Quadrivalent Afluria® Influenza Vaccine

Adult (18 years of age and older) Study

CSLCT-QIV-13-01 Study Results

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ACIP 2016 October Meeting
Atlanta, GA

Burden of Disease

- **Influenza** is a highly infectious respiratory infection [1].

- Seasonal epidemics occur predominantly during winter, with an annual incidence of 5 to 10% in adults [2]
  - Infection is associated with significant morbidity and mortality, with an estimated 250,000 to 500,000 deaths directly attributed to influenza annually worldwide [2]

- Conventionally, influenza vaccines are trivalent, consisting of two influenza A subtypes and one influenza B lineage. However, two antigenically distinct B lineages co-circulate from year to year [3]

[1] Bouvier NM, Palese P. Vaccine. 2008;26 Suppl 4:D49-53.
[2] World Health Organisation. Influenza. factsheets/fs211/en/. 13 July, 2016.
[3] Beran J, Wertzova V, Honegr K, Kaliskova E, Havlickova M, Havlik J, et al. BMC Infect Dis. 2009;9:2.

AFLURIA:

- Egg-derived, purified, inactivated, split virion influenza vaccine
- Manufactured at Parkville, Australia
- Vaccine formulations:
  - 0.5mL pre-filled syringe, thimerosal-free
  - 5mL multi-dose vial, thimerosal-containing
- FDA approved indications
  - ≥ 18 years TIV: approval Nov 2007
  - ≥ 5 to 18 years TIV: approval Dec 2011*
  - ≥ 18 years QIV: approval Aug 2016

*** Current ACIP Recommendation for Afluria is for ≥ 9 years and older**

Afluria Stepwise Clinical Development Plan

2013	2014-15	2015-16	2016-17

TIV TDOC Study (18 to 60 yrs)
CSL-TIV; n= 120
Ph 4
Immunogenicity*

TIV Pediatric (5 to < 9yrs)
CSL-TIV: QIV comparator; 3:1; n= 402
Ph 4, randomised, observer-blinded, comparator controlled
Safety

QIV Adult (≥ 18 yrs)
QIV: CSL-TIV-1: CSL-TIV-2; 2:1:1; n= 3484
Ph 3, randomised, double-blinded, comparator controlled
Immunogenicity and safety

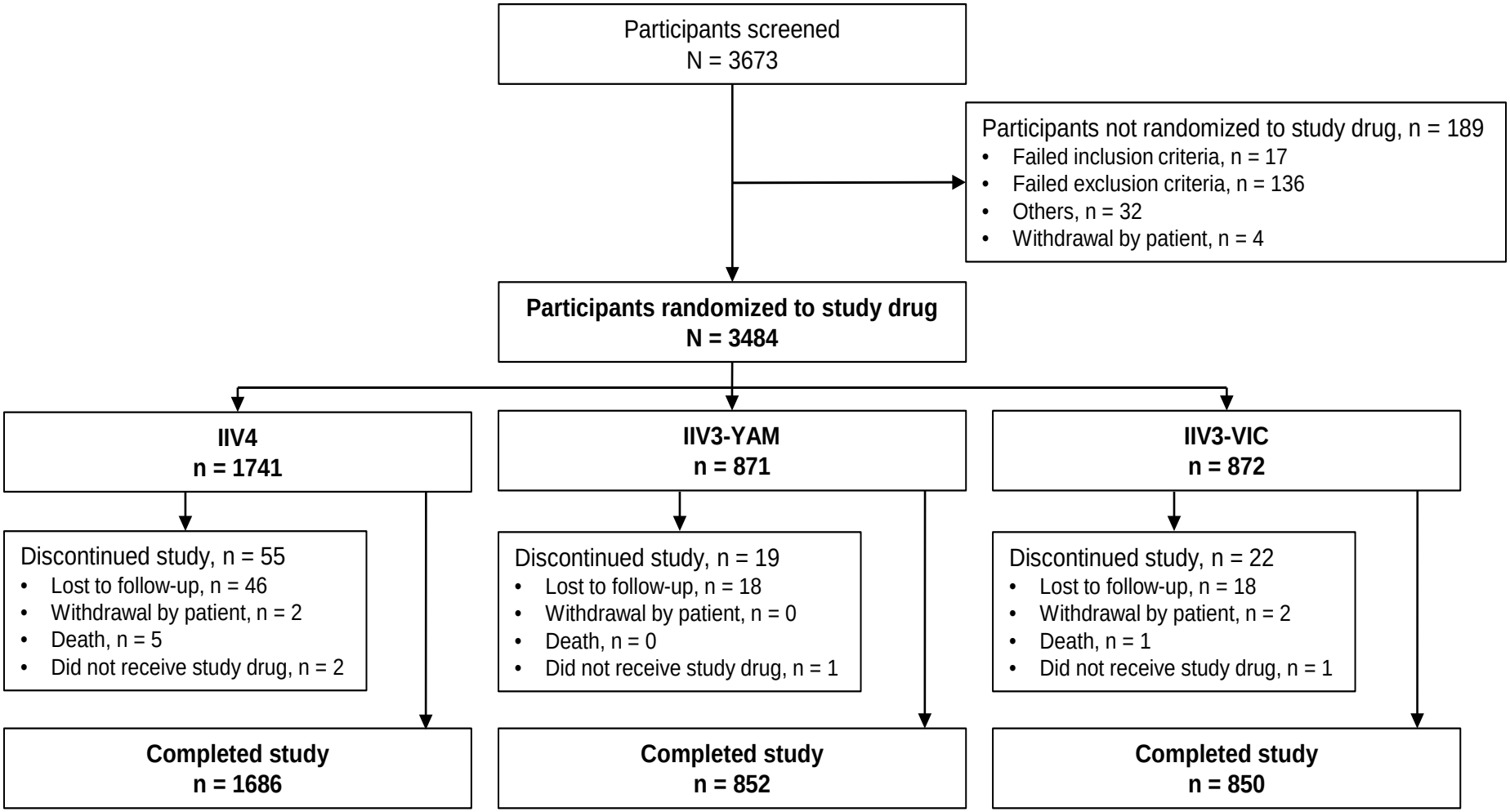
- QIV adult study / approved
- 5-18 QIV study / completed, pending FDA submission
- 6mo-5yr QIV study underway

QIV Pediatric (5 to <18 yrs)
QIV: QIV comparator; 3:1; n= 2278
Ph 3, randomised, observer-blinded, comparator controlled,
Immunogenicity and safety

QIV Pediatric (6 mths to <5 yrs)
QIV: QIV comparator; 3:1, n= 2222
Ph 3, randomised, observer-blinded, comparator controlled,
Immunogenicity and safety

QIV Safety and Immunogenicity in Adults

Phase III, randomized, double-blind, multicenter study



Comparison between IIV4 with a US-licensed 2014-2015 IIV3 (IIV3-YAM) and an IIV3 containing the alternate Victoria B strain (IIV3-VIC) in healthy adults aged ≥18 years

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Adults Demographics (full analysis set)

	IIV4 N=1741	IIV3-YAM N=871	IIV3-VIC N=872	IIV3 (pooled) N=1743	Overall N=3484
Age, mean ± SD, years	58.3 ± 18.10	58.2 ± 18.10	58.3 ± 17.89	58.2 ± 17.99	58.3 ± 18.04
Age group, (%)					
18 to 49 years	29.3	29.3	29.2	29.3	29.3
50 to 64 years	20.7	20.6	20.8	20.7	20.7
65 to 74 years	31.1	31.1	31.0	31.0	31.1
≥ 75 years	18.9	19.1	19.0	19.0	19.0
Gender, (%)					
Female	55.8	58.7	58.5	58.6	57.2
Ethnicity, (%)					
Hispanic or Latino	4.8	6.5	3.6	5.0	4.9
Not Hispanic or Latino	94.9	93.3	96.2	94.8	94.9
Unknown	0.2	0.1	0.2	0.2	0.2
Race, (%)					
White	82.0	82.5	82.8	82.7	82.3
Black or African American	16.3	15.0	15.5	15.3	15.8
Asian	0.7	0.8	0.5	0.6	0.7
Other	0.6	0.7	0.7	0.7	0.7
Native Hawaiian or Pacific Islander	0.1	0.5	0	0.2	0.2
Weight, mean ± SD, kg	85.48 ± 21.45	85.58 ± 21.30	85.08 ± 22.78	85.33 ± 22.05	85.40 ± 21.74
Subjects reporting history of ever received an influenza vaccine, (%)	87.2	87.3	87.2	87.2	87.2
Subjects reporting having received an influenza vaccine during the 12 months before the study start, (%)	62.4	66.0	62.4	64.2	63.3

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Healthy Adults

- **Exclusion Criteria**
  - Allergic to egg proteins or any study vaccine component
  - Acutely ill
  - Immunocompromised
  - Influenza vaccine within the preceding 6 months or any licensed vaccine (within 14 days for inactivated vaccines or 28 days for live vaccines)
  - Immunoglobulins or blood products within the last 3 months
  - Investigational product within the last 28 days
  - Anticoagulant therapy (except antiplatelet agents)
  - History of Guillain-Barre Syndrome or demyelinating disease
  - History of drug or alcohol abuse
  - Clinically significant disease, in the investigator's opinion precluded study participation

QIV Safety and Immunogenicity in Adults
Primary Immunogenicity & Safety Endpoints

- Non-inferiority Immunogenicity for eight co-primary endpoints (2 endpoints, 4 viral strains)
  - **Geometric mean titer (GMT)**
    - upper bound of the 95% CI of the **GMT ratios** should **not exceed 1.5**
  - **Seroconversion rate (SCR)**
    - the upper bound of the 95% CI of the **SCR differences** should be **≤ 10%**

Safety: Frequency and Intensity of Adverse Events

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QIV Immunogenicity in Adults
Secondary Endpoints

- **Non-inferiority (HI GMTs & SCRs) in each age group 18 to 64 years and ≥ 65 years**

- **Superiority (GMTs and SCRs) for the unmatched B strain included in the QIV, but not in the respective TIVs----Overall and in each age group; 18 to 64 years and ≥ 65 years**

  - **Geometric mean titer (GMT)**
    - the lower bound of the 95% CI of the **GMT ratio** should be **greater than 1**

  - **Seroconversion rate (SCR)**
    - the lower bound of the 95% CI of the **SCR differences** should be **greater than 0%**

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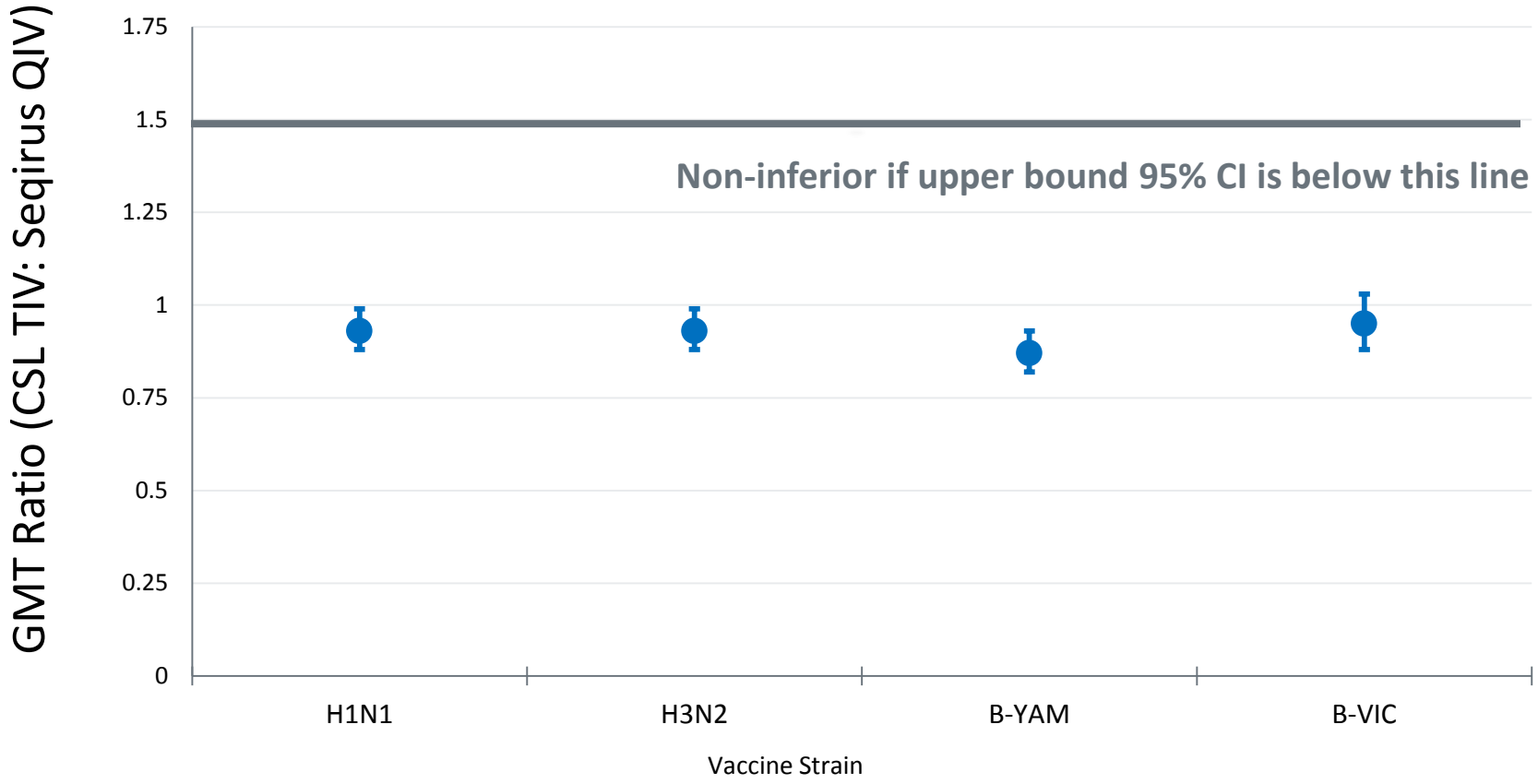
QIV Immunogenicity in Adults

Ratio of HI Geometric Mean Titers: ≥ 18 years



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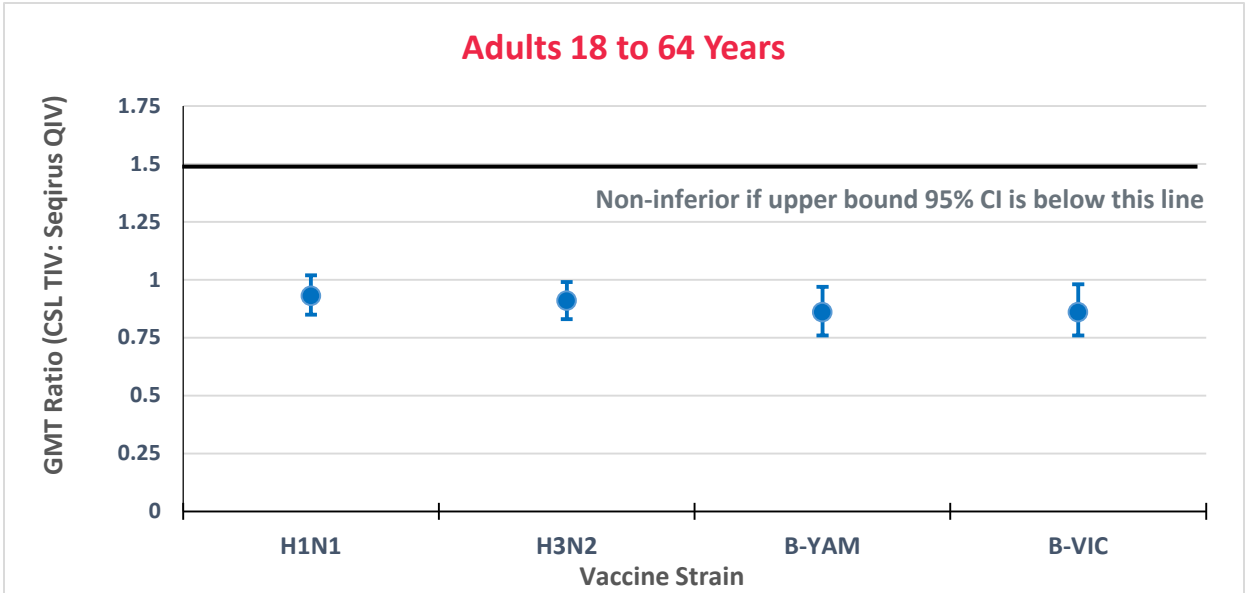
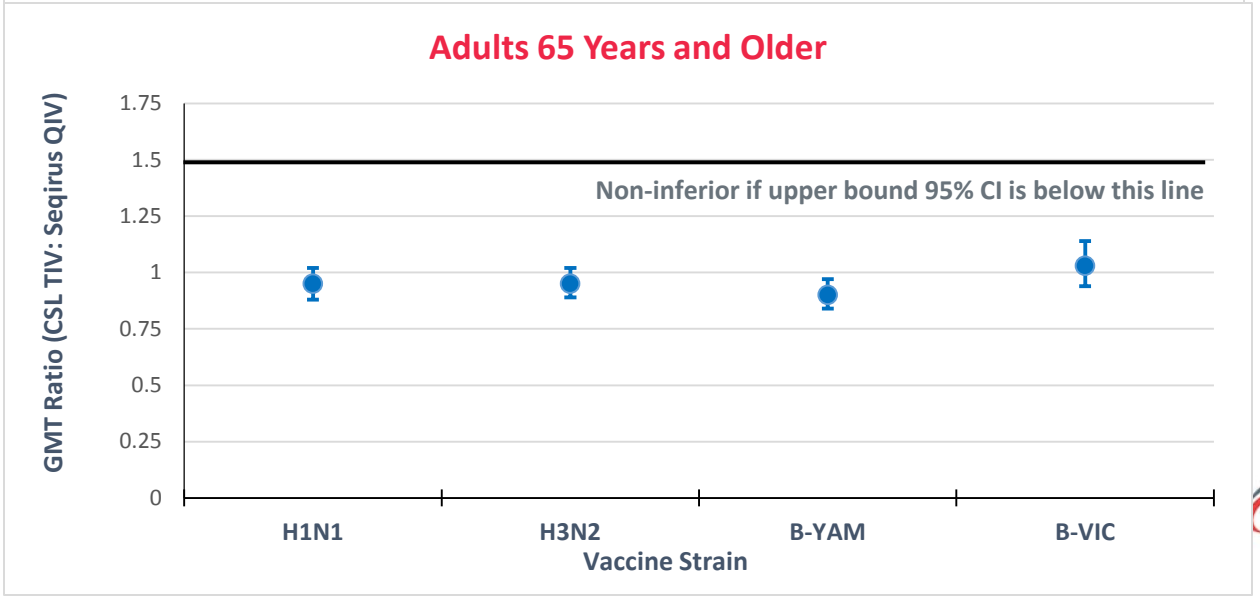
QIV Immunogenicity in Adults

Ratio of HI Geometric Mean Titers: 18 to 64 yrs and ≥ 65 yrs





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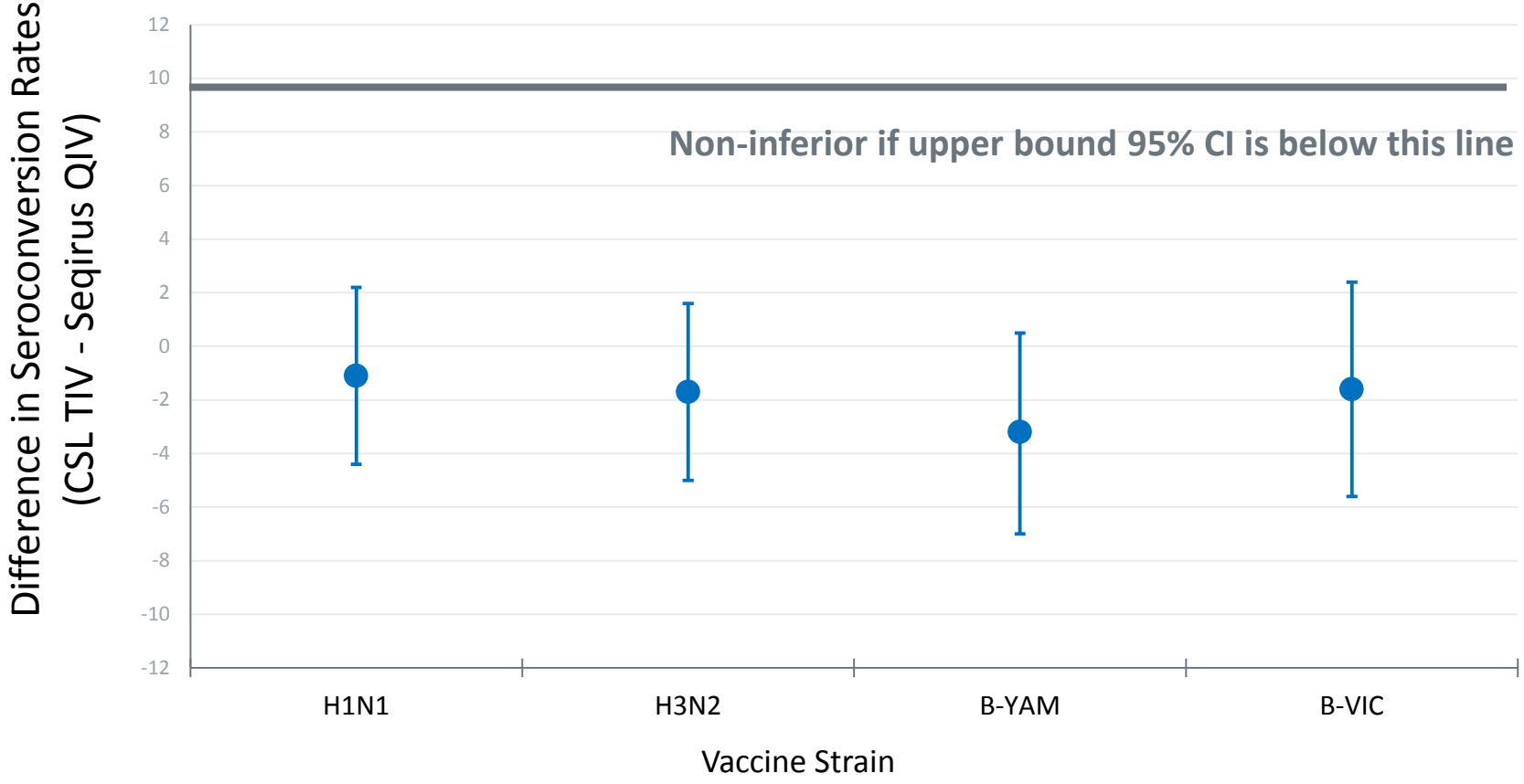
QIV Immunogenicity in Adults

Difference in Seroconversion Rates: ≥ 18 years



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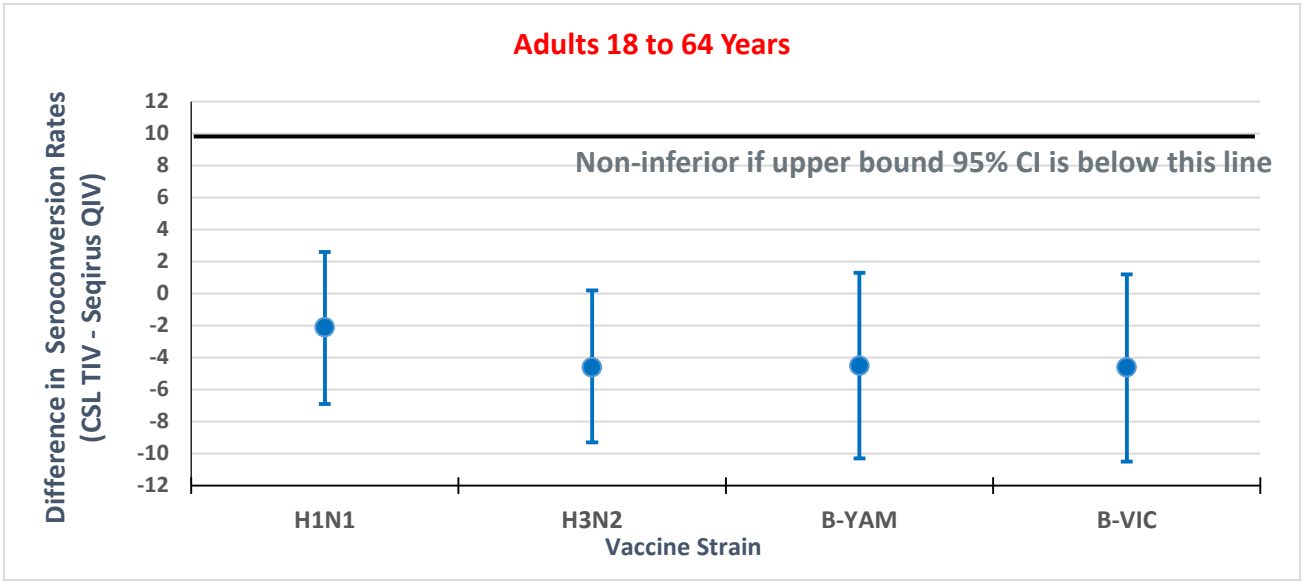
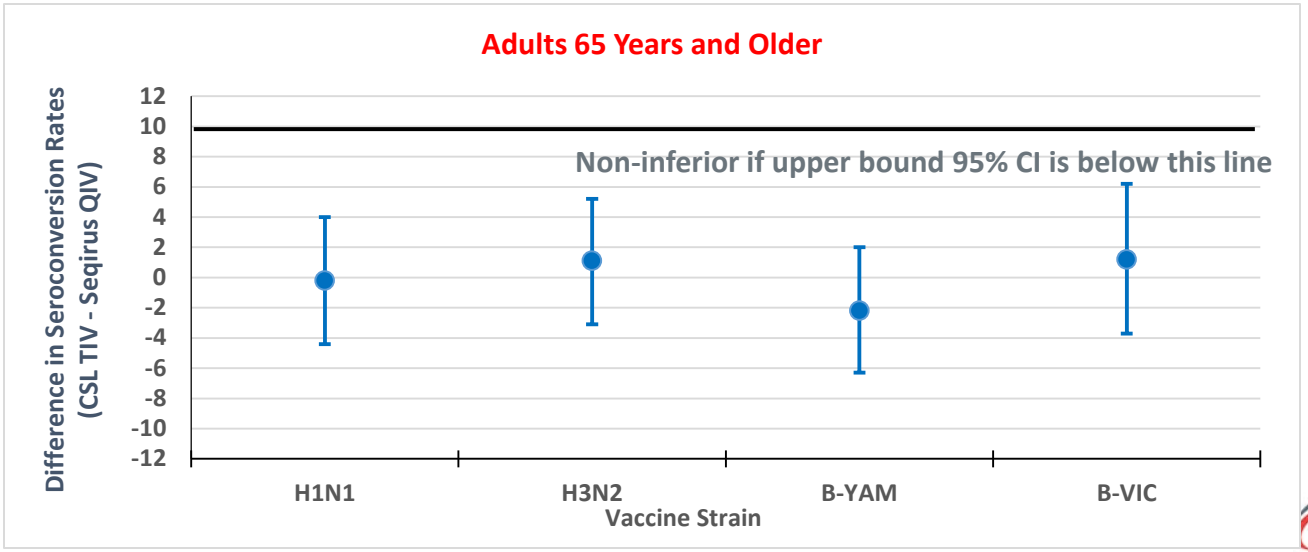
QIV Immunogenicity in Adults

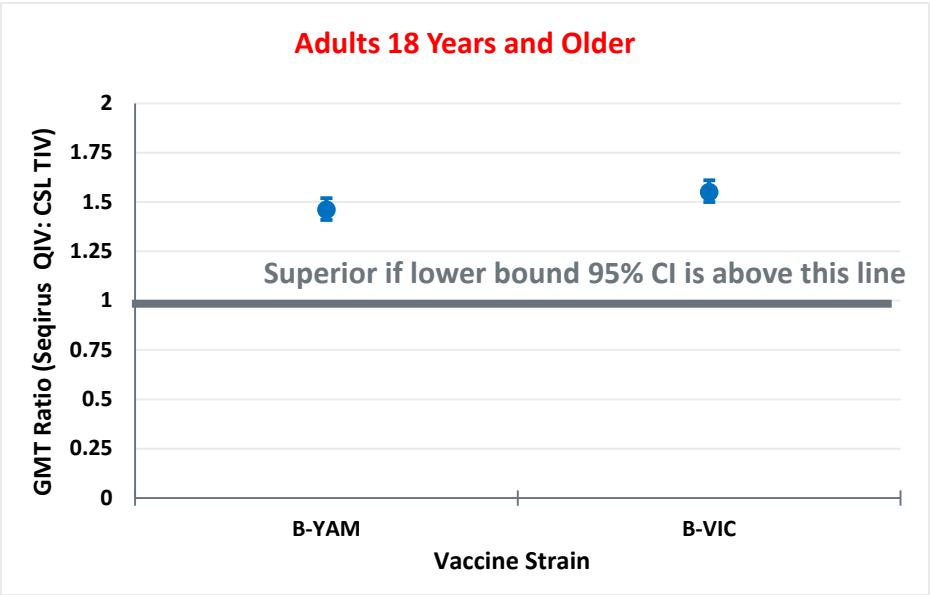
Difference in Seroconversion Rates: 18 - 64 yrs and ≥ 65 yrs

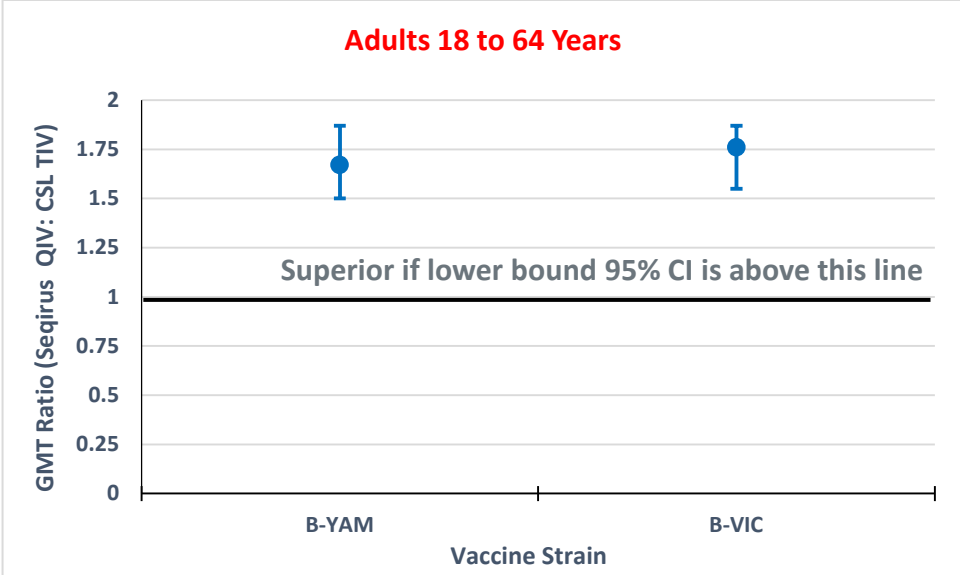


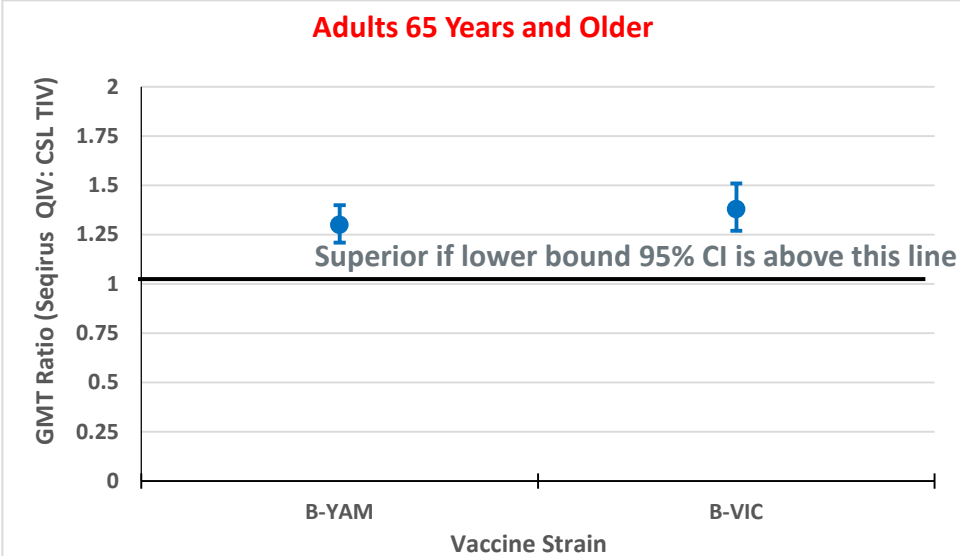


QIV Immunogenicity in Adults

Superiority against alternate B strain/Ratio of HI Geometric Mean Titers: ≥ 18 yrs, 18 to 64 yrs and ≥ 65 yrs



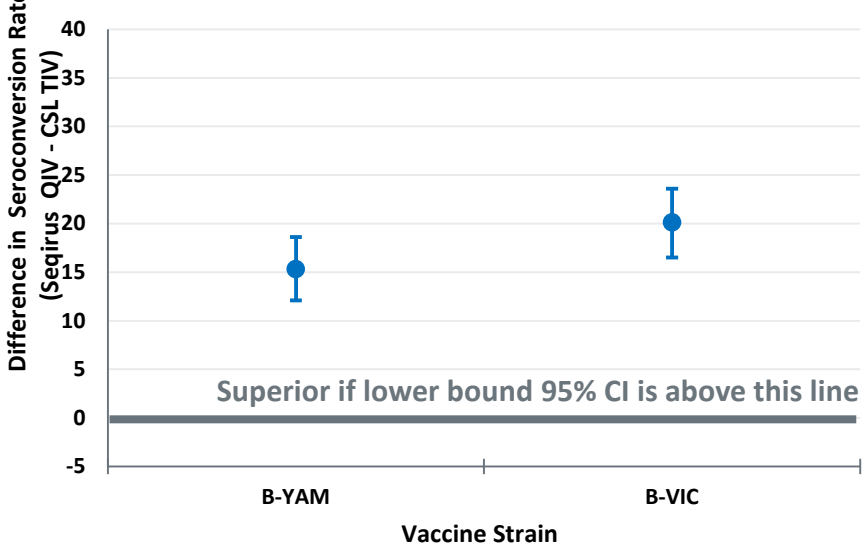




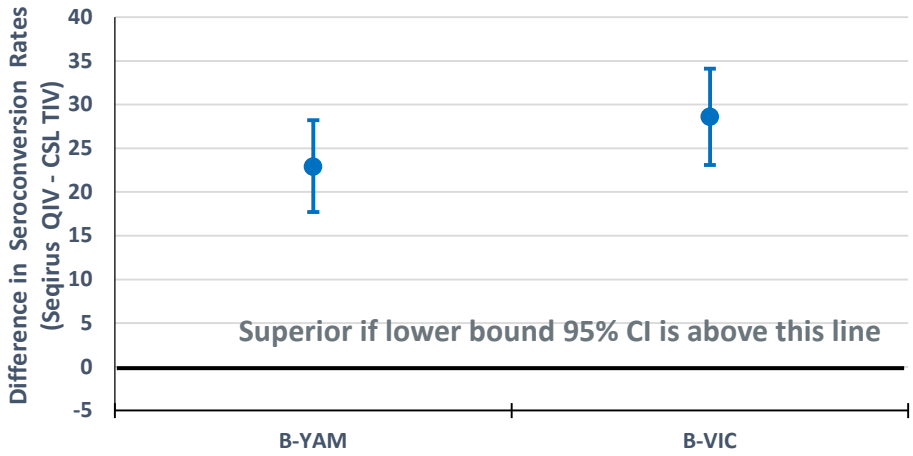
QIV Immunogenicity in Adults

Superiority against alternate B strain/Difference in Seroconversion Rates: ≥ 18 yrs, 18 to 64 yrs and ≥ 65 yrs

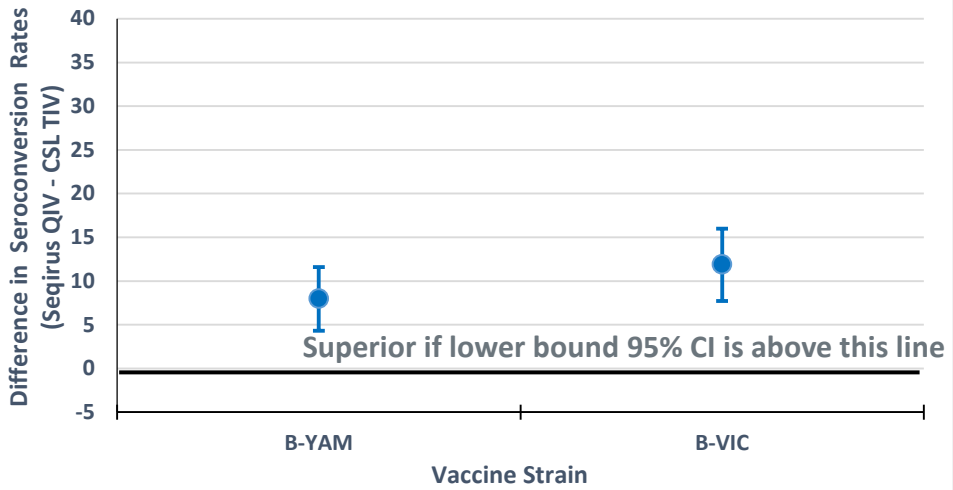
Adults 18 Years and Older



Adults 18 to 64 Years



Adults 65 Years and Older



QIV Safety in Adults

Solicited and unsolicited adverse events (safety population)[a]

	IIV4 N=1721 (%)	IIV3-YAM * N=864 (%)	IIV3-VIC N=864 (%)	Overall N=3449 (%)
Any adverse event				
One or more AEs [b]	52.9	53.1	52.5	52.9
Grade 1	47.0	45.4	45.4	46.2
Grade 2	18.4	17.9	17.2	18.0
Grade 3	6.2	4.9	6.0	5.8
Vaccine-related	43.8	42.1	42.4	43.0
Discontinuation due to an AE	0	0	0	0
Solicited adverse events				
Any solicited AE [b]	46.7	45.3	45.9	46.1
Grade 1	42.8	41.7	40.5	41.9
Grade 2	11.6	9.1	11.0	10.8
Grade 3	2.4	1.7	2.8	2.3
Solicited local adverse reactions [c]	37.4	34.6	36.6	36.5
Solicited systemic AEs	28.9	28.4	27.2	28.4
Vaccine-related	20.4	19.1	20.6	20.1

[a] Proportion of participants based on the number of participants in the respective group

[b] Intensity of AEs

Grade 1 (symptoms were easily tolerated, did not interfere with normal , everyday activities)

Grade 2 (discomfort enough to cause some interference with normal , everyday activities)

Grade 3 (symptoms that prevent normal, everyday activities)

Redness and swelling/lump reactions were graded by size

Grade 1: ≥20 - <50mm; Grade 2: ≥50 - <100mm; Grade 3: ≥100mm

Fever by oral temperature

Grade 1: ≥38.0°C - <38.5°C; Grade 2: ≥38.5°C - <39.0°C; Grade 3: ≥39.0°C

[c] All solicited local adverse reactions were considered related to study vaccine

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QIV Safety in Adults

Solicited and unsolicited adverse events (safety population)[a]

	IIV4 N=1721 (%)	IIV3-YAM * N=864 (%)	IIV3-VIC N=864 (%)	Overall N=3449 (%)
Unsolicited adverse events				
Any unsolicited AE [b]	20.5	22.1	20.4	20.8
Grade 1	10.7	11.8	12.0	11.3
Grade 2	9.5	11.0	8.6	9.7
Grade 3	4.2	3.4	3.8	3.9
Vaccine-related	3.5	2.4	2.1	2.9
Serious adverse events				
Any SAE	2.3	1.6	1.5	1.9
Vaccine-related	0.2	0	0	0.1
Discontinuation due to an SAE	0	0	0	0
Deaths	0.3	0	0.1	0.2
Adverse events of special interest	0	0	0	0

[a] Proportion of participants based on the number of participants in the respective group

[b] Intensity of AEs

Grade 1 (symptoms were easily tolerated, did not interfere with normal, everyday activities)

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Grade 3 (symptoms that prevent normal, everyday activities)

Redness and swelling/lump reactions were graded by size

Grade 1: ≥20 - <50mm; Grade 2: ≥50 - <100mm; Grade 3: ≥100mm

Fever by oral temperature

Grade 1: ≥38.0°C - <38.5°C; Grade 2: ≥38.5°C - <39.0°C; Grade 3: ≥39.0°C

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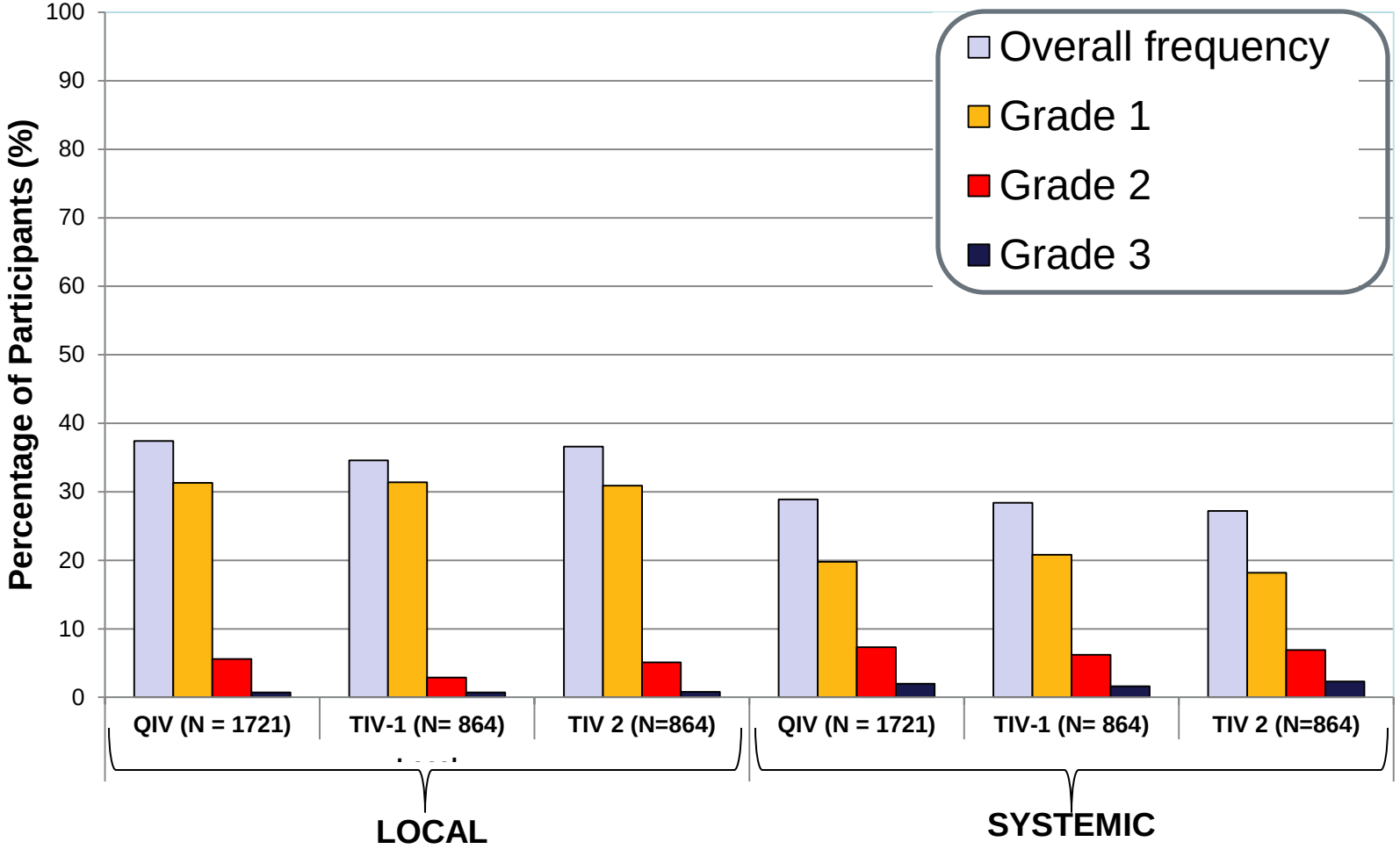
Solicited Local Reactions and Systemic Adverse Events- Overall Frequency and Intensity



Strengths

Trial Design

- Prospective
- Double blinded
- Randomized
- Phase 3
- Active-control
- Multicenter

Sufficient Power to meet primary endpoints

Potential Limitations

Use of immunogenicity as a surrogate for protection

- may not be a true representation of clinical efficacy

Participants with moderate to severe acute illnesses were excluded

Summary of QIV Safety and Immunogenicity in Adults

- Afluria Quadrivalent® Influenza Vaccine met non-inferior immunogenicity for all strains to both comparator TIVs in adults ≥ 18 years, and in each age group 18 to 64 years and ≥ 65 years
- Immunologic superiority of the alternate B strain (B/Yamagata and B/Victoria strain) was also met for both the age cohorts by the GMT ratios and SCR for each virus strain
- Acceptable Safety Profile
- U.S. FDA approval on August 24, 2016

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Thank you