



Clinical trial results: COMBinAtion Therapy in Myocardial Infarction: The COMBAT-MI trial Summary

EudraCT number	2015-001000-58
Trial protocol	ES
Global end of trial date	29 June 2020

Results information

Result version number	v1 (current)
This version publication date	20 March 2021
First version publication date	20 March 2021

Trial information

Trial identification

Sponsor protocol code	COMBAT-MI
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02404376
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	HOSPITAL UNIVERSITARI VALL D`HEBRON
Sponsor organisation address	PASSEIG VALL D`HEBRON 119-129, BARCELONA, Spain, 08035
Public contact	Ignacio Ferreira González, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), +34 9327461346134, nachoferreira@secardiologia.es
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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	07 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effectiveness of combination therapy with RIC and exenatide to limit MI size in patients with STEMI receiving pPCI.

Protection of trial subjects:

measures to minimise pain

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2016
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: 378
Worldwide total number of subjects	378
EEA total number of subjects	378

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)	219
From 65 to 84 years	150
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Patients eligible were enrolled in the catheterization laboratory and were randomly assigned to one of four groups.

Pre-assignment

Screening details:

Patients may be considered eligible by Haemodynamics after verification of eligible criteria and exclusion criteria (screening).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PLACEBO+RIC

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intracavernous use

Dosage and administration details:

All patients will receive saline, 180mL was intravenously administered, prior to the PPCI, at a flow rate of 72mL/h. After 15 min, the flow rate was reduced to 26mL/h and maintained for additional 6 hours.

Arm title	PLACEBO+ SHAM-RIC
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients receive saline , 180mL was intravenously administered, prior to the PPCI, at a flow rate of 72mL/h. After 15 min, the flow rate was reduced to 26mL/h and maintained for additional 6 hours.

Arm title	EXENATIDE+RIC
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	EXENATIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients will receive intravenous infusion of exenatide (18µg) diluted in saline (vehicle, 180mL) was intravenously administered, prior to the PPCI, at a flow rate of 72mL/h (0.12µg/min). After 15 min, the flow rate was reduced to 26mL/h (0.043µg/min) and maintained for additional 6 hours.

Arm title	EXENATIDE+SHAM RIC
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	EXENATIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients will receive intravenous infusion of exenatide (18µg) diluted in saline (vehicle, 180mL) was intravenously administered, prior to the PPCI, at a flow rate of 72mL/h (0.12µg/min). After 15 min, the flow rate was reduced to 26mL/h (0.043µg/min) and maintained for additional 6 hours.

Number of subjects in period 1	PLACEBO+RIC	PLACEBO+ SHAM- RIC	EXENATIDE+RIC
Started	96	93	91
Completed	54	58	48
Not completed	42	35	43
Primary Outcome not performed	1	2	1
CRM not performed	2	3	7
Exclusion Criteria	39	30	35

Number of subjects in period 1	EXENATIDE+SHAM RIC
Started	98
Completed	62
Not completed	36
Primary Outcome not performed	1
CRM not performed	5
Exclusion Criteria	30

Baseline characteristics

Reporting groups

Reporting group title	PLACEBO+RIC
Reporting group description: -	
Reporting group title	PLACEBO+ SHAM-RIC
Reporting group description: -	
Reporting group title	EXENATIDE+RIC
Reporting group description: -	
Reporting group title	EXENATIDE+SHAM RIC
Reporting group description: -	

Reporting group values	PLACEBO+RIC	PLACEBO+ SHAM-RIC	EXENATIDE+RIC
Number of subjects	96	93	91
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	60	47
From 65-84 years	43	32	40
85 years and over	1	1	4
Gender categorical			
Units: Subjects			
Female	15	10	15
Male	81	83	76

Reporting group values	EXENATIDE+SHAM RIC	Total	
Number of subjects	98	378	
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)	52	211	
From 65-84 years	43	158	
85 years and over	3	9	

Gender categorical Units: Subjects			
Female	39	79	
Male	59	299	

Subject analysis sets

Subject analysis set title	Placebo+ RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo+ RIC	
Subject analysis set title	Placebo+ Sham RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo+ Sham RIC	
Subject analysis set title	EXENATIDE+ RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: EXENATIDE+ RIC	
Subject analysis set title	EXENATIDE+ Sham RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: EXENATIDE+ Sham RIC	

Reporting group values	Placebo+ RIC	Placebo+ Sham RIC	EXENATIDE+ RIC
Number of subjects	54	58	48
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	40	27
From 65-84 years	21	18	19
85 years and over	0	0	2
Gender categorical Units: Subjects			
Female	6	8	8
Male	48	50	40

