



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
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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, Data analyst, Carer, 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 $10^7 \pm 0.5$ 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 $10^7 \pm 0.5$ 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)
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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 $10^7 \pm 0.5$ 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 $10^7 \pm 0.5$ 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)
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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 $10^7 \pm 0.5$ 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 $10^7 \pm 0.5$ 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)
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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 $10^7 \pm 0.5$ 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)
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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 $10^7 \pm 0.5$ 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)
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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 $10^7 \pm 0.5$ 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			
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			
Units: months			
arithmetic mean	35.96	34.96	34.94
standard deviation	± 6.41	± 6.78	± 6.80
Sex: Female, Male			
Units: Subjects			
Female	27	32	35
Male	40	34	32
Race (NIH/OMB)			
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)			
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			
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			
Units: months			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	94		
Male	106		
Race (NIH/OMB)			
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)			
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 $10^7 \pm 0.5$ 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 $10^7 \pm 0.5$ 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 $10^7 \pm 0.5$ 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 (\geq) 4-fold rise from baseline in A/H1N1 HAI antibody titer. Percentage of subjects with \geq 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]
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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
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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 \geq 4-fold rise from baseline in B/Yamagata HAI antibody titer. Percentage of subjects with \geq 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 \geq 4-fold rise from baseline in B/Victoria HAI antibody titer. Percentage of subjects with \geq 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 Subjects With A/H1N1 HAI Antibody Seroconversion Rate at Day 56

End point title	Percentage of Subjects 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]
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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
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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]
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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
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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]
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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
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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)
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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
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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
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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
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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
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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
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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
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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 (\leq) 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
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End point description:

Seroconversion rate is defined as ≥ 2 -fold rise from baseline in strain specific nasal IgA antibody titer. Percentage of subjects with ≥ 2 -fold rise in strain specific 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
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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
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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
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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)
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	FluMist Trivalent (2015-2016)
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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 $10^{7\pm 0.5}$ 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)
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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 $10^{7\pm 0.5}$ 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)
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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 $10^{7\pm 0.5}$ 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 occurrences (all)	1 / 67 (1.49%) 1	0 / 67 (0.00%) 0	1 / 66 (1.52%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4	9 / 67 (13.43%) 9	7 / 66 (10.61%) 7
Sneezing subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	1 / 67 (1.49%) 1	1 / 66 (1.52%) 1
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	1 / 67 (1.49%) 1	0 / 66 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	1 / 67 (1.49%) 1	0 / 66 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1	1 / 67 (1.49%) 1	2 / 66 (3.03%) 2
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2	1 / 67 (1.49%) 1	2 / 66 (3.03%) 2
Laceration subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1	0 / 67 (0.00%) 0	0 / 66 (0.00%) 0
Radial head dislocation subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	0 / 67 (0.00%) 0	1 / 66 (1.52%) 1
Thermal burn subjects affected / exposed occurrences (all)	0 / 67 (0.00%) 0	0 / 67 (0.00%) 0	1 / 66 (1.52%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1	0 / 67 (0.00%) 0	1 / 66 (1.52%) 1
Lethargy			

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