



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-outcome |
| 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-outcome |
| 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 |
| Number of subjects analysed | 3528 | 3537 | 3534 | 3525 |
| Units: number | 322 | 183 | 327 | 220 |

Statistical analyses

| Statistical analysis title | Primary outocme |
|---|--------------------------|
| 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) |

| Statistical analysis title | Primary-outcome |
|---|--------------------|
| 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) |

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 | Colchicine vs Placebo |
|-----------------------|-----------------------|

Reporting group description: -

| | |
|-----------------------|---------------------------|
| Reporting group title | Spironolactone vs placebo |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events | Colchicine 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 gastrointestinal 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 | Colchicine 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 | 0 / 7062 (0.00%) | 67 / 7062 (0.95%) | |
| occurrences (all) | 0 | 67 | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 594 / 7062 (8.41%) | 0 / 7062 (0.00%) | |
| occurrences (all) | 594 | 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>