Reporting group values	EXENATIDE+ Sham RIC		
Number of subjects	62		
Age categorical 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)	36		
From 65-84 years	25		
85 years and over	1		
Gender categorical			
Units: Subjects			
Female	14		
Male	48		

End points

End points reporting groups

Reporting group title	PLACEBO+RIC
Reporting group description: -	
Reporting group title	PLACEBO+ SHAM-RIC
Reporting group description: -	
Reporting group title	EXENATIDE+RIC
Reporting group description: -	
Reporting group title	EXENATIDE+SHAM RIC
Reporting group description: -	
Subject analysis set title	Placebo+ RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo+ RIC	
Subject analysis set title	Placebo+ Sham RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo+ Sham RIC	
Subject analysis set title	EXENATIDE+ RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: EXENATIDE+ RIC	
Subject analysis set title	EXENATIDE+ Sham RIC
Subject analysis set type	Intention-to-treat
Subject analysis set description: EXENATIDE+ Sham RIC	

Primary: Myocardial Infarct Size measured by late gadolinium enhancement in CMRI 3-7 days after pPCI, and expressed as percent of left ventricular mass

End point title	Myocardial Infarct Size measured by late gadolinium enhancement in CMRI 3-7 days after pPCI, and expressed as percent of left ventricular mass
End point description:	
End point type	Primary
End point timeframe: 3-7 days	

End point values	PLACEBO+RIC	PLACEBO+ SHAM-RIC	EXENATIDE+RIC	EXENATIDE+S HAM RIC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	58	48	62
Units: percentage	54	58	48	62

Statistical analyses

Statistical analysis title	Factorial
Comparison groups	PLACEBO+RIC v PLACEBO+ SHAM-RIC v EXENATIDE+RIC v EXENATIDE+SHAM RIC
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	> 0.05 ^[2]
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Variability estimate	Standard deviation

Notes:

[1] - Two by two factorial analysis

[2] - Negative clinical trial

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 year

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Placebo+ RIC
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Reporting group description: -

Reporting group title	Placebo+ RIC
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Reporting group description: -

Reporting group title	EXENATIDE + RIC
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Reporting group description: -

Reporting group title	EXENATIDE + Sham RIC
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Reporting group description: -

Serious adverse events	Placebo+ RIC	Placebo+ RIC	EXENATIDE + RIC
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 54 (12.96%)	15 / 58 (25.86%)	13 / 48 (27.08%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Cardiac disorders			
Death			
subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 54 (1.85%)	2 / 58 (3.45%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	4 / 54 (7.41%)	8 / 58 (13.79%)	8 / 48 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Transient ischaemic attack alternative dictionary used: MedDRA 23.1 subjects affected / exposed	0 / 54 (0.00%)	2 / 58 (3.45%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Myocardial infarction subjects affected / exposed	1 / 54 (1.85%)	1 / 58 (1.72%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EXENATIDE + Sham RIC		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 62 (11.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Cardiac disorders			
Death			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Transient ischaemic attack alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo+ RIC	Placebo+ RIC	EXENATIDE + RIC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 54 (12.96%)	15 / 58 (25.86%)	7 / 48 (14.58%)
Cardiac disorders			
Percutaneous coronary intervention			
subjects affected / exposed	1 / 54 (1.85%)	0 / 58 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 54 (1.85%)	6 / 58 (10.34%)	2 / 48 (4.17%)
occurrences (all)	0	0	0
Arrhythmia supraventricular			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 54 (9.26%)	4 / 58 (6.90%)	3 / 48 (6.25%)
occurrences (all)	0	0	0

Non-serious adverse events	EXENATIDE + Sham RIC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 62 (9.68%)		
Cardiac disorders			
Percutaneous coronary intervention			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	0		
Atrial fibrillation			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	0		

Arrhythmia supraventricular alternative dictionary used: MedDRA 23.1 subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 0		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2016	Amendment n°1 Update of participating centers Number of patients is increased Modification of extension of time to perform the CMR
07 March 2017	Amendment n°2 Update of CMR machine Update of participating Investigators sites
31 May 2017	Amendment n°3 Update of participating investigator sites Revision of patient`s information letter
08 March 2018	Amendment n°4 Number of patients is increased
19 September 2019	Amendment n°5 Updated of participating investigator site

Notes:

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 trial could not be finished according with the prespecified sample size because of recruitment problems. Final sample size included in the analyses underpowered.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33495853>