Clinical trial results:
CLEAR SYNERGY (OASIS 9)
A 2x2 factorial randomized controlled trial of CoLchicine and spironolactonE in patients with ST elevation myocARdial infarction/SYNERGY Stent Registry –Organization to Assess Strategies for Ischemic Syndromes 9

Summary

EudraCT number	2017-000487-15
Trial protocol	ES FI CZ NL HU
Global end of trial date	09 August 2024

Results information

Result version number	v1 (current)
This version publication date	09 April 2025
First version publication date	09 April 2025
Summary attachment (see zip file)	OASIS_NEJM 2024 (OASIS_NEJM colchicine.pdf) OASIS_NEJM Spiro (OASIS_NEJM Spiro.pdf)

Trial information

Trial identification

Sponsor protocol code	CLSYN.1702

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03048825
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Population Health Research Institute (PHRI)
Sponsor organisation address	237 Barton Street East ON L8L 2x2 Hamilton (Canadá), Hamilton, Ontario, Canada,
Public contact	CLEAR SYNERGY Project Office, Population Health Research Institute, 1 9055274322 x41079, clear@phri.ca
Scientific contact	CLEAR SYNERGY Project Office, Population Health Research Institute, 1 9055274322 x41079, clear@phri.ca

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 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2024
Global end of trial reached?	Yes
Global end of trial date	09 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine the rate of major adverse cardiac events (MACE) in STEMI patients who have received a SYNERGY everolimus eluting stent compared to performance goal.
2. To determine if colchicine can reduce the incidence of cardiovascular (CV) death, myocardial infarction (MI), or stroke.
3. To determine if spironolactone can reduce the incidence of cardiovascular death or new or worsening heart failure.

Protection of trial subjects:

After the first 90 days of treatment, all patients received the trial product once a day. However, after blinded interim analyses showed higher-than-expected rates of discontinuation and the Colchicine Cardiovascular Outcomes
Trial (COLCOT) showed efficacy with once-daily colchicine, the steering committee adopted the regimen of once-daily colchicine at a dose of 0.5 mg or matching placebo throughout the remainder of the treatment period, beginning in September 2020

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2018
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	Egypt: 143
Country: Number of subjects enrolled	Canada: 1860
Country: Number of subjects enrolled	Australia: 59
Country: Number of subjects enrolled	United States: 162
Country: Number of subjects enrolled	Switzerland: 93
Country: Number of subjects enrolled	Nepal: 123
Country: Number of subjects enrolled	Serbia: 507
Country: Number of subjects enrolled	North Macedonia: 2589
Country: Number of subjects enrolled	Netherlands: 487
Country: Number of subjects enrolled	Spain: 374
Country: Number of subjects enrolled	United Kingdom: 413
Country: Number of subjects enrolled	Czechia: 86

Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Hungary: 40
Worldwide total number of subjects	7062
EEA total number of subjects	1113

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)	4395
From 65 to 84 years	2589
85 years and over	78

Subject disposition

Recruitment

Recruitment details:

Between February 1, 2018, and November 8, 2022, we enrolled 7062 patients from 104 centers in 14 countries; 3528 patients were assigned to receive colchicine and 3534 to receive placebo. 3537 were assigned to receive spironolactone and 3525 to receive placebo.

Pre-assignment

Screening details:

Patients were randomly assigned in a factorial 1:1:1:1 allocation to receive spironolactone and colchicine, colchicine and placebo, spironolactone and placebo, or placebo only as soon as possible after the index percutaneous coronary intervention. Randomization was stratified according the type of myocardial infarction: STEMI or NSTEMI.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Colchine

Arm description:

Colchine

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

Dosage and administration details:

Colchicine tablets of 0.5 mg

Arm title	Placebo

Arm description:

Placebo vs Colchine

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets of 0.5 mg

Arm title	Spironolactone

Arm description:

Spironolactone

Arm type	Experimental

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

Dosage and administration details:
Spironolactone tablets of 25 mg

Arm title	Placebo

Arm description:
Placebo vs Spironolactone

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Tablets of 25 mg

Number of subjects in period 1	Colchine	Placebo	Spironolactone
Started	3528	3534	3537
Completed	3517	3523	3526
Not completed	11	11	11
Lost to follow-up	11	11	11

Number of subjects in period 1	Placebo
Started	3525
Completed	3513
Not completed	12
Lost to follow-up	12

Baseline characteristics

Reporting groups	
Reporting group title	Colchine
Reporting group description: Colchine	
Reporting group title	Placebo
Reporting group description: Placebo vs Colchine	
Reporting group title	Spironolactone
Reporting group description: Spironolactone	
Reporting group title	Placebo
Reporting group description: Placebo vs Spironolactone	

Reporting group values	Colchine	Placebo	Spironolactone
Number of subjects	3528	3534	3537
Age categorical Units: Subjects			
18-64 years	2202	2193	2161
From 65-84 year	1296	1293	1333
85 years and over	30	48	43
Age continuous Units: years			
arithmetic mean	60.6211305	60.6500288	60.8817807
standard deviation	± 10.3297764	± 10.3235369	± 10.3477658
Gender categorical Units: Subjects			
Female	725	713	760
Male	2803	2821	2777

Reporting group values	Placebo	Total	
Number of subjects	3525	7062	
Age categorical Units: Subjects			
18-64 years	2234	4395	
From 65-84 year	1256	2589	
85 years and over	35	78	
Age continuous Units: years			
arithmetic mean	60.3885651		
standard deviation	± 10.2995335	-	
Gender categorical Units: Subjects			
Female	678	1438	
Male	2847	5624	

Subject analysis sets	
Subject analysis set title	Colchicine
Subject analysis set type	Per protocol

Subject analysis set description:

At the beginning of the trial, colchicine dosage was based on weight for the first 90 days of treatment; patients weighing 70 kg or more received a dose of 0.5 mg of colchicine or matching placebo twice a day, and patients weighing less than 70 kg received a dose of 0.5 mg or matching placebo once a day. After the first 90 days of treatment, all patients received the trial product once a day

Subject analysis set title	Spironolactone
Subject analysis set type	Per protocol

Subject analysis set description:

We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of spironolactone as compared with placebo and colchicine as compared with placebo in patients with acute myocardial infarction.

Subject analysis set title	Placebo (vs Colchine)
Subject analysis set type	Per protocol

Subject analysis set description:

At the beginning of the trial, colchicine dosage was based on weight for the first 90 days of treatment; patients weighing 70 kg or more received a dose of 0.5 mg of colchicine or matching placebo twice a day, and patients weighing less than 70 kg received a dose of 0.5 mg or matching placebo once a day. After the first 90 days of treatment, all patients received the trial product once a day

Subject analysis set title	Placebo (vs Spironolactone)
Subject analysis set type	Per protocol

Subject analysis set description:

We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of spironolactone as compared with placebo and colchicine as compared with placebo in patients with acute myocardial infarction.

Reporting group values	Colchicine	Spironolactone	Placebo (vs Colchine)
Number of subjects	3528	3537	3534
Age categorical Units: Subjects			
18-64 years	2202	2161	2193
From 65-84 year	1296	1333	1293
85 years and over	30	43	48
Age continuous Units: years			
arithmetic mean	60.6211305	60.8817807	60.6500288
standard deviation	± 10.3297764	± 10.3477658	± 10.3235369
Gender categorical Units: Subjects			
Female	725	760	713
Male	2803	2777	2821

Reporting group values	Placebo (vs Spironolactone)		
Number of subjects	3525		
Age categorical Units: Subjects			
18-64 years	2234		
From 65-84 year	1256		
85 years and over	35		

Age continuous Units: years			
arithmetic mean	60.3885651		
standard deviation	± 10.2995335		
Gender categorical Units: Subjects			
Female	678		
Male	2847		

End points

End points reporting groups

Reporting group title	Colchine
Reporting group description: Colchine	
Reporting group title	Placebo
Reporting group description: Placebo vs Colchine	
Reporting group title	Spironolactone
Reporting group description: Spironolactone	
Reporting group title	Placebo
Reporting group description: Placebo vs Spironolactone	
Subject analysis set title	Colchicine
Subject analysis set type	Per protocol
Subject analysis set description: At the beginning of the trial, colchicine dosage was based on weight for the first 90 days of treatment; patients weighing 70 kg or more received a dose of 0.5 mg of colchicine or matching placebo twice a day, and patients weighing less than 70 kg received a dose of 0.5 mg or matching placebo once a day. After the first 90 days of treatment, all patients received the trial product once a day	
Subject analysis set title	Spironolactone
Subject analysis set type	Per protocol
Subject analysis set description: We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of spironolactone as compared with placebo and colchicine as compared with placebo in patients with acute myocardial infarction.	
Subject analysis set title	Placebo (vs Colchine)
Subject analysis set type	Per protocol
Subject analysis set description: At the beginning of the trial, colchicine dosage was based on weight for the first 90 days of treatment; patients weighing 70 kg or more received a dose of 0.5 mg of colchicine or matching placebo twice a day, and patients weighing less than 70 kg received a dose of 0.5 mg or matching placebo once a day. After the first 90 days of treatment, all patients received the trial product once a day	
Subject analysis set title	Placebo (vs Spironolactone)
Subject analysis set type	Per protocol
Subject analysis set description: We used a 2-by-2 factorial design in this international, investigator-initiated, prospective, randomized, placebo-controlled trial of spironolactone as compared with placebo and colchicine as compared with placebo in patients with acute myocardial infarction.	

Primary: Death from cardiovascular causes or new or worsening heart failure

End point title	Death from cardiovascular causes or new or worsening heart failure
End point description:	
End point type	Primary
End point timeframe: The median time from symptom onset to randomization was 26.8 hours (interquartile range, 15.9 to 42.4), and the median time from randomization to the first dose of the trial product was 1.6 hours (interquartile range, 0.6 to 7.4)	

End point values	Colchine	Placebo	Spironolactone	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3528	3534	3537	3525
Units: number	322	327	183	220

End point values	Colchicine	Spironolactone	Placebo (vs Colchine)	Placebo (vs Spironolactone)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3528	3537	3534	3525
Units: number	322	183	327	220

Statistical analyses

Statistical analysis title	Primary-outocome
Comparison groups	Colchine v Placebo
Number of subjects included in analysis	7062
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.93
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Statistical analysis title	Primary-outocome
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	7062
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.51
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Primary: Death from cardiovascular causes or new or worsening heart failure

End point title	Death from cardiovascular causes or new or worsening heart failure

End point description:

End point type	Primary

End point timeframe:

The median time from symptom onset to randomization was 26.8 hours (interquartile range, 15.9 to 42.4), and the median time from randomization to the first dose of the trial product was 1.6 hours (interquartile range, 0.6 to 7.4)

End point values	Colchine	Placebo	Spironolactone	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3528	3534	3537	3525
Units: number	322	327	183	220

End point values	Colchicine	Spironolactone	Placebo (vs Colchine)	Placebo (vs Spironolactone)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
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Method	Logrank
Parameter estimate	Hazard ratio (HR)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All SAEs were reported to the Sponsor by completing the SAE CRF within 24 hours of knowledge of the event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Colchinine vs Placebo
Reporting group description: -	
Reporting group title	Spironolactone vs placebo

Reporting group description: -

Serious adverse events	Colchinine vs Placebo	Spironolactone vs placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 7062 (0.96%)	59 / 7062 (0.84%)	
number of deaths (all causes)	322	183	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 7062 (0.00%)	59 / 7062 (0.84%)	
occurrences causally related to treatment / all	0 / 0	59 / 59	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Serious adverse gastrointentinal event			
subjects affected / exposed	68 / 7062 (0.96%)	0 / 7062 (0.00%)	
occurrences causally related to treatment / all	68 / 68	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Colchinine vs Placebo	Spironolactone vs placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	594 / 7062 (8.41%)	67 / 7062 (0.95%)	

Vascular disorders Hypotension subjects affected / exposed occurrences (all)	 0 / 7062 (0.00%) 0	 67 / 7062 (0.95%) 67	
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	 594 / 7062 (8.41%) 594	 0 / 7062 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2019	Approval Amendments Part I - Authorisation for new batches of Spinorolactone test batch 17C07O2A - 17C07P2A
08 January 2021	Protocol amendment v.5
08 November 2023	Protocol amendment v 6.0 Modification the study efficacy outcome definitions for colchicine and spironolactone arms and update outcome analysis accordingly. Updates to outcome event definitions for newly added outcome events of interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39555823