Clinical trial results:
A phase IIb study to determine the safety and efficacy of candidate INfluenza Vaccine MVA-NP+M1 in combination with licensed InaCTivated inflUenza vaccine in adultS aged 65 years and above

Summary

EudraCT number	2017-001103-77
Trial protocol	GB
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	11 November 2019
First version publication date	11 November 2019

Trial information

Trial identification

Sponsor protocol code	FLU007 INVICTUS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03300362
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vaccitech Limited
Sponsor organisation address	The Schrodinger Building, Heatley Avenue, Oxford Science Park, Oxford, United Kingdom, OX4 4GE
Public contact	Dr Thomas Evans, Vaccitech Limited, 44 1865 818008, enquiries@vaccitech.co.uk
Scientific contact	Dr Thomas Evans, Vaccitech Limited, 44 1865 818008, tom.evans@vaccitech.co.uk

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	20 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of MVA-NP+M1 in combination with licensed inactivated influenza vaccine in adults ≥65 years.

Protection of trial subjects:

standard procedures for emergency care were followed for any adverse events if clinically needed. The study also incorporated stopping rules and IDMC reviews at pre-defined time points.

Background therapy:

annual licensed QIV influenza vaccine

Evidence for comparator: -

Actual start date of recruitment	29 September 2017
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	United Kingdom: 862
Worldwide total number of subjects	862
EEA total number of subjects	862

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)	0
From 65 to 84 years	862
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

participants aged 65 years or over who were eligible for the annual seasonal influenza vaccine were approached after screening by their General Practitioner. If interest was obtained, they were brought into their GP practice for screening, consenting and vaccination on the same day. They were then sent home with a diary card.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	1020[1]
Number of subjects completed	862

Pre-assignment subject non-completion reasons

Reason: Number of subjects	On anti-coagulants: 2
Reason: Number of subjects	Did not attend appointment: 77
Reason: Number of subjects	History of anaphlyaxis: 2
Reason: Number of subjects	Attended visit and changed mind: 44
Reason: Number of subjects	Other medical reason: 2
Reason: Number of subjects	Involved in other trial: 1
Reason: Number of subjects	Previous allergic reaction to vaccine: 1
Reason: Number of subjects	Unknown: 20
Reason: Number of subjects	Physician decision: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1020 people screened and invited to participate, only 862 decided or were eligible to participate.

Period 1

Period 1 title	Enrolment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

MVA-NP+M1 plus seasonal influenza vaccine

Arm type	Experimental
Investigational medicinal product name	MVA-NP+M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details: MVA dose 1.5x10*8 pfu given into deltoid muscle	
Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details: Influenza virus (inactivated, split) of the following strains*: Per 0.5 ml dose * propagated in fertilised hens' eggs from healthy chicken flocks ** haemagglutinin	
Arm title	Placebo
Arm description: 0.9% Saline placebo and seasonal influenza vaccine	
Arm type	Placebo
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: 0.9% saline 0.5mL given into deltoid muscle	
Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details: Each dose was 0.5ml and administered via intramuscular injection	

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the appearance of MVA it was not possible to conduct a double blind trial, however, to maintain as much blind as possible all study roles that could be kept blind were as shown here.

Number of subjects in period 1	Active	Placebo
Started	432	430
Completed	431	429
Not completed	1	1
Consent withdrawn by subject	1	-
ineligible	-	1

Period 2

Period 2 title	Vaccination
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[3]
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

MVA-NP+M1 plus seasonal influenza vaccine

Arm type	Experimental
Investigational medicinal product name	MVA-NP+M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MVA dose 1.5x10*8 pfu given into deltoid muscle

Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Influenza virus (inactivated, split) of the following strains*:

Per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin

Arm title	Placebo

Arm description:

0.9% Saline placebo and seasonal influenza vaccine

Arm type	Placebo
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.9% saline 0.5mL given into deltoid muscle

Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose was 0.5ml and administered via intramuscular injection

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the appearance of MVA it was not possible to conduct a double blind trial, however, to maintain as much blind as possible all study roles that could be kept blind were as shown here.

Number of subjects in period 2	Active	Placebo
Started	431	429
Completed	420	426
Not completed	11	3
Consent withdrawn by subject	3	-
unknown reason	1	1
non adherence	7	2

Period 3

Period 3 title	Diary Card Completion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[4]
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

MVA-NP+M1 plus seasonal influenza vaccine

Arm type	Experimental
Investigational medicinal product name	MVA-NP+M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MVA dose 1.5x10*8 pfu given into deltoid muscle

Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Influenza virus (inactivated, split) of the following strains*:

Per 0.5 ml dose

* propagated in fertilised hens' eggs from healthy chicken flocks

** haemagglutinin

Arm title	Placebo

Arm description:	
0.9% Saline placebo and seasonal influenza vaccine	
Arm type	Placebo
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.9% saline 0.5mL given into deltoid muscle	
Investigational medicinal product name	Quadrivalent Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Each dose was 0.5ml and administered via intramuscular injection	

Notes:

[4] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the appearance of MVA it was not possible to conduct a double blind trial, however, to maintain as much blind as possible all study roles that could be kept blind were as shown here.

Number of subjects in period 3	Active	Placebo
Started	420	426
Completed	413	420
Not completed	7	6
Adverse event, serious fatal	1	1
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	1
non adherence	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
MVA-NP+M1 plus seasonal influenza vaccine	
Reporting group title	Placebo
Reporting group description:	
0.9% Saline placebo and seasonal influenza vaccine	

Reporting group values	Active	Placebo	Total
Number of subjects	432	430	862
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 Units: years			
arithmetic mean	72.5	72.4	
standard deviation	± 5.1	± 4.9	-
Gender categorical Units: Subjects			
Female	192	193	385
Male	240	237	477

End points

End points reporting groups	
Reporting group title	Active
Reporting group description: MVA-NP+M1 plus seasonal influenza vaccine	
Reporting group title	Placebo
Reporting group description: 0.9% Saline placebo and seasonal influenza vaccine	
Reporting group title	Active
Reporting group description: MVA-NP+M1 plus seasonal influenza vaccine	
Reporting group title	Placebo
Reporting group description: 0.9% Saline placebo and seasonal influenza vaccine	
Reporting group title	Active
Reporting group description: MVA-NP+M1 plus seasonal influenza vaccine	
Reporting group title	Placebo
Reporting group description: 0.9% Saline placebo and seasonal influenza vaccine	

Primary: Number of Days with Moderate/Severe Influenza-like Symptoms during ILI	
End point title	Number of Days with Moderate/Severe Influenza-like Symptoms during ILI
End point description:	
End point type	Primary
End point timeframe: Day 8 until end of influenza season which was 30th April 2018	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	426		
Units: days				
arithmetic mean (standard deviation)	1.1 (± 3.8)	1.1 (± 3.3)		

Statistical analyses

Statistical analysis title	Unadjusted Linear Mixed Effect Model
Comparison groups	Placebo v Active

Number of subjects included in analysis	846
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.872
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.954
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.537
upper limit	1.694

Notes:

[1] - unadjusted linear mixed effect model for presence of moderate or severe symptoms

Secondary: Incidence of Influenza like Illness

End point title	Incidence of Influenza like Illness

End point description:

Protocol defined ILI episodes

End point type	Secondary

End point timeframe:

Day 8 to 30th April 2018

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	426		
Units: episodes	83	94		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Influenza like Illness

End point title	Duration of Influenza like Illness

End point description:

End point type	Secondary

End point timeframe:

Day 08 to 30th April 2018

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	94		
Units: Days				
median (full range (min-max))	7.0 (1.0 to 58.0)	5.0 (1.0 to 28.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

date of consent to day 28 for non-serious events
date of consent until end of study for serious adverse events

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 860 (3.02%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Elective surgery			

subjects affected / exposed	6 / 860 (0.70%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 860 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Physical assault			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis relapsing			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive pancreatitis			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cyst			

subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	2 / 860 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Abscess limb			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 860 (0.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 860 (6.98%)		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 860 (1.05%)		
occurrences (all)	10		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 860 (1.28%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 860 (1.63%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 860 (1.63%)		
occurrences (all)	14		
Myalgia			

subjects affected / exposed occurrences (all)	12 / 860 (1.40%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2017	Sponsor Address 24 Hour Safety Hotline number and safety email Treatment duration and follow-up duration ILI definition Clarification of trial design for immunology cohort Date to start recording their illness diary cards Criteria for postponement of vaccination. Details of randomisation for immunology cohort Randomisation details not recorded in eCRF Illness reporting and safety follow-up – details of ILI symptoms given here. Medical Notes Review includes: chest imaging results when available Deleted: Guidelines for assessing the relationship of vaccine administration to an AE Start date for data analysis Primary Outcome definition Interim analysis: to include after the first 100 participants have been randomised
27 March 2018	Updated information on previous clinical use of MVA-NP+M1. Added laboratory confirmed influenza as a secondary trial endpoint. Addition of nasal swab procedure to collect laboratory confirmed influenza secondary endpoint Clarifications on secondary endpoints and immunology endpoints. Clarifications on trial design, AE reporting and causality assessment procedures Updated list of solicited AEs and ILI symptoms recorded Updated safety reporting information: GP consultations due to respiratory illness only, collected from week 5 onward. Previously scheduled elective procedures will not be reported as SAEs. Clarification of which investigators will be blinded to group allocation. Clarifications on study procedures for data collection on defined endpoints. Updated compensation amount to reflect additional screening visit needed for participants recruited into the Immunology Cohort via general advertisements. Increased window from 90 to 120 days between screening and vaccination visit for participants recruited via general advertisements Update clarification of the statistical analysis of ILI

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported