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## Package insert

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA® QUADRIVALENT safely and effectively. See full prescribing information for AFLURIA QUADRIVALENT.

#### AFLURIA QUADRIVALENT, Influenza Vaccine

#### Suspension for Intramuscular Injection

#### 2018-2019 Formula

#### Initial U.S. Approval (AFLURIA QUADRIVALENT): 2016

#### RECENT MAJOR CHANGES

Indications and Usage (1) 07/2017  
Dosage and Administration (2) 07/2017

#### INDICATIONS AND USAGE

- AFLURIA QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)
- AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older. (1)

#### DOSAGE AND ADMINISTRATION

For intramuscular injection only, by needle and syringe (6 months and older) or by PharmaJet®Stratis® Needle-Free Injection System (18 through 64 years). (2)

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5 mL	Not Applicable

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2)

#### DOSAGE FORMS AND STRENGTHS

AFLURIA QUADRIVALENT is a suspension for injection supplied in three presentations:

- 0.25 mL pre-filled syringe (single dose) (3, 11)
- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (ten 0.5 mL doses) (3, 11)

#### CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)

#### WARNINGS AND PRECAUTIONS

- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.2)

#### ADVERSE REACTIONS

AFLURIA QUADRIVALENT administered by needle and syringe:

- In adults 18 through 64 years, the most commonly reported injection-site adverse reaction was pain (≥ 40%). The most common systemic adverse events were myalgia and headache (≥ 20%). (6.1)
- In adults 65 years of age and older, the most commonly reported injection-site adverse reaction was pain (≥ 20%). The most common systemic adverse event was myalgia (≥ 10%). (6.1)
- In children 5 through 8 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse event was headache (≥ 10%). (6.1)
- In children 9 through 17 years, the most commonly reported injection-site adverse reactions were pain (≥ 50%), redness and swelling (≥ 10%). The most common systemic adverse events were headache, myalgia, and malaise and fatigue (≥ 10%). (6.1)
- In children 6 months through 35 months of age, the most commonly reported injection-site reactions were pain and redness (≥ 20%). The most common systemic adverse events were irritability (≥ 30%), diarrhea and loss of appetite (≥ 20%). (6.1)
- In children 36 through 59 months of age, the most commonly reported injection site reactions were pain (≥ 30%) and redness (≥ 20%). The most commonly reported systemic adverse events were malaise and fatigue, and diarrhea (≥ 10%). (6.1)

AFLURIA (trivalent formulation) administered by the PharmaJet Stratis Needle-Free Injection System:

- In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions were tenderness (≥ 80%), swelling, pain, redness (≥ 60%), itching (≥ 20%) and bruising (≥ 10%). The most common systemic adverse events were myalgia, malaise (≥ 30%), and headache (≥ 20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Seqirus USA Inc. at 1-855-358-8966 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

#### USE IN SPECIFIC POPULATIONS

- The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of age have not been established. (8.4)
- Antibody responses were lower in geriatric subjects than in younger adults. (8.5)
- Pregnancy: There is a pregnancy exposure registry that monitors outcomes in women exposed to AFLURIA QUADRIVALENT during pregnancy. Enroll in the pregnancy registry by calling 1-855-358-8966 or sending an email to [us.medicalinformation@seqirus.com](mailto:us.medicalinformation@seqirus.com). (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2018

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**1 FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

AFLURIA<sup>®</sup> QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

AFLURIA QUADRIVALENT is approved for use in persons 6 months of age and older.

**2 DOSAGE AND ADMINISTRATION****For intramuscular (IM) use only.**

- By needle and syringe (6 months of age and older)
- By PharmaJet<sup>®</sup> Stratis<sup>®</sup> Needle-Free Injection System (18 through 64 years of age)

The dose and schedule for AFLURIA QUADRIVALENT are presented in Table 1.

**Table 1: AFLURIA QUADRIVALENT Dosage and Schedule**

Age	Dose	Schedule
6 months through 35 months	One or two doses <sup>a</sup> , 0.25 mL each	If 2 doses, administer at least 1 month apart
36 months through 8 years	One or two doses <sup>a</sup> , 0.5 mL each	If 2 doses, administer at least 1 month apart
9 years and older	One dose, 0.5mL	Not Applicable

<sup>a</sup>1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

Immediately before use, shake thoroughly and inspect visually. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, the vaccine should not be administered.

When using the single-dose pre-filled syringe, shake the syringe thoroughly and administer the dose immediately.

When using the multi-dose vial, shake the vial thoroughly before withdrawing each dose, and administer the dose immediately.

- Needle and Syringe: Draw up the exact dose using a separate sterile needle and syringe for each individual patient. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss.
- PharmaJet Stratis Needle-Free Injection System: For instructions on withdrawal of a 0.5 mL dose and use of the PharmaJet Stratis Needle-Free Injection System, refer to the Instructions For Use for the PharmaJet Stratis Needle-Free Injection System.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in

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32 infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid  
33 muscle of the upper arm if muscle mass is adequate) in persons 12 months through 35 months  
34 of age, or the deltoid muscle of the upper arm in persons  $\geq$  36 months of age.

### 35 **3 DOSAGE FORMS AND STRENGTHS**

36 AFLURIA QUADRIVALENT is a sterile suspension for intramuscular injection (*see*  
37 *Description [11]*).

38 AFLURIA QUADRIVALENT is supplied in three presentations:

- 39 • 0.25 mL pre-filled syringe (single dose, for persons 6 months through 35 months of  
40 age)
- 41 • 0.5 mL pre-filled syringe (single dose, for persons 36 months of age and older).
- 42 • 5 mL multi-dose vial ( for persons 6 months of age and older).

### 43 **4 CONTRAINDICATIONS**

44 AFLURIA QUADRIVALENT is contraindicated in individuals with known severe allergic  
45 reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a  
46 previous dose of any influenza vaccine (*see Description [11]*).

### 47 **5 WARNINGS AND PRECAUTIONS**

#### 48 **5.1 Guillain-Barré Syndrome**

49 If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza  
50 vaccination, the decision to give AFLURIA QUADRIVALENT should be based on careful  
51 consideration of the potential benefits and risks.

52 The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence  
53 for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is  
54 unclear. If influenza vaccine does pose a risk, it is probably slightly more than one additional  
55 case per 1 million persons vaccinated.

#### 56 **5.2 Preventing and Managing Allergic Reactions**

57 Appropriate medical treatment and supervision must be available to manage possible  
58 anaphylactic reactions following administration of the vaccine.

#### 59 **5.3 Altered Immunocompetence**

60 If AFLURIA QUADRIVALENT is administered to immunocompromised persons, including  
61 those receiving immunosuppressive therapy, the immune response may be diminished.

#### 62 **5.4 Limitations of Vaccine Effectiveness**

63 Vaccination with AFLURIA QUADRIVALENT may not protect all individuals.

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**6 ADVERSE REACTIONS**

64  
65 In adults 18 through 64 years of age, the most commonly reported injection-site adverse reaction  
66 observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and  
67 syringe was pain ( $\geq 40\%$ ). The most common systemic adverse events observed were myalgia  
68 and headache ( $\geq 20\%$ ).

69 In adults 65 years of age and older, the most commonly reported injection-site adverse reaction  
70 observed in clinical studies with AFLURIA QUADRIVALENT administered by needle and  
71 syringe was pain ( $\geq 20\%$ ). The most common systemic adverse event observed was myalgia ( $\geq$   
72 10%).

73 The safety experience with AFLURIA (trivalent formulation) is relevant to AFLURIA  
74 QUADRIVALENT because both vaccines are manufactured using the same process and have  
75 overlapping compositions (see *Description [11]*).

76 In adults 18 through 64 years of age, the most commonly reported injection-site adverse reactions  
77 observed in a clinical study with AFLURIA (trivalent formulation) using the PharmaJet Stratis  
78 Needle-Free Injection System were tenderness ( $\geq 80\%$ ), swelling, pain, redness ( $\geq 60\%$ ), itching  
79 ( $\geq 20\%$ ) and bruising ( $\geq 10\%$ ). The most common systemic adverse events were myalgia,  
80 malaise ( $\geq 30\%$ ) and headache ( $\geq 20\%$ ).

81 In children 5 through 8 years, the most commonly reported injection-site adverse reactions when  
82 AFLURIA QUADRIVALENT was administered by needle and syringe were pain ( $\geq 50\%$ ) and  
83 redness and swelling ( $\geq 10\%$ ). The most common systemic adverse event was headache ( $\geq 10\%$ ).

84 In children 9 through 17 years, the most commonly reported injection-site adverse reactions  
85 when AFLURIA QUADRIVALENT was administered by needle and syringe were pain ( $\geq 50\%$ )  
86 and redness and swelling ( $\geq 10\%$ ). The most common systemic adverse events were headache,  
87 myalgia, and malaise and fatigue ( $\geq 10\%$ ).

88 In children 6 months through 35 months of age, the most frequently reported injection site  
89 reactions in the clinical study with AFLURIA QUADRIVALENT administered by needle and  
90 syringe were pain and redness ( $\geq 20\%$ ). The most common systemic adverse events were  
91 irritability ( $\geq 30\%$ ), diarrhea and loss of appetite ( $\geq 20\%$ ).

92 In children 36 through 59 months of age, the most commonly reported injection site reactions  
93 were pain ( $\geq 30\%$ ) and redness ( $\geq 20\%$ ). The most commonly reported systemic adverse events  
94 were malaise and fatigue, and diarrhea ( $\geq 10\%$ ).

95

**6.1 Clinical Trials Experience**

96 Because clinical studies are conducted under widely varying conditions, adverse reaction rates  
97 observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical  
98 studies of another vaccine and may not reflect the rates observed in clinical practice.  
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100 *Adults*

101 Clinical safety data for AFLURIA QUADRIVALENT in adults have been collected in one  
102 clinical trial, Study 1, a randomized, double-blind, active-controlled trial conducted in the U.S.  
103 in 3449 subjects ages 18 years and older. Subjects in the safety population received one dose of  
104 either AFLURIA QUADRIVALENT (N=1721) or one of two formulations of comparator  
105 trivalent influenza vaccine (AFLURIA, TIV-1 N=864 or TIV-2 N=864) each containing an  
106 influenza type B virus that corresponded to one of the two B viruses in AFLURIA  
107 QUADRIVALENT (a type B virus of the Yamagata lineage or a type B virus of the Victoria  
108 lineage), respectively. The mean age of the population was 58 years, 57% were female, and  
109 racial groups consisted of 82% White, 16% Black, and 2% other; 5% of subjects were  
110 Hispanic/Latino. The age sub-groups were 18 through 64 years and 65 years and older with  
111 mean ages of 43 years and 73 years, respectively. In this study, AFLURIA QUADRIVALENT  
112 and comparator trivalent influenza vaccines were administered by needle and syringe (*see*  
113 *Clinical Studies [14]*).

114 Local (injection-site) adverse reactions and systemic adverse events were solicited for 7 days  
115 post-vaccination (Table 2). Injection site cellulitis, cellulitis-like reactions (defined as  
116 concurrent Grade 3 pain, redness, and swelling/lump), and Grade 3 swelling/lump were  
117 monitored for 28 days post-vaccination. Unsolicited adverse events were collected for 28 days  
118 post-vaccination. Serious adverse events (SAEs), including deaths, were collected for 180 days  
119 post-vaccination.

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120 **Table 2: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**  
 121 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
 122 **AFLURIA QUADRIVALENT or Trivalent Influenza Vaccine (Study 1)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event											
	Subjects 18 through 64 years						Subjects ≥ 65 years					
	AFLURIA Quadrivalent N= 854 <sup>c</sup>		TIV-1 N= 428 <sup>c</sup>		TIV-2 N= 430 <sup>c</sup>		AFLURIA Quadrivalent N= 867 <sup>c</sup>		TIV-1 N= 436 <sup>c</sup>		TIV-2 N= 434 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>												
Pain	47.9	0.7	43.7	1.4	50.7	1.2	24.6	0.1	22.7	0	21.0	0.2
Swelling/Lump	3.7	0.1	2.3	0	3.5	0.2	3.2	0.5	1.8	0	1.6	0
Redness	2.9	0	2.8	0	2.8	0	4.2	0.3	2.1	0	2.5	0.2
<b>Systemic Adverse Events <sup>e</sup></b>												
Myalgia (muscle ache)	25.5	1.9	23.4	1.4	24.2	1.2	12.7	0.3	14.0	0.7	12.2	0.5
Headache	21.7	1.7	15.2	0.9	19.1	1.2	8.4	0	7.1	0.2	7.8	0.7
Malaise	8.9	0.7	9.1	0	9.3	0.7	4.4	0.5	5.0	0.2	5.1	0.2
Nausea	6.9	0.6	7.7	0.5	6.3	1.2	1.6	0	1.8	0	2.1	0.2
Chills	4.8	0.6	4.4	0.2	4.7	0.5	2.0	0	2.1	0.5	1.4	0.2
Vomiting	1.5	0.4	0.9	0	2.3	0.7	0.5	0.1	0	0	0.7	0.2
Fever	1.1	0.4	0.9	0	0.5	0	0.2	0	0.9	0	0.5	0.2

123 Abbreviations: Gr 3, Grade 3.

124 <sup>a</sup> NCT02214225

125 <sup>b</sup> Proportion of subjects reporting each solicited local adverse reaction or systemic adverse event by study vaccine group based  
 126 on the number of subjects contributing any follow up safety information for at least one data value of an individual  
 127 sign/symptom.

128 <sup>c</sup> N = number of subjects in the Safety Population for each study vaccine group.

129 <sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 20mm  
 130 diameter, Grade 3 = ≥ 100mm diameter.

131 <sup>e</sup> Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is  
 132 that which prevents daily activity.

133 In the 28 days following vaccination, no subject experienced cellulitis or a cellulitis-like reaction.  
 134 All Grade 3 swelling/lump reactions began within 7 days of vaccination and are included in  
 135 Table 2.

136 In the 28 days following vaccination, 20.5%, 20.1%, and 20.7% of adults 18 through 64 years  
 137 and 20.3%, 24.1%, and 20.0% of adults ≥ 65 years who received AFLURIA QUADRIVALENT,  
 138 TIV-1, and TIV-2, respectively, reported unsolicited adverse events. Rates of individual events  
 139 were similar between treatment groups, and most events were mild to moderate in severity.

140 In the 180 days following vaccination, 2.3%, 1.6%, and 1.5% of all subjects who received  
 141 AFLURIA QUADRIVALENT, TIV-1, and TIV-2, respectively, experienced SAEs, including

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142 six deaths, five in the AFLURIA QUADRIVALENT group and one in the TIV-2 group. The  
143 majority of SAEs occurred after Study Day 28 and in subjects  $\geq 65$  years of age who had co-  
144 morbid illnesses. No SAEs or deaths appeared related to the study vaccines.

145 Safety information has also been collected in a clinical study of AFLURIA (trivalent  
146 formulation) administered using the PharmaJet Stratis Needle-Free Injection System (Study 2).  
147 Study 2 included 1,247 subjects for safety analysis, ages 18 through 64 years, randomized to  
148 receive AFLURIA by either the PharmaJet Stratis Needle-Free Injection System (624 subjects)  
149 or needle and syringe (623 subjects). No deaths or vaccine-related serious adverse events were  
150 reported in Study 2. Local (injection-site) adverse reactions and systemic adverse events were  
151 solicited for 7 days post-vaccination (Table 3).

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152 **Table 3: Proportion of Subjects 18 through 64 Years of Age with Solicited Local Adverse**  
 153 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
 154 **AFLURIA (trivalent formulation) by PharmaJet Stratis Needle-Free Injection**  
 155 **System or Needle and Syringe (Study 2)<sup>a</sup>**

	Percentage <sup>b</sup> of Subjects Reporting Event			
	Subjects 18 through 64 years			
	AFLURIA (trivalent formulation)			
	PharmaJet Stratis Needle-Free Injection System N=540-616 <sup>c</sup>		Needle and Syringe N=599-606 <sup>c</sup>	
	Any	Grade 3	Any	Grade 3
<b>Local Adverse Reactions <sup>d</sup></b>				
Tenderness	89.4	2.1	77.9	1.0
Swelling	64.8	1.7	19.7	0.2
Pain	64.4	0.8	49.3	0.7
Redness	60.1	1.3	19.2	0.3
Itching <sup>f</sup>	28.0	0.0	9.5	0.2
Bruising	17.6	0.2	5.3	0.0
<b>Systemic Adverse Events <sup>e</sup></b>				
Myalgia	36.4	0.8	35.5	1.0
Malaise	31.2	0.7	28.4	0.5
Headache	24.7	1.3	22.1	1.3
Chills	7.0	0.2	7.2	0.2
Nausea	6.6	0.2	6.5	0.0
Vomiting	1.3	0.0	1.8	0.2
Fever	0.3	0.0	0.3	0.0

156 <sup>a</sup> NCT01688921

157 <sup>b</sup> Proportion of subjects reporting each local adverse reaction or systemic adverse event by treatment group based on the number  
 158 of subjects contributing at least one data value for an individual sign/symptom (individual event denominators).

159 <sup>c</sup> N = number of subjects in the Safety Population for each treatment group. Denominators for the PharmaJet Stratis Needle-Free  
 160 Injection System group were: N=540 for itching and N=605-616 for all other parameters. Denominators for the needle and  
 161 syringe group were: N=527 for itching and N=599-606 for all other parameters.

162 <sup>d</sup> Local adverse reactions: Grade 3 is pain, tenderness or itching that prevents daily activity; Swelling, redness or bruising: any =  
 163 ≥ 25mm diameter, Grade 3 = > 100mm diameter.

164 <sup>e</sup> Systemic adverse events: Fever: any = ≥ 100.4°F (Oral), Grade 3 = ≥ 102.2°F (Oral); Grade 3 for all other adverse events is  
 165 that which prevents daily activity.

166 <sup>f</sup> A total of 155 subjects (approximately randomly distributed between PharmaJet Stratis Needle-Free Injection System and  
 167 needle and syringe groups) received Diary Cards without itching listed as a solicited symptom.

168 In adults 18 through 64 years who received AFLURIA (trivalent formulation) administered by  
 169 PharmaJet Stratis Needle-Free Injection System, commonly reported unsolicited adverse events  
 170 were headache (4.2%), injection site hematoma (1.8%), injection site erythema (1.1%), myalgia  
 171 (1.0%) and nausea (1.0%).

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172 ***Children 5 Years Through 17 Years of Age***

173 Clinical safety data for AFLURIA QUADRIVALENT in older children and adolescents have  
174 been collected in one clinical trial, Study 3, a randomized, observer-blinded, comparator-  
175 controlled trial conducted in the U.S. in 2278 subjects aged 5 through 17 years. Subjects were  
176 stratified into one of two age cohorts of 5 through 8 years or 9 through 17 years (51.2% and  
177 48.8% of the study population, respectively). The mean age of the population was 9.5 years,  
178 52.1% were male, and racial groups consisted of 73.3% White, 20.7% Black, 0.8% Asian, 0.3%  
179 American Indian/Native American, and 0.7% Native Hawaiian/Pacific Islander; 23.8% of  
180 subjects were Hispanic/Latino. The mean ages of subjects 5 through 8 years and 9 through 17  
181 years were 6.7 years and 12.5 years, respectively. Subjects in the safety population (N=2252)  
182 received either AFLURIA QUADRIVALENT (N=1692) or a U.S.-licensed comparator  
183 quadrivalent influenza vaccine (N=560). Study subjects were scheduled to receive either a single  
184 vaccination or two vaccinations 28 days apart based on their previous vaccination history. In  
185 this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle  
186 and syringe (see *Clinical Studies [14]*).

187 Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days  
188 post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and  
189 swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects  
190 were instructed to report and return to clinic within 24 hours in the event of a cellulitis-like  
191 reaction. Unsolicited adverse events were collected for 28 days post-vaccination. All solicited  
192 local adverse reactions and systemic adverse events following any vaccination (first or second  
193 dose) are presented in Table 4.

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194 **Table 4: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**  
195 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
196 **AFLURIA QUADRIVALENT or Comparator (Study 3)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event							
	Subjects 5 through 8 years				Subjects 9 through 17 years			
	AFLURIA Quadrivalent N= 828-829 <sup>c</sup>		Comparator N= 273-274 <sup>c</sup>		AFLURIA Quadrivalent N= 790-792 <sup>c</sup>		Comparator N= 261 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions <sup>d</sup></b>								
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
<b>Systemic Adverse Events <sup>e</sup></b>								
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

197 Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluarix<sup>®</sup> Quadrivalent  
198 (GlaxoSmithKline Biologicals)]

199 <sup>a</sup> NCT02545543

200 <sup>b</sup> Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited  
201 Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

202 <sup>c</sup> N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety data)  
203 for each study vaccine group.

204 <sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity; swelling/lump and redness: any = > 0mm diameter,  
205 Grade 3 = > 30mm diameter.

206 <sup>e</sup> Systemic adverse events: Fever: any =  $\geq 100.4^{\circ}\text{F}$  (Oral), Grade 3 =  $\geq 102.2^{\circ}\text{F}$  (Oral); Grade 3 for all other adverse events is  
207 that which prevents daily activity or requires significant medical intervention.  
208

209 In subjects 5 through 8 years of age, all solicited local adverse reactions and systemic adverse  
210 events were reported at lower frequencies after the second vaccination than after the first  
211 vaccination with AFLURIA QUADRIVALENT with the exception of vomiting (which occurred  
212 at the same rate of 2.2% after each vaccination).

213 One subject, 8 years of age, experienced a cellulitis-like reaction at the injection site after  
214 vaccination with AFLURIA QUADRIVALENT.

215 The most commonly reported unsolicited adverse events in the 28 days following the first or  
216 second dose of AFLURIA QUADRIVALENT in subjects 5 through 8 years of age were cough  
217 (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%), and were similar to the  
218 comparator.

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219 For subjects ages 9 through 17 years who received AFLURIA QUADRIVALENT, the most  
220 commonly reported unsolicited adverse events in the 28 days following vaccination were  
221 oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%), and were  
222 similar to the comparator.

223 No deaths were reported in Study 3. In the 180 days following vaccinations, AFLURIA  
224 QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious  
225 adverse events (SAEs). None of the SAEs appeared related to the study vaccines except for one  
226 case of influenza B infection (considered a vaccine failure) in an AFLURIA QUADRIVALENT  
227 recipient.

**228 *Children 6 Months Through 59 Months of Age***

229 Clinical safety data for AFLURIA QUADRIVALENT in infants and young children have been  
230 collected in one clinical trial, Study 4, a randomized, observer-blind, comparator-controlled trial  
231 conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into  
232 one of two age cohorts of 6 through 35 months or 36 through 59 months (41.6% and 58.4% of  
233 the study population, respectively). The mean age of the population was 36.6 months, 51.6%  
234 were male, and racial groups consisted of 71.0% White, 21.5% Black, 1.1% Asian, 0.7% Native  
235 Hawaiian/Pacific Islander, and 0.3% American Indian/Native American; 26.4% of subjects were  
236 Hispanic/Latino. The mean ages of subjects 6 through 35 months and 36 through 59 months  
237 were 21.7 months and 47.1 months, respectively. Subjects in the safety population (N=2232)  
238 received either AFLURIA QUADRIVALENT (N=1673) or a U.S.-licensed comparator  
239 quadrivalent influenza vaccine (N=559). Study subjects were scheduled to receive either a single  
240 vaccination or two vaccinations 28 days apart based on their previous vaccination history. In  
241 this study, AFLURIA QUADRIVALENT and comparator vaccine were administered by needle  
242 and syringe (see *Clinical Studies [14]*).

243 Local (injection site) adverse reactions and systemic adverse events were solicited for 7 days  
244 post-vaccination. Cellulitis-like reactions (defined as concurrent Grade 3 pain, redness, and  
245 swelling/lump) at the injection site were monitored for 28 days post-vaccination. Subjects were  
246 instructed to report and return to clinic within 24 hours in the event of a cellulitis-like reaction.  
247 Unsolicited adverse events were collected for 28 days post-vaccination, and SAEs for 6 months  
248 following the last vaccination. All solicited local adverse reactions and systemic adverse events  
249 following any vaccination (first or second dose) are presented in Table 5.

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250 **Table 5: Proportion of Subjects Per Age Cohort with Any Solicited Local Adverse**  
251 **Reactions or Systemic Adverse Events within 7 Days after Administration of**  
252 **AFLURIA QUADRIVALENT or Comparator QIV (Study 4)<sup>a</sup>**

	Percentage (%) <sup>b</sup> of Subjects in each Age Cohort Reporting an Event							
	6 through 35 months				36 through 59 months			
	AFLURIA Quadrivalent N= 668-669 <sup>c</sup>		Comparator N= 226-227 <sup>c</sup>		AFLURIA Quadrivalent N= 947-949 <sup>c</sup>		Comparator N= 317-318 <sup>c</sup>	
	Any	Gr 3	Any	Gr 3	Any	Gr 3	Any	Gr 3
<b>Local Adverse Reactions<sup>d</sup></b>								
Pain	20.8	0.1	25.6	0.4	35.5	0	31.4	0.6
Redness	20.8	0.6	17.6	1.8	22.4	2.3	20.8	5.3
Swelling/Lump	6.1	0.4	6.2	0.9	10.1	1.7	12.9	2.5
<b>Systemic Adverse Events<sup>e</sup></b>								
Irritability	32.9	0.7	28.2	0.4	-	-	-	-
Diarrhea	24.2	0.1	25.6	0.4	12.1	0.1	8.8	0.6
Loss of Appetite	20.0	0.3	19.4	0.4	-	-	-	-
Malaise and Fatigue	-	-	-	-	14.3	0.5	13.2	0.3
Myalgia	-	-	-	-	9.9	0.1	9.4	0
Nausea and/or vomiting	9.4	0.7	11.0	0	9.2	0.4	6.6	0.3
Headache	-	-	-	-	6.2	0.4	5.0	0
Fever <sup>f</sup>	7.2	2.5	11.9	2.6	4.8	1.2	6.0	0.9

253 Abbreviations: Gr 3, Grade 3 (severe); Comparator, Comparator quadrivalent influenza vaccine [Fluzone<sup>®</sup> Quadrivalent (Sanofi  
254 Pasteur)]

255 <sup>a</sup> NCT02914275

256 <sup>b</sup> Percent (%) is derived from the number of subjects that reported the event divided by the number of subjects in the Solicited  
257 Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

258 <sup>c</sup> N = number of subjects in the Solicited Safety Population (subjects who were vaccinated and provided any solicited safety  
259 data) for each study vaccine group.

260 <sup>d</sup> Local adverse reactions: Grade 3 pain is that which prevents daily activity (36 through 59 month subjects); or cried when limb  
261 was moved or spontaneously painful (6 through 35 month subjects); Swelling/Lump and redness: any = ≥ 0mm diameter, Grade  
262 3 = ≥ 30mm diameter.

263 <sup>e</sup> Systemic adverse events: Fever: any = ≥ 99.5°F (Axillary), Grade 3 = ≥ 101.3°F (Axillary); Grade 3 for all other adverse events  
264 is that which prevents daily activity; Irritability, Loss of Appetite, Malaise and Fatigue, Myalgia and Headache are age specific  
265 systemic adverse events, where “-” denotes event was not applicable to that age cohort.

266 <sup>f</sup> Prophylactic antipyretics (acetaminophen or ibuprofen-containing medications) were not permitted. Antipyretics used to treat  
267 fever were permitted and rates of use were as follows: 6 through 35 months (Afluria QIV 5.9%, Comparator QIV 9.0%); 36  
268 through 59 months (Afluria QIV 3.7%, Comparator QIV 2.5%).

269 In subjects 6 through 35 months of age, all solicited local adverse reactions and systemic adverse  
270 events were reported at lower frequencies after the second vaccination than after the first  
271 vaccination with AFLURIA QUADRIVALENT.

272 In subjects 36 through 59 months of age, all solicited local adverse reactions and systemic adverse  
273 events were reported at lower frequencies after the second vaccination than after the first  
274 vaccination with AFLURIA QUADRIVALENT.

275 The most commonly reported unsolicited adverse events in the 28 days following the first or  
276 second dose of AFLURIA QUADRIVALENT in subjects 6 through 35 months of age were  
277 rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%),

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278 diarrhea (3.7%), otitis media (2.4%), vomiting (2.4%), nasal congestion (2.4%), nasopharyngitis  
279 (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash  
280 (1.2%), influenza like illness (1.0%) and fatigue (1.0%), and were similar to comparator.

281 The most commonly reported unsolicited adverse events in the 28 days following the first or  
282 second dose of AFLURIA QUADRIVALENT in subjects 36 through 59 months of age were  
283 cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%),  
284 vomiting (2.1%), nasal congestion (1.6%), nasopharyngitis (1.7%), oropharyngeal pain (1.2%)  
285 diarrhea (1.1%) and fatigue (1.1%), and were similar to the comparator.

286 No deaths were reported in Study 4. In the 180 days following vaccinations, AFLURIA  
287 QUADRIVALENT and comparator vaccine recipients experienced similar rates of serious  
288 adverse events (SAEs), none of which were related to study vaccines. No vaccine-related febrile  
289 seizures occurred in Study 4. Unrelated SAEs of febrile seizures occurred in two AFLURIA  
290 QUADRIVALENT recipients (6 through 35 months age group) at 43 and 104 days post-  
291 vaccinations.

292

## 293 **6.2 Postmarketing Experience**

294 Because postmarketing reporting of adverse events is voluntary and from a population of  
295 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal  
296 relationship to vaccine exposure. The adverse events described have been included in this  
297 section because they: 1) represent reactions that are known to occur following immunizations  
298 generally or influenza immunizations specifically; 2) are potentially serious; or 3) have been  
299 reported frequently. There are limited postmarketing data available for AFLURIA  
300 QUADRIVALENT. The adverse events listed below reflect experience in both children and  
301 adults and include those identified during post-approval use of AFLURIA (trivalent formulation)  
302 outside the U.S. since 1985.

303 The post-marketing experience with AFLURIA (trivalent formulation) included the following:

### 304 **Blood and lymphatic system disorders**

305 Thrombocytopenia

### 306 **Immune system disorders**

307 Allergic or immediate hypersensitivity reactions including anaphylactic shock and serum  
308 sickness

### 309 **Nervous system disorders**

310 Neuralgia, paresthesia, convulsions (including febrile seizures), encephalomyelitis,  
311 encephalopathy, neuritis or neuropathy, transverse myelitis, and GBS

### 312 **Vascular disorders**

313 Vasculitis which may be associated with transient renal involvement

### 314 **Skin and subcutaneous tissue disorders**

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315 Pruritus, urticaria, and rash

316 **General disorders and administration site conditions**

317 Cellulitis and large injection site swelling

318 Influenza-like illness

319 **7 DRUG INTERACTIONS**

320 No interaction studies have been performed on interaction between influenza vaccines in general  
321 and other vaccines or medications.

322 **8 USE IN SPECIFIC POPULATIONS**

323 **8.1 Pregnancy**

324 Pregnancy Exposure Registry

325 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to  
326 AFLURIA QUADRIVALENT during pregnancy. Women who are vaccinated with AFLURIA  
327 QUADRIVALENT during pregnancy are encouraged to enroll in the registry by calling 1-855-  
328 358-8966 or sending an email to Seqirus at us.medicalinformation@seqirus.com.

329

330 Risk summary

331 All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general  
332 population, the estimated background risk of major birth defects and miscarriage in clinically  
333 recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data for AFLURIA  
334 (trivalent formulation) administered to pregnant women are relevant to AFLURIA  
335 QUADRIVALENT because both vaccines are manufactured using the same process and have  
336 overlapping compositions (see *Description [11]*). There are limited data for AFLURIA  
337 QUADRIVALENT administered to pregnant women, and available data for AFLURIA  
338 (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-  
339 associated risks in pregnancy.

340 There were no developmental toxicity studies of AFLURIA QUADRIVALENT performed in  
341 animals. A developmental toxicity study of AFLURIA (trivalent formulation) has been  
342 performed in female rats administered a single human dose [0.5 mL (divided)] of AFLURIA  
343 (trivalent formulation) prior to mating and during gestation. This study revealed no evidence of  
344 harm to the fetus due to AFLURIA (trivalent formulation) (*see 8.1 Data*).

345 Clinical Considerations

346 *Disease-associated Maternal and/or Embryo-Fetal Risk*

347 Pregnant women are at increased risk for severe illness due to influenza compared to non-  
348 pregnant women. Pregnant women with influenza may be at increased risk for adverse  
349 pregnancy outcomes, including preterm labor and delivery.

350 Data

351 *Animal Data*

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352 In a developmental toxicity study, female rats were administered a single human dose [0.5 mL  
353 (divided)] of AFLURIA (trivalent formulation) by intramuscular injection 21 days and 7 days  
354 prior to mating, and on gestation day 6. Some rats were administered an additional dose on  
355 gestation day 20. No vaccine-related fetal malformations or variations and no adverse effects on  
356 pre-weaning development were observed in the study.

**357 8.2 Lactation****358 Risk Summary**

359 It is not known whether AFLURIA QUADRIVALENT is excreted in human milk. Data are  
360 not available to assess the effects of AFLURIA QUADRIVALENT on the breastfed infant or  
361 on milk production/excretion.

362 The developmental and health benefits of breastfeeding should be considered along with the  
363 mother's clinical need for AFLURIA QUADRIVALENT and any potential adverse effects on  
364 the breastfed child from AFLURIA QUADRIVALENT or from the underlying maternal  
365 condition. For preventive vaccines, the underlying maternal condition is susceptibility to  
366 disease prevented by the vaccine.

**367 8.4 Pediatric Use**

368 The safety and effectiveness of AFLURIA QUADRIVALENT in persons less than 6 months of  
369 age have not been established.

370 The PharmaJet Stratis Needle-Free Injection System is not approved as a method of  
371 administering AFLURIA QUADRIVALENT to children and adolescents less than 18 years of  
372 age due to lack of adequate data supporting safety and effectiveness in this population.

**373 8.5 Geriatric Use**

374 In clinical studies, AFLURIA QUADRIVALENT has been administered to, and safety  
375 information collected for, 867 subjects aged 65 years and older (*see Adverse Reactions [6]*). The  
376 65 years and older age group included 539 subjects 65 through 74 years and 328 subjects 75  
377 years and older. After administration of AFLURIA QUADRIVALENT, hemagglutination-  
378 inhibiting antibody responses were non-inferior to comparator trivalent influenza (TIV-1 and  
379 TIV-2) in persons 65 years of age and older, but were lower than younger adult subjects (*see*  
380 *Clinical Studies [14]*).

381 The PharmaJet Stratis Needle-Free Injection System is not approved as a method of  
382 administering AFLURIA QUADRIVALENT to adults 65 years of age and older due to lack of  
383 adequate data supporting safety and effectiveness in this population.

**384 11 DESCRIPTION**

385 AFLURIA QUADRIVALENT, Influenza Vaccine for intramuscular injection, is a sterile, clear,  
386 colorless to slightly opalescent suspension with some sediment that resuspends upon shaking to  
387 form a homogeneous suspension. AFLURIA QUADRIVALENT is prepared from influenza

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388 virus propagated in the allantoic fluid of embryonated chicken eggs. Following harvest, the virus  
389 is purified in a sucrose density gradient using continuous flow zonal centrifugation. The purified  
390 virus is inactivated with beta-propiolactone, and the virus particles are disrupted using sodium  
391 taurodeoxycholate to produce a “split virion”. The disrupted virus is further purified and  
392 suspended in a phosphate buffered isotonic solution.

393 AFLURIA QUADRIVALENT is standardized according to USPHS requirements for the 2018-  
394 2019 influenza season and is formulated to contain 60 mcg hemagglutinin (HA) per 0.5 mL dose  
395 in the recommended ratio of 15 mcg HA for each of the four influenza strains recommended for  
396 the 2018-2019 Northern Hemisphere influenza season:

397 A/Singapore/GP1908/2015 IVR 180A (H1N1) (an A/Michigan/45/2015 – like virus),  
398 A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2) (an A/Singapore/INFIMH-16-  
399 0019/2016 – like virus), B/Maryland/15/2016 (a B/Colorado/06/2017 – like virus) and  
400 B/Phuket/3073/2013 BVR-1B (a B/Phuket/3073/2013 – like virus). A 0.25 mL dose contains  
401 7.5 mcg HA of each of the same four influenza strains.

402 Thimerosal, a mercury derivative, is not used in the manufacturing process for the single dose  
403 presentation. This presentation does not contain preservative. The multi-dose presentation  
404 contains thimerosal added as a preservative; each 0.5 mL dose contains 24.5 mcg of mercury  
405 and each 0.25 mL dose contains 12.25 mcg of mercury.

406 A single 0.5 mL dose of AFLURIA QUADRIVALENT contains sodium chloride (4.1 mg),  
407 monobasic sodium phosphate (80 mcg), dibasic sodium phosphate (300 mcg), monobasic  
408 potassium phosphate (20 mcg), potassium chloride (20 mcg), and calcium chloride (0.5 mcg).  
409 From the manufacturing process, each 0.5 mL dose may also contain residual amounts of sodium  
410 taurodeoxycholate ( $\leq 10$  ppm), ovalbumin ( $< 1$  mcg), sucrose ( $< 10$  mcg), neomycin sulfate  
411 ( $\leq 81.8$  nanograms [ng]), polymyxin B ( $\leq 14$  ng), and beta-propiolactone ( $\leq 1.5$  ng). A single  
412 0.25 mL dose of AFLURIA QUADRIVALENT contains half of these quantities.

413 The rubber tip cap and plunger used for the preservative-free, single-dose syringes and the  
414 rubber stoppers used for the multi-dose vial were not made with natural rubber latex.

**415 12 CLINICAL PHARMACOLOGY****416 12.1 Mechanism of Action**

417 Influenza illness and its complications follow infection with influenza viruses. Global  
418 surveillance of influenza identifies yearly antigenic variants. For example, since 1977 antigenic  
419 variants of influenza A (H1N1 and H3N2) and influenza B viruses have been in global  
420 circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages)  
421 have co-circulated worldwide. Specific levels of hemagglutination inhibition (HI) antibody titers  
422 post-vaccination with inactivated influenza vaccine have not been correlated with protection  
423 from influenza virus. In some human studies, antibody titers of 1:40 or greater have been  
424 associated with protection from influenza illness in up to 50% of subjects.<sup>2,3</sup>

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425 Antibody against one influenza virus type or subtype confers limited or no protection against  
426 another. Furthermore, antibody to one antigenic variant of influenza virus might not protect  
427 against a new antigenic variant of the same type or subtype. Frequent development of antigenic  
428 variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for  
429 the usual change to one or more new strains in each year's influenza vaccine. Therefore,  
430 inactivated influenza vaccines are standardized to contain the HA of four strains (i.e., typically  
431 two type A and two type B) representing the influenza viruses likely to be circulating in the U.S.  
432 during the upcoming winter.

433 Annual revaccination with the current vaccine is recommended because immunity declines  
434 during the year after vaccination and circulating strains of influenza virus change from year to  
435 year.<sup>1</sup>

**436 13 NONCLINICAL TOXICOLOGY****437 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

438 AFLURIA QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential,  
439 or male infertility in animals. A developmental toxicity study conducted in rats vaccinated with  
440 AFLURIA (trivalent formulation) revealed no impact on female fertility (see *Pregnancy [8.1]*).

**441 14 CLINICAL STUDIES****442 14.1 Efficacy Against Laboratory-Confirmed Influenza**

443 The efficacy of AFLURIA (trivalent formulation) is relevant to AFLURIA QUADRIVALENT  
444 because both vaccines are manufactured using the same process and have overlapping  
445 compositions (see *Description [11]*).

446 The efficacy of AFLURIA (trivalent formulation) was demonstrated in Study 5, a randomized,  
447 observer-blind, placebo-controlled study conducted in 15,044 subjects. Healthy subjects 18  
448 through 64 years of age were randomized in a 2:1 ratio to receive a single dose of AFLURIA  
449 (trivalent formulation) (enrolled subjects: 10,033; evaluable subjects: 9,889) or placebo (enrolled  
450 subjects: 5,011; evaluable subjects: 4,960). The mean age of all randomized subjects was 35.5  
451 years. 54.4% were female and 90.2% were White. Laboratory-confirmed influenza was  
452 assessed by active and passive surveillance of influenza-like illness (ILI) beginning 2 weeks  
453 post-vaccination until the end of the influenza season, approximately 6 months post-vaccination.  
454 ILI was defined as at least one respiratory symptom (e.g., cough, sore throat, nasal congestion)  
455 and at least one systemic symptom (e.g., oral temperature of 100.0°F or higher, feverishness,  
456 chills, body aches). Nasal and throat swabs were collected from subjects who presented with an  
457 ILI for laboratory confirmation by viral culture and real-time reverse transcription polymerase  
458 chain reaction. Influenza virus strain was further characterized using gene sequencing and  
459 pyrosequencing.

460 Attack rates and vaccine efficacy, defined as the relative reduction in the influenza infection rate  
461 for AFLURIA (trivalent formulation) compared to placebo, were calculated using the per  
462 protocol population. Vaccine efficacy against laboratory-confirmed influenza infection due to

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463 influenza A or B virus strains contained in the vaccine was 60% with a lower limit of the 95%  
464 CI of 41% (Table 6).

465 **Table 6: AFLURIA (trivalent formulation): Laboratory-Confirmed Influenza Infection**  
466 **Rate and Vaccine Efficacy in Adults 18 through 64 Years of Age (Study 5)<sup>a</sup>**

	Subjects <sup>b</sup>	Laboratory-Confirmed Influenza Cases	Influenza Infection Rate	Vaccine Efficacy <sup>c</sup>	
	N	N	n/N %	%	Lower Limit of the 95% CI
<b>Vaccine-matched Strains</b>					
AFLURIA	9889	58	0.59	60	41
Placebo	4960	73	1.47		
<b>Any Influenza Virus Strain</b>					
AFLURIA	9889	222	2.24	42	28
Placebo	4960	192	3.87		

467 Abbreviations: CI, confidence interval.

468 <sup>a</sup>NCT00562484

469 <sup>b</sup> The Per Protocol Population was identical to the Evaluable Population in this study.

470 <sup>c</sup> Vaccine efficacy = 1 minus the ratio of AFLURIA (trivalent formulation) /placebo infection rates. The objective of the study  
471 was to demonstrate that the lower limit of the CI for vaccine efficacy was greater than 40%.

472 **14.2 Immunogenicity of AFLURIA QUADRIVALENT in Adults and Older Adults**  
473 **Administered by Needle and Syringe**

474 Study 1 was a randomized, double-blind, active-controlled trial conducted in the U.S. in adults  
475 aged 18 years of age and older. Subjects received one dose of either AFLURIA  
476 QUADRIVALENT (N=1691) or one of two formulations of comparator trivalent influenza  
477 vaccine (AFLURIA, TIV-1 N=854 or TIV-2 N=850) each containing an influenza type B virus  
478 that corresponded to one of the two B viruses in AFLURIA QUADRIVALENT (a type B virus  
479 of the Yamagata lineage or a type B virus of the Victoria lineage, respectively).

480 Post-vaccination immunogenicity was evaluated on sera obtained 21 days after administration  
481 of a single dose of AFLURIA QUADRIVALENT or TIV comparator. The co-primary endpoints  
482 were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers) and the difference  
483 in seroconversion rates for each vaccine strain, 21 days after vaccination. Pre-specified non-  
484 inferiority criteria required that the upper bound of the 2-sided 95% CI of the GMT ratio  
485 (TIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound of the 2-sided 95%  
486 CI of the seroconversion rate difference (TIV minus AFLURIA QUADRIVALENT) did not  
487 exceed 10.0% for each strain.

488 Serum HI antibody responses to AFLURIA QUADRIVALENT were non-inferior to both TIVs  
489 for all influenza strains for subjects 18 years of age and older. Additionally, non-inferiority was  
490 demonstrated for both endpoints in both age sub-groups, adults aged 18 through 64 years and 65  
491 years and older, for all strains (Table 7). Superiority of the immune response to each of the  
492 influenza B strains contained in AFLURIA QUADRIVALENT was shown relative to the



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493 antibody response after vaccination with TIV formulations not containing that B lineage strain  
494 for subjects 18 years of age and older. Superiority against the alternate B strain was also  
495 demonstrated for each of the influenza B strains in both age sub-groups; 18 through 64 years and  
496 65 years and older. Post-hoc analyses of immunogenicity endpoints by gender did not  
497 demonstrate meaningful differences between males and females. The study population was not  
498 sufficiently diverse to assess differences between races or ethnicities.

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499 **Table 7: Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of**  
500 **Non-Inferiority of AFLURIA QUADRIVALENT Relative to Trivalent Influenza**  
501 **Vaccine (TIV) by Age Cohort (Study 1)<sup>a</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>b</sup>	Seroconversion % <sup>c</sup>		Difference	Met both pre-defined non-inferiority criteria? <sup>d</sup>
	AFLURIA Quadrivalent	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1691	Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria)	Pooled TIV or TIV-1 or TIV-2 minus AFLURIA Quadrivalent (95% CI)	
<b>18 through 64 years</b>	<b>AFLURIA Quadrivalent N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421</b>						
A(H1N1)	432.7	402.8	0.93 <sup>e</sup> (0.85, 1.02)	51.3	49.1	-2.1 <sup>h</sup> (-6.9, 2.7)	Yes
A(H3N2)	569.1	515.1	0.91 <sup>e</sup> (0.83, 0.99)	56.3	51.7	-4.6 <sup>h</sup> (-9.4, 0.2)	Yes
B/Massachusetts/2/2012 (B Yamagata)	92.3	79.3	0.86 <sup>f</sup> (0.76, 0.97)	45.7	41.3	-4.5 <sup>i</sup> (-10.3, 1.4)	Yes
B/Brisbane/60/2008 (B Victoria)	110.7	95.2	0.86 <sup>g</sup> (0.76, 0.98)	57.6	53.0	-4.6 <sup>j</sup> (-10.5, 1.2)	Yes
<b>≥ 65 years</b>	<b>AFLURIA Quadrivalent N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429</b>						
A(H1N1)	211.4	199.8	0.95 <sup>e</sup> (0.88, 1.02)	26.6	26.4	-0.2 <sup>h</sup> (-5.0, 4.5)	Yes
A(H3N2)	419.5	400.0	0.95 <sup>e</sup> (0.89, 1.02)	25.9	27.0	1.1 <sup>h</sup> (-3.7, 5.8)	Yes
B/Massachusetts/2/2012 (B Yamagata)	43.3	39.1	0.90 <sup>f</sup> (0.84, 0.97)	16.6	14.4	-2.2 <sup>i</sup> (-8.0, 3.6)	Yes
B/Brisbane/60/2008 (B Victoria)	66.1	68.4	1.03 <sup>g</sup> (0.94, 1.14)	23.5	24.7	1.2 <sup>j</sup> (-4.6, 7.0)	Yes

502 Abbreviations: CI, confidence interval; GMT, geometric mean titer.

503 <sup>a</sup> NCT02214225

504 <sup>b</sup> GMT ratio was computed after fitting a multi-variable model on the post-vaccination titers including sex, vaccination history,  
505 pre-vaccination HI titers and other factors.

506 <sup>c</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an  
507 increase in titer from  $< 1:10$  to  $\geq 1:40$ .

508 <sup>d</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Pooled TIV or TIV-1 (B  
509 Yamagata) or TIV-2 (B Victoria)/AFLURIA Quadrivalent should not exceed 1.5. NI criterion for the SCR difference: upper  
510 bound of 2-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B Yamagata) or TIV-2 (B Victoria) minus  
511 AFLURIA Quadrivalent should not exceed 10%.

512 <sup>e</sup> Pooled TIV/AFLURIA Quadrivalent

513 <sup>f</sup> TIV-1 (B Yamagata)/AFLURIA Quadrivalent

514 <sup>g</sup> TIV-2 (B Victoria)/AFLURIA Quadrivalent

515 <sup>h</sup> Pooled TIV – AFLURIA Quadrivalent

516 <sup>i</sup> TIV-1 (B Yamagata) - AFLURIA Quadrivalent

517 <sup>j</sup> TIV-2 (B Victoria) - AFLURIA Quadrivalent

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**14.3 Immunogenicity of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System**

Study 2 was a randomized, comparator-controlled, non-inferiority study that enrolled 1,250 subjects 18 through 64 years of age. This study compared the immune response following administration of AFLURIA (trivalent formulation) when delivered intramuscularly using either the PharmaJet Stratis Needle-Free Injection System or needle and syringe. Immunogenicity assessments were performed prior to vaccination and at 28 days after vaccination in the immunogenicity population (1130 subjects, 562 PharmaJet Stratis Needle-Free Injection System group, 568 needle and syringe group). The co-primary endpoints were HI GMT ratios for each vaccine strain and the absolute difference in seroconversion rates for each vaccine strain 28 days after vaccination. As shown in Table 8, non-inferiority of administration of AFLURIA (trivalent formulation) by the PharmaJet Stratis Needle-Free Injection System compared to administration of AFLURIA (trivalent formulation) by needle and syringe was demonstrated in the immunogenicity population for all strains. Post-hoc analyses of immunogenicity by age showed that younger subjects (18 through 49 years) elicited higher immunological responses than older subjects (50 through 64 years). Post-hoc analyses of immunogenicity according to sex and body mass index did not reveal significant influences of these variables on immune responses. The study population was not sufficiently diverse to assess immunogenicity by race or ethnicity.

**Table 8: Baseline and Post-Vaccination HI Antibody GMTs, Seroconversion Rates, and Analyses of Non-Inferiority of AFLURIA (trivalent formulation) Administered by PharmaJet Stratis Needle-Free Injection System or Needle and Syringe, Adults 18 through 64 Years of Age (Study 2)<sup>a</sup>**

Strain	Baseline GMT		Post-vaccination GMT		GMT Ratio <sup>b</sup>	Seroconversion % <sup>c</sup>		Difference	Met both pre-defined non-inferiority criteria? <sup>d</sup>
	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe over PharmaJet Stratis Needle-Free Injection System (95% CI)	Needle and Syringe N=568	PharmaJet Stratis Needle-Free Injection System N=562	Needle and Syringe minus PharmaJet Stratis Needle-Free Injection System (95% CI)	
A(H1N1)	79.5	83.7	280.6	282.9	0.99 (0.88, 1.12)	38.4	37.5	0.8 (-4.8, 6.5)	Yes
A(H3N2)	75.4	68.1	265.9	247.3	1.08 (0.96, 1.21)	45.1	43.8	1.3 (-4.5, 7.1)	Yes
B	12.6	13.5	39.7	42.5	0.94 (0.83, 1.06)	35.2	34.9	0.3 (-5.2, 5.9)	Yes

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

<sup>a</sup> NCT01688921

<sup>b</sup> GMT ratio is defined as post-vaccination GMT for Needle and Syringe/PharmaJet Stratis Needle-Free Injection System.

<sup>c</sup> Seroconversion rate is defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer  $\geq 1:10$  or an increase in titer from  $< 1:10$  to  $\geq 1:40$ .

<sup>d</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of 2-sided 95% CI on the GMT ratio of Needle and Syringe/PharmaJet Stratis Needle-Free Injection System should not exceed 1.5. NI criterion for the seroconversion rate (SCR) difference: upper bound of 2-sided 95% CI on the difference between SCR Needle and Syringe – SCR PharmaJet Stratis Needle-Free Injection System should not exceed 10%.

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**549 14.4 Immunogenicity of AFLURIA QUADRIVALENT in Children 5 through 17**  
**550 Years Administered by Needle and Syringe**

551 Study 3 was a randomized, observer-blinded, comparator-controlled trial conducted in the U.S.  
552 in children 5 through 17 years of age. A total of 2278 subjects were randomized 3:1 to receive  
553 one or two doses of AFLURIA QUADRIVALENT (N=1709) or a U.S.-licensed comparator  
554 quadrivalent influenza vaccine (N=569). Subjects 5 through 8 years of age were eligible to  
555 receive a second dose at least 28 days after the first dose depending on their influenza vaccination  
556 history, consistent with the 2015-2016 recommendations of the Advisory Committee on  
557 Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines.  
558 Approximately 25% of subjects in each treatment group in the 5 through 8 years of age sub-  
559 group received two vaccine doses.

560 Baseline serology for HI assessment was collected prior to vaccination. Post-vaccination  
561 immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination  
562 dose.

563 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT  
564 elicits an immune response that is not inferior to that of a comparator vaccine containing the  
565 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT  
566 n=1605, Comparator n=528) was used for the primary endpoint analyses. The co-primary  
567 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other  
568 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.  
569 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the  
570 GMT ratio (Comparator/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper bound  
571 of the 2-sided 95% CI of the seroconversion rate difference (Comparator minus AFLURIA  
572 QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody responses to  
573 AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and seroconversion rates  
574 relative to the comparator vaccine for all influenza strains (Table 9). Analyses of  
575 immunogenicity endpoints by gender did not demonstrate meaningful differences between males  
576 and females. The study population was not sufficiently diverse to assess differences among races  
577 or ethnicities.

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578 **Table 9: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of**  
579 **AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**  
580 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last Vaccination**  
581 **Among a Pediatric Population 5 through 17 Years of Age (Per Protocol**  
582 **Population) (Study 3) <sup>a,b</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup>	Met both pre-defined non-inferiority criteria? <sup>f</sup>
	AFLURIA Quadrivalent N=1605	Comparator N=528	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1605 (95% CI)	Comparator N=528 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	952.6 (n=1604 <sup>g</sup> )	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A(H3N2)	886.4 (n=1604 <sup>g</sup> )	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Phuket/3073/2013 (B Yamagata)	60.9 (n=1604 <sup>g</sup> )	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Brisbane/60/2008 (B Victoria)	145.0 (n=1604 <sup>g</sup> )	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

583 Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluarix<sup>®</sup> Quadrivalent  
584 [GlaxoSmithKline Biologicals]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

585 <sup>a</sup> NCT02545543

586 <sup>b</sup> The Per-Protocol Population comprised all subjects in the Evaluable Population who did not have any protocol deviations  
587 that were medically assessed as potentially impacting on immunogenicity results.

588 <sup>c</sup> GMT Ratio = Comparator /AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI  
589 Titer=Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer +  
590 Site + Number of Doses (1 vs 2) + Age Strata\*Vaccine. The Age Strata\*Vaccine interaction term was excluded from the  
591 model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square  
592 means were back transformed.

593 <sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a  
594 postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

595 <sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

596 <sup>f</sup> Non-inferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator  
597 /AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95%  
598 CI on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

599 <sup>g</sup> Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio since  
600 the subject did not have information on all covariates (unknown prevaccination history).

601 **14.5 Immunogenicity of AFLURIA QUADRIVALENT in Children 6 Months**  
602 **through 59 Months Administered by Needle and Syringe**

603 Study 4 was a randomized, observer-blind, comparator-controlled trial conducted in the U.S. in  
604 children 6 months through 59 months of age. A total of 2247 subjects were randomized 3:1 to  
605 receive AFLURIA QUADRIVALENT (N=1684) or a U.S.-licensed comparator quadrivalent  
606 influenza vaccine (N=563). Children 6 months through 35 months received one or two 0.25  
607 mL doses and children 36 months through 59 months received one or two 0.5 mL doses.  
608 Subjects were eligible to receive a second dose at least 28 days after the first dose depending  
609 on their influenza vaccination history, consistent with the 2016-2017 recommendations of the  
610 Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal

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611 Influenza with Vaccines. Approximately 40% of subjects in each treatment group received two  
612 vaccine doses.

613 Baseline serology for HI assessment was collected prior to vaccination. Postvaccination  
614 immunogenicity was evaluated by HI assay on sera obtained 28 days after the last vaccination  
615 dose.

616 The primary objective was to demonstrate that vaccination with AFLURIA QUADRIVALENT  
617 elicits an immune response that is not inferior to that of a comparator vaccine containing the  
618 same recommended virus strains. The Per Protocol Population (AFLURIA QUADRIVALENT  
619 n=1456, Comparator QIV n=484) was used for the primary endpoint analyses. The co-primary  
620 endpoints were HI Geometric Mean Titer (GMT) ratios (adjusted for baseline HI titers and other  
621 covariates) and seroconversion rates for each vaccine strain, 28 days after the last vaccination.  
622 Pre-specified non-inferiority criteria required that the upper bound of the 2-sided 95% CI of the  
623 GMT ratio (Comparator QIV/AFLURIA QUADRIVALENT) did not exceed 1.5 and the upper  
624 bound of the 2-sided 95% CI of the seroconversion rate difference (Comparator QIV minus  
625 AFLURIA QUADRIVALENT) did not exceed 10.0% for each strain. Serum HI antibody  
626 responses to AFLURIA QUADRIVALENT were non-inferior for both GMT ratio and  
627 seroconversion rates relative to the comparator vaccine for all influenza strains (Table 10).  
628 Analyses of immunogenicity endpoints by gender did not demonstrate meaningful differences  
629 between males and females. The study population was not sufficiently diverse to assess  
630 differences among races or ethnicities.

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631 **Table 10: Post-Vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority**  
 632 **of AFLURIA QUADRIVALENT Relative to a U.S.-Licensed Comparator**  
 633 **Quadrivalent Influenza Vaccine for each Strain 28 Days after Last**  
 634 **Vaccination Among a Pediatric Population 6 through 59 Months of Age (Per**  
 635 **Protocol Population) (Study 4)<sup>a, b</sup>**

Strain	Post-vaccination GMT		GMT Ratio <sup>c</sup>	Seroconversion % <sup>d</sup>		SCR Difference <sup>e</sup>	Met both pre-defined non-inferiority criteria? <sup>f</sup>
	AFLURIA Quadrivalent N=1456	Comparator N=484	Comparator over AFLURIA Quadrivalent (95% CI)	AFLURIA Quadrivalent N=1456 (95% CI)	Comparator N=484 (95% CI)	Comparator minus AFLURIA Quadrivalent (95% CI)	
A(H1N1)	353.5 (n=1455 <sup>g</sup> )	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A(H3N2)	393.0 (n=1454 <sup>g</sup> )	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455 <sup>h</sup> )	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Phuket/3073/2013 (B Yamagata)	23.7 (n=1455 <sup>g</sup> )	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Brisbane/60/2008 (B Victoria)	54.6 (n=1455 <sup>g</sup> )	52.9 (n=483 <sup>h</sup> )	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483 <sup>h</sup> )	0.9 (-4.2, 6.1)	Yes

636 Abbreviations: CI, confidence interval; Comparator, Comparator quadrivalent influenza vaccine (Fluzone Quadrivalent  
 637 [Sanofi Aventis]); GMT (adjusted), geometric mean titer; SCR, seroconversion rate.

638 <sup>a</sup> NCT02914275

639 <sup>b</sup> The Per-Protocol Population comprised all subjects (6 through 35 months of age receiving one or two 0.25 mL doses and 36  
 640 through 59 months of age receiving one or two 0.5 mL doses) in the Evaluable Population who did not have any protocol  
 641 deviations that were medically assessed as potentially impacting on immunogenicity results.

642 <sup>c</sup> GMT Ratio = Comparator / AFLURIA QUADRIVALENT. Adjusted analysis model: Log-transformed Post-Vaccination HI  
 643 Titer=Vaccine + Age Cohort [6 through 35 months or 36 through 59 months] + Gender + Vaccination History [y/n] + Log-  
 644 transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Cohort\*Vaccine. The Age Cohort\*Vaccine  
 645 interaction term was excluded from the model fit for the strains A(H1N1), A(H3N2) and B/Yamagata as the interaction result  
 646 was non-significant (p>0.05). Least square means were back transformed.

647 <sup>d</sup> Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a  
 648 postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

649 <sup>e</sup> Seroconversion rate difference = Comparator SCR percentage minus AFLURIA QUADRIVALENT SCR percentage.

650 <sup>f</sup> Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the GMT ratio of Comparator /  
 651 AFLURIA QUADRIVALENT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI  
 652 on the difference between SCR Comparator – AFLURIA QUADRIVALENT should not exceed 10%.

653 <sup>g</sup> Subject 8400402-0073 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio  
 654 because the subject did not have information on all covariates (unknown prevaccination history).

655 <sup>h</sup> Subject 8400427-0070 had missing B/Victoria Antigen pre-vaccination titer.

656 <sup>i</sup> Subject 8400402-0074 had missing A/H3N2 post-vaccination titer.

657 **15 REFERENCES**

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**Package insert**666 **16 HOW SUPPLIED/STORAGE AND HANDLING**667 **16.1 How Supplied**

668 Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
Pre-Filled Syringe	33332-218-20	<ul style="list-style-type: none"><li>Ten 0.25 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-218-21]</li></ul>
Pre-Filled Syringe	33332-318-01	<ul style="list-style-type: none"><li>Ten 0.5 mL single-dose syringes fitted with a Luer-Lok™ attachment without needles [NDC 33332-318-02]</li></ul>
Multi-Dose Vial	33332-418-10	<ul style="list-style-type: none"><li>One 5 mL vial, which contains ten 0.5 mL doses [NDC 33332-418-11]</li></ul>

669 **16.2 Storage and Handling**

- 670 • Store refrigerated at 2–8°C (36–46°F).
- 671 • Do not freeze. Discard if product has been frozen.
- 672 • Protect from light.
- 673 • Do not use AFLURIA QUADRIVALENT beyond the expiration date printed on the
- 674 label.
- 675 • Between uses, return the multi-dose vial to the recommended storage conditions.
- 676 • Once the stopper of the multi-dose vial has been pierced the vial must be discarded within
- 677 28 days.

678 **17 PATIENT COUNSELING INFORMATION**

- 679 • Inform the vaccine recipient or guardian of the potential benefits and risks of
- 680 immunization with AFLURIA QUADRIVALENT.
- 681 • Inform the vaccine recipient or guardian that AFLURIA QUADRIVALENT is an
- 682 inactivated vaccine that cannot cause influenza but stimulates the immune system to
- 683 produce antibodies that protect against influenza, and that the full effect of the vaccine
- 684 is generally achieved approximately 3 weeks after vaccination.
- 685 • Instruct the vaccine recipient or guardian to report any severe or unusual adverse
- 686 reactions to their healthcare provider.
- 687 • Encourage women who receive AFLURIA QUADRIVALENT while pregnant to enroll
- 688 in the pregnancy registry. Pregnant women can enroll in the pregnancy registry by
- 689 calling 1-855-358-8966 or sending an email to Seqirus at
- 690 us.medicalinformation@seqirus.com.
- 691 • Provide the vaccine recipient Vaccine Information Statements prior to immunization.
- 692 These materials are available free of charge at the Centers for Disease Control and
- 693 Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).
- 694 • Instruct the vaccine recipient that annual revaccination is recommended.



**Package insert**

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695 Manufactured by:  
696 **Seqirus Pty Ltd.** Parkville, Victoria, 3052, Australia  
697 U.S. License No. 2044

698 Distributed by:  
699 **Seqirus USA Inc.** 25 Deforest Avenue, Summit, NJ 07901, USA  
700 1-855-358-8966

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