Older Adult (65+) Adjuvanted Quadrivalent Influenza Vaccine (aIIV4) Phase III Trial

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Gregg C. Sylvester, MD, MPH

Medical Affairs

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Agenda

- Background
- Pivotal Phase III Trial (aIIV4/Fluad Quadrivalent)
  - Study Design & Objectives
  - Immunogenicity
  - Efficacy
  - Safety
- Conclusion





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Background

- **MF59® Adjuvanted influenza vaccine (aIIV3/Fluad Trivalent) indicated for individuals 65 years and older was licensed based on immunogenicity and safety and has been in use for >20 years**

- **Effectiveness studies have provided evidence of clinical benefit of aIIV3 vaccine vs non-adjuvanted vaccines[1-4]**

- **To fulfill post-marketing commitments for aIIV3, an efficacy trial was conducted to evaluate absolute efficacy of MF59® adjuvanted quadrivalent seasonal influenza vaccine (aIIV4)**

1.Mannino S, et al. *Am J Epidemiol*. 2012;176:527-533.
2. Van Buynder PG, et al. *Vaccine*. 2013;31:6122-6128.
3. Lapi F, et al. Expert Rev Vaccines. 2019 Jun;18(6):663-670
4. Peabody R, et al. *Vaccine*. 2019

OBJECTIVES

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Study Overview

- **Phase III study to evaluate the immunogenicity, efficacy and safety of aIIV4 compared to non-influenza vaccine comparator in adults**

  ≥ 65 years of age

  – **1:1 randomization (aIIV4 vs Boostrix®)**

- **2 seasons: 2016/17 Northern and 2017 Southern Hemisphere (predominant influenza A/H3N2 virus circulation)**

- **Conducted in 12 countries:**

  – **Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand and Turkey**

Efficacy Objectives

- Case-driven
  - 238 PCR-confirmed cases
- Primary Efficacy Objective
  - Vaccine efficacy (VE) against any PCR-confirmed influenza
    - CBER Criteria: Lower Limit 95% CI >40%
- Secondary Efficacy Objective
  - VE against culture-confirmed influenza, due to antigenically matched strains
    - CBER Criteria: Lower Limit 95% CI >40%

CI=Confidence Interval
RT-PCR= Reverse Transcriptase Polymerase Chain Reaction

Immunogenicity & Safety Objectives

Immunogenicity

- Measured by HI titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine

Safety

- Local and systemic solicited AEs from day 1 to 7
- Unsolicited AEs for 21 days after vaccination and AEs leading to withdrawal, SAEs, AESIs, NOCD for 365 days after vaccination

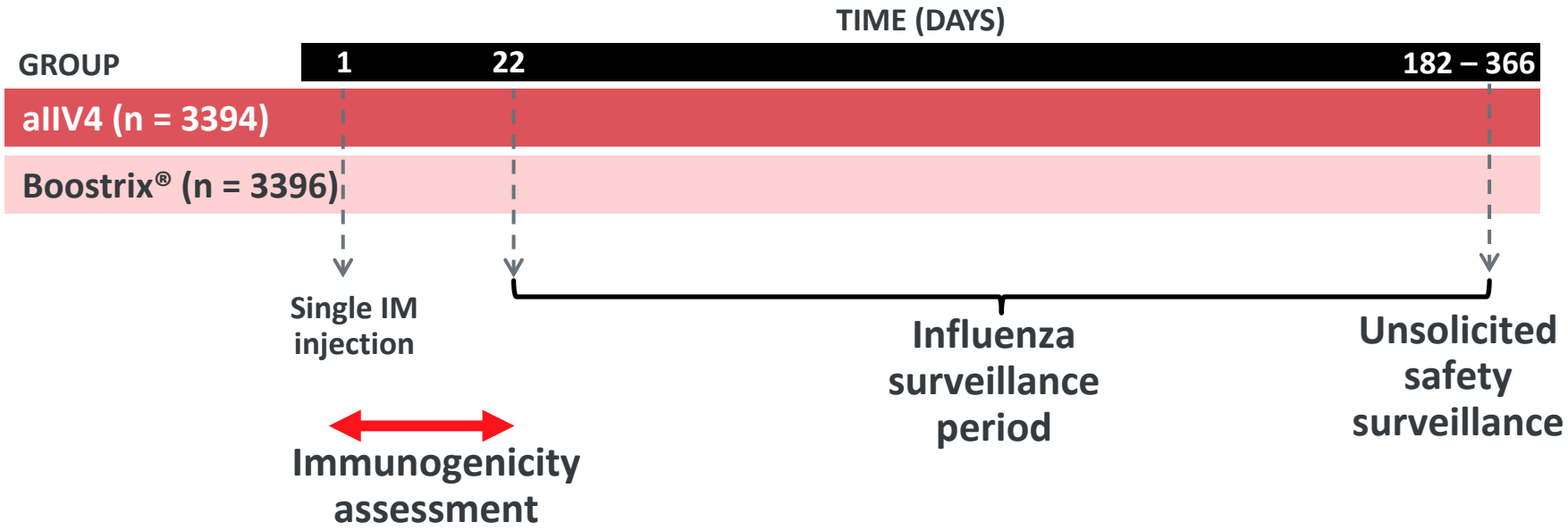
HI – hemagglutinin inhibition
AE – adverse event
SAE – serious adverse event
AESI – adverse events of special interest
NOCD – new onset of chronic disease

Demographics and Baseline Characteristics

	aIIV4 (n = 3394)	Boostrix® (n = 3396)	Total (n = 6790)
Age (years)			
Mean (SD)	**71.9 (5.53)**	**71.8 (5.36)**	**71.9 (5.44)**
• 65 to 74 years	2416 (71.2%)	2406 (70.8%)	4822 (71.0%)
• 75 to 84 years	893 (26.3%)	928 (27.3%)	1821 (26.8%)
• ≥ 85 years	85 (2.5%)	62 (1.8%)	147 (2.2%)
Sex			
• Male	1289 (38.0%)	1307 (38.5%)	2596 (38.2%)
Race			
• White	1642 (48.4%)	1629 (48.0%)	3271 (48.2%)
• Asian	1139 (33.6%)	1159 (34.1%)	2298 (33.8%)
• Black/African Amer.	1 (0.0%)	0	1 (0.0%)
• Alaska/Native Amer.	62 (1.8%)	59 (1.7%)	121 (1.8%)
• Other	550 (16.2%)	549 (16.2%)	1099 (16.2%)
Comorbidity Score[1]			
• < 50	2472 (72.8%)	2474 (72.9%)	4946 (72.8%)

1. Hak E, et al. *J Infect Dis*. 2004 Feb 1;189(3):450-8

Study to evaluate immunogenicity, efficacy, and safety in older adults (65+)



PRIMARY OBJECTIVE	SECONDARY OBJECTIVE
• Absolute vaccine efficacy against PCR-confirmed influenza due to any strain	• Absolute vaccine efficacy against culture-confirmed influenza due to strains antigenically matched to the vaccine strains

Results

Immunogenicity

Strain	aIIV4 (n=1313-1324)			Boostrix® (n=330-331)		
	GMT Day 22	Seroconversion rate % (95% CI)	HI titer ≥1:40 % (95% CI)	GMT Day 22	Seroconversion rate % (95% CI)	HI titer ≥1:40 % (95% CI)
A/H1N1	439	78 (75 - 80)	96 (95 - 97)	29	2 (1 - 4)	47 (41 - 52)
A/H3N2	573	85 (83 - 86)	96 (94 - 97)	27	4 (2 - 7)	42 (36 - 47)
B/Yam	87	61 (58 - 63)	79 (77 - 81)	12	4 (2 - 6)	22 (17 - 26)
B/Vic	104	66 (63- 68)	82 (79 - 84)	11	2 (1 - 4)	18 (14 - 23)

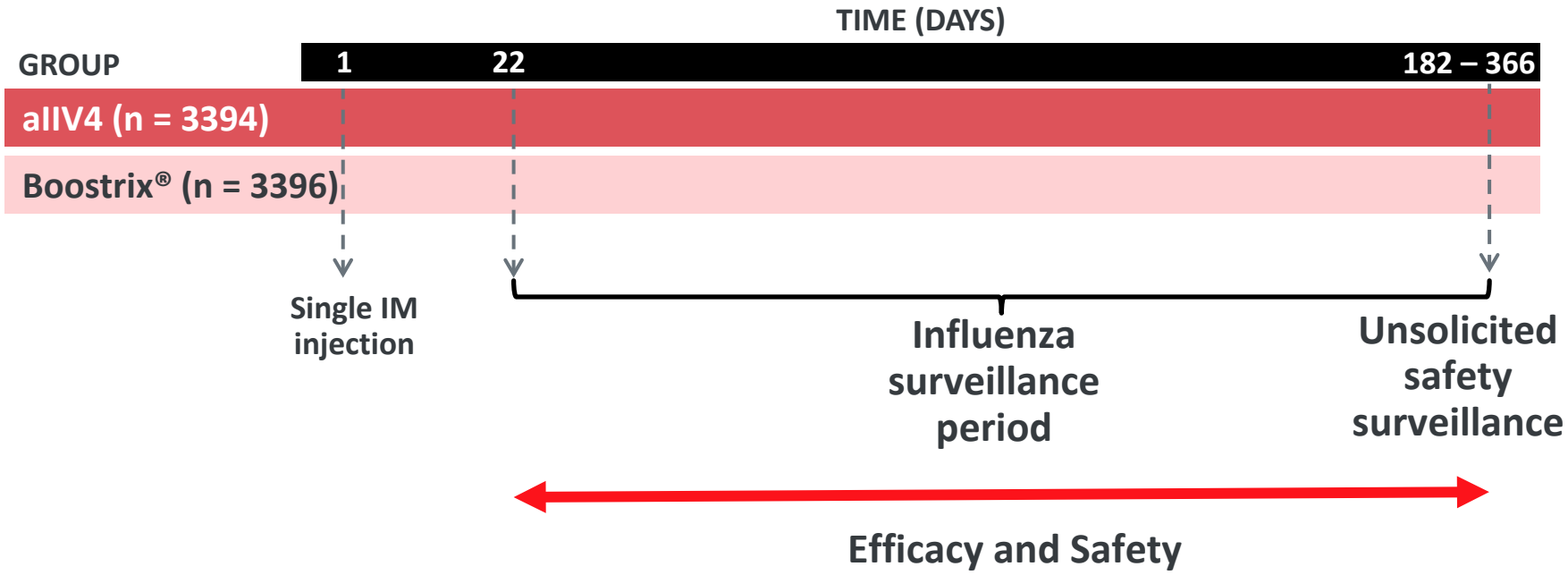
CBER criteria met for aIIV4:

- **LL of > 30% for SCR for All strains**
- **LL of > 60% for HI titer ≥1:40 for All strains**

LL – lower limit
SCR – seroconversion rate
HI – hemagluttinin inhibition
CBER – Center for Biologics Evaluation and Research

Pivotal Phase III Trial (aIIV4)

Study to evaluate immunogenicity, efficacy, and safety in older adults (65+)



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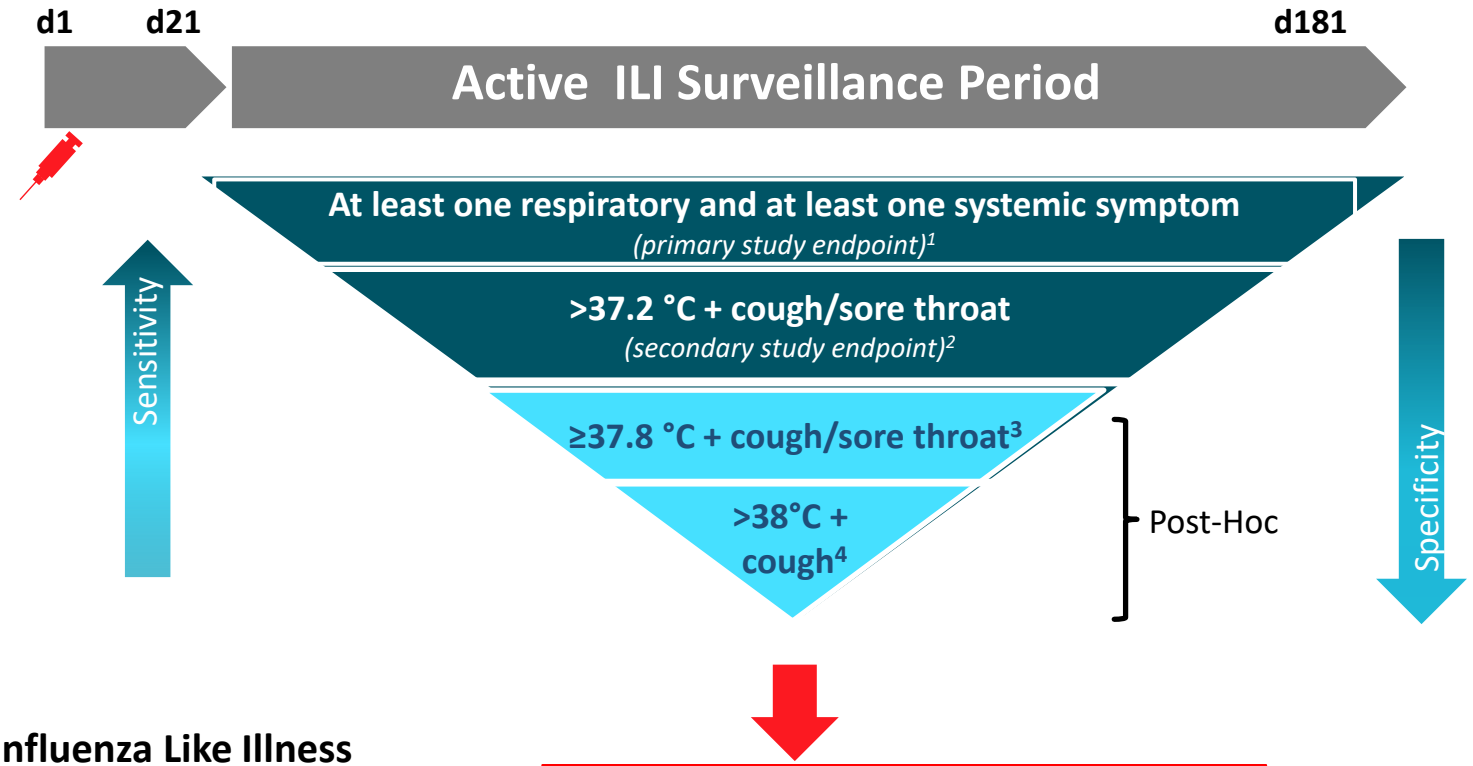
Influenza Like Illness Case Accrual



ILI = Influenza Like Illness

1. Primary Protocol Defined ILI
2. Secondary Protocol Defined ILI
3. CDC Defined ILI
4. WHO Defined ILI

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Influenza Cases Accrued By ILI Definition – aIIV4 Arm

Influenza Like Illness (ILI) Definition	Clinically Defined ILI	PCR Confirmed Influenza (% of ILI)	Antigenically Matched Influenza (% of PCR +ve)
Protocol			
At least one systemic + at least one respiratory symptom (Primary Endpoint)	801	122 (15.2%)	7 (5.7%)
Protocol			
>37.2°C with cough or sore throat (Secondary Endpoint)	396	83 (20.9%)	5 (6.0%)
Post-hoc analysis			
≥37.8°C with cough or sore throat (CDC Defined ILI)	164	54 (32.9%)	3 (5.6%)
≥38°C with cough (WHO Defined ILI)	114	39 (34.2%)	2 (5.1%)

Protocol ILI definition:
At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.

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Absolute Vaccine Efficacy – PCR Confirmed Cases

ILI Definition	RT-PCR confirmed influenza		
	aIIV4 Cases N (Attack Rate)	Tdap Cases N (Attack Rate)	Absolute VE % (95%CI)
Respiratory + Systemic Symptom[1]	122 (3.6%)	151 (4.5%)	19.8 (-5.3, 38.9)*
>37.2 °C + cough/sore throat[2]	83 (2.5%)	121 (3.6%)	32.1 (10.2, 48.7)
≥37.8 °C + cough/sore throat[3]	54 (1.6%)	92 (2.7%)	41.9 (18.7, 58.5)
>38°C + cough[4]	39 (1.2%)	79 (2.3%)	51.1 (28.2, 66.7)

*Primary study objective; *Pre-specified CBER Criteria: LL 95% CI for VE >40%*

1. Primary Protocol Defined ILI
2. Secondary Protocol Defined ILI
3. CDC Defined ILI
4. WHO Defined ILI

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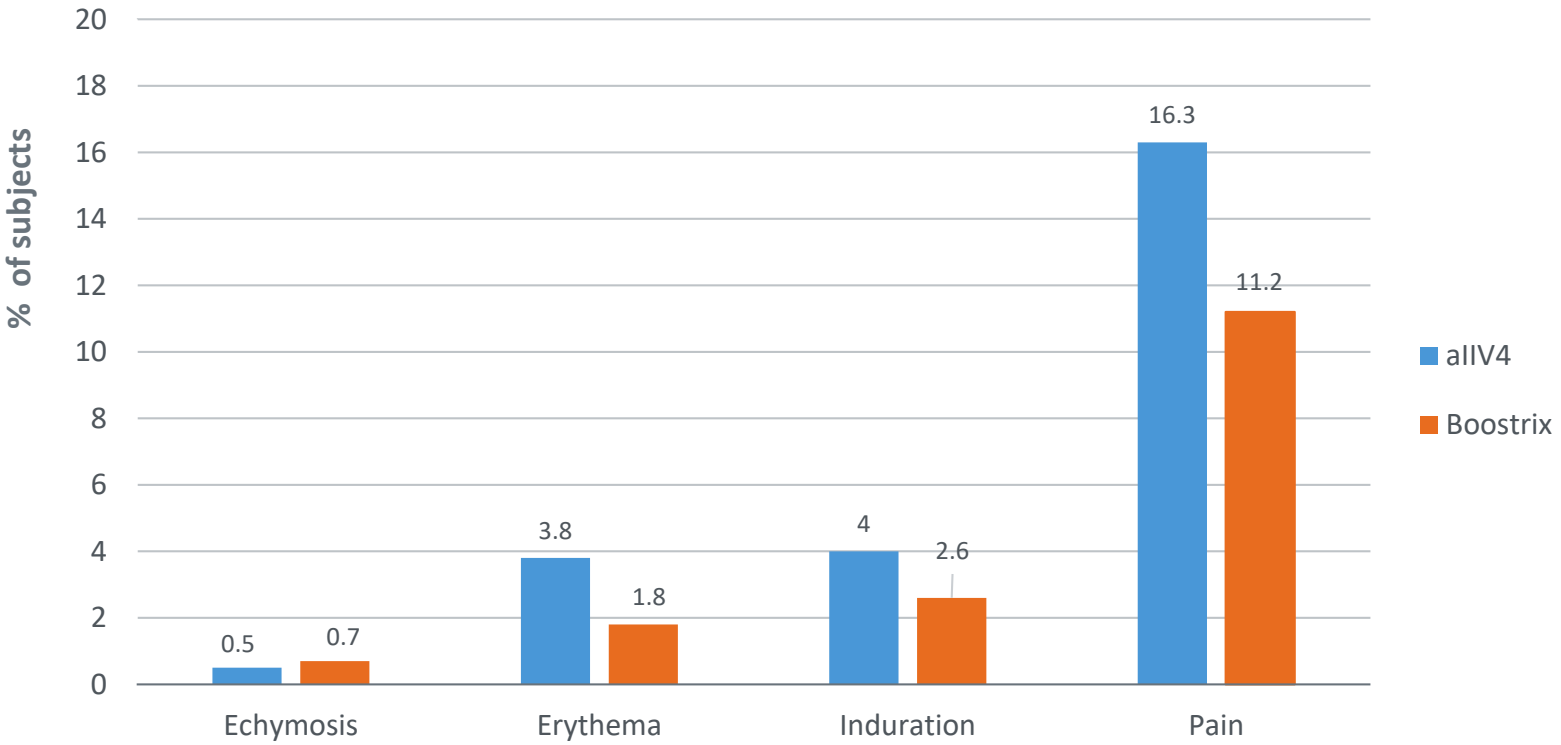
Absolute Vaccine Efficacy : Culture Confirmed Matched Cases

ILI Definition	Antigenically matched influenza		
	aIIV4 Cases N (Attack Rate)	Tdap Cases N (Attack Rate)	Absolute VE % (95%CI)
Respiratory + Systemic Symptom[1]	7 (0.2%)	14 (0.4%)	49.9 (-24.0, 79.8)
>37.2 °C + cough/sore throat[2]	5 (0.1%)	13 (0.4%)	61.5 (-8.0, 86.3)
≥37.8 °C + cough/sore throat[3]	3 (0.1%)	9 (0.3%)	66.6 (-23.3, 91.0)
>38°C + cough[4]	2 (0.1%)	8 (0.2%)	75.0 (-17.9, 94.7)

1. Primary Protocol Defined ILI
2. Secondary Protocol Defined ILI
3. CDC Defined ILI
4. WHO Defined ILI

Solicited local adverse events



- **Higher local solicited AE in aIIV4 group compared to the Boostrix® group**
- **Majority of reactions mild to moderate intensity**
- **Most commonly reported local solicited AE: Injection site pain**

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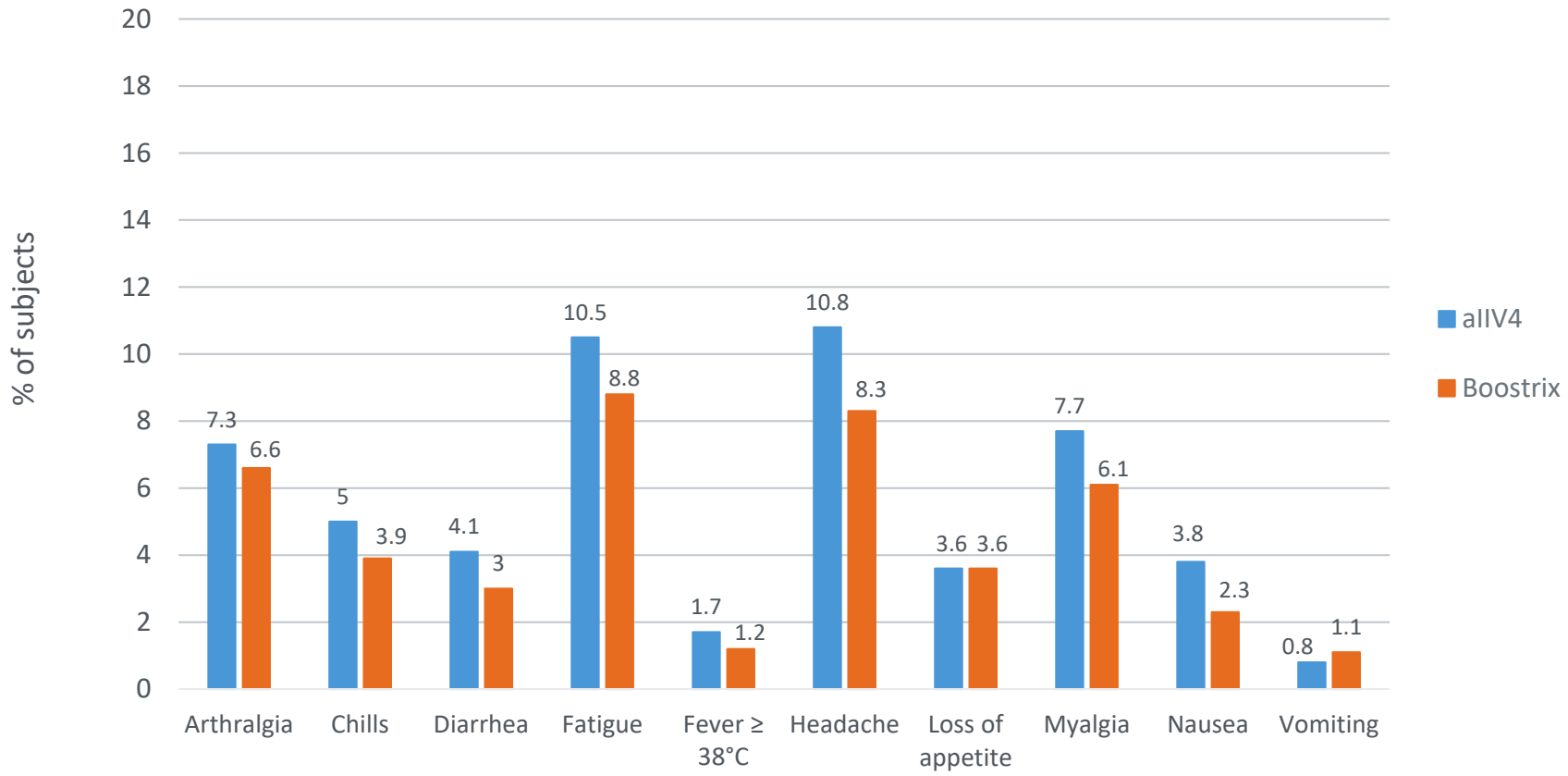
Solicited systemic adverse events



- **Higher systemic solicited AEs in aIIV4 group compared to the Boostrix® group**
- **Majority of reactions mild to moderate intensity**
- **Most commonly reported systemic solicited AEs: headache and fatigue**

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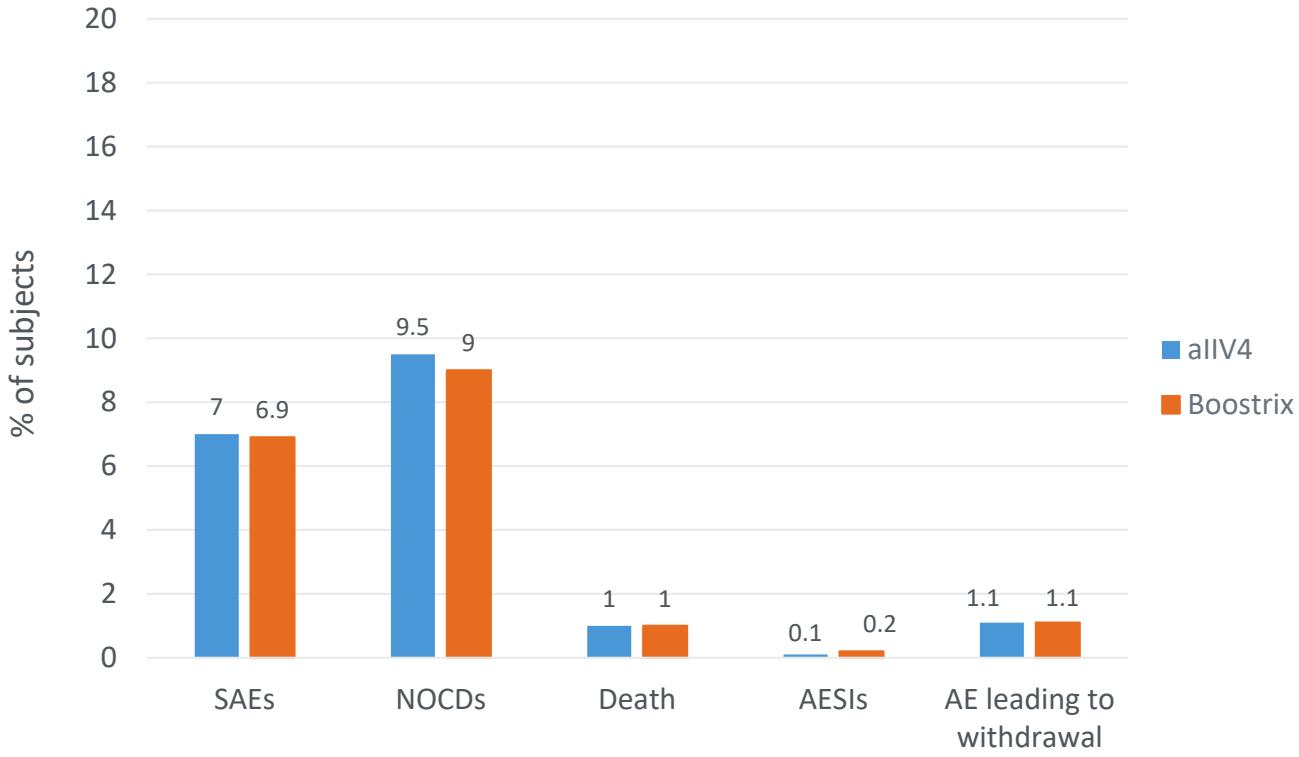
Specific unsolicited adverse events (Day 1-366)



SAE; Serious adverse Event
NOCD; New Onset Chronic Disease
AESI; Adverse Events Special Interest
AE; Adverse Event

- **Safety data consistent with aIIV3 profile**
- **aIIV4 has an acceptable safety profile in older adults**

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Discussion

Vaccine Efficacy Data

Influenza Like Illness (ILI) Definition	aIIV4 Cases n (attack rate)	Boostrix® Cases n (attack rate)	Absolute VE % (95%CI)
Protocol			
At least one systemic + at least one respiratory symptom • Primary Protocol defined ILI	**122 (3.6%)**	**151 (4.5%)**	**19.8 (-5.3, 38.9)**
Protocol			
>37.2°C with cough or sore throat • Secondary Protocol defined ILI	**83 (2.5%)**	**121 (3.6%)**	**32.1 (10.2, 48.7)**
Post-hoc analysis			
≥37.8°C with cough or sore throat • CDC defined ILI	**54 (1.6%)**	**92 (2.7%)**	**41.9 (18.7, 58.5)**
≥38°C with cough • WHO defined ILI	**39 (1.2%)**	**79 (2.3%)**	**51.1 (28.2, 66.7)**

At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.

Vaccine Effectiveness: 2016-17 NH & 2017 SH Influenza Seasons

Region	Overall % VE 95% CI	65+ %VE 95% CI
Europe	38% (21-51)	23% (-15-49)
USA	40% (32-46)	20% (-11-43)
AUS	33% (17-46)	-12% (-47-13)

Primary Phase 3 study objective for aIIV4 ; *Pre-specified CBER Criteria: LL 95% CI for VE >40%*

Sullivan et al. Euro Surveill. 2017;22(43):pii=17-00707; Flannery B, Clin Infect Dis. 2018 Sep 11. doi: 10.1093/cid/ciy775; Pebody R, Euro Surveill. 2017 Nov;22(44). Seki Y, J Infect Chemother. 2018 Nov;24(11):873-880; Noh JY et al PLoS One. 2017 May 25;12(5):e0178010; Zhang D, et al Vaccine. 2019 Mar 22;37(13):1853-1858; Wu S, Vaccine. 2018 Sep 11;36(38):5774-5780. Rondy M, Euro Surveill. 2017 Oct;22(41); .Souty C, et al J Clin Virol. 2017 Oct;95:1-4; Castilla J, et al Euro Surveill. 2017 Feb 16;22(7); Trebbien R, et al J Clin Virol. 2017 Sep;94:1-7.; Stein Y, et al Clin Infect Dis. 2018 Apr 17;66(9):1383-1391

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Study Limitations

- **Study period was relatively short and dominated by H3N2 circulating strains**

- **A wide range of circulating antigenically and genetically different strains of Influenza A/H3N2**
  - ~90% of the culture-confirmed influenza isolates were antigenically different to the strains in the vaccine

- **Study population was relatively healthy**

Conclusion

- aIIV4 elicited a robust immune response for all 4 strains satisfying the CBER criteria for immunogenicity
- aIIV4 VE results were 19.8% - 51% depending on ILI definition
- aIIV4 had an expected, and acceptable tolerability profile similar to aIIV3
- aIIV4 received FDA licensure on Feb 21, 2020