Supplemental Data

Supplemental Table S1a. Local and systemic reactions after first and second doses in participants with a history of food and/or drug allergies

	First dose (*n* = 19,792)		Second dose (*n* = 19,592)	
	With a history of food and/or drug allergies *n* = 806, *n* (%)	Without a history of food and/or drug allergies *n* = 18,986, *n* (%)	With a history of food and/or drug allergies *n* =791, *n* (%)	Without a history of food and/or drug allergies *n* =18,801, *n* (%)
Local reactions	758 (94.0)	17,558 (92.5)	726 (91.8)	17,039 (90.6)
Redness	143 (17.7)	2,599 (13.7)	172 (21.6)	2,952 (15.7)
Swelling	146 (18.1)	2,324 (12.2)	152 (19.2)	2,606 (13.9)
Induration	128 (15.9)	1,978 (10.4)	128 (16.2)	1,844 (9.8)
Pain	746 (92.6)	17,457 (91.9)	710 (89.8)	16,824 (89.5)
Warmth	151 (18.7)	2,393 (12.6)	221 (27.9)	3,501 (18.6)
Pruritus	92 (11.4)	1,493 (7.9)	146 (18.5)	2,189 (11.6)
Systemic reactions	390 (48.4)	6,688 (35.2)	652 (82.4)	14,107 (75.0)
Headache	246 (30.5)	3,979 (21.0)	485 (61.3)	9,926 (52.8)
Malaise	275 (34.1)	4,309 (22.7)	607 (76.7)	12,871 (68.5)
Rhinorrhea	128 (15.9)	1,892 (10.0)	155 (19.6)	2,674 (14.2)
Fever ≥ 37.5 ℃	39 (4.8)	615 (3.2)	338 (42.7)	7,132 (37.9)
Fever ≥ 38.0 ℃	8 (1.0)	166 (0.9)	193 (24.4)	3,986 (21.2)

Local reactions include redness, swelling, induration, pain, warmth, and pruritus. Systemic reactions include headache, malaise, and rhinorrhea.

Allergies include 1) food allergy to wheat, egg, shrimp, and crab, among others, and 2) drug allergy to penicillin, contrast media, and fluoroquinolones, among others.

Supplemental Table S1b. Local and systemic reactions after the first and second doses in participants with a history of asthma and/or atopic disorders

	First dose (*n* = 19,792)		Second dose (*n* = 19,592)	
	With a history of asthma and/or atopic disorders *n* = 2,370, *n* (%)	Without a history of asthma and/or atopic disorders *n* = 17,422, *n* (%)	With a history of asthma and/or atopic disorders *n* = 2,335, *n* (%)	Without a history of asthma and/or atopic disorders *n* = 17,257, *n* (%)
Local reactions	2,239 (94.5)	16,077 (92.3)	2,150 (92.1)	15,615 (90.5)
Redness	371 (15.7)	2,371 (13.6)	428 (18.3)	2,695 (15.6)
Swelling	355 (15.0)	2,115 (12.1)	391 (16.7)	2,367 (13.7)
Induration	317 (13.4)	1,789 (10.3)	299 (12.8)	1,673 (9.7)
Pain	2,225 (93.9)	15,978 (91.7)	2,119 (90.7)	15,415 (89.3)
Warmth	348 (14.7)	2,196 (12.6)	517 (22.1)	3,205 (18.6)
Pruritus	222 (9.4)	1,363 (7.8)	306 (13.1)	2,029 (11.8)
Systemic reactions	997 (42.1)	6,081 (34.9)	1,863 (79.8)	12,896 (74.7)
Headache	589 (24.9)	3,636 (20.9)	1,370 (58.7)	9,041 (52.4)
Malaise	662 (27.9)	3,922 (22.5)	1,690 (72.4)	11,788 (68.3)
Rhinorrhea	310 (13.1)	1,710 (9.8)	432 (18.5)	2,397 (13.9)
Fever ≥ 37.5 ℃	101 (4.3)	553 (3.2)	976 (41.8)	6,494 (37.6)
Fever ≥ 38.0 ℃	17 (0.7)	157 (0.9)	547 (23.4)	3,632 (21.0)

Local reactions include redness, swelling, induration, pain, warmth, and pruritus. Systemic reactions include headache, malaise, and rhinorrhea.

Supplemental Table S2a. FDA evaluation criteria for Local Reactions and Fever

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/Redness *	2.5-5 cm	5.1-10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Fever (°C) ***	38.0-38.4	38.5-38.9	39.0-40	> 40

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

*** Oral temperature; no recent hot or cold beverages or smoking. Fever is defined as a body temperature of 38℃ or higher in foreign countries.

Excerpt criteria statements from the "Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007",

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical

Supplemental Table S2b. Japan evaluation criteria for Local Reactions and Fever

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Serious or Life Threatening (Grade 4)
Pain	Feels pain, but does not interfere with activity	Used single-dose oral analgesics for pain	Used multiple-dose oral analgesics for pain	
Redness	Smaller than 2.0 cm in diameter	2.0-5.0 cm in diameter	Larger than 2.0-5.0 cm in diameter	Severe or persistent ulcer, or necrosis, or requires surgery
Swelling	Smaller than 2.0 cm in diameter	2.0-5.0 cm in diameter	Larger than 2.0-5.0 cm in diameter	
Induration	Smaller than 2.0 cm in diameter	2.0-5.0 cm in diameter	Larger than 2.0-5.0 cm in diameter	

Fever is divided into two groups, body temperature ≥ 37.5 °C and ≥ 38.0 °C.

Excerpt criteria statements from a document of the investigator-initiated clinical trial for a new influenza vaccine in 2006.