



Clinical trial results:

Influenza vaccination After Myocardial Infarction (IAMI trial).

A multicenter, prospective, randomized controlled clinical trial based on national angiography and angioplasty registries

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-001354-42 |
| Trial protocol | SE DK LV CZ NO GB |
| Global end of trial date | 02 March 2021 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 28 September 2022 |
| First version publication date | 28 September 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | IAMI-2014 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02831608 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Örebro University Hospital |
| Sponsor organisation address | Södra Grev Rosengatan, Örebro, Sweden, 70185 |
| Public contact | Department of Cardiology, Örebro University Hospital, 46 19 602 10 00, ole.frobert@regionorebrolan.se |
| Scientific contact | Department of Cardiology, Örebro University Hospital, 46 19 602 10 00, ole.frobert@regionorebrolan.se |

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 | 02 March 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 March 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 March 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

In a multicenter, prospective, randomized registry-based controlled clinical trial based on the SCAAR and SWEDEHEART platforms and other national registries in the participating countries to compare influenza vaccination and placebo in reducing future major adverse cardiac and cerebrovascular events in patients with myocardial infarction or stable coronary artery disease and an increased risk of future cardiovascular events.

Protection of trial subjects:

The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

Background therapy:

All patients in the study received guideline-directed medical therapy without restrictions for myocardial infarction/chronic ischemic heart disease. Information of medical therapy at baseline was not recorded. Heart disease-relevant medications at discharge for the two treatment groups was recorded.

Evidence for comparator:

Because influenza vaccination carries a Class I, Level of Evidence B recommendation in both American and European secondary prevention cardiovascular guidelines, it could be considered controversial to conduct a randomized clinical trial in which half of the patients received placebo. However, current guidelines are based mostly on evidence from observational studies, timing of influenza vaccination following an acute cardiovascular event is unknown, and influenza immunization rates remain low. In the IAMI study only patients not routinely receiving yearly influenza vaccination and not planning to be vaccinated during the current influenza season could be enrolled. Also, participants were allowed to obtain influenza vaccination after study enrollment on their own behalf.

| | |
|---|-----------------|
| Actual start date of recruitment | 11 October 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 | Australia: 47 |
| Country: Number of subjects enrolled | Bangladesh: 620 |
| Country: Number of subjects enrolled | Norway: 21 |
| Country: Number of subjects enrolled | Sweden: 999 |
| Country: Number of subjects enrolled | United Kingdom: 162 |
| Country: Number of subjects enrolled | Czechia: 110 |
| Country: Number of subjects enrolled | Denmark: 574 |
| Country: Number of subjects enrolled | Latvia: 38 |

| | |
|------------------------------------|------|
| Worldwide total number of subjects | 2571 |
| EEA total number of subjects | 1742 |

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) | 1694 |
| From 65 to 84 years | 833 |
| 85 years and over | 44 |

Subject disposition

Recruitment

Recruitment details:

From October 11, 2016, to March 1, 2020, 6696 patients were screened, of whom 2571 provided written informed consent and underwent randomization; 2532 received influenza vaccination or placebo and were included in the modified intention-to-treat analysis.

Pre-assignment

Screening details:

6696 patients were screened, of whom 2571 provided written informed consent and underwent randomization. 4125 patients were not enrolled, due to the following reasons: already vaccinated or intending vaccination (N=1439), patient declined (N=1202), patient not eligible (N=580), other medical reason (N=430), logistical reasons (N=326), other (N=148)

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, Carer, Assessor |

Blinding implementation details:

According to randomization, The IMP or placebo was prepared by an unblinded study nurse at each center, not otherwise involved or participating in the study. To ascertain blinding, the nurse could lay a piece of foil around the syringe to ensure that the patient could not see what was administered during the vaccination.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vaccine |

Arm description:

Subjects randomized to receive a single dose of influenza vaccine

| | |
|--|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | VaxigripTetra |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Injection , Subcutaneous use |

Dosage and administration details:

0.5 mL suspension for injection administered as a subcutaneous injection in a single dose.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects randomized to receive a single dose of placebo

| | |
|--|------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Sodium chloride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Injection , Subcutaneous use |

Dosage and administration details:

0.5 mL solution for injection administered as a subcutaneous injection in a single dose.

| Number of subjects in period 1 | Vaccine | Placebo |
|---------------------------------------|---------|---------|
| Started | 1290 | 1281 |
| Randomization | 1290 | 1281 |
| Treatment | 1272 | 1260 |
| Completed | 1272 | 1260 |
| Not completed | 18 | 21 |
| Consent withdrawn by subject | 11 | 10 |
| Transferred | 4 | 3 |
| Other | - | 3 |
| Incorrectly randomized | 3 | 5 |

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Vaccine |
| Reporting group description: | |
| Subjects randomized to receive a single dose of influenza vaccine | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects randomized to receive a single dose of placebo | |

| Reporting group values | Vaccine | Placebo | Total |
|---|---------|---------|-------|
| Number of subjects | 1290 | 1281 | 2571 |
| 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Age is reported for the subjects included in the m-ITT analysis, defined as all randomized patients according to their randomized treatment assignment and who received the study medication. Total number of subjects: 2532 Arm 1, Vaccine: 1272 Arm 2, Placebo: 1260 | | | |
| Units: years | | | |
| arithmetic mean | 60.1 | 59.6 | |
| standard deviation | ± 11.0 | ± 11.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 236 | 226 | 462 |
| Male | 1036 | 1034 | 2070 |
| Not reported | 18 | 21 | 39 |
| Diagnosis at inclusion | | | |
| Units: Subjects | | | |
| ST-segment elevation myocardial infarction | 665 | 683 | 1348 |
| Non-ST-segment elevation myocardial infarction | 568 | 551 | 1119 |
| Stable coronary artery disease | 6 | 2 | 8 |
| Not reported | 51 | 45 | 96 |
| Diabetes | | | |
| Units: Subjects | | | |
| Yes | 281 | 247 | 528 |
| No | 972 | 1007 | 1979 |

| | | | |
|--|-----------|-----------|------|
| Not reported | 37 | 27 | 64 |
| Smoking status | | | |
| Units: Subjects | | | |
| Never smoked | 463 | 461 | 924 |
| Former smoker | 332 | 328 | 660 |
| Current smoker | 437 | 433 | 870 |
| Not reported | 58 | 59 | 117 |
| Hyperlipidemia | | | |
| Units: Subjects | | | |
| Yes | 427 | 409 | 836 |
| No | 830 | 840 | 1670 |
| Not reported | 33 | 32 | 65 |
| Hypertension | | | |
| Units: Subjects | | | |
| Yes | 650 | 595 | 1245 |
| No | 601 | 656 | 1257 |
| Not reported | 39 | 30 | 69 |
| Previous myocardial infarction | | | |
| Units: Subjects | | | |
| Yes | 191 | 172 | 363 |
| No | 1062 | 1077 | 2139 |
| Not reported | 37 | 32 | 69 |
| Previous percutaneous coronary intervention | | | |
| Units: Subjects | | | |
| Yes | 138 | 129 | 267 |
| No | 1119 | 1128 | 2247 |
| Not reported | 33 | 24 | 57 |
| Previous coronary artery bypass grafting | | | |
| Units: Subjects | | | |
| Yes | 28 | 37 | 65 |
| No | 1230 | 1220 | 2450 |
| Not reported | 32 | 24 | 56 |
| Killip class ≥ 2 | | | |
| Units: Subjects | | | |
| Yes | 50 | 45 | 95 |
| No | 1107 | 1110 | 2217 |
| Not reported | 133 | 126 | 259 |
| Number of diseased vessels | | | |
| Units: Subjects | | | |
| Normal | 33 | 27 | 60 |
| 1-vessel disease | 546 | 590 | 1136 |
| 2-vessel disease | 268 | 228 | 496 |
| 3-vessel disease | 148 | 148 | 296 |
| Left main disease | 67 | 57 | 124 |
| Not reported | 228 | 231 | 459 |
| Body mass index | | | |
| Body-mass index is based on data reported for 1207 subjects in the vaccine group and 1201 subjects in the placebo group. | | | |
| Units: kilogram(s)/square metre | | | |
| arithmetic mean | 27.5 | 27.4 | |
| standard deviation | ± 5.0 | ± 5.1 | - |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | Vaccine |
| Reporting group description: | |
| Subjects randomized to receive a single dose of influenza vaccine | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects randomized to receive a single dose of placebo | |

Primary: All-cause death, myocardial infarction, stent thrombosis

| | |
|---|--|
| End point title | All-cause death, myocardial infarction, stent thrombosis |
| End point description: | |
| The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months after randomization, assessed during a telephone interview with participants or next of kin. If the patient or relatives could not be contacted, information was collected through review of hospital records. | |
| Definitions: | |
| <ul style="list-style-type: none">- Death: All reasons for death, i.e. cardiac, non-cardiac or unknown.- Myocardial infarction: ICD codes I21, I21.4 and I22, heart failure as I50 and stroke as I63.9.- New PCIs and stent thromboses are followed in SCAAR and the other national PCI registries. | |
| End point type | Primary |
| End point timeframe: | |
| Primary endpoint was measured at 1 year after treatment. | |

| End point values | Vaccine | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1272 | 1260 | | |
| Units: subjects | 67 | 91 | | |

Statistical analyses

| | |
|---|-------------------|
| Statistical analysis title | Primary endpoint |
| Comparison groups | Vaccine v Placebo |
| Number of subjects included in analysis | 2532 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.99 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting of AE started after informed consent and when treatment with study medication had been given and continued until the patient left the hospital after the coronary angiography/PCI procedure up to a minimum of 7 days following influenza vaccination

Adverse event reporting additional description:

Medical occurrences that were symptoms of existing disease, including exacerbations, or the PCI procedure were not defined as AE's. Also elective hospitalisations for pre-treatment conditions were not AE's nor expected reactions to vaccinations. AEs not to be reported were also those defined as study endpoints.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Vaccine |
|-----------------------|---------|

Reporting group description:

Subjects randomized to receive a single dose of influenza vaccine

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects randomized to receive a single dose of placebo

| Serious adverse events | Vaccine | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1272 (0.00%) | 0 / 1260 (0.00%) | |
| number of deaths (all causes) | 37 | 61 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0.2 %

| Non-serious adverse events | Vaccine | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 1272 (2.36%) | 16 / 1260 (1.27%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 1272 (0.31%) | 0 / 1260 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Headache | | | |

| | | | |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 1272 (0.16%) 2 | 2 / 1260 (0.16%) 2 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1272 (0.00%) | 2 / 1260 (0.16%) | |
| occurrences (all) | 0 | 2 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 1272 (0.00%) | 2 / 1260 (0.16%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 0 / 1260 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 0 / 1260 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Sore injection site | | | |
| subjects affected / exposed | 5 / 1272 (0.39%) | 1 / 1260 (0.08%) | |
| occurrences (all) | 5 | 1 | |
| Urticaria | | | |
| subjects affected / exposed | 4 / 1272 (0.31%) | 1 / 1260 (0.08%) | |
| occurrences (all) | 4 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 2 / 1260 (0.16%) | |
| occurrences (all) | 2 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 2 / 1260 (0.16%) | |
| occurrences (all) | 2 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 1 / 1260 (0.08%) | |
| occurrences (all) | 2 | 1 | |
| Infections and infestations | | | |
| Fever | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 3 / 1272 (0.24%) | 2 / 1260 (0.16%) | |
| occurrences (all) | 3 | 2 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 1272 (0.16%) | 1 / 1260 (0.08%) | |
| occurrences (all) | 2 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 21 December 2016 | Study protocol, Version 6.0: <ul style="list-style-type: none">• Changed timeframes for vaccination from 42 hours following coronary angiography/PCI (NSTEMI and STEMI patients) to 72 hours to optimize compliance and facilitate the implementation of the study.• Clarification regarding unblinding |
| 11 September 2017 | Study protocol, Version 7.0: <ul style="list-style-type: none">• Change of study title from Swedish national registries to national registries• Change of vaccine from Vaxigrip to VaxigripTetra and from Sanofi Pasteur MSD to Sanofi Pasteur Europe• Additional countries and sites• Clarification of exclusion criteria• Change in timeframe for enrolment and vaccination from 24 hours prior to coronary angiography/PCI (NSTEMI patients) up to 72 hours following coronary angiography/PCI for both NSTEMI and STEMI patients• Clarification that Informed consent shall be obtained by a medical doctor participating in the study.• Change in timeframe for vaccination (24 hours prior to coronary angiography/PCI (NSTEMI patients) since there is a risk that complications that arise after the procedure may be difficult to derive from the procedure itself or for study treatment, so no vaccination performed before coronary angiography/PCI procedure. |
| 10 July 2018 | Study protocol, Version 8.0: <ul style="list-style-type: none">• Change in study period• Change in exclusion criteria |
| 11 October 2018 | Study protocol, Version 9.0: <ul style="list-style-type: none">• Prolonged study period, inclusion to 2021 and follow up (exploratory endpoints) to 2026• Additional study population, patients with stable coronary artery disease and an increased risk of future cardiovascular events.• Additional inclusion criteria; Patients with stable coronary artery disease ≥ 75 years of age undergoing angiography/PCI AND with at least one additional risk criterion• Addition that primary endpoints also can be obtained by telephone interviews and hospital records not only from national health registries,• Clarifications regarding secondary endpoints• Clarification regarding randomization in study-specific online Web-system for non-Swedish centers.• Addition that all endpoints will be adjudicated according to a separate Adjudication Charter.• Addition of text regarding additional study population |

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.

Due to the COVID-19 pandemic, the DSMB decided on April 7 2020, to recommend a halt of the inclusion, since transmission of influenza was expected to decrease, and COVID-19 related deaths were deemed likely to make the results difficult to interpret.

Notes: