Clinical trial results:
A phase II, open label trial to describe immune and transcriptional responses to MF59 adjuvanted trivalent influenza vaccine (ATIV) in 13-24 month healthy children and adults 18-65 years

Summary

EudraCT number	2015-001648-12
Trial protocol	GB
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	16 November 2019
First version publication date	16 November 2019

Trial information

Trial identification

Sponsor protocol code	OVG2015/02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02529904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford. Clinical Trials and Research Governance Team (CTRG).
Sponsor organisation address	Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington, Oxford, United Kingdom, OX3 7GB
Public contact	Professor Andrew J Pollard, Oxford Vaccine Group, 0044 1865 611400, andrew.pollard@paediatrics.ox.ac.uk
Scientific contact	Professor Andrew J Pollard, Oxford Vaccine Group, 0044 1865 611400, andrew.pollard@paediatrics.ox.ac.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	15 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective of this study was to identify the specific 'immune response' genes which are activated by the ATIV vaccine and to correlate them to the immune response (level of antibodies - these are specific proteins against a virus which are part of the immune response) which occur when these genes are 'switched on' (this is also called gene expression). We were interested in assessing the difference between the response in children (aged 13-24 months) compared to adults (aged 18 -65 years).

Protection of trial subjects:

Ethical, Legal and Management Protection: Every effort was made to ensure that participants, parents or guardians giving informed consent were able to understand fully the nature of the study including the risks,burdens, benefits and implications that taking part would have. The study involved the vaccination and the collection of blood samples that would not normally be part of routine care. In order to minimise any discomfort, local anaesthetic cream was offered to numb children's skin prior to the sample being collected.
The members of the study team undertaking vaccination and venepuncture had specific training and experience. With the participant/parent/guardians agreement two attempts at blood sampling were made and if unsuccessful a further visit was arranged by the study team.
Strict inclusion and exclusion criteria applied to the enrolment of each study participant.
The study complied with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so ensuring that the participant's anonymity was maintained throughout the trial.

Background therapy:

Not applicable.

Evidence for comparator:

The study aimed to assess early gene transcriptional responses to priming and boosting with ATIV in children aged 13-24 months and adults aged 18 - 65 years, and to establish correlations with HAI titers. This study adds to the initial ADITEC Flu pilot study conducted in 2012 (EudraCT Number: 2012-002443-26, Ethics Ref: OxREC C 12/SC/0407); a phase 2, randomised, open label study, also demonstrated increased immunogenicity and a relatively similar reactogenicity profile following ATIV immunisation compared to TIV.

This current study adds to the initial study by collecting immunogenicity and gene expression data following the first ATIV dose (the initial study only collected blood samples for gene analysis post-second ATIV dose) and directly comparing child to adult data by enrolling both child and adult cohorts. Children received 2 doses (0.25ml) approximately 2 weeks apart and adults received a single dose (0.5ml) of the Fluad vaccine (MF59 Adjuvanted trivalent influenza vaccine (MF59-ATIV)) by -intramuscular injection.

Actual start date of recruitment	05 October 2015
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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	90
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on the 5th of October 2015. Screening visits started on the 3rd November 2015. Recruitment was completed on the 22nd February 2016.

Eligible participants were identified within the Thames Valley area of England (UK) using a variety of recruitment methods including posters, leaflets, website and mail outs.

Pre-assignment

Screening details:

Full inclusion/exclusion criteria assessed by the study doctor.Screening assessment included: physical examination, medical history, concomitant medication, temperature measurement, demographics.

Period 1

Period 1 title	Study Duration (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Children aged 13 to 24 months of age

Arm description:

Children received 2 half doses of the vaccine (0.25ml) at V1 (Day 0) and V4 (Day 28)

Arm type	Experimental
Investigational medicinal product name	FLUAD
Investigational medicinal product code	J07BB02
Other name	FLUAD (Influenza Vaccine, Adjuvanted)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Children received a 0.25 ml dose administered at visit 1 and visit 4, intramuscularly into the upper lateral aspect of either thigh muscle using a 0.6 x 25 mm 23 gauge needle.

Adults received a 0.5ml administered at visit 1 intramuscularly into the deltoid area of either arm using a 25mm 23 gauge needle.

Arm title	Adults aged 18 to 65 years of age

Arm description:

Adults received a single full dose of the vaccine (0.5ml) at V1 (Day 0)

Arm type	Experimental
Investigational medicinal product name	FLUAD
Investigational medicinal product code	J07BB02
Other name	FLUAD (Influenza Vaccine, Adjuvanted)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Children received a 0.25 ml dose administered at visit 1 and visit 4, intramuscularly into the upper lateral aspect of either thigh muscle using a 0.6 x 25 mm 23 gauge needle.

Adults received a 0.5ml administered at visit 1 intramuscularly into the deltoid area of either arm using a 25mm 23 gauge needle.

Number of subjects in period 1	Children aged 13 to 24 months of age	Adults aged 18 to 65 years of age
Started	90	30
Completed	86	30
Not completed	4	0
Consent withdrawn by subject	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Study Duration

Reporting group description: -

Reporting group values	Study Duration	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	90	90	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	30	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	71	71	
Male	49	49	

Subject analysis sets	
Subject analysis set title	Group 1 (aged 13 - 24 months)
Subject analysis set type	Per protocol

Subject analysis set description:

Children 13-24 months of age.

Baseline Visit (Day -7 to Day 0) = Blood sample for HAI, innate responses and transcriptomics, V1 (Day 0) = ATIV dose 1, V2 (Day 1) = Blood sample for innate responses and transcriptomics, V4 (Day 28) = ATIV dose 2, V7 (Day 56) = blood sample for HAI

Subject analysis set title	Group 2 (aged 13 - 24 months)
Subject analysis set type	Per protocol

Subject analysis set description:

Children 13-24 months of age.

V1 (Day 0) = ATIV dose 1, V3 (Day 21 to Day 28) = Blood sample for HAI, innate responses and transcriptomics, V4 (Day 28) = ATIV dose 2, V5 (Day 29) = blood sample for innate response and transcriptomics, V7 (Day 56) = blood sample for HAI

Subject analysis set title	Group 3 (aged 13 - 24 months)
Subject analysis set type	Per protocol

Subject analysis set description:

Children 13-24 months of age.

V1 (Day 0) = ATIV dose 1, V4 (Day 28) = Blood sample for HAI, innate responses and transcriptomics and ATIV dose 2, V6 (Day 31) = blood sample for innate response and transcriptomics, V7 (Day 56) =

blood sample for HAI

Subject analysis set title	Group 4 (aged 18 - 65 years)
Subject analysis set type	Per protocol

Subject analysis set description:

Adults 18-65 years of age.

Baseline Visit (Day -7 to Day 0) = Blood sample for HAI, V1 (Day 0) = ATIV, V2 (Day 1) = blood sample for innate responses and transcriptomics, V3 (Day 3) = blood sample for innate responses and transcriptomics, V4 (Day 28) = blood sample for HAI

Reporting group values	Group 1 (aged 13 - 24 months)	Group 2 (aged 13 - 24 months)	Group 3 (aged 13 - 24 months)
Number of subjects	30	30	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	30	30	30
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	17	18	11
Male	13	12	19

Reporting group values	Group 4 (aged 18 - 65 years)		
Number of subjects	30		
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)	30		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	25		
Male	5		

End points

End points reporting groups

Reporting group title	Children aged 13 to 24 months of age
Reporting group description:	
Children received 2 half doses of the vaccine (0.25ml) at V1 (Day 0) and V4 (Day 28)	
Reporting group title	Adults aged 18 to 65 years of age
Reporting group description:	
Adults received a single full dose of the vaccine (0.5ml) at V1 (Day 0)	
Subject analysis set title	Group 1 (aged 13 - 24 months)
Subject analysis set type	Per protocol
Subject analysis set description:	
Children 13-24 months of age. Baseline Visit (Day -7 to Day 0) = Blood sample for HAI, innate responses and transcriptomics, V1 (Day 0) = ATIV dose 1, V2 (Day 1) = Blood sample for innate responses and transcriptomics, V4 (Day 28) = ATIV dose 2, V7 (Day 56) = blood sample for HAI	

Subject analysis set title	Group 2 (aged 13 - 24 months)
Subject analysis set type	Per protocol
Subject analysis set description:	
Children 13-24 months of age. V1 (Day 0) = ATIV dose 1, V3 (Day 21 to Day 28) = Blood sample for HAI, innate responses and transcriptomics, V4 (Day 28) = ATIV dose 2, V5 (Day 29) = blood sample for innate response and transcriptomics, V7 (Day 56) = blood sample for HAI	
Subject analysis set title	Group 3 (aged 13 - 24 months)
Subject analysis set type	Per protocol
Subject analysis set description:	
Children 13-24 months of age. V1 (Day 0) = ATIV dose 1, V4 (Day 28) = Blood sample for HAI, innate responses and transcriptomics and ATIV dose 2, V6 (Day 31) = blood sample for innate response and transcriptomics, V7 (Day 56) = blood sample for HAI	
Subject analysis set title	Group 4 (aged 18 - 65 years)
Subject analysis set type	Per protocol
Subject analysis set description:	
Adults 18-65 years of age. Baseline Visit (Day -7 to Day 0) = Blood sample for HAI, V1 (Day 0) = ATIV, V2 (Day 1) = blood sample for innate responses and transcriptomics, V3 (Day 3) = blood sample for innate responses and transcriptomics, V4 (Day 28) = blood sample for HAI	

Primary: Gene Expression

End point title	Gene Expression[1]
End point description:	
Differential gene expression following ATIV at baseline and days 1 (children and adults) and 3 (adults only) post initial immunization and at baseline and days 1 and 3 post boost immunization (children only).	
End point type	Primary
End point timeframe:	
Endpoint 1: Differential gene expression following ATIV at baseline and days 1 (children and adults) and 3 (adults only) post initial immunization and at baseline and days 1 and 3 post boost immunization (children only).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistics will be descriptive and will be included in the trial publication.

End point values	Group 1 (aged 13 - 24 months)	Group 2 (aged 13 - 24 months)	Group 3 (aged 13 - 24 months)	Group 4 (aged 18 - 65 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: Description				
number (not applicable)	30	30	30	30

Statistical analyses

No statistical analyses for this end point

Primary: HAI Titres

End point title	HAI Titres[2]

End point description:

HAI titers (for strains influenza A H1N1,influenza A H3N2 and influenza B) ≥ defined thresholds (1:40, 1:110 and 1:620), the HAI geometric mean titers (GMT) and the mean geometric fold rise in HAI titers from baseline to day 28 (adults and children) and to day 56 (children only).

End point type	Primary

End point timeframe:

Group 1 = Baseline (Day -7 to Day 0) and V7 (Day 56)
Group 2 = V3 (Day 21 to Day 28) and V7 (Day 56)
Group 3 = V4 (Day 28) and V7 (Day 56)
Group 4 = Baseline (Day -7 to 0) and V4 (Day 28)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistics will be descriptive and will be included in the trial publication.

End point values	Group 1 (aged 13 - 24 months)	Group 2 (aged 13 - 24 months)	Group 3 (aged 13 - 24 months)	Group 4 (aged 18 - 65 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: Description				
number (not applicable)	30	30	30	30

Statistical analyses

No statistical analyses for this end point

Secondary: Innate Immune Cells

End point title	Innate Immune Cells

End point description:

Analysis of the frequency and activation of granulocytes, monocytes, and dendritic cells as measured in

the peripheral whole blood at the following time points: baseline, day 1 and day 28 (children and adults), and also day 3 (adults only) post initial immunization and at day 1 and 3 post-boost immunization (children only).

End point type	Secondary

End point timeframe:

Group 1 = Baseline (Day -7 to Day 0) and V2 (Day 1)
Group 2 = V3 (Day 21 to Day 28) and V5 (Day 29)
Group 3 = V4 (Day 28) and V6 (Day 31)
Group 4 = Baseline (Day -7 to 0), V2 (Day 1) and V3 (Day 3)

End point values	Group 1 (aged 13 - 24 months)	Group 2 (aged 13 - 24 months)	Group 3 (aged 13 - 24 months)	Group 4 (aged 18 - 65 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: Description				
number (not applicable)	30	30	30	30

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of ATIV

End point title	Immunogenicity of ATIV

End point description:

The percentage of participants with HAI titers (for strains influenza A H1N1, influenza A H3N2 and influenza B) ≥ defined thresholds (1:40, 1:110 and 1:620), the HAI geometric mean titers (GMT) and the mean geometric fold rise in HAI titers from baseline to day 28 (adults and children) and to day 56 (children only).

End point type	Secondary

End point timeframe:

Group 1 = Baseline (Day -7 to Day 0) and V2 (Day 1)
Group 2 = V3 (Day 21 to Day 28) and V5 (Day 29)
Group 3 = V4 (Day 28) and V6 (Day 31)
Group 4 = Baseline (Day -7 to 0), V2 (Day 1) and V3 (Day 3)

End point values	Group 1 (aged 13 - 24 months)	Group 2 (aged 13 - 24 months)	Group 3 (aged 13 - 24 months)	Group 4 (aged 18 - 65 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: Description				
number (not applicable)	30	30	30	30

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting in this study were reported from the point of first study intervention. The time frame for adverse event reporting was from the baseline visit or 2 days prior to V1 when the electronic diary (ediary) entries commenced.

Adverse event reporting additional description:

All AEs occurring on the day of vaccine administration and three days following, and all AEs resulting in withdrawal from the study occurring within 1 month after vaccination, whether or not attributed to study medication, will be reported on the CRF/source document. AEs will be divided up into solicited and unsolicited reactions.

Assessment type	Systematic

Dictionary used

Dictionary name	Protocol
Dictionary version	3.0

Reporting groups

Reporting group title	Systemic Local AE's: redness and swelling

Reporting group description:

Redness and swelling will be measured and recorded in the eDiary. They will be categorised as absent, mild, moderate and severe based on the size of affected area. A ruler will be given to the parent/participant with instructions for measuring any redness or swelling at the injection site. The parent/participant will be asked to measure the largest diameter of a local reaction and record this in the eDiary.

Reporting group title	Systemic Local AE's: Tenderness

Reporting group description:

The parent/participant will be asked to assess and record in the eDiary whether tenderness is present at the injection site and grade it based on the degree to which the tenderness affects movement of the limb and routine daily activities.

Reporting group title	Solicited Systemic AE's: Temperature

Reporting group description:

Temperature will be measured by the parent/participant and recorded from day of immunisation until three days post-vaccination. A digital thermometer will be provided by the study team at the screening visit. Temperature will be considered as fever if equal to or greater than 38.0°C. In the event of fever, the highest value measured throughout each day should be recorded in the eDiary.

Reporting group title	Solicited Systemic AE's: Systemic AE's

Reporting group description:

Systemic AEs for children include: reduced feeding, reduced activity, irritability, vomiting or diarrhoea. For adults, systemic AEs include: headache, nausea/vomiting, malaise, myalgia and arthralgia. The severity of these solicited systemic AEs will be graded as follows: 0 if none, 1 if mild symptoms, 2 if moderate symptoms and 3 if severe symptoms.

Reporting group title	Unsolicited AE's

Reporting group description:

Unsolicited AEs are any adverse events that are not pre-listed in the eDiary but may be reported in the eDiary in the three days following vaccination (in addition to day of vaccine administration) by the parent/participant or through interview.

The following information will be recorded for medically significant, unsolicited AEs: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant’s parents/participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe. The relationship of AEs to the study medication will be assessed.

Serious adverse events	Systemic Local AE's: redness and swelling	Systemic Local AE's: Tenderness	Solicited Systemic AE's: Temperature
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 117 (0.00%)	0 / 117 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Solicited Systemic AE's: Systemic AE's	Unsolicited AE's	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 120 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Systemic Local AE's: redness and swelling	Systemic Local AE's: Tenderness	Solicited Systemic AE's: Temperature
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 117 (29.91%)	62 / 117 (52.99%)	6 / 117 (5.13%)
General disorders and administration site conditions			
Administration site reaction	Additional description: Redness and swelling		
alternative dictionary used: Protocol 3.0			
alternative assessment type: Non-systematic			
subjects affected / exposed	35 / 117 (29.91%)	62 / 117 (52.99%)	6 / 117 (5.13%)
occurrences (all)	1	1	1

Non-serious adverse events	Solicited Systemic AE's: Systemic AE's	Unsolicited AE's	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 117 (77.78%)	0 / 120 (0.00%)	
General disorders and administration site conditions			
Administration site reaction	Additional description: Redness and swelling		
alternative dictionary used: Protocol 3.0			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	91 / 117 (77.78%) 1	0 / 120 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	The addition of Thames Valley General Practitioner (GP) surgeries for study recruitment purposes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported