Quadrivalent Afluria® Influenza Vaccine
Adult (18 years of age and older) Study

CSLCT-QIV-13-01 Study Results

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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]

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>TIV TDOC Study (18 to 60 yrs)</td>
<td>CSL-TIV; n= 120 Ph 4 Immunogenicity*</td>
</tr>
<tr>
<td>2014-15</td>
<td>TIV Pediatric (5 to &lt; 9 yrs)</td>
<td>CSL-TIV: QIV comparator; 3:1; n= 402 Ph 4, randomised, observer-blinded, comparator controlled Safety</td>
</tr>
<tr>
<td>2015-16</td>
<td>QIV Adult (≥ 18 yrs)</td>
<td>QIV: CSL-TIV-1: CSL-TIV-2; 2:1:1; n= 3484 Ph 3, randomised, double-blinded, comparator controlled Immunogenicity and safety</td>
</tr>
<tr>
<td>2016-17</td>
<td>QIV Pediatric (5 to &lt; 18 yrs)</td>
<td>QIV: QIV comparator; 3:1; n= 2278 Ph 3, randomised, observer-blinded, comparator controlled Immunogenicity and safety</td>
</tr>
<tr>
<td></td>
<td>QIV Pediatric (6 mths to &lt; 5 yrs)</td>
<td>QIV: QIV comparator; 3:1; n= 2222 Ph 3, randomised, observer-blinded, comparator controlled, Immunogenicity and safety</td>
</tr>
</tbody>
</table>

- QIV adult study / approved
- 5-18 QIV study / completed, pending FDA submission
- 6mo-5yr QIV study underway
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.
### Adults Demographics (full analysis set)

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

Ratio of HI Geometric Mean Titers: ≥ 18 years

Non-inferior if upper bound 95% CI is below this line
QIV Immunogenicity in Adults
Ratio of HI Geometric Mean Titers: 18 to 64 yrs and ≥ 65 yrs

**Adults 18 to 64 Years**

- **H1N1**
- **H3N2**
- **B-YAM**
- **B-VIC**

**Adults 65 Years and Older**

- **H1N1**
- **H3N2**
- **B-YAM**
- **B-VIC**

Non-inferior if upper bound 95% CI is below this line.
QIV Immunogenicity in Adults
Difference in Seroconversion Rates: ≥ 18 years

Difference in Seroconversion Rates (CSL TIV - Seqirus QIV)

Non-inferior if upper bound 95% CI is below this line

Vaccine Strain

H1N1  H3N2  B-YAM  B-VIC
QIV Immunogenicity in Adults

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

Adults 18 to 64 Years

Non-inferior if upper bound 95% CI is below this line

Adults 65 Years and Older

Non-inferior if upper bound 95% CI is below this line
QIV Immunogenicity in Adults
Superiority against alternate B strain/Ratio of HI Geometric Mean Titers: 
≥ 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 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)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>IIV4 N=1721 (%)</th>
<th>IIV3-YAM * N=864 (%)</th>
<th>IIV3-VIC N=864 (%)</th>
<th>Overall N=3449 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more AEs</td>
<td>52.9</td>
<td>53.1</td>
<td>52.5</td>
<td>52.9</td>
</tr>
<tr>
<td>Grade 1</td>
<td>47.0</td>
<td>45.4</td>
<td>45.4</td>
<td>46.2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>18.4</td>
<td>17.9</td>
<td>17.2</td>
<td>18.0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6.2</td>
<td>4.9</td>
<td>6.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Vaccine-related</td>
<td>43.8</td>
<td>42.1</td>
<td>42.4</td>
<td>43.0</td>
</tr>
<tr>
<td>Discontinuation due to an AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## Solicited adverse events

<table>
<thead>
<tr>
<th></th>
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<th>IIV3-VIC N=864 (%)</th>
<th>Overall N=3449 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any solicited AE</td>
<td>46.7</td>
<td>45.3</td>
<td>45.9</td>
<td>46.1</td>
</tr>
<tr>
<td>Grade 1</td>
<td>42.8</td>
<td>41.7</td>
<td>40.5</td>
<td>41.9</td>
</tr>
<tr>
<td>Grade 2</td>
<td>11.6</td>
<td>9.1</td>
<td>11.0</td>
<td>10.8</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.4</td>
<td>1.7</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Solicited local adverse reactions</td>
<td>37.4</td>
<td>34.6</td>
<td>36.6</td>
<td>36.5</td>
</tr>
<tr>
<td>Solicited systemic AEs</td>
<td>28.9</td>
<td>28.4</td>
<td>27.2</td>
<td>28.4</td>
</tr>
<tr>
<td>Vaccine-related</td>
<td>20.4</td>
<td>19.1</td>
<td>20.6</td>
<td>20.1</td>
</tr>
</tbody>
</table>

\(^a\) 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
# QIV Safety in Adults

## Solicited and unsolicited adverse events (safety population)\

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

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

Overall frequency

Grade 1

Grade 2

Grade 3

Percentage of Participants (%)
**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
Thank you