VAP00027
Immunogenicity and Safety of Quadrivalent Recombinant Influenza Vaccine (RIV4) in Children and Adolescents Aged 9 to 17 Years and Adults Aged 18 to 49 Years

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For the Advisory Committee of Immunization Practices (ACIP) Influenza Working Group

sanofi

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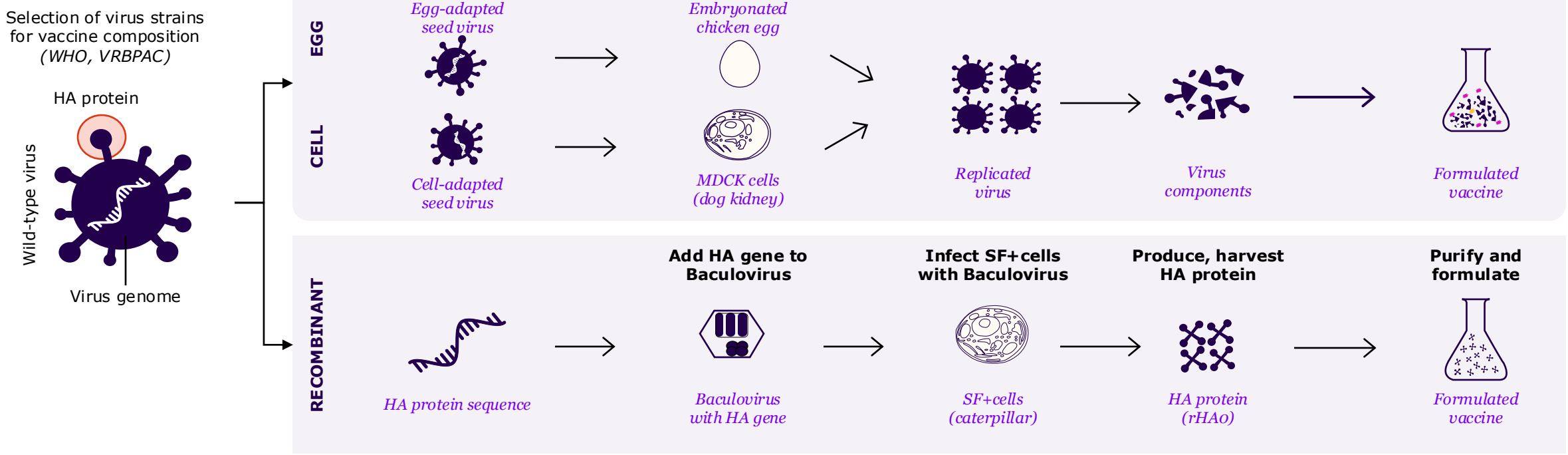
Presenter’s disclosures

Pedro Folegatti, MD DTM&H MSc Dphil

is a full-time employee of Sanofi and may hold shares in the company

Recombinant technology ensures sequence integrity of antigens consistent with WHO-identified strains for seasonal vaccine formulation



RIV is produced using **the exact genetic sequence** of the HA protein derived from the WHO selected influenza strains; **no live virus** is used in the manufacturing process

In this novel production platform, rHA is expressed in insect cells using **BEVS**

rHA molecules are subsequently **extracted** from the infected insect cells and **purified** from the clarified cell extract before formulation

BEVS, baculovirus expression vector system; CBER, Center for Biologics Evaluation and Research; HA, hemagglutinin; MDCK, Madin-Darby Canine Kidney; NIBSC, National Institute for Biological Standards and Control; rHA, recombinant haemagglutinin; rHA0, recombinant influenza virus hemagglutinins; SF+, spodoptera frugiperda (fall armyworm)-positive; TGA, Therapeutic Goods Administration; VRBPAC, Vaccines and Related Biological Products Advisory Committee; WHO, World Health Organization.

Reference: Arunachalam AB, *et al*. *NPJ Vaccines*.2021;6:144.

Safety and efficacy of RIV in clinical studies and real-world data

Clinical data (RIV4)

- 2 Phase III studies
  - Adults *50 years of age and older*[1] during a season with predominantly antigenically drifted H3N2 strains
    - RIV4 provided *30%* (95% CI, 10 to 47) *to 43%* (95% CI, 21 to 59) *enhanced protection* against influenza disease vs IIV4
  - Adults *18 to 49 years of age*[2]
    - Non-inferior to the same IIV4 comparator vaccine for 3 of 4 influenza (SC rates and GMTs)

First license and recommendation

- *RIV3* was first licensed in the US in 2013, followed by approval of RIV4 *in 2016 for adults ≥18 years of age*
- ACIP recommends use of recombinant influenza vaccination from 2013[3]

Real-world safety data:

- *~38 million doses of RIV3 and RIV4 distributed* cumulatively (Sanofi internal data as of 31 Jan 2024)
- Established clinical safety profile, well tolerated with *no safety concerns*[4]

GMT, geometric mean titers; IIV4, quadrivalent inactivated influenza vaccine; RIV3, trivalent recombinant influenza vaccine; RIV4, quadrivalent recombinant influenza vaccine; SC, seroconversion; US, United States

References: 1. Dunkle LM, *et al*. *N Engl J Med*. 2017;376(25):2427-36. **2.** Dunkle LM, *et al*. *J Infect Dis.* 2017;216(10):1219-26. **3.** Prevention and Control of Influenza with Vaccines: Interim Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2013. Accessed August 2024. 4. Flublok® Influenza Vaccine. Product Insert.

Trial design (1/2)

Study design

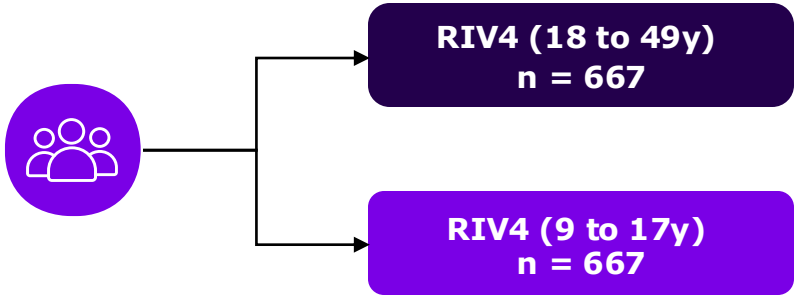
- Phase III parallel, multi-center, open-label, non-randomized
- *Immuno-bridging* study
- *36 centers* in Europe (Spain, Poland, Czech Republic) and the United States
- *2022/2023* northern hemisphere influenza

Study population:

- Healthy children & adults; n=1334
- **Aged 9-49 years**

Intervention:

- To receive a single dose of:



Objectives & endpoints

Primary:

- To demonstrate the non-inferior HAI immune response of RIV4 for 4 strains in participants aged 9 to 17 years vs participants aged 18 to 49 years
  - HAI titers at D29
  - Seroconversion rates

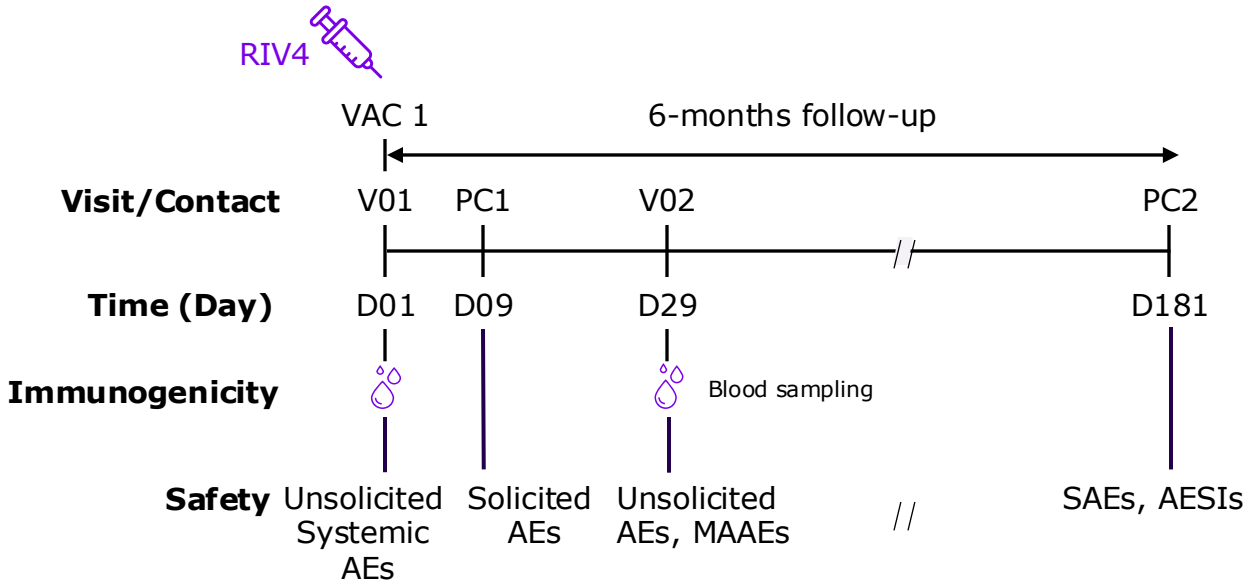
Secondary:

- To describe the safety profile of RIV4 vaccine in all participants and by age group
  - Solicited & Unsolicited AEs
  - MAAEs
  - SAEs and AESIs
- To describe HAI immune responses induced by RIV4

Ab, antibody; AE, adverse event; AESI, adverse events of special interest; HAI, hemagglutination inhibiting antibody; MAAEs, medically attended adverse events; NAb, neutralizing antibody; RIV4, recombinant influenza vaccine quadrivalent; SAEs, serious adverse events; US, United States.

Trial design (2/2)

Graphical Study design



Key exclusion criteria

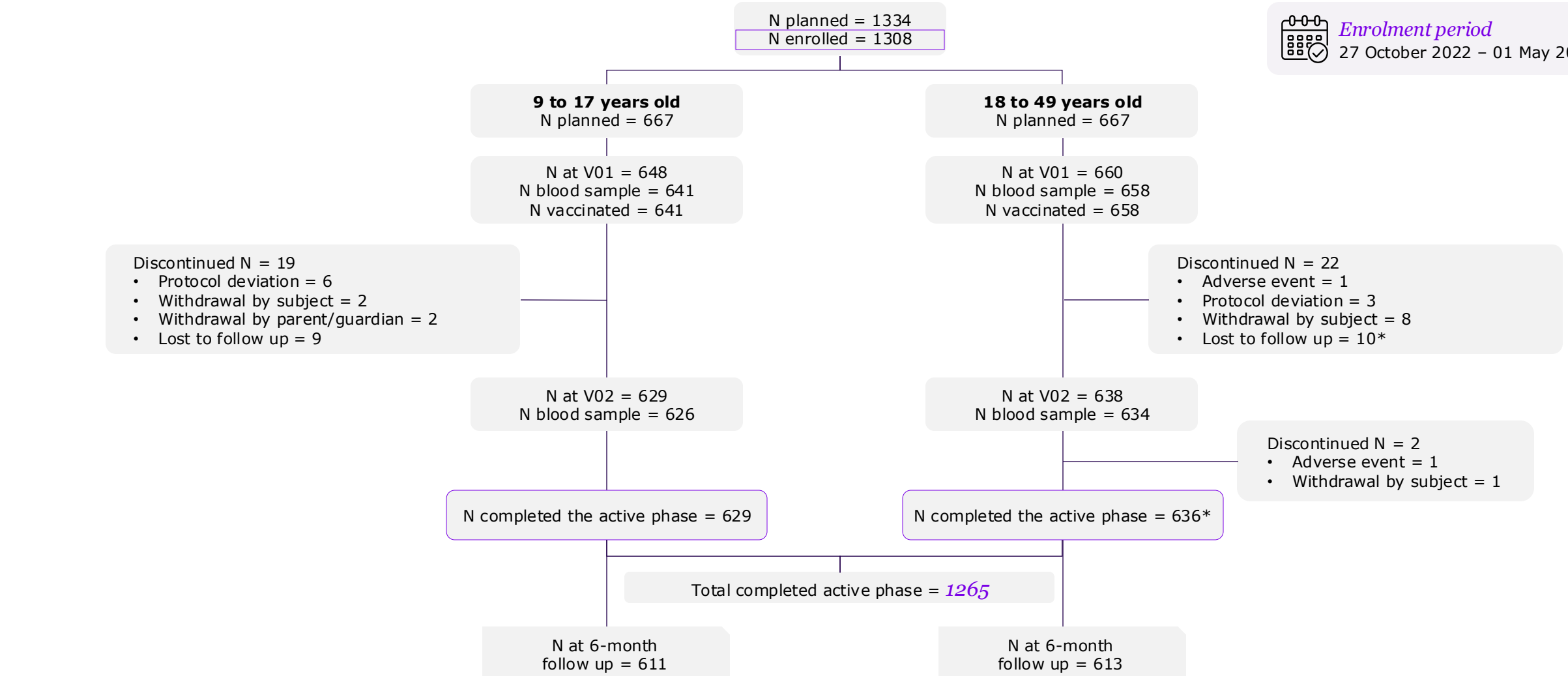
- Receipt of any vaccine in the 4 weeks before or after enrolment
  - COVID-19 vaccines were allowed within 2 weeks (before or after enrolment)
- Influenza vaccine receipt in the 6 months preceding enrolment

Statistical considerations

- Overall study power of 80%
  - type II error <20% for the 8 NI tests (GMTs and SC on 4 strains)
- Non-Inferiority Margin
  - Lower bound of the two-sided 95% CI of the ratio of GMTs between groups >0.667 for each strain
  - Lower bound of the two-sided 95% CI of seroconversion rates ≥-10% for the 4 strains

AEs, adverse events; AESIs, adverse events of special interest; CI, confidence interval; D, Day; PC, Phone Call; GMTs, geometric mean titers; MAAEs, medically attended adverse event; NI, non-inferiority; RIV4, quadrivalent recombinant influenza vaccine; SAEs, serious adverse events; VAC, vaccination

Participant disposition



N, number of participants; V, visit

Baseline Characteristics

Overall, there were more *females* than males (653 females [53.7%] and 562 males [46.3%]) and the male/female ratio was 0.86

The overall mean age of participants was *23.5 years (± 12.5)*

- *13 years (±2.48) in the 9-17s and 34 years in the 18-49s (±9.20)*

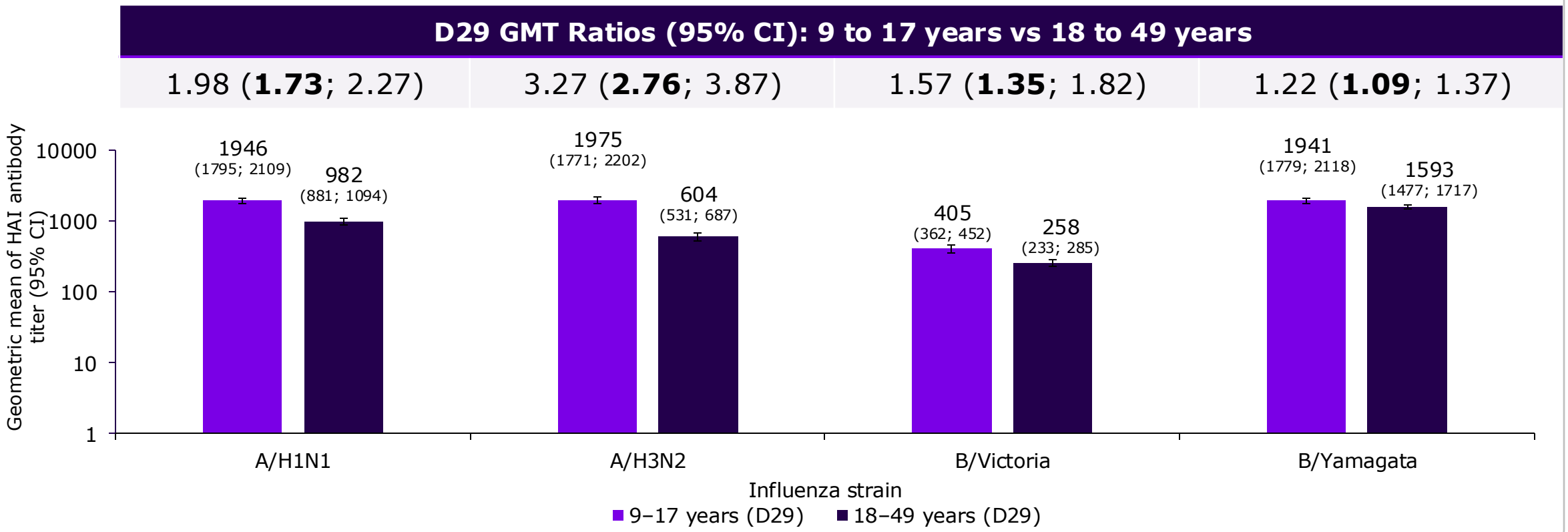
Most participants were *White* (77.4%), followed by *Black or African American* participants (18.9%)

Most participants (87.0%) were of *"Not Hispanic or Latino"* ethnicity

Primary objective met
Non-inferiority of immune response: GMTs at Day 29

- Non-inferiority of RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age was demonstrated for GMT ratios of all *4 strains*

GMTs at D29 after vaccination of 9 to 17 years vs 18 to 49 years



CI, confidence interval; GMT, geometric mean titers; HAI, hemagglutination inhibition; RIV4, quadrivalent recombinant influenza vaccine

Primary objective met
Non-inferiority of immune response: Seroconversion

- Non-inferiority of RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age was demonstrated for *seroconversion* of all *4 strains of influenza*

Immunogenicity primary objective: Non-inferiority of immune response in terms of seroconversion rates after vaccination of 9 to 17 years vs 18 to 49 years

	9 to 17 years minus 18 to 49 years		
Antigen/ strain	**Difference (%)**	**(95% CI)**	**Non-inferiority[§]**
A/H1N1	1.92	(-2.78; 6.62)	Y
A/H3N2	-0.59	(-4.41; 3.23)	Y
B/Victoria	3.29	(-1.57; 8.14)	Y
B/Yamagata	14.3	(9.17; 19.3)	Y

M, number of participants with available data for the considered endpoint; N, total number of participants included in the study; [§]Non-inferiority for SC rates is demonstrated if the lower limit of the 2-sided 95% CI is ≥-10% for the 4 strains

CI, confidence interval; RIV4, quadrivalent recombinant influenza vaccine; SC, seroconversion

Safety overview

During the study, 10 participants (0.8%) reported at least 1 SAE and 66 participants (5.1%) reported at least 1 MAAE. None of the SAEs and MAAEs were considered as related to the vaccine

No deaths and no AESIs were reported during the study

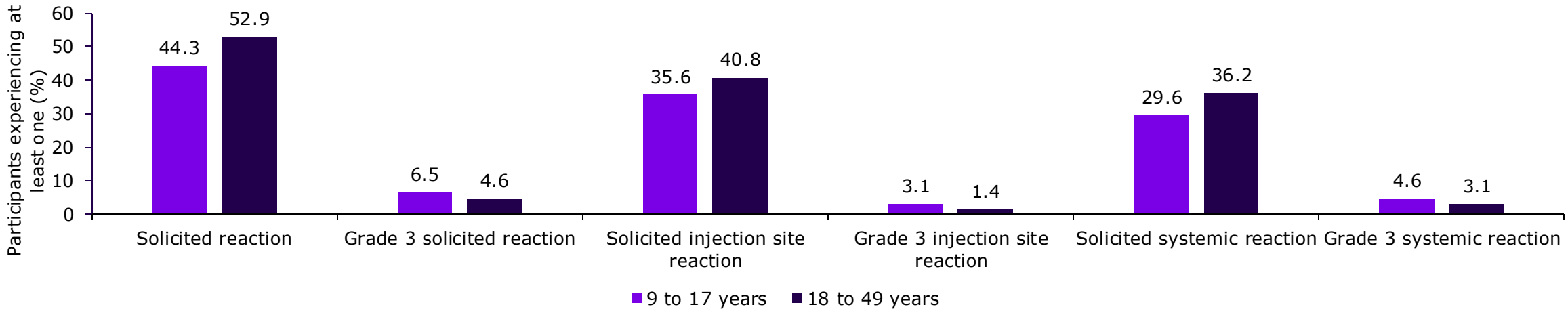
No substantial differences in safety profile was observed between groups

AR, adverse reactions; AESI, adverse event of special interest; CI, confidence interval; MAAE, medically attended adverse event; SAE, serious adverse event

Solicited reactions within 7 days of vaccinations

- Most solicited reactions were of Grade 1 or Grade 2 intensity, started within D1-D4, and resolved (spontaneously) after 1-3 days
- Within 28 days of vaccination, *0.9% of participants* in both age groups experienced at least 1 unsolicited injection site AR rated as Grade 3
- Grade 3 solicited injection site reactions consisted predominantly of *swelling* in 9 participants of 9 to 17 years group (1.5%) and *induration* in 5 participants of 18 to 49 years (0.8%)
- Grade 3 solicited systemic reactions consisted predominantly of *headache* and *malaise* reported by 16 participants (2.6%, each) in 9 to 17 years group. Grade 3 *malaise* was reported by 10 participants (1.6%) in 18 to 49 years groups

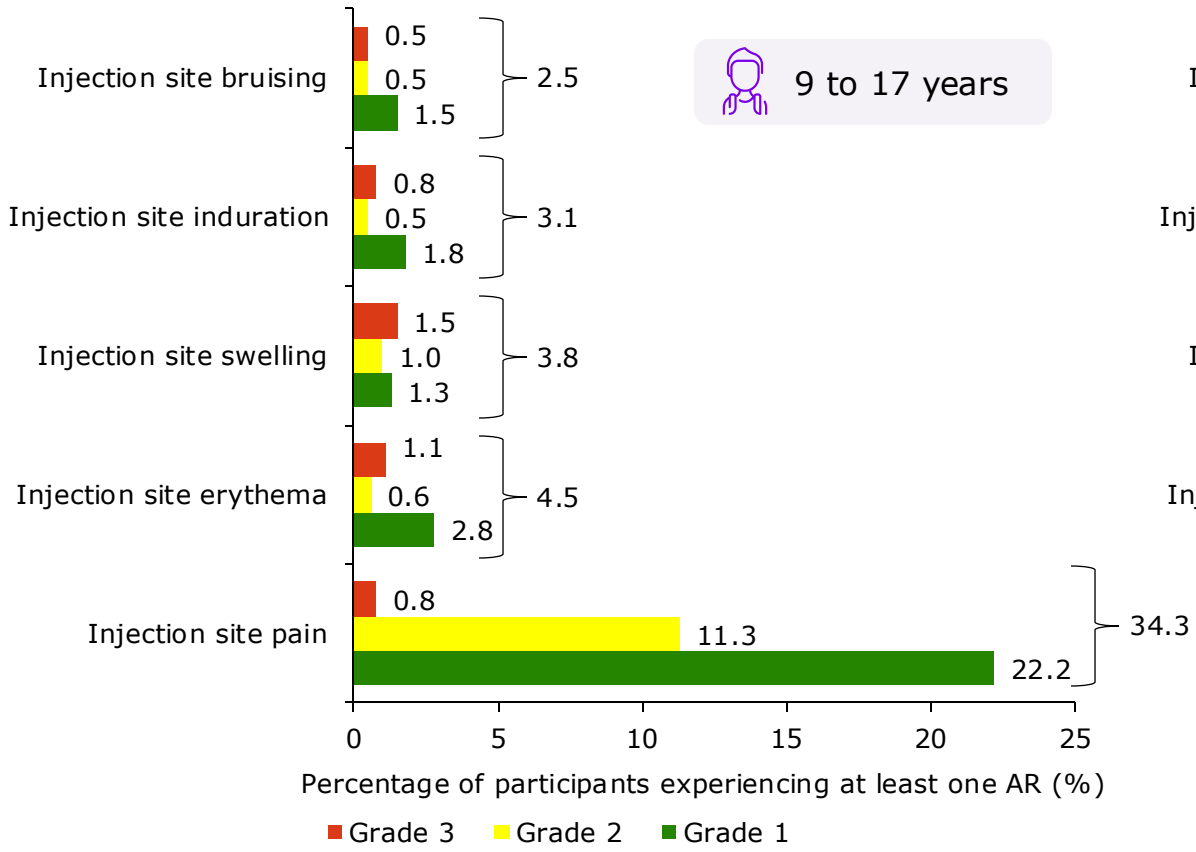
Summary of solicited reactions within 7 days after vaccine injection

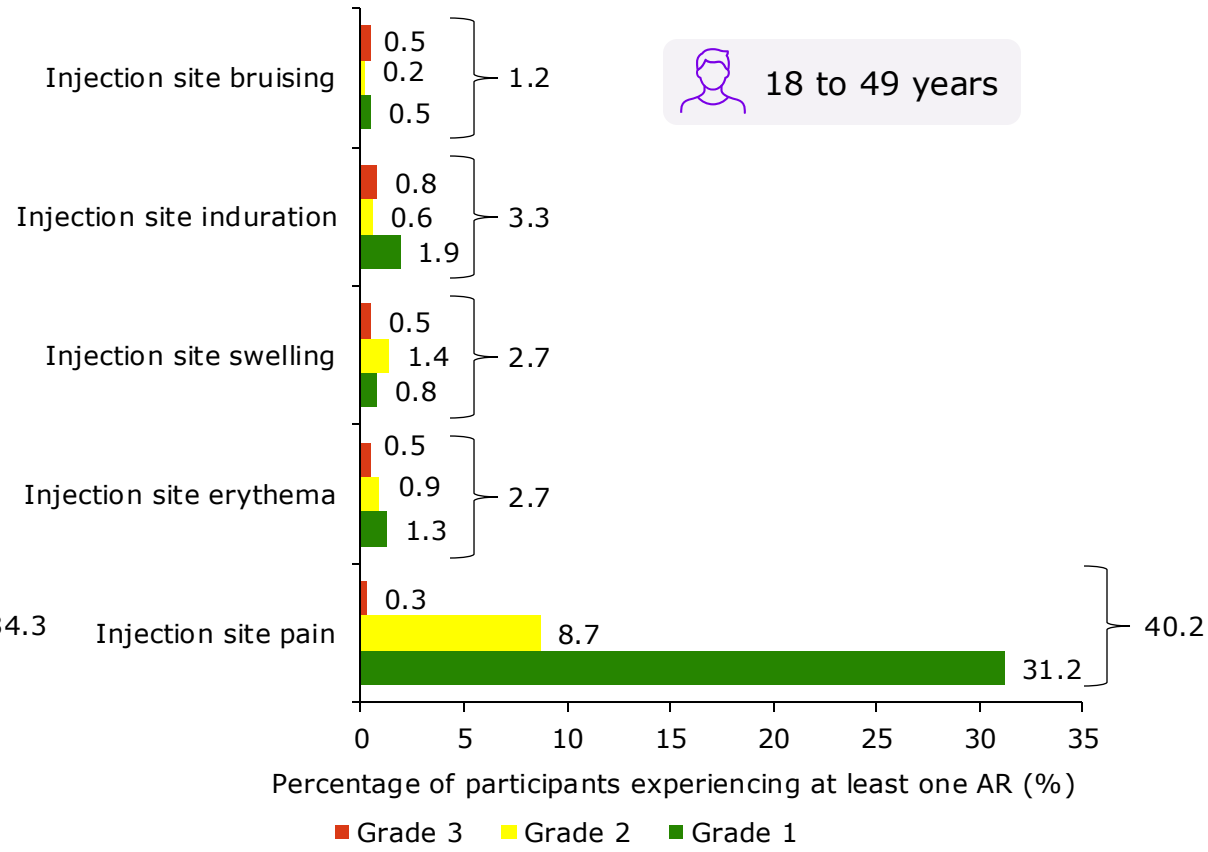


AR, adverse reaction; D, day

Solicited injection site reactions after vaccine injection

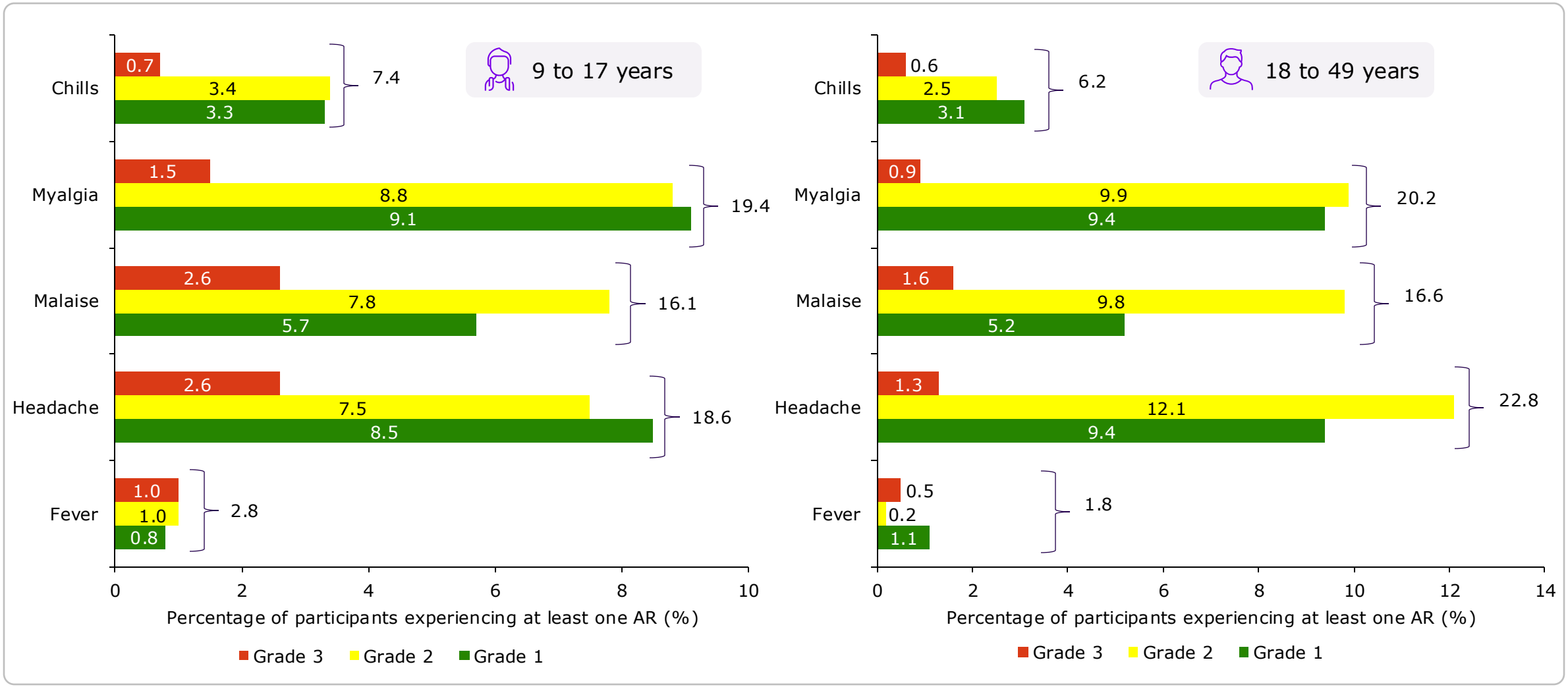
Summary of solicited injection site reactions after vaccination





AR, adverse reaction

Solicited systemic reactions after vaccine injection



AR, adverse reaction

13 SAEs reported in the study:

All events classified as unrelated by Sponsor and Investigator

18-49 years of age

- 7 participants reported 9 SAEs
- Within 28 days
  - Major Depression and Intentional Overdose*
  - Gastric Cancer Recurrent
  - Suicidal Ideation*
  - Seizure^
  - Acute Respiratory Failure and Overdose
- During Follow-up
  - Kidney Infection
  - Obstructive Pancreatitis

9-17 years of age

- 3 participants reported 4 SAEs
- Within 28 days
  - Suicidal Ideation and worsening of Suicidal Ideation*
- During Follow-up
  - Suicidal Ideation*
  - Spinal Fracture (post trauma)

*All participants reporting Psychiatric Disorders SAEs had past medical history of mental health disorders prior to enrollment
^Neurology review attributed event to amphetamine use, sleep deprivation and metabolic disorder

Conclusion

- RIV induced a *robust immune response* in participants 9 to 17 years and 18 to 49 years
- These findings are consistent with previous research[1-5]
- *Non-Inferiority* of HAI immune response induced in those 9 to 17 years of age versus those 18 to 49 years of age as assessed by GMTs and SC rates at D29 was *met for all 4 influenza strains*
- The *safety profile of the RIV4 vaccine was comparable in both age groups*

D, Day; GMT, geometric mean titer; HAI, hemagglutination inhibition; NI, non-inferiority; RIV, recombinant influenza vaccine; SC, seroconversion

References: 1. Hasio A, *et al*. *N Engl J Med.* 2023;389:2245-2255. **2.** Zimmerman RK, *et al*. *Vaccine*. 2023;41(35):5134-5140. **3.** Dunkle LM *et al*. *N Engl J Med.* 2017;376:2427-2436. **4.** Dunkle *et al*. *Pediatrics*.2018;141(5):3021. **5.** James C King *et al*. *Vaccine*. 2009 Nov 5;27(47):6589-94.

Funding

Funding

This study was funded and sponsored by Sanofi

Thank you

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Baseline demographics by age group

	9 to 17 years (N=609)	18 to 49 years (N=606)	All (N=1215)
Sex, n (%)			
Male	316 (51.9)	246 (40.6)	562 (46.3)
Female	293 (48.1)	360 (59.4)	653 (53.7)
Age, mean (SD), Year	13.0 (2.48)	34.1 (9.20)	23.5 (12.5)
Racial origin, n (%)			
American Indian or Alaska Native	4 (0.7)	0	4 (0 .3)
Asian	1 (0.2)	6 (1.0)	7 (0 .6)
Black or African American	140 (23.0)	90 (14.9)	230 (18.9)
Native Hawaiian or Other Pacific Islander	1 (0.2)	2 (0.3)	3 (0.2)
White	447 (73.4)	493 (81.4)	940 (77.4)
Not Reported	0	2 (0.3)	2 (0.2)
Unknown	1 (0.2)	1 (0.2)	2 (0.2)
Multiple	15 (2.5)	12 (2.0)	27 (2.2)
Ethnicity, n (%)			
Hispanic or Latino	107 (17.6)	35 (5.8)	142 (11.7)
Not Hispanic or Latino	494 (81.1)	563 (92.9)	1057 (87.0)
Not reported	7 (1.1)	8 (1.3)	15 (1.2)
Unknown	1 (0.2)	0	1 (<0.1)

n, number of study participants fulfilling the item listed; N, total number of participants included in the study; SD, standard deviation

HAI antibody titers

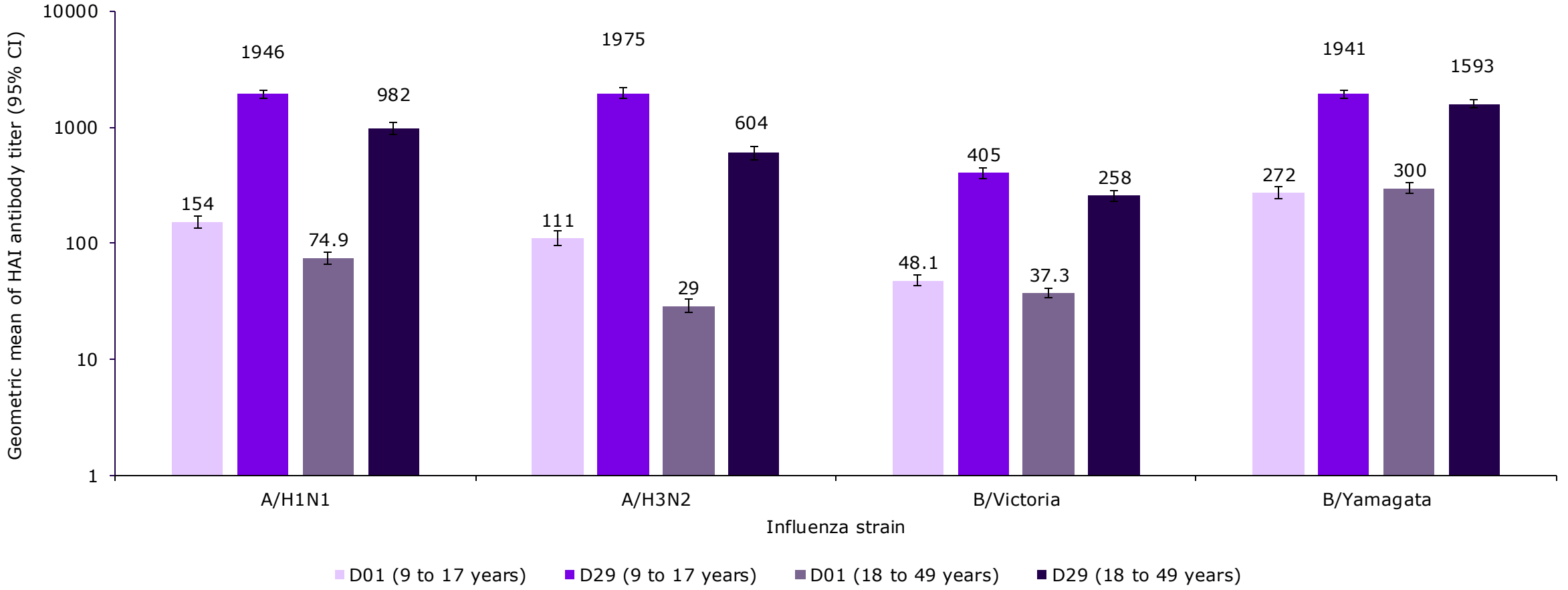
- At baseline, the HAI Ab GMTs were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for the A/H1N1, A/H3N2, B/Victoria lineage, and were similar in both age groups for B/Yamagata lineage strain
- At D29, the HAI Ab GMTs increased in both age groups and were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for all virus strains

GMTs at baseline and D29 after vaccination of 9 to 17 years vs 18 to 49 years

	HAI Ab GMTs (95% CI) at baseline		HAI Ab GMTs (95% CI) at D29	
Antigen/ strain	**9 to 17 years**	**18 to 49 years**	**9 to 17 years**	**18 to 49 years**
A/H1N1	154 (137; 173)	74.9 (65.8; 85.1)	1946 (1795; 2109)	982 (881; 1094)
A/H3N2	111 (95.4; 128)	29.0 (25.7; 32.8)	1975 (1771; 2202)	604 (531; 687)
B/Victoria	48.1 (43.0; 53.8)	37.3 (34.0; 40.9)	405 (362; 452)	258 (233; 285)
B/Yamagata	272 (243; 305)	300 (269; 335)	1941 (1779; 2118)	1593 (1477; 1717)

Ab, antibody; CI, confidence interval; D, day; GMT, geometric mean titer; GMTRs, HAI Ab GMT ratios; HAI, hemagglutination inhibition

Geometric mean of HAI antibody titer



CI, confidence interval; D, day; HAI, hemagglutination inhibition

Non-inferiority of immune response: GMTs at Day 29

- Non-inferiority of RIV4 in participants 9 to 17 years of age versus participants 18 to 49 years of age was demonstrated for all *4 ratios of GMTs*

GMTs at D29 after vaccination of 9 to 17 years vs 18 to 49 years

	9 to 17 years (N=609)			18 to 49 years (N=606)			9 to 17 years / 18 to 49 years		
Antigen/ strain	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**GMT Ratio**	**(95% CI)**	**Non-inferiority§**
A/H1N1	609	1946	(1795; 2109)	606	982	(881; 1094)	l.98	(1.73; 2.27)	Y
A/H3N2	609	1975	(1771; 2202)	606	604	(531; 687)	3.27	(2.76; 3.87)	Y
B/Victoria	609	405	(362; 452)	606	258	(233; 285)	1.57	(1.35; 1.82)	Y
B/Yamagata	609	1941	(1779; 2118)	606	1593	(1477; 1717)	1.22	(1.09; 1.37)	Y

; §Non-inferiority is concluded if the lower limit of the two-sided 95% CI of the ratio of GMTs between groups (9 to 17 years/18 to 49 years) is > 0.667 for each strain

CI, confidence interval; D, day; GMT, geometric mean titers; M, number of participants with available data for the considered endpoint; N, total number of participants; RIV4, quadrivalent recombinant influenza vaccine

Individual HAI antibody titer ratios

- The post-vaccination GMTRs (D29/D01) were similar in both age groups for A/H1N1, A/H3N2, and B/Victoria lineage strains and were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for B/Yamagata lineage strain

	GMTRs (95% CI)	
Antigen/ strain	**9 to 17 years**	**18 to 49 years**
A/H1N1	12.7 (11.1; 14.5)	13.1 (11.4; 15.0)
A/H3N2	17.9 (15.7; 20.3)	20.8 (18.4; 23.6)
B/Victoria	8.41 (7.55; 9.37)	6.91 (6.25; 7.64)
B/Yamagata	**7.13 (6.46; 7.87)**	5.31 (4.79; 5.88)

CI, confidence interval; D, day; GMT, geometric mean titer; GMTRs, HAI Ab GMT ratios; HAI, hemagglutination inhibition

HAI antibody titer ≥40 (1/dil) and HAI antibody titer ≥10 (1/dil)

- At baseline, the percentages of participants with HAI Ab titer ≥40 (1/dil) and HAI antibody titer ≥10 (1/dil) were higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for the A/H1N1 and A/H3N2, and were similar in both age groups for B/Victoria and B/Yamagata lineage strains
- At D29, the percentages of participants with HAI Ab titer ≥40 (1/dil) and HAI antibody titer ≥10 (1/dil) increased for all 4 virus strains and were high in both age groups

		D01		D29	
	Antigen/ strain	**9 to 17 years**	**18 to 49 years**	**9 to 17 years**	**18 to 49 years**
Percentage of participants with HAI antibody titer ≥ 40 (95% CI)	A/H1N1	87.2 (84.3; 89.7)	71.8 (68.0; 75.3)	99.7 (98.8; 100)	97.5 (96.0; 98.6)
	A/H3N2	74.7 (71.1; 78.1)	45.0 (41.0; 49.1)	99.0 (97.9; 99.6)	95.0 (93.0; 96.6)
	B/Victoria	61.4 (57.4; 65.3)	59.8 (55.8; 63.8)	95.6 (93.6; 97.1)	97.0 (95.3;98.2)
	B/Yamagata	93.1 (90.8; 95.0)	95.2 (93.2; 96.8)	99.5 (98.6; 99.9)	100 (99.4; 100)
Percentage of participants with HAI antibody titer ≥ 10 (95% CI)	A/H1N1	97.0 (95.4; 98.2)	89.8 (87.1; 92.1)	100 (99.4;100)	99.3 (98.3; 99.8)
	A/H3N2	89.2 (86.4; 91.5)	77.7 (74.2; 81.0)	100 (99.4; 100)	99.7 (98.8; 100)
	B/Victoria	92.1 (89.7; 94.1)	91.7 (89.2; 93.8)	99.5 (98.6; 99.9)	99.8 (99.1; 100)
	B/Yamagata	97.9 (96.4; 98.9)	99.5 (98.6;99.9)	100 (99.4; 100)	100 (99.4; 100)

CI, confidence interval; D, day; HAI, hemagglutination inhibition

Seroconversion

- The SC rates were similar in both age groups for A/H1N1, A/H3N2, B/Victoria lineage strains and higher in participants 9 to 17 years of age than in participants 18 to 49 years of age for B/Yamagata lineage strain

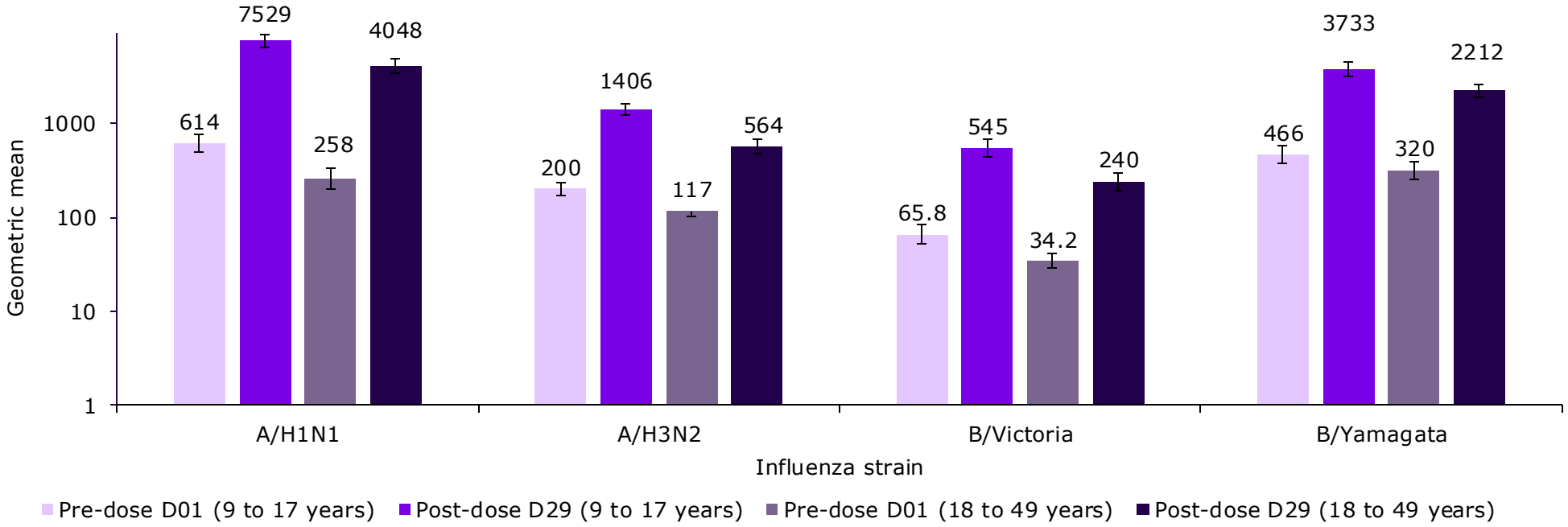
	SC (% [95% CI])	
Antigen/ strain	**9 to 17 years**	**18 to 49 years**
A/H1N1	78.3 (74.8; 81.5)	76.4 (72.8; 79.7)
A/H3N2	86.5 (83.6; 89.1)	87.1 (84.2; 89.7)
B/Victoria	76.8 (73.3; 80.1)	73.6 (69.8; 77.0)
B/Yamagata	77.2 (73.6; 80.5)	62.9 (58.9; 66.7)

SC, seroconversion

Neutralizing Ab titers (SN assay) at D01 and D29 after vaccination

- The post-vaccination SN Ab GMTRs were *similar in both age groups for A/H1N1, B/Victoria lineage,* and *B/Yamagata lineage* strains
- It was *higher* in participants *9 to 17 years* of age than in participants 18 to 49 years of age for *A/H3N2 strain*

GMTRs (D29/D01) per strain and age group							
12.2 (9.4; 15.8)	15.5 (11.8; 20.3)	7.0 (5.9; 8.3)	4.8 (4.1; 5.6)	8.3 (6.7; 10.3)	7.1 (5.8; 8.6)	8.0 (6.5; 9.8)	6.8 (5.5; 8.5)



Ab, antibody; D, day; GMTR, geometric mean titer ratio; HAI, hemagglutination inhibition; SN, seroneutralization

Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by age subgroup

Table 5: Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by age subgroup

		9 to 11 years (N=186)			12 to 17 years (N=423)			18 to 34 years (N=303)			35 to 49 years (N-303)		
Strain	**Time Point**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
A/H1N1	V01 (D01)	186	139	(112; 173)	423	160	(139; 184)	303	102	(85.2; 122)	303	55.0	(46.0; 65.7)
	V02 (D29)	186	2101	(1786; 2472)	423	1881	(1717; 2062)	303	1499	(1313; 1711)	303	643	(549; 753)
A/H3N2	V01 (D01)	186	152	(117; 198)	423	96.1	(80.6; 115)	303	27.7	(23.2; 33.0)	303	30.4	(25.6; 36.0)
	V02 (D29)	186	2550	(2129; 3055)	423	1765	(1543; 2019)	303	644	(536; 775)	303	567	(473; 679)
B/Victoria	V01 (D01)	186	36.3	(30.4; 43.4)	423	54.4	(47.4; 62.6)	303	36.5	(32.0; 41.7)	303	38.1	(33.6; 43.3)
	V02 (D29)	186	308	(248; 383)	423	456	(402; 517)	303	270	(232; 315)	303	247	(216; 281)
B/Yamagata	V01 (D01)	186	169	(136; 210)	423	336	(296; 381)	303	435	(377; 501)	303	207	(178; 242)
	V02 (D29)	186	1339	(1101; 1627)	423	2286	(2094; 2496)	303	2211	(2026; 2414)	303	1147	(1026; 1282)

Ab, antibody; CI, confidence interval; D, day; GM, geometric mean; HAI, hemagglutination inhibition; M, number of participants with available data for the considered endpoint; V, visit

Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by priming status

Table 17: Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by priming status

		9 to 17 years						18 to 49 years					
		Previously unvaccinated* (N-425)			Previously vaccinated† (N=180)			Previously unvaccinated* (N=409)			Previously vaccinated† (N=193)		
Strain	**Time Point**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**	**M**	**GM**	**(95% CI)**
A/H1N1	V01 (D01)	425	123	(107; 142)	180	255	(208; 313)	409	50.1	(43.2; 58.1)	193	168	(137; 207)
	V02 (D29)	425	2276	(2072; 2501)	180	1351	(1169; 1561)	409	1152	(1004; 1322)	193	698	(591; 824)
A/H3N2	V01 (D01)	425	103	(85.5; 123)	180	135	(105; 173)	409	24.7	(21.3; 28.5)	193	39.9	(31.9; 49.7)
	V02 (D29)	425	2054	(1804; 2339)	180	1838	(1502; 2250)	409	648	(553; 759)	193	518	(414; 647)
B/Victoria	V01 (D01)	425	37.7	(32.9; 43.1)	180	86.7	(72.8; 103)	409	29.8	(26.7; 33.1)	193	59.0	(50.6; 68.7)
	V02 (D29)	425	399	(348; 457)	180	422	(348; 512)	409	270	(238; 306)	193	236	(199; 280)
B/Yamagata	V01 (D01)	425	215	(187; 247)	180	474	(401; 560)	409	240	(210; 275)	193	478	(406; 564)
	V02 (D29)	425	1995	(1785; 2229)	180	1803	(1575; 2064)	409	1784	(1629; 1955)	193	1266	(1113; 1441)

CI, confidence interval; D, day; GM, geometric mean; HAI, hemagglutination inhibition; M, number of participants with available data for the considered endpoint; V, visit

Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by baseline seropositivity

Table 21: Summary of geometric mean of HAI antibody titer at baseline (D01) and D29 by baseline seropositivity

		9 to 17 years						18 to 49 years					
		Baseline seropositive for			Baseline seronegative for			Baseline seropositive for			Baseline seronegative for		
Strain	Time Point	M	GM	(95% CI)	M	GM	(95% CI)	M	GM	(95% CI)	M	GM	(95% CI)
A/H1N1	V01 (D01)	591	170	(153; 190)	18	5.00	(NC; NC)	544	102	(90.6; 115)	62	5.00	(NC; NC)
	V02 (D29)	591	1989	(1839; 2152)	18	941	(391; 2265)	544	1181	(1071; 1303)	62	193	(123; 305)
A/H3N2	V01 (D01)	543	161	(141; 184)	66	5.00	(NC; NC)	471	48.0	(42.4; 54.4)	135	5.00	(NC; NC)
	V02 (D29)	543	2518	(2289; 2770)	66	268	(184; 390)	471	915	(809; 1036)	135	142	(109; 186)
B/Victoria	V01 (D01)	561	58.4	(52.5; 65.0)	48	5.00	(NC; NC)	555	44.7	(41.1; 48.6)	50	5.00	(NC; NC)
	V02 (D29)	561	471	(424; 524)	48	68.3	(45.1; 103)	555	280	(253; 310)	50	101	(69.0; 149)
B/Yamagata	V01 (D01)	596	297	(268; 330)	13	5.00	(NC; NC)	603	306	(275; 341)	3	5.00	(NC; NC)
	V02 (D29)	596	2076	(1918; 2248)	13	89.0	(37.3; 212)	603	1596	(1480; 1722)	3	1016	(NC; NC)

Ci, confidence interval; D, day; GM, geometric mean; HAI, hemagglutination inhibition; M, number of participants with available data for the considered endpoint; V, visit

Safety overview

- During the study, 10 participants (0.8%) reported at least 1 SAE and 66 participants (5.1%) reported at least 1 MAAE. None of the SAEs and MAAEs were considered as related to the vaccine
- No deaths and no AESIs were reported during the study

Safety overview after vaccine injection

	9 to 17 years (N=641)			18 to 49 years (N=658)			All (N=1299)		
Period/Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Within 28 days after vaccine injection									
Unsolicited AR	30/641	4.7	(3.2; 6.6)	26/658	4.0	(2.6; 5.7)	56/1299	4.3	(3.3; 5.6)
AE leading to discontinuation	0/641	0	(0; 0.6)	2/658	0.3	(0; 1.1)	2/1299	0.2	(0; 0.6)
During the study									
SAE	3/641	0.5	(0.1; 1.4)	7/658	1.1	(0.4; 2.2)	10/1299	0.8	(0.4; 1.4)
Death	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
AESI	0/641	0	(0; 0.6)	0/658	0	(0; 0.6)	0/1299	0	(0; 0.3)
MAAE	29/641	4.5	(3.1; 6.4)	37/658	5.6	(4.0; 7.7)	66/1299	5.1	(4.0; 6.4)

M, number of participants with available data for the relevant endpoint; n, number of participants experiencing the endpoint listed in the first column; N, total number of participants included in the study

AR, adverse reactions; AESI, adverse event of special interest; CI, confidence interval; MAAE, medically attended adverse event; SAE, serious adverse event