



Clinical trial results: Safety of Nasal Influenza Immunisation in Children with Asthma: The SNIFFLE 4 study

Summary

EudraCT number	2016-002352-24
Trial protocol	GB
Global end of trial date	31 March 2017

Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

Trial information

Trial identification

Sponsor protocol code	16SM3348
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02866942
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	24 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2017
Global end of trial reached?	Yes
Global end of trial date	31 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess changes in asthma symptoms / symptom control following LAIV in children with asthma / recurrent wheezing, including children with difficult/severe asthma

Protection of trial subjects:

Participants were recruited through local asthma clinics and informed consent obtained. Participants were immunised in the hospital environment, by personnel qualified in the recognition and treatment of anaphylaxis, and observed for at least 20 minutes following a dose. Families were then contacted at 72 hours after immunisation to establish the occurrence of any delayed effects, and also contacted 4 weeks later to complete a validated questionnaire to re-assess asthma control. Participating families had contact details for their local paediatric respiratory/research team during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 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	United Kingdom: 478
Worldwide total number of subjects	478
EEA total number of subjects	478

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)	320
Adolescents (12-17 years)	154
Adults (18-64 years)	4
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Subjects were recruited through 2 routes: existing specialist paediatric asthma/allergy outpatient services or from prior participation in SNIFFLE studies at 14 hospitals with paediatric services in England.

Pre-assignment

Screening details:

Inclusion criteria: age 2-18 years; physician diagnosis of asthma and prescribed regular inhaled corticosteroids (ICS) OR if <5yrs, 2+ exacerbations in previous 12 mths requiring oral steroids or hospitalisation.

Exclusion criteria: invasive ventilation due to a respiratory illness in the preceding 2 years; acute wheeze not an exclusion criteria

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LAIV
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Arm description:

Participant received at least 1 dose of LAIV for 2016/17 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)

Number of subjects in period 1	LAIV
Started	478
Completed	478

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	478	478	
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	154	154	
Adults (18-64 years)	4	4	
Children (2-4 years)	85	85	
Children (5-11 years)	235	235	
Gender categorical			
Units: Subjects			
Female	190	190	
Male	288	288	
Asthma control			
"Persistent poor control" defined as: <ul style="list-style-type: none"> • Age 2-4yrs: ICS>200µg + LRTA or ≥2 exacerbations in past year requiring oral steroids/hospitalisation • Age 5-11yr: ICS>400µg/day • Age 12+yr: ICS>800µg/day (BTS criteria, 2014)			
Units: Subjects			
Persistent poor asthma control	229	229	
Not persistent	249	249	
Treatment with high dose ICS			
High dose inhaled corticosteroids (ICS), defined as <ul style="list-style-type: none"> • Age 2-4yrs: ICS≥400µg/day • Age 5+yrs: ICS>800µg/day 			
Units: Subjects			
High dose ICS	208	208	
Not high dose ICS	270	270	
Difficult asthma			
"Difficult asthma" defined as persistence of asthma symptoms despite treatment with high-dose therapies (BTS definition)			
Units: Subjects			
Difficult asthma	142	142	
Not difficult asthma	336	336	

End points

End points reporting groups

Reporting group title	LAIV
Reporting group description:	
Participant received at least 1 dose of LAIV for 2016/17 influenza season	
Subject analysis set title	Full dataset for subjects age >5yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
For participants aged 5+ years only	

Primary: Change in asthma control

End point title	Change in asthma control
End point description:	
No. of participants with a significant change in TRACK or (c-)ACT score comparing pre to 4 weeks post LAIV.	
The minimum important difference (MID) for the ACT score is around 2 points in children and 3 points in adults, and 10 points for TRACK. For the purpose of this analysis, a change in ACT of at least 3 points, or 10 points for TRACK will be determined to be a significant change, where this results in an ACT score changing to $< / \geq 20$ or TRACK score to $< / \geq 80$ points.	
End point type	Primary
End point timeframe:	
4 weeks post LAIV administration	

End point values	LAIV	Full dataset for subjects age >5yrs		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	319 ^[1]	259 ^[2]		
Units: No. cases				
Improvement \geq MID	28	25		
No change	254	205		
Deterioration \geq MID	37	29		

Notes:

[1] - 4 week follow-up data available in 319/478 participants

[2] - Follow-up data available for 259 participants aged 5+ years

Statistical analyses

Statistical analysis title	Change in asthma control
Statistical analysis description:	
For the primary outcome, the change in TRACK or ACT score pre- and 4 weeks post LAIV is assessed by McNemar's test for paired data for combined ages for TRACK/ACT.	
Comparison groups	LAIV v Full dataset for subjects age >5yrs

Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.26 ^[3]
Method	Mcnemar

Notes:

[3] - Overall the proportion with a significant deterioration was 37/319 (11.6%, 95% CI 8.3% - 15.6%). But this did not significantly differ to the proportion that improved of 28/319 (8.8%), $p=0.26$, so there is no evidence this is due to LAIV.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 72hr of LAIV administration for AEs and SAEs unrelated to asthma symptoms

Within 4 weeks of LAIV for SAEs related or possibly related to asthma symptoms

Assessment type	Systematic
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Dictionary used

Dictionary name	Internal PHE categor
Dictionary version	1

Reporting groups

Reporting group title	LAIV
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Reporting group description:

Participant received at least 1 dose of LAIV for 2016/17 influenza season

Serious adverse events	LAIV		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 478 (0.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Wheezing	Additional description: Asthma exacerbation		
subjects affected / exposed	4 / 478 (0.84%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LAIV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 478 (31.38%)		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	42 / 478 (8.79%)		
occurrences (all)	42		
Rhinitis			

subjects affected / exposed occurrences (all)	54 / 478 (11.30%) 54		
Infections and infestations			
Cough			
subjects affected / exposed	27 / 478 (5.65%)		
occurrences (all)	27		
Wheezing			
subjects affected / exposed	27 / 478 (5.65%)		
occurrences (all)	27		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2016	Substitution of "surveillance nasal swabs" during influenza season with nasal swabs to be taken during the 7 days post vaccination to assess for viral shedding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported