Clinical trial results:
Efficacy & Safety of Nasal Influenza Immunisation in Children - The SNIFFLE-3 study

Summary

EudraCT number	2015-003019-39
Trial protocol	GB
Global end of trial date	27 May 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2018
First version publication date	14 October 2018

Trial information

Trial identification

Sponsor protocol code	15SM2801

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02549365
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Norfolk Place, London, United Kingdom,
Public contact	Dr Paul Turner, Imperial College London, 44 02033127754, p.turner@imperial.ac.uk
Scientific contact	Dr Paul Turner, Imperial College London, 44 02033127754, p.turner@imperial.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	21 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2016
Global end of trial reached?	Yes
Global end of trial date	27 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of LAIV in children and their siblings in the 2015/16 influenza season, through documentation of the incidence of laboratory confirmed influenza and other respiratory viruses, in children receiving LAIV (recruited to both the intervention and surveillance phases of the study), compared to their household sibling controls (recruited to only the surveillance phase).

Protection of trial subjects:

Study undertaken by research team on paediatric research unit. Partipants who were consented to provide blood samples were offered local anaesthetic cream prior to venepuncture.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 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: 276
Worldwide total number of subjects	276
EEA total number of subjects	276

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)	13
Children (2-11 years)	195
Adolescents (12-17 years)	68
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 164 Index cases (who received LAIV) and 122 siblings (household controls) were recruited.

Pre-assignment

Screening details:

Subjects were recruited through 2 routes: existing paediatric outpatient services at St Mary's Hospital or from prior participation in SNIFFLE studies.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LAIV

Arm description:

Participant received at least 1 dose of LAIV for 2015/16 influenza season

Arm type	Experimental
Investigational medicinal product name	Live Attenuated Influenza Vaccine
Investigational medicinal product code	EU/1/13/887/001
Other name	Fluenz Tetra
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

0.2ml (administered as 0.1ml per nostril)

Arm title	Household control

Arm description:

Household sibling of index case

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	LAIV	Household control
Started	164	112
Completed	164	112

Period 2	
Period 2 title	Surveillance
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	LAIV

Arm description:

Participant received at least 1 dose of LAIV for 2015/16 influenza season

Arm type	Experimental
Investigational medicinal product name	Live Attenuated Influenza Vaccine
Investigational medicinal product code	EU/1/13/887/001
Other name	Fluenz Tetra
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

0.2ml (administered as 0.1ml per nostril)

Arm title	Household control

Arm description:

Household sibling of index case

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	LAIV	Household control
Started	164	112
Completed	164	112

Baseline characteristics

Reporting groups	
Reporting group title	LAIV
Reporting group description:	
Participant received at least 1 dose of LAIV for 2015/16 influenza season	
Reporting group title	Household control
Reporting group description:	
Household sibling of index case	

Reporting group values	LAIV	Household control	Total
Number of subjects	164	112	276
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)	0	13	13
Children (2-11 years)	32	75	107
Adolescents (12-17 years)	132	24	156
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	65	48	113
Male	99	64	163
Prior influenza vaccination in previous 3 years Units: Subjects			
No prior vaccination	96	107	203
1 vaccine	37	4	41
2 vaccines	22	1	23
3 vaccines	9	0	9

End points

End points reporting groups	
Reporting group title	LAIV
Reporting group description:	
Participant received at least 1 dose of LAIV for 2015/16 influenza season	
Reporting group title	Household control
Reporting group description:	
Household sibling of index case	
Reporting group title	LAIV
Reporting group description:	
Participant received at least 1 dose of LAIV for 2015/16 influenza season	
Reporting group title	Household control
Reporting group description:	
Household sibling of index case	

Primary: Laboratory positive infuenza infection	
End point title	Laboratory positive infuenza infection
End point description:	
End point type	Primary
End point timeframe:	
Influenza season 2015/2016	

End point values	LAIV	Household control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164[1]	112[2]		
Units: Number of cases				
number (not applicable)				
Positive for H1N1	4	2		
Positive for 'flu B	4	0		

Notes:

[1] - 39 swabs collected in 29 children

[2] - 19 swabs in 17 children

Attachments (see zip file)	Vaccine Efficacy/Sniffle 3 Vaccine Efficacy.docx

Statistical analyses

Statistical analysis title	Efficacy
Statistical analysis description:	
Incidence of laboratory confirmed influenza is compared between those vaccinated and household controls. VE will be calculated as 1 – RR with 95% confidence intervals using Poisson regression. Adjustment for age will be included and the influence of prior vaccinations.	
Comparison groups	LAIV v Household control

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Odds ratio (OR)
Point estimate	2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	13.9
Variability estimate	Standard deviation

Notes:

[3] - Incidence of laboratory confirmed influenza is compared between those vaccinated and household controls. VE will be calculated as 1 – RR with 95% confidence intervals using Poisson regression. Adjustment for age will be included and the influence of prior vaccinations.

Secondary: Immunogenicity pre/post LAIV

End point title	Immunogenicity pre/post LAIV[4]

End point description:

End point type	Secondary

End point timeframe:

3-6 weeks post LAIV

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Household controls did not undergo venepuncture in this protocol (since no intervention was administered)

End point values	LAIV			
Subject group type	Reporting group			
Number of subjects analysed	41[5]			
Units: antibody titre				
geometric mean (confidence interval 95%)	1.06 (0.95 to 1.19)			

Notes:

[5] - 41 participants consented to venepuncture

Attachments (see zip file)	Sniffle 3 Immunogenicity.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - serious adverse events

End point title	Safety - serious adverse events[6]

End point description:

End point type	Secondary

End point timeframe:

Up to 4 weeks post LAIV

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: AE data was not collected in the household controls (since no intervention was administered)

End point values	LAIV			
Subject group type	Reporting group			
Number of subjects analysed	164			
Units: No. cases	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - adverse events

End point title	Safety - adverse events[7]

End point description:

End point type	Secondary

End point timeframe:

Up 72 hours post LAIV

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: AE data was not collected in the household controls (since no intervention was administered)

End point values	LAIV			
Subject group type	Reporting group			
Number of subjects analysed	164			
Units: No. cases	63			

Attachments (see zip file)	Safety/Sniffle 3 Safety.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 72 hours following LAIV for non-serious AEs
Up to 4 weeks following LAIV for SAEs

Adverse event reporting additional description:

Questionnaire after 72 hours
Asthma control questionnaire 4 weeks following LAIV.

Assessment type	Systematic

Dictionary used

Dictionary name	Internal PHE categor
Dictionary version	1

Reporting groups

Reporting group title	Atopic status: positive

Reporting group description:

Existing atopic disease e.g. asthma, food allergy, eczema

Reporting group title	Non-atopic participants

Reporting group description: -

Serious adverse events	Atopic status: positive	Non-atopic participants	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 116 (0.00%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	

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

Non-serious adverse events	Atopic status: positive	Non-atopic participants	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 116 (39.66%)	12 / 48 (25.00%)	
General disorders and administration site conditions			
Rhinitis			
subjects affected / exposed	23 / 116 (19.83%)	5 / 48 (10.42%)	
occurrences (all)	19	5	
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 116 (11.21%)	3 / 48 (6.25%)	
occurrences (all)	13	3	
Fever			

subjects affected / exposed	4 / 116 (3.45%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Malaise			
subjects affected / exposed	3 / 116 (2.59%)	1 / 48 (2.08%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Sniffle 3 was unable to demonstrate a protective effect of LAIV in 2015/16 when comparing vaccinated children with siblings. In fact there were more positive flu swabs in those vaccinated, perhaps indicating a reporting bias.

Notes: