# Clinical trial results:
# A Phase 4 Double-blind Study to Evaluate the Shedding and Immunogenicity of Trivalent and Quadrivalent Formulations of FluMist in Children 24 to < 48 Months of Age

## Summary

| | |
|---|---|
| EudraCT number | 2018-003701-26 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 29 September 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 01 December 2018 |
| First version publication date | 01 December 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | D2560C00013 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03143101 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | MedImmune, LLC |
| Sponsor organisation address | One MedImmune Way, Gaithersburg, United States, 20878 |
| Public contact | Raburn Mallory, MedImmune, LLC, +1 3013 985799, information.center@astrazeneca.com |
| Scientific contact | Raburn Mallory, MedImmune, LLC, +1 3013 985799, information.center@astrazeneca.com |

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 | 29 September 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to describe the level of serum hemagglutination inhibition (HAI) antibody responses induced by trivalent and quadrivalent formulations of FluMist against antigenically matched influenza strains.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Subjects signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 08 May 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 200 |
| Worldwide total number of subjects | 200 |
| EEA total number of subjects | 0 |

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) | 200 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |

| | |
|---|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted from 08 May 2017 through 29 Sep 2017 in the USA.

### Pre-assignment

Screening details:

A total of 200 subjects were randomized and participated in the study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | FluMist trivalent (2015-2016) |

Arm description:

Subjects received intranasal spray of 0.2 milliliter (mL) (total dose in both nostrils) FluMist trivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 fluorescent focus units (FFU) of each vaccine strain. Strains included in the trivalent vaccine were: A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), and B/Phuket/3073/2013 (B/Yamagata-lineage).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FluMist trivalent vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Intranasal use |

Dosage and administration details:

Intranasal spray of 0.2 mL (total dose in both nostrils) FluMist trivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the trivalent vaccine were: A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), and B/Phuket/3073/2013 (B/Yamagata-lineage).

| | |
|---|---|
| **Arm title** | FluMist Quadrivalent (2015-2016) |

Arm description:

Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FluMist quadrivalent vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Intranasal use |

Dosage and administration details:

Intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage).

| | |
|---|---|
| **Arm title** | FluMist Quadrivalent (2017-2018) |

Arm description:

Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were the new A/H1N1 (A/Slovenia/2903/2015), A/H3N2 (A/New Caledonia/71/2014), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FluMist quadrivalent vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Intranasal use |

Dosage and administration details:

Intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were the new A/H1N1 (A/Slovenia/2903/2015), A/H3N2 (A/New Caledonia/71/2014), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage).

| **Number of subjects in period 1** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) |
|---|---|---|---|
| Started | 67 | 66 | 67 |
| Completed | 65 | 63 | 67 |
| Not completed | 2 | 3 | 0 |
| Consent withdrawn by subject | - | 1 | - |
| Lost to follow-up | 2 | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | FluMist trivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 milliliter (mL) (total dose in both nostrils) FluMist trivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 fluorescent focus units (FFU) of each vaccine strain. Strains included in the trivalent vaccine were: A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), and B/Phuket/3073/2013 (B/Yamagata-lineage). | |
| Reporting group title | FluMist Quadrivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |
| Reporting group title | FluMist Quadrivalent (2017-2018) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were the new A/H1N1 (A/Slovenia/2903/2015), A/H3N2 (A/New Caledonia/71/2014), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |

| **Reporting group values** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) |
|---|---|---|---|
| Number of subjects | 67 | 66 | 67 |
| Age categorical<br>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 | 0 | 0 |
| Children (2-11 years) | 67 | 66 | 67 |
| 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 |
| Age Continuous<br>Units: months | | | |
| arithmetic mean | 35.96 | 34.96 | 34.94 |
| standard deviation | ± 6.41 | ± 6.78 | ± 6.80 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 27 | 32 | 35 |
| Male | 40 | 34 | 32 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 0 |
| Asian | 1 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 2 | 0 | 1 |
| Black or African American | 9 | 9 | 13 |

| | | | |
|---|---|---|---|
| White | 52 | 55 | 49 |
| More than one race | 3 | 1 | 3 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 11 | 9 | 14 |
| Not Hispanic or Latino | 56 | 57 | 53 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 200 | | |
| Age categorical<br>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) | 200 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous<br>Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 94 | | |
| Male | 106 | | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | | |
| Asian | 1 | | |
| Native Hawaiian or Other Pacific Islander | 3 | | |
| Black or African American | 31 | | |
| White | 156 | | |
| More than one race | 7 | | |
| Unknown or Not Reported | 1 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 34 | | |
| Not Hispanic or Latino | 166 | | |
| Unknown or Not Reported | 0 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | FluMist trivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 milliliter (mL) (total dose in both nostrils) FluMist trivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 fluorescent focus units (FFU) of each vaccine strain. Strains included in the trivalent vaccine were: A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), and B/Phuket/3073/2013 (B/Yamagata-lineage). | |
| Reporting group title | FluMist Quadrivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |
| Reporting group title | FluMist Quadrivalent (2017-2018) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were the new A/H1N1 (A/Slovenia/2903/2015), A/H3N2 (A/New Caledonia/71/2014), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |

### Primary: Percentage of Subjects With A/H1N1 Hemagglutination Inhibition (HAI) Antibody Seroconversion Rate at Day 28

| | |
|---|---|
| End point title | Percentage of Subjects With A/H1N1 Hemagglutination Inhibition (HAI) Antibody Seroconversion Rate at Day 28 |
| End point description: | |
| Seroconversion rate is defined as at least (>=) 4-fold rise from baseline in A/H1N1 HAI antibody titer. Percentage of subjects with >= 4-fold rise in A/H1N1 HAI antibody titer at Day 28 is reported. Immunogenicity population included all subjects in the as-treated population (ATP) who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point. Comparative statistical analysis was planned only for 'FluMist Quadrivalent (2015-2016)' and 'FluMist Quadrivalent (2017-2018)' arms. | |
| End point type | Primary |
| End point timeframe: | |
| Day 28 | |

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 56 | 64 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 10.0 (3.8 to 20.5) | 5.4 (1.1 to 14.9) | 23.4 (13.8 to 35.7) | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | FluMist Quadrivalent (2015-2016) v FluMist Quadrivalent (2017-2018) |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 [1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (net) |
| Point estimate | 18.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.8 |
| upper limit | 30.9 |

Notes:

[1] - p-value is calculated from the Cochran–Mantel–Haenszel (CMH) test adjusting for the prior influenza vaccination status.

## Primary: Percentage of Subjects With A/H3N2 HAI Antibody Seroconversion Rate at Day 28

| End point title | Percentage of Subjects With A/H3N2 HAI Antibody Seroconversion Rate at Day 28[2] |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in A/H3N2 HAI antibody titer. Percentage of subjects with >= 4-fold rise in A/H3N2 HAI antibody titer at Day 28 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| End point type | Primary |
|---|---|

End point timeframe:

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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 56 | 64 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 51.7 (38.4 to 64.8) | 64.3 (50.4 to 76.6) | 31.3 (20.2 to 44.1) | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects With B/Yamagata HAI Antibody Seroconversion Rate at Day 28

| End point title | Percentage of Subjects With B/Yamagata HAI Antibody Seroconversion Rate at Day 28[3] |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in B/Yamagata HAI antibody titer. Percentage of subjects with >= 4-fold rise in B/Yamagata HAI antibody titer at Day 28 is reported. Immunogenicity population included all subject in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| End point type | Primary |
|---|---|

End point timeframe:

Day 28

Notes:

[3] - 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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| **End point values** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 56 | 64 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 50.0 (36.8 to 63.2) | 42.9 (29.7 to 56.8) | 57.8 (44.8 to 70.1) | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects With B/Victoria HAI Antibody Seroconversion Rate at Day 28

| End point title | Percentage of Subjects With B/Victoria HAI Antibody Seroconversion Rate at Day 28[4] |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in B/Victoria HAI antibody titer. Percentage of subjects with >= 4-fold rise in B/Victoria HAI antibody titer at Day 28 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| End point type | Primary |
|---|---|

End point timeframe:

Day 28

Notes:

[4] - 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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[5] | 56 | 64 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | ( to ) | 14.3 (6.4 to 26.2) | 35.9 (24.3 to 48.9) | |

Notes:

[5] - B/Victoria strain was not included in this arm.

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjecs With A/H1N1 HAI Antibody Seroconversion Rate at Day 56

| End point title | Percentage of Subjecs With A/H1N1 HAI Antibody Seroconversion Rate at Day 56 |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in A/H1N1 HAI antibody titer. Percentage of subjects with >= 4-fold rise in A/H1N1 HAI antibody titer at Day 56 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point. Comparative statistical analysis was planned only for 'FluMist Quadrivalent (2015-2016)' and 'FluMist Quadrivalent (2017-2018)' arms.

| End point type | Primary |
|---|---|

End point timeframe:

Day 56

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59 | 56 | 62 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 23.7 (13.6 to 36.6) | 12.5 (5.2 to 24.1) | 45.2 (32.5 to 58.3) | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | FluMist Quadrivalent (2015-2016) v FluMist Quadrivalent (2017-2018) |

| | |
|---|---|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (net) |
| Point estimate | 32.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.4 |
| upper limit | 47.8 |

Notes:

[6] - p-value is calculated from the CMH test adjusting for the prior influenza vaccination status.

## Primary: Percentage of Subjects With A/H3N2 HAI Antibody Seroconversion Rate at Day 56

| | |
|---|---|
| End point title | Percentage of Subjects With A/H3N2 HAI Antibody Seroconversion Rate at Day 56[7] |

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in A/H3N2 HAI antibody titer. Percentage of subjects with >= 4-fold rise in A/H3N2 HAI antibody titer at Day 56 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 56

Notes:

[7] - 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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59 | 56 | 62 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 54.2 (40.8 to 67.3) | 66.1 (52.2 to 78.2) | 40.3 (28.1 to 53.6) | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects With B/Yamagata HAI Antibody Seroconversion Rate at Day 56

| | |
|---|---|
| End point title | Percentage of Subjects With B/Yamagata HAI Antibody Seroconversion Rate at Day 56[8] |

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in B/Yamagata HAI antibody titer. Percentage of subjects with >= 4-fold rise in B/Yamagata HAI antibody titer at Day 56 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| End point type | Primary |
|---|---|

End point timeframe:

Day 56

Notes:

[8] - 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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| **End point values** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 56 | 62 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 50.0 (36.8 to 63.2) | 53.6 (39.7 to 67.0) | 54.8 (41.7 to 67.5) | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Subjects With B/Victoria HAI Antibody Seroconversion Rate at Day 56

| End point title | Percentage of Subjects With B/Victoria HAI Antibody Seroconversion Rate at Day 56[9] |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in B/Victoria HAI antibody titer. Percentage of subjects with >= 4-fold rise in B/Victoria HAI antibody titer at Day 56 is reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. Here, "N" signifies number of subjects analyzed for this end point.

| End point type | Primary |
|---|---|

End point timeframe:

Day 56

Notes:

[9] - 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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

| **End point values** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[10] | 56 | 62 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | ( to ) | 25.0 (14.4 to 38.4) | 40.3 (28.1 to 53.6) | |

Notes:

[10] - B/Victoria strain was not included in this arm.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Who Shed Vaccine Virus by Formulation, Strain, Dose Number, and Baseline Serostatus as Measured by Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR)

| End point title | Percentage of Subjects Who Shed Vaccine Virus by Formulation, Strain, Dose Number, and Baseline Serostatus as Measured by Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR) |
|---|---|

End point description:

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) was used to measure viral shedding from the nasopharyngeal swabs. Percentage of subjects who shed virus are reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 2, 3, 4, 5, and 7 after Dose 1 (Day 1 dose) and on Days 2, 4, and 6 after Dose 2 (Day 28 dose)

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 66 | 67 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| A/H1N1/HAI:negative/Dose 1 (n=30,43,39) | 86.7 | 81.4 | 94.9 | |
| A/H1N1/HAI:negative/Dose 2 (n=29,43,39) | 17.2 | 25.6 | 46.2 | |
| A/H1N1/HAI:positive/Dose 1 (n=36,22,28) | 86.1 | 63.6 | 71.4 | |
| A/H1N1/HAI positive/Dose 2 (n=35,21,27) | 22.9 | 23.8 | 29.6 | |
| A/H3N2/HAI:negative/Dose 1 (n=21,35,24) | 100.0 | 100.0 | 95.8 | |
| A/H3N2/HAI:negative/Dose 2 (n=20,35,24) | 55.0 | 60.0 | 79.2 | |
| A/H3N2/HAI:positive/Dose 1 (n=45,30,43) | 95.6 | 83.3 | 95.3 | |
| A/H3N2/HAI:positive/Dose 2 (n=44,29,42) | 47.7 | 44.8 | 59.5 | |
| B/Yamagata/HAI:negative/Dose 1 (n=51,54,51) | 100.0 | 98.1 | 100.0 | |

| | | | | |
|---|---|---|---|---|
| B/Yamagata/HAI:negative/Dose 2 (n=50,53,51) | 42.0 | 39.6 | 31.4 | |
| B/Yamagata/HAI:positive/Dose 1 (n=15,11,16) | 73.3 | 81.8 | 93.8 | |
| B/Yamagata/HAI:positive/Dose 2 (n=14,11,15) | 50.0 | 54.5 | 53.3 | |
| B/Victoria/HAI:negative/Dose 1 (n=0,59,39) | 99999 | 100.0 | 100.0 | |
| B/Victoria/HAI:negative/Dose 2 (n=0,58,39) | 99999 | 44.8 | 53.8 | |
| B/Victoria/HAI:positive/Dose 1 (n=0,6,28) | 99999 | 83.3 | 100.0 | |
| B/Victoria/HAI:positive/Dose 2 (n=0,6,27) | 99999 | 50.0 | 37.0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Days of Vaccine Virus Shedding by Formulation, Strain, Dose Number, and Baseline Serostatus as Measured by qRT-PCR

| | |
|---|---|
| End point title | Number of Days of Vaccine Virus Shedding by Formulation, Strain, Dose Number, and Baseline Serostatus as Measured by qRT-PCR |

End point description:

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) was used to measure viral shedding from the nasopharyngeal swabs. Number of days of virus shedding are reported. Subjects included in immunogenicity population and who shed vaccine virus were analyzed for this end point. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Days 2, 3, 4, 5, and 7 after Dose 1 (Day 1 dose) and on Days 2, 4 and 6 after Dose 2 (Day 28 dose)

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 65 | 67 | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | | | | |
| A/H1N1/HAI:negative/Dose 1 (n=26,35,37) | 2.2 (± 1.2) | 2.2 (± 1.0) | 2.8 (± 1.3) | |
| A/H1N1/HAI:negative/Dose 2 (n=5,11,18) | 1.2 (± 0.4) | 1.4 (± 0.7) | 1.3 (± 0.5) | |
| A/H1N1/HAI:positive/Dose 1 (n=31,14,20) | 2.2 (± 1.0) | 1.9 (± 0.7) | 2.0 (± 1.3) | |
| A/H1N1/HAI:positive/Dose 2 (n=8,5,8) | 1.1 (± 0.4) | 1.0 (± 0.0) | 1.1 (± 0.4) | |
| A/H3N2/HAI:negative/Dose 1 (n=21,35,23) | 4.5 (± 1.0) | 4.5 (± 0.9) | 3.9 (± 1.2) | |
| A/H3N2/HAI:negative/Dose 2 (n=11,21,19) | 1.3 (± 0.6) | 1.1 (± 0.4) | 1.7 (± 0.8) | |

| | | | | |
|---|---|---|---|---|
| A/H3N2/HAI: positive/Dose 1 (n=43,25,41) | 3.8 (± 1.5) | 3.4 (± 1.6) | 2.5 (± 1.4) | |
| A/H3N2/HAI: positive/Dose 2 (n=21,13,25) | 1.3 (± 0.6) | 1.5 (± 0.8) | 1.4 (± 0.6) | |
| B/Yamagata/HAI:negative/Dose 1 (n=51,53,51) | 3.6 (± 1.3) | 3.6 (± 1.3) | 4.0 (± 1.1) | |
| B/Yamagata/HAI:negative/Dose 2 (n=21,21,16) | 1.3 (± 0.6) | 1.3 (± 0.7) | 1.1 (± 0.3) | |
| B/Yamagata/HAI:positive/Dose 1 (n=11,9,15) | 2.5 (± 1.2) | 3.3 (± 1.0) | 3.1 (± 1.6) | |
| B/Yamagata/HAI:positive/Dose 2 (n=7,6,8) | 1.1 (± 0.4) | 1.0 (± 0.0) | 1.3 (± 0.5) | |
| B/Victoria/HAI:negative/Dose 1 (n=0,59,39) | 99999 (± 99999) | 3.9 (± 1.2) | 4.6 (± 0.8) | |
| B/Victoria/HAI:negative/Dose 2 (n=0,26,21) | 99999 (± 99999) | 1.4 (± 0.6) | 1.4 (± 0.6) | |
| B/Victoria/HAI:positive/Dose 1 (n=0,5,28) | 99999 (± 99999) | 2.0 (± 1.0) | 3.5 (± 1.5) | |
| B/Victoria/HAI:positive/Dose 2 (n=0,3,10) | 99999 (± 99999) | 1.0 (± 0.0) | 1.1 (± 0.3) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Titer by Day, Strain, Dose Number, and Baseline Serostatus as Measured by qRT-PCR

| | |
|---|---|
| End point title | Viral Titer by Day, Strain, Dose Number, and Baseline Serostatus as Measured by qRT-PCR |

End point description:

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) was used to measure viral titer from the nasopharyngeal swabs. Viral titers are reported. Subjects included in immunogenicity population and who shed vaccine virus were analyzed for this end point. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group and an arbitrary value '999999' signifies standard deviation data not applicable as only one subject was evaluable for the specified arm group.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day (D) 2, D3, D4, D5, and D7 after Dose 1 (D1 dose) and on D2, D4 and D6 after Dose 2 (D28 dose)

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 65 | 67 | |
| Units: log10 viral particles/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| A/H1N1/HAI:negative/Dose 1 D2 (n=13,16,16) | 3.79 (± 0.56) | 3.76 (± 0.71) | 3.70 (± 0.49) | |
| A/H1N1/HAI:negative/Dose 1 D3 (n=16,20,25) | 3.66 (± 0.55) | 3.81 (± 0.83) | 4.21 (± 0.97) | |

| | | | | |
|---|---|---|---|---|
| A/H1N1/HAI:negative/Dose 1 D4 (n=4,6,19) | 3.63 (± 0.34) | 3.34 (± 0.56) | 3.81 (± 0.94) | |
| A/H1N1/HAI:negative/Dose 1 D5 (n=3,3,9) | 3.12 (± 0.16) | 3.17 (± 0.10) | 3.85 (± 0.48) | |
| A/H1N1/HAI:negative/Dose 1 D7 (n=2,0,3) | 3.17 (± 0.40) | 99999 (± 99999) | 2.93 (± 0.23) | |
| A/H1N1/HAI:negative/Dose 2 D2 (n=4,7,6) | 3.68 (± 0.88) | 3.29 (± 0.30) | 3.90 (± 1.04) | |
| A/H1N1/HAI:negative/Dose 2 D4 (n=0,3,4) | 99999 (± 99999) | 3.49 (± 0.37) | 4.02 (± 1.24) | |
| A/H1N1/HAI:negative/Dose 2 D6 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| A/H1N1/ HAI:positive/Dose 1 D2 (n=17,9,13) | 3.66 (± 0.46) | 3.48 (± 0.62) | 3.14 (± 0.45) | |
| A/H1N1/ HAI:positive/Dose 1 D3 (n=17,7,7) | 3.39 (± 0.57) | 4.03 (± 0.91) | 3.99 (± 0.84) | |
| A/H1N1/HAI:positive/Dose 1 D4 (n=5,2,6) | 3.09 (± 0.62) | 3.39 (± 0.25) | 3.97 (± 0.73) | |
| A/H1N1/HAI:positive/Dose 1 D5 (n=3,0,3) | 3.35 (± 0.64) | 99999 (± 99999) | 3.73 (± 0.62) | |
| A/H1N1/HAI:positive/Dose 1 D7 (n=1,0,0) | 3.10 (± 999999) | 99999 (± 99999) | 99999 (± 99999) | |
| A/H1N1/HAI:positive/Dose 2 D2 (n=6,1,5) | 3.38 (± 0.78) | 2.86 (± 999999) | 3.36 (± 0.56) | |
| A/H1N1/HAI:positive/Dose 2 D4 (n=0,0,1) | 99999 (± 99999) | 99999 (± 99999) | 3.65 (± 999999) | |
| A/H1N1/HAI:positive/Dose 2 D6 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| A/H3N2/HAI:negative/Dose 1 D2 (n=19,29,15) | 4.20 (± 0.99) | 4.15 (± 0.93) | 3.52 (± 0.77) | |
| A/H3N2/HAI:negative/Dose 1 D3 (n=19,30,18) | 5.20 (± 1.12) | 5.39 (± 1.19) | 4.34 (± 0.86) | |
| A/H3N2/HAI:negative/Dose 1 D4 (n=20,33,18) | 4.86 (± 0.99) | 4.51 (± 1.14) | 4.51 (± 1.05) | |
| A/H3N2/HAI :negative/Dose 1 D5 (n=18,31,17) | 4.04 (± 1.09) | 4.16 (± 1.20) | 3.67 (± 1.06) | |
| A/H3N2/HAI:negative/Dose 1 D7 (n=14,24,9) | 4.10 (± 0.97) | 4.12 (± 0.88) | 3.58 (± 1.26) | |
| A/H3N2/HAI:negative/Dose 2 D2 (n=7,12,12) | 3.67 (± 1.03) | 3.33 (± 0.67) | 3.01 (± 0.49) | |
| A/H3N2/HAI:negative/Dose 2 D4 (n=0,2,8) | 99999 (± 99999) | 3.41 (± 0.26) | 3.68 (± 0.70) | |
| A/H3N2/HAI:negative/Dose 2 D6 (n=0,1,3) | 99999 (± 99999) | 2.72 (± 999999) | 3.05 (± 0.61) | |
| A/H3N2/HAI:positive/Dose 1 D2 (n=38,18,28) | 3.80 (± 1.07) | 3.98 (± 1.02) | 3.19 (± 0.67) | |
| A/H3N2/HAI:positive/Dose 1 D3 (n=33,16,17) | 4.79 (± 1.29) | 5.06 (± 1.20) | 3.54 (± 0.98) | |
| A/H3N2/HAI:positive/Dose 1 D4 (n=31,17,14) | 4.34 (± 1.03) | 4.45 (± 1.14) | 4.00 (± 1.24) | |
| A/H3N2/HAI:positive/Dose 1 D5 (n=26,11,13) | 3.99 (± 1.05) | 4.01 (± 0.98) | 3.98 (± 0.72) | |
| A/H3N2/HAI:positive/Dose 1 D7 (n=21,5,6) | 3.92 (± 1.06) | 4.10 (± 1.36) | 3.30 (± 0.55) | |
| A/H3N2/HAI:positive/Dose 2 D2 (n=16,9,9) | 3.30 (± 0.89) | 3.55 (± 0.93) | 3.54 (± 0.78) | |
| A/H3N2/HAI:positive/Dose 2 D4 (n=3,4,4) | 2.71 (± 0.62) | 3.38 (± 0.90) | 3.26 (± 0.60) | |
| A/H3N2/HAI:positive/Dose 2 D6 (n=1,1,1) | 3.82 (± 999999) | 2.32 (± 999999) | 3.17 (± 999999) | |
| B/Yamagata/HAI:negative/Dose1D2 (n=18,20,21) | 3.93 (± 0.40) | 4.09 (± 0.53) | 4.16 (± 0.58) | |

| | | | | |
|---|---|---|---|---|
| B/Yamagata/HAI:negative/Dose1D3 (n=26,29,29) | 4.10 (± 0.60) | 4.60 (± 0.77) | 4.72 (± 0.92) | |
| B/Yamagata/HAI:negative/Dose1D4 (n=27,29,33) | 4.04 (± 0.61) | 4.60 (± 0.83) | 4.72 (± 0.88) | |
| B/Yamagata/HAI:negative/Dose1D5 (n=19,22,29) | 4.56 (± 0.53) | 4.42 (± 0.72) | 4.59 (± 0.80) | |
| B/Yamagata/HAI:negative/Dose1D7 (n=19,14,23) | 4.37 (± 0.86) | 3.93 (± 0.50) | 3.98 (± 0.62) | |
| B/Yamagata/HAI:negative/Dose2D2 (n=4,5,5) | 3.92 (± 0.31) | 4.10 (± 0.55) | 3.80 (± 0.35) | |
| B/Yamagata/HAI:negative/Dose2D4 (n=4,5,0) | 3.74 (± 0.60) | 3.85 (± 0.52) | 99999 (± 99999) | |
| B/Yamagata/HAI:negative/Dose2D6 (n=2,0,0) | 3.83 (± 0.35) | 99999 (± 99999) | 99999 (± 99999) | |
| B/Yamagata/HAI:positive/Dose1D2 (n=3,7,5) | 3.93 (± 0.20) | 3.57 (± 0.19) | 4.15 (± 0.78) | |
| B/Yamagata/HAI:positive/Dose1D3 (n=5,6,5) | 3.93 (± 0.58) | 3.92 (± 0.51) | 4.67 (± 0.79) | |
| B/Yamagata/HAI:positive/Dose1D4 (n=2,2,7) | 3.46 (± 0.04) | 4.60 (± 1.44) | 4.94 (± 1.28) | |
| B/Yamagata/HAI:positive/Dose1D5 (n=1,1,7) | 3.84 (± 999999) | 5.01 (± 999999) | 4.82 (± 0.65) | |
| B/Yamagata/HAI:positive/Dose1D7 (n=1,0,5) | 5.46 (± 999999) | 99999 (± 99999) | 3.91 (± 0.63) | |
| B/Yamagata/HAI:positive/Dose2D2 (n=0,1,3) | 99999 (± 99999) | 3.38 (± 999999) | 3.70 (± 0.11) | |
| B/Yamagata/HAI:positive/Dose2D4 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| B/Yamagata/HAI:positive/Dose2D6 (n=1,0,0) | 3.92 (± 999999) | 99999 (± 99999) | 99999 (± 99999) | |
| B/Victoria/HAI:negative/Dose1D2 (n=0,33,25) | 99999 (± 99999) | 3.41 (± 0.58) | 3.49 (± 0.72) | |
| B/Victoria/HAI:negative/Dose1D3 (n=0,44,31) | 99999 (± 99999) | 4.12 (± 1.02) | 4.39 (± 0.98) | |
| B/Victoria/HAI:negative/Dose1D4 (n=0,41,35) | 99999 (± 99999) | 4.02 (± 1.13) | 4.58 (± 1.24) | |
| B/Victoria/HAI:negative/Dose1D5 (n=0,29,34) | 99999 (± 99999) | 3.98 (± 1.05) | 4.09 (± 1.02) | |
| B/Victoria/HAI:negative/Dose1D7 (n=0,30,26) | 99999 (± 99999) | 3.57 (± 0.79) | 4.14 (± 0.84) | |
| B/Victoria/HAI:negative/Dose2D2 (n=0,10,6) | 99999 (± 99999) | 3.43 (± 1.01) | 2.94 (± 0.36) | |
| B/Victoria/HAI:negative/Dose2D4 (n=0,5,3) | 99999 (± 99999) | 3.48 (± 0.88) | 2.67 (± 0.29) | |
| B/Victoria/HAI:negative/Dose2D6 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| B/Victoria/HAi:positive/Dose1D2 (n=0,2,11) | 99999 (± 99999) | 2.73 (± 0.01) | 3.10 (± 0.53) | |
| B/Victoria/HAI:positive/Dose1D3 (n=0,3,14) | 99999 (± 99999) | 3.09 (± 0.42) | 3.96 (± 1.08) | |
| B/Victoria/HAI:positive/Dose1D4 (n=0,1,16) | 99999 (± 99999) | 2.73 (± 999999) | 4.40 (± 0.98) | |
| B/Victoria/HAI:positive/Dose1D5 (n=0,0,15) | 99999 (± 99999) | 99999 (± 99999) | 4.26 (± 0.90) | |
| B/Victoria/HAI:positive/Dose1D7 (n=0,0,12) | 99999 (± 99999) | 99999 (± 99999) | 4.00 (± 0.96) | |
| B/Victoria/HAI:positive/Dose2D2 (n=0,0,4) | 99999 (± 99999) | 99999 (± 99999) | 3.41 (± 0.51) | |
| B/Victoria/HAI:positive/Dose2D4 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |
| B/Victoria/HAI:positive/Dose2D6 (n=0,0,0) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Strain-specific Neutralizing Antibody Seroconversion Rates From Baseline Through Days 28 and 56 by Baseline Serostatus

| End point title | Percentage of Subjects With Strain-specific Neutralizing Antibody Seroconversion Rates From Baseline Through Days 28 and 56 by Baseline Serostatus |
|---|---|

End point description:

Seroconversion rate is defined as >= 4-fold rise from baseline in strain specific microneutralizing antibody titer. Baseline microneutralization values of less than or equal to (<=) 10 were considered as microneutralization status negative and values greater than (>) 10 were considered microneutralization positive. Percentage of subjects with >= 4-fold rise in strain specific neutralizing antibody titer at Days 28 and 56 are reported. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 28 and 56

| **End point values** | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 65 | 67 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| A/H1N1/Seronegative/Day 28 (n=8,20,0) | 0.0 (0.0 to 36.9) | 10.0 (1.2 to 31.7) | 99999 (99999 to 99999) | |
| A/H1N1/Seronegative/Day 56 (n=8,20,0) | 37.5 (8.5 to 75.5) | 25.0 (8.7 to 49.1) | 99999 (99999 to 99999) | |
| A/H1N1/Seropositive/Day 28 (n=52,36,63) | 3.8 (0.5 to 13.2) | 2.8 (0.1 to 14.5) | 15.9 (7.9 to 27.3) | |
| A/H1N1/Seropositive/Day 56 (n=51,36,60) | 11.8 (4.4 to 23.9) | 2.8 (0.1 to 14.5) | 31.7 (20.3 to 45.0) | |
| A/H3N2/Seronegative/Day 28 (n=14,27,15) | 100.0 (76.8 to 100.0) | 100.0 (87.2 to 100.0) | 46.7 (21.3 to 73.4) | |
| A/H3N2/Seronegative/Day 56 (n=16,26,13) | 93.8 (69.8 to 99.8) | 100.0 (86.8 to 100.0) | 84.6 (54.6 to 98.1) | |
| A/H3N2/Seropositive/Day 28 (n=46,29,48) | 47.8 (32.9 to 63.1) | 34.5 (17.9 to 54.3) | 25.0 (13.6 to 39.6) | |
| A/H3N2/Seropositive/Day 56 (n=43,30,47) | 44.2 (29.1 to 60.1) | 43.3 (25.5 to 62.6) | 14.9 (6.2 to 28.3) | |
| B/Yamagata/Seronegative/Day 28 (n=44,46,50) | 59.1 (43.2 to 73.7) | 45.7 (30.9 to 61.0) | 58.0 (43.2 to 71.8) | |

| | | | | |
|---|---|---|---|---|
| B/Yamagata/Seronegative/Day 56 (n=44,47,49) | 77.3 (62.2 to 88.5) | 68.1 (52.9 to 80.9) | 75.5 (61.1 to 86.7) | |
| B/Yamagata/Seropositive/Day 28 (n=16,10,14) | 18.8 (4.0 to 45.6) | 0.0 (0.0 to 30.8) | 14.3 (1.8 to 42.8) | |
| B/Yamagata/Seropositive/Day 56 (n=16,9,13) | 18.8 (4.0 to 45.6) | 0.0 (0.0 to 33.6) | 7.7 (0.2 to 36.0) | |
| B/Victoria/Serosnegative/Day 28 (n-0,48,53) | 99999 (99999 to 99999) | 20.8 (10.5 to 35.0) | 18.9 (9.4 to 32.0) | |
| B/Victoria/Seronegative/Day 56 (n=0,49,51) | 99999 (99999 to 99999) | 16.3 (7.3 to 29.7) | 23.5 (12.8 to 37.5) | |
| B/Victoria/Seropositive/Day 28 (n=0,8,10) | 99999 (99999 to 99999) | 12.5 (0.3 to 52.7) | 10.0 (0.3 to 44.5) | |
| B/Victoria/Seropositive/Day 56 (n=0,7,9) | 99999 (99999 to 99999) | 14.3 (0.4 to 57.9) | 11.1 (0.3 to 48.2) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Strain-specific Nasal Immunoglobulin A (IgA) seroconversion Rate From Baseline Through Days 28 and 56

| | |
|---|---|
| End point title | Percentage of Subjects With Strain-specific Nasal Immunoglobulin A (IgA) seroconversion Rate From Baseline Through Days 28 and 56 |

End point description:

Seroconversion rate is defined as >= 2-fold rise from baseline in strain speciific nasal IgA antibody titer. Percentage of subjects with >= 2-fold rise in strain speciific nasal IgA antibody titer at Days 28 and 56 are reported for this end point. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Days 28 and 56

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 65 | 67 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| A/H1N1/Day 28 (n=62,63,67) | 33.9 (22.3 to 47.0) | 31.7 (20.6 to 44.7) | 40.3 (28.5 to 53.0) | |
| A/H1N1//Day 56 (n=64,60,65) | 40.6 (28.5 to 53.6) | 46.7 (33.7 to 60.0) | 67.7 (54.9 to 78.8) | |
| A/H3N2//Day 28 (n=63,62,67) | 79.4 (67.3 to 88.5) | 79.0 (66.8 to 88.3) | 44.8 (32.6 to 57.4) | |
| A/H3N2/Day 56 (n=64,61,65) | 89.1 (78.8 to 95.5) | 88.5 (77.8 to 95.3) | 55.4 (42.5 to 67.7) | |
| B/Yamagata//Day 28 (n=63,63,67) | 69.8 (57.0 to 80.8) | 79.4 (67.3 to 88.5) | 77.6 (65.8 to 86.9) | |

| | | | | |
|---|---|---|---|---|
| B/Yamagata//Day 56 (n=64,61,66) | 81.3 (69.5 to 89.9) | 88.5 (77.8 to 95.3) | 86.4 (75.7 to 93.6) | |
| B/Victoria//Day 28 (0,63,67) | 99999 (99999 to 99999) | 73.0 (60.3 to 83.4) | 79.1 (67.4 to 88.1) | |
| B/Victoria//Day 56 (n=0,61,66) | 99999 (99999 to 99999) | 91.8 (81.9 to 97.3) | 84.8 (73.9 to 92.5) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Any Post Dose Strain-specific Antibody Response

| End point title | Percentage of Subjects With Any Post Dose Strain-specific Antibody Response |
|---|---|

End point description:

Strain specific antibody response defined as >= 4-fold increase in HAI antibodies or >= 4-fold increase in neutralizing antibodies (NA) or >= 2-fold increase in IgA antibodies titer. Immunogenicity population included all subjects in the ATP who had no major protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response to investigational product. B/Victoria strain was not included in the 'FluMist trivalent (2015-2016)' arm. Here, "n" signifies number of subjects analyzed for specified category. An arbitrary value '99999' signifies data not applicable, as no subjects were analyzed for specified arm group.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 28 and 56

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 65 | 67 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| A/H1N1/HAI response/Day 28 (n=60,56,64) | 10.0 | 5.4 | 23.4 | |
| A/H1N1/NA response/Day 28 (n=60,56,63) | 3.3 | 5.4 | 15.9 | |
| A/H1N1/Nasal IgA response/Day 28 (n=63,63,67) | 46.0 | 52.4 | 35.8 | |
| A/H1N1/HAI response/Day 56 (n=59,56,62) | 23.7 | 12.5 | 45.2 | |
| A/H1N1/NA response/Day 56 (n=59,56,60) | 15.3 | 10.7 | 31.7 | |
| A/H1N1/Nasal IgA response/Day 56 (n=64,60,65) | 46.9 | 53.3 | 61.5 | |
| A/H3N2/HAI response/Day 28 (n=60,56,64) | 51.7 | 64.3 | 31.3 | |
| A/H3N2/NA response/Day 28 (n=60,56,63) | 60.0 | 66.1 | 30.2 | |
| A/H3N2/Nasal IgA response/Day 28 (n=64,62,67) | 81.3 | 85.5 | 38.8 | |

| | | | | |
|---|---|---|---|---|
| A/H3N2/HAI response/Day 56 (n=59,56,62) | 54.2 | 66.1 | 40.3 | |
| A/H3N2/NA response/Day 56 (n=59,56,60) | 57.6 | 69.6 | 30.0 | |
| A/H3N2/Nasal IgA response/Day 56 (n=64,61,65) | 76.6 | 82.0 | 50.8 | |
| B/Yamagata/HAI response/Day 28 (n=60,56,64) | 50.0 | 42.9 | 57.8 | |
| B/Yamagata/NA response/Day 28 (n=60,56,64) | 48.3 | 37.5 | 48.4 | |
| B/Yamagata/Nasal IgA response/Day 28 (n=64,63,67) | 65.6 | 87.3 | 61.2 | |
| B/Yamagata/HAI response/Day 56 (n=60,56,62) | 50.0 | 53.6 | 54.8 | |
| B/Yamagata/NA response/Day 56 (n=60,56,62) | 61.7 | 57.1 | 61.3 | |
| B/Yamagata/Nasal IgA response/Day 56 (n=64,61,66) | 70.3 | 83.6 | 77.3 | |
| B/Victoria/HAI response/Day 28 (n=0,56,64) | 99999 | 14.3 | 35.9 | |
| B/Victoria/NA response/Day 28 (n=0,56,63) | 99999 | 19.6 | 17.5 | |
| B/Victoria/Nasal IgA response/Day 28 (n=0,63,67) | 99999 | 76.2 | 55.2 | |
| B/Victoria/HAI response/Day 56 (n=0,56,62) | 99999 | 25.0 | 40.3 | |
| B/Victoria/NA response/Day 56 (n=0,56,60) | 99999 | 16.1 | 21.7 | |
| B/Victoria/Nasal IgA response/Day 56 (n=0,61,66) | 99999 | 83.6 | 78.8 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Any Solicited Symptoms

| | |
|---|---|
| End point title | Percentage of Subjects With Any Solicited Symptoms |

End point description:

Solicited symptoms included fever by any route (temperature ≥ 100.4 degrees Fahrenheit), runny/stuffy nose, sore throat, cough, headache, generalized muscle aches, lethargy or tiredness/weakness, and decreased appetite. ATP included all subjects who received any amount of investigational drug.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 1 through Day 14 after Dose 1 (Day 1 dose) and Dose 2 (Day 28 dose)

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 66 | 67 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |

| | | | | |
|---|---|---|---|---|
| Fever: Dose 1 (n=67,65,67) | 3.0 | 1.5 | 10.4 | |
| Fever: Dose 2 (n=63,61,63) | 3.2 | 8.2 | 6.3 | |
| Runny/Stuffy Nose: Dose 1 (n=67,65,67) | 34.3 | 41.5 | 43.3 | |
| Runny/Stuffy Nose: Dose 2 (n=63,60,64) | 33.3 | 36.7 | 34.4 | |
| Sore Throat: Dose 1 (n=67,65,67) | 6.0 | 1.5 | 4.5 | |
| Sore Throat: Dose 2 (n=63,60,64) | 3.2 | 3.3 | 4.7 | |
| Cough: Dose 1 (n=67,65,67) | 19.4 | 15.4 | 10.4 | |
| Cough: Dose 2 (n=63,60,64) | 19.0 | 21.7 | 10.9 | |
| Headache: Dose 1 (n=67,65,67) | 1.5 | 4.6 | 6.0 | |
| Headache: Dose 2 (n=63,60,64) | 3.2 | 5.0 | 3.1 | |
| Generalized Muscle Aches: Dose 1 (n=67,65,67) | 4.5 | 4.6 | 1.5 | |
| Generalized Muscle Aches: Dose 2 (n=63,60,64) | 0.0 | 3.3 | 0.0 | |
| Lethargy/Tiredness/Weakness: Dose 1 (n=67,65,67) | 13.4 | 13.8 | 16.4 | |
| Lethargy/Tiredness/Weakness: Dose 2 (n=63,60,64) | 12.7 | 11.7 | 7.8 | |
| Decreased Appetite: Dose 1 (n=67,65,67) | 13.4 | 12.3 | 11.9 | |
| Decreased Appetite: Dose 2 (n=63,60,64) | 9.5 | 8.3 | 7.8 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) |
|---|---|

End point description:

An Adverse Event (AE) is any unfavourable and unintended sign, symptoms, or diseases temporally associated with use of study drug, whether or not considered related to study drug. A serious adverse event (SAE) is an AE that results in death, initial or prolonged inpatient hospitalization, life-threatening, persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event. TEAEs and TESAEs are defined as AEs and SAEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug. ATP included all subjects who received any amount of investigational drug.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 through Day 28 after Dose 1 (Day 1 dose) and Dose 2 (Day 28 dose)

| End point values | FluMist trivalent (2015-2016) | FluMist Quadrivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 66 | 67 | |
| Units: Subjects | | | | |
| TEAEs\| | 29 | 31 | 34 | |
| TESAEs\| | 0 | 0 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Day 1 through Day 28 after Dose 1 (Day 1 dose) and Dose 2 (Day 28 dose) | |
| Adverse event reporting additional description: | |
| ATP included all subjects who received any investigational drug. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

| Reporting groups | |
|---|---|
| Reporting group title | FluMist Trivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist trivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the trivalent vaccine were: A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), and B/Phuket/3073/2013 (B/Yamagata-lineage). | |
| Reporting group title | FluMist Quadrivalent (2017-2018) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were the new A/H1N1 (A/Slovenia/2903/2015), A/H3N2 (A/New Caledonia/71/2014), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |
| Reporting group title | FluMist Quadrivalent (2015-2016) |
| Reporting group description: | |
| Subjects received intranasal spray of 0.2 mL (total dose in both nostrils) FluMist quadrivalent vaccine on Days 1 and 28. Each 0.2 mL dose contained 10^7±0.5 FFU of each vaccine strain. Strains included in the vaccine were A/H1N1 (A/Bolivia/559/2013), A/H3N2 (A/Switzerland/9715293/2013), B/Phuket/3073/2013 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage). | |

| **Serious adverse events** | FluMist Trivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | FluMist Quadrivalent (2015-2016) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | FluMist Trivalent (2015-2016) | FluMist Quadrivalent (2017-2018) | FluMist Quadrivalent (2015-2016) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 67 (43.28%) | 34 / 67 (50.75%) | 31 / 66 (46.97%) |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Chills | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Developmental delay | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 67 (2.99%) | 7 / 66 (10.61%) |
| occurrences (all) | 1 | 2 | 7 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 2 / 67 (2.99%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 4 / 67 (5.97%) | 5 / 66 (7.58%) |
| occurrences (all) | 4 | 4 | 5 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 67 (1.49%) | 3 / 66 (4.55%) |
| occurrences (all) | 3 | 2 | 3 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 67 (1.49%) | 1 / 66 (1.52%) |
| occurrences (all) | 1 | 1 | 1 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngeal erythema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 9 / 67 (13.43%) | 7 / 66 (10.61%) |
| occurrences (all) | 4 | 9 | 7 |
| Sneezing | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 1 | 1 |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritability | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 67 (1.49%) | 2 / 66 (3.03%) |
| occurrences (all) | 1 | 1 | 2 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 1 / 67 (1.49%) | 2 / 66 (3.03%) |
| occurrences (all) | 2 | 1 | 2 |
| Laceration | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Radial head dislocation | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 1 | 0 | 1 |
| Lethargy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Tympanic membrane perforation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Eye oedema | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Strabismus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 1 | 0 | 1 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 67 (13.43%) | 4 / 67 (5.97%) | 5 / 66 (7.58%) |
| occurrences (all) | 10 | 5 | 5 |
| Haematochezia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral discomfort | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 2 / 66 (3.03%) |
| occurrences (all) | 0 | 0 | 2 |
| Toothache | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 4 / 67 (5.97%) | 5 / 66 (7.58%) |
| occurrences (all) | 4 | 5 | 6 |
| Skin and subcutaneous tissue disorders | | | |
| Cold sweat | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Neck pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 67 (2.99%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Croup infectious | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 67 (1.49%) | 1 / 66 (1.52%) |
| occurrences (all) | 4 | 1 | 1 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Otitis media acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 3 / 67 (4.48%) | 1 / 66 (1.52%) |
| occurrences (all) | 1 | 4 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 67 (0.00%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 3 / 67 (4.48%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 2 / 67 (2.99%) | 2 / 66 (3.03%) |
| occurrences (all) | 4 | 2 | 2 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 2 / 67 (2.99%) | 0 / 66 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 67 (1.49%) | 0 / 66 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 67 (0.00%) | 1 / 66 (1.52%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 June 2017 | Inclusion Criterion 1 (subject age criterion) was amended from "Age 24 months to less than (<) 48 months of age at the time of randomization" to "Age 24 months to < 48 months of age at the time of screening". The screening period was extended from 30 days to 75 days. The duration of subject participation was extended from "2 to 3 months" to "3 to 4 months". Updated Table 4.2-1 (Schedule of Study Procedures), study days for screening study period amended from "-30 to 1" to "-75 to 1". |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported