



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. Participants 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 |
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| 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 influenza infection

| | |
|--|---|
| End point title | Laboratory positive influenza 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: