



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
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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
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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:	
- 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Vaccine
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Reporting group description:

Subjects randomized to receive a single dose of influenza vaccine

Reporting group title	Placebo
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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: • 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: • 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: • Change in study period • Change in exclusion criteria
11 October 2018	Study protocol, Version 9.0: • 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: