Clinical trial results:
EVOlocumab in stable Heart Failure with reduced ejection fraction of ischemic etiology: EVO-HF Pilot

Summary

EudraCT number	2017-004656-30
Trial protocol	ES
Global end of trial date	20 July 2022

Results information

Result version number	v1 (current)
This version publication date	24 April 2024
First version publication date	24 April 2024

Trial information

Trial identification

Sponsor protocol code	ICOR-2016-05

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	FUNDACIÓ INSTITUT D'INVESTIGACIÓ EN CIÈNCIES DE LA SALUT GERMANS TRIAS I PUJOL (IGTP)
Sponsor organisation address	Carretera de Canyet s/n, Badalona, Spain, 08916
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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 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess if LDL-C lowering at 1 year with monthly subcutaneous (SC) evolocumab 420 mg for 1 year will result in a significant reduction of high-sensitivity troponin T (hs-TnT), surrogate marker of myocyte injury and atherosclerosis progression, compared with current Standard of care (SOC) in subjects with elevated LDL-C, stable coronary artery disease (CAD) and stable heart failure with reduced ejection fraction (HFrEF).

Protection of trial subjects:

Not specified

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2018
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	12
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited in three Spanish Sites:
- Hospital Universitario Germans Trias i Pujol.
- Hospital Clínico Universitario de Valencia.
- Hospital Universitario Virgen del Rocío de Sevilla

Pre-assignment

Screening details:

1. Signing of the informed consent
2. Patient ≥18 years and ≤80 years of age
3. LVEF <40%
4. Ischemic etiology (evidence of at least one acute coronary event and/or CAD by coronary angiography or multi slice CT)
5. New York Heart Association (NYHA) class II
6. NT-proBNP ≥400 pg/mL
7. Hs-TnT ≥10 pg/mL
8. LDL ≥ 70 mg/dL
9. Stable CAD

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Investigators will be blinded for the biomarkers results

Arms

Are arms mutually exclusive?	Yes
Arm title	Evolocumab + GDMT

Arm description:

Patients in arm 1 will receive 12 subcutaneous injections of 420 mg of evolocumab, once every month, along with GDMT during 1 year.

Arm type	Experimental
Investigational medicinal product name	Evolocumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

evolocumab 420 mg/month on top of guideline-driven medical treatment (GDMT)

Arm title	GDMT

Arm description:

Guideline-driven medical treatment according to each participant

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Evolocumab + GDMT	GDMT
Started	17	22
Completed	16	22
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	39	39	
Age categorical 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)	12	12	
From 65-84 years	27	27	
85 years and over	0	0	
Subjects	0	0	
Age continuous Units: years			
median	67.7		
standard deviation	± 9.7	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	31	31	

End points

End points reporting groups

Reporting group title	Evolocumab + GDMT
Reporting group description:	
Patients in arm 1 will receive 12 subcutaneous injections of 420 mg of evolocumab, once every month, along with GDMT during 1 year.	
Reporting group title	GDMT
Reporting group description:	
Guideline-driven medical treatment according to each participant	

Primary: The Change in hs-TnT levels at 1 year

End point title	The Change in hs-TnT levels at 1 year
End point description:	
Statistical differences among patients in each treatment group were compared using the paired Student’s t-test or Wilcoxon test according to normal or non-normal distribution of the observed changes. No significant changes in hs-TnT levels were measured at 1 year in either of the two groups.	
End point type	Primary
End point timeframe:	
At 1 year	

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: hs-TnT levels				
median (standard deviation)	0.63 (± 8.6)	1.42 (± 7.3)		

Statistical analyses

Statistical analysis title	Paired Student’s t-test
Statistical analysis description:	
Mean±standard deviation was used only when all of the values for one variable had a normal distribution, including changes between baseline and 1 year. Statistical differences among patients in each treatment group were compared using the paired Student’s t-test or Wilcoxon test according to normal or non-normal distribution of the observed changes.	
Comparison groups	GDMT v Evolocumab + GDMT
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.539
Method	t-test, 2-sided

Secondary: Change in NT-proBNP levels

End point title	Change in NT-proBNP levels

End point description:

The NT-proBNP levels decreased only in the evolocumab plus GDMT group (p=0.045), but the differences between treatment groups were non-significant.

End point type	Secondary

End point timeframe:

at 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: NT-proBNP levels				
log mean (standard deviation)	-882 (± 1676)	-117 (± 545)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hs-CRP levels

End point title	Change in hs-CRP levels

End point description:

There were no significant changes in hs-CRP in either of the two groups

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: hs-CRP levels				
median (inter-quartile range (Q1-Q3))	-0.3 (-3.55 to 0.15)	-0.7 (-3.75 to 0.235)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LDL-C levels

End point title	Change in LDL-C levels

End point description:

Changes in total cholesterol and LDL-C were significantly different between groups, with higher decrease in the GDMT plus evolocumab group (p=0.003).

End point type	Secondary

End point timeframe:

at 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: LDL-C levels				
log mean (standard deviation)	-46.1 (± 35)	-15.3 (± 23.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change LDLR levels

End point title	Change LDLR levels

End point description:

There were no significant changes in LDLR in either of the two groups

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: LDLR levels				
log mean (standard deviation)	7.5 (± 23.1)	1.04 (± 12.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HDL-C levels

End point title	Change in HDL-C levels

End point description:

There were no significant changes in HDL-C in either of the two groups

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: HDL-C levels				
log mean (standard deviation)	-0.98 (± 9.4)	1.86 (± 9.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PCSK9 Levels

End point title	Change in PCSK9 Levels

End point description:

PCSK9 blood levels increased only in the intervention group

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: PCSK9 Levels				
log mean (standard deviation)	2307 (± 1366)	111.6 (± 479)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 6 minutes walking test

End point title	Change in 6 minutes walking test

End point description:

No significant differences were measured in the distance walked in the 6-min walking test between groups

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: meters				
log mean (standard deviation)	371 (± 120)	367 (± 104)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in quality of life test (KCCQ)

End point title	Change in quality of life test (KCCQ)

End point description:

There were also no significant changes in the scoring on the KCCQ. However, a non-significant trend for better evolution in quality of life perception in the intervention group was observed.

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: score				
log mean (standard deviation)	74.9 (± 18.7)	78.7 (± 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ST2 levels

End point title	Change in ST2 levels

End point description:

ST2 levels decreased significantly in the evolocumab plus GDMT group (p=0.008) and not in the GDMT alone group, and the difference between groups was significant (p=0.013).

End point type	Secondary

End point timeframe:

At 1 year

End point values	Evolocumab + GDMT	GDMT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: ST2 levels				
median (inter-quartile range (Q1-Q3))	-3 (-7.5 to 0)	1 (-3 to 2.25)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events that occur during the period comprehended from the time of enrollment of the patient in the study (signing of the consent form) to 30 days after discontinuation of the investigational products will be recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Experimental Group
Reporting group description: -	
Reporting group title	Control Group
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The AEs report is not included in the EudraCT results. In total 14 non-serious AEs have been recorded by the control group and 18 non-serious AEs have been recorded by the experimental group. In total 32 non-serious AEs have been recorded during the study.

Serious adverse events	Experimental Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 17 (29.41%)	5 / 22 (22.73%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Sustained ventricular tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	3 / 22 (13.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			

subjects affected / exposed	0 / 17 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac dysfunction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Failure	Additional description: NYHA Class III		
subjects affected / exposed	1 / 17 (5.88%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Temporal artery stenosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia by covid-19			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden onset dyspnea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haematoma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal gland operation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical Herniation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 22 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2019	Two changes in the criteria inclusion. The value of LDL cholesterol will be reduced to ≥ 70 mg/dL and the troponin T (Hs-TnT) value high sensitivity will be reduced to #8805; 10 pg/ml. It is decided to reduce These two criteria values inclusion to be able to include more patients in the study and benefit of the treatment, and extrapolate further faithfully the results of the study the real population.
13 February 2020	Change of inclusion criterion #6, duration update study and addition of a new site recruiter
11 February 2021	Update of the number of subjects of the rehearsal and communication of the termination of collaboration AMGEN in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 July 2021	The corresponding competent authority requested the sponsor the verification of compliance with Good Manufacturing Standards by the Pharmacy Service Hospital involved in the manufacture of Investigational Drug(s) after the AMGEN discontinuation in the study.	14 September 2021

Notes:

Limitations and caveats

None reported