorized legal representative, the nature of the study, its purposes, procedures, estimated duration, the potential risks and benefits related to the participation in the study, as well as any inconvenience that this may cause. can suppose. Each of the participants should be warned that their participation in the study is voluntary and that they can leave the study at any time, without this affecting their subsequent treatment or their relationship with the professionals who treat them. For this, an information / consent sheet has been designed for the patient or the authorized legal representative, which is attached.

Background therapy:

Carvedilol (Cv), a non-selective β -blockers (NSBBs) with capacity to ameliorate hepatic vascular resistance (HVR), is more effective than traditional-NSBBs to reduce the hepatic venous pressure gradient (HVPG). Statins may also decrease portal hypertension by reducing the HVR by improving endothelial function. Whether the addition of statins may improve the hemodynamic effects of carvedilol in cirrhosis with clinically significant portal hypertension (CSPH) has not been clarified. This study aimed to evaluate whether the addition of simvastatin (Sv) can improve the hemodynamic effects of carvedilol in cirrhosis with CSPH and without previous HVPG response to NSBBs.

Evidence for comparator: -

Actual start date of recruitment	20 October 2011
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	Spain: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	82
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients of both sexes, with liver cirrhosis, older than 18 years and younger than 80 years who meet all the inclusion criteria and do not meet any exclusion criteria.

Pre-assignment

Screening details:

- Liver cirrhosis diagnosed by previous biopsy or by clinical, analytical and ultrasound criteria.
- PPG >10 mmHg.
- Presence of large esophageal varices or small esophageal varices with red dots, esophageal varices of any size and Pugh C, and/or fundic gastric varices of any size, in a recent gastroscopy (< 1 month)

Period 1

Period 1 title	BASELINE (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	CARVEDIOL + PLACEBO

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	CARVEDIOL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

6.25 mg/ 24h

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

XXXXX

Arm title	CARVEDIOL + SIMVASTATINA
------------------	--------------------------

Arm description: -

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

Dosage and administration details:

6.25 mg/ 24

Investigational medicinal product name	SIMVASTATINA
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg/ 24h

Number of subjects in period 1	CARVEDILOL + PLACEBO	CARVEDILOL + SIMVASTATINA
Started	41	41
INICIAL	41	41
Completed	41	41

Baseline characteristics

End points

End points reporting groups

Reporting group title	CARVEDIOL + PLACEBO
Reporting group description: -	
Reporting group title	CARVEDIOL + SIMVASTATINA
Reporting group description: -	

Primary: hepatic venous pressure gradient

End point title	hepatic venous pressure gradient
End point description:	
End point type	Primary
End point timeframe:	
OVERALL PERIOD	

End point values	CARVEDIOL + PLACEBO	CARVEDIOL + SIMVASTATINA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: mmHg	2	3		

Statistical analyses

Statistical analysis title	Descriptive statistical analysis
Comparison groups	CARVEDIOL + PLACEBO v CARVEDIOL + SIMVASTATINA
Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16
--------------------	----

Reporting groups

Reporting group title	CARVEDILOL + PLACEBO
-----------------------	----------------------

Reporting group description: -

Reporting group title	CARVEDILOL + SIMVASTATINA
-----------------------	---------------------------

Reporting group description: -

Serious adverse events	CARVEDILOL + PLACEBO	CARVEDILOL + SIMVASTATINA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (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: 5 %

Non-serious adverse events	CARVEDILOL + PLACEBO	CARVEDILOL + SIMVASTATINA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 41 (21.95%)	11 / 41 (26.83%)	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 41 (19.51%)	4 / 41 (9.76%)	
occurrences (all)	8	4	

Hepatobiliary disorders Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 41 (2.44%) 1	
Musculoskeletal and connective tissue disorders Increase of Creatin Kinase subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 41 (2.44%) 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