AFLURIA QUADRIVALENT
(AFLURIA QIV)

PHASE III, RANDOMIZED, OBSERVER-BLIND COMPARATOR-CONTROLLED STUDY, CHILDREN 6 – 59 MONTHS

GREGG C. SYLVESTER, MD, MPH
MEDICAL AFFAIRS
AGENDA

• Background Afluria Clinical Development Program

• Afluria QIV: Phase 3, Randomized, Observer-Blind Comparator-Controlled Study, children 6 – 59 months
  • Study Design & Objectives
  • Immunogenicity
  • Safety
  • Conclusion
CLINICAL DEVELOPMENT PROGRAM
BRIEF OVERVIEW
AFLURIA QIV: STEPWISE CLINICAL DEVELOPMENT PROGRAM

- The TIV’s formulation in 2010 Southern Hemisphere: reported increases in fever rates & febrile seizures
- Increasing the concentration of the splitting agent reduced the pyrogenicity of the reformulated vaccine QIV

2014-15

Afluria QIV (≥ 18 yrs)
Phase III, RCT
Immunogenicity and safety
FDA approval in Aug. 2016

2015-16

Afluria QIV Ped. (5 to <18 yrs)
Phase III, RCT
Immunogenicity and safety
FDA approval in Aug. 2017

2016-17

Afluria QIV Ped. (6 m to <5 yrs)
Phase III, RCT
Immunogenicity and safety
FDA approval in Oct. 2018
AFLURIA QIV: STUDY DESIGN & ENROLLMENT

Phase 3, randomized, observer-blinded, comparator-controlled, multicenter study during the Northern Hemisphere during 2016 - 2017

Total Subjects\(^a\)
N = 2247

6 to 35 months of age
n = 935

- Afluria QIV 0.25 mL
  n = 700
- Comparator QIV 0.25 mL
  n = 235

36 to 59 months of age
n = 1312

- Afluria QIV 0.5 mL
  n = 984
- Comparator QIV 0.5 mL
  n = 328

\(^a\) Randomized 3:1 Afluria QIV: Comparator QIV (Fluzone)
Afluria QIV: Study Objectives

• Primary Immunogenicity Objective
  – Non-inferiority of Afluria QIV compared with a US-licensed Comparator QIV in 6 to 59 months of age
    • 6 to 35 months and 36 to 59 months

• Primary Safety Objective
  – Safety and tolerability of Afluria QIV and Comparator QIV in two age strata:
    • 6 to 35 months and 36 to 59 months, and overall
## Afluria QIV: Demographics and Baseline Characteristics

**Full Analysis Set**

<table>
<thead>
<tr>
<th></th>
<th>6-59 months</th>
<th></th>
<th>6-35 months</th>
<th></th>
<th>36-59 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afluria QIV</td>
<td>Comp QIV</td>
<td>Afluria QIV</td>
<td>Comp QIV</td>
<td>Afluria QIV</td>
<td>Comp QIV</td>
</tr>
<tr>
<td></td>
<td>N=1684</td>
<td>N=563</td>
<td>N=700</td>
<td>N=235</td>
<td>N=984</td>
<td>N=328</td>
</tr>
<tr>
<td>Age, median, months</td>
<td>38.0</td>
<td>39.0</td>
<td>22.0</td>
<td>22.0</td>
<td>47.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Sex, female</td>
<td>48.7%</td>
<td>47.6%</td>
<td>48.9%</td>
<td>43.4%</td>
<td>48.6%</td>
<td>50.6%</td>
</tr>
<tr>
<td>White</td>
<td>71.6%</td>
<td>69.4%</td>
<td>73.1%</td>
<td>74.0%</td>
<td>70.4%</td>
<td>66.2%</td>
</tr>
<tr>
<td>Black or Afr. Am.</td>
<td>21.4%</td>
<td>21.8%</td>
<td>20.9%</td>
<td>18.7%</td>
<td>21.8%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Asian</td>
<td>0.9%</td>
<td>1.8%</td>
<td>0.9%</td>
<td>1.7%</td>
<td>0.9%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Pre-vax temp, median (°F)</td>
<td>97.25</td>
<td>97.40</td>
<td>97.20</td>
<td>97.30</td>
<td>97.30</td>
<td>97.40</td>
</tr>
<tr>
<td>Indicated for 2 doses</td>
<td>40.2%</td>
<td>38.7%</td>
<td>61.1%</td>
<td>61.3%</td>
<td>25.3%</td>
<td>22.6%</td>
</tr>
</tbody>
</table>
Non-inferior criteria are met if all eight (8) co-primary endpoints (2 endpoints, 4 strains) meet the following:

– Geometric mean titer (GMT)
  • upper bound of the 2-sided 95% CI of the geometric mean titer ratios (Comp QIV/ Afluria QIV) should not exceed 1.5

– Seroconversion rate (SCR)
  • the upper bound of the 2-sided 95% CI of the seroconversion rate* differences (Comp QIV – Afluria QIV) should be ≤10%

*SCR is defined as baseline seronegative subjects (<1:10) with a post-vaccination GMT ≥ 40 or baseline seropositive subjects (≥1:10) with a 4-fold increase
**AFLURIA QIV: IMMUNOGENICITY RESULTS**

*(GEOMETRIC MEAN TITER RATIO & DIFFERENCE IN SEROCONVERSION RATES, PER-PROTOCOL POPULATION)*

**Ratio of HI Geometric Mean Titer**

- Non-inferior if upper bound 95% CI is $\leq 10$

**Difference in Seroconversion Rates**

- Non-inferior if upper bound 95% CI is $\leq 10$

---

**GMT Ratio (Comp QIV: Afluria QIV)**

- H1N1: 0.75
- H3N2: 0.5
- B-YAM: 0.25
- B-VIC: 1.25

**Difference in SCRS (Comp QIV: Afluria QIV)**

- H1N1: -16
- H3N2: -14
- B-YAM: -12
- B-VIC: -10
Solicited local adverse reactions were similar between groups.
Most reactions were mild or moderate.
AFLURIA QIV: SOLICITED LOCAL ADVERSE REACTIONS
36 – 59 MONTHS AGE GROUP, AFTER ANY VACCINATION

- Solicited local adverse reactions similar between groups
- Most reactions mild or moderate for both vaccines
AFLURIA QIV: SOLICITED SYSTEMIC ADVERSE EVENTS

6 – 35 MONTHS AGE GROUP, AFTER ANY VACCINATION

- Solicited systemic adverse events similar between groups; most events mild or moderate in intensity
AFLURIA QIV: SOLICITED SYSTEMIC ADVERSE EVENTS

36 – 59 MONTHS AGE GROUP, AFTER ANY VACCINATION

- Solicited systemic adverse events similar between groups
- Most events mild or moderate in intensity
AFLURIA QIV: SUMMARY OF FEVER EVENTS
6 – 35 MONTHS AGE GROUP, AFTER ANY VACCINATION

- Overall any fever rate for Afluria QIV was 7.2% and 11.9% for comparator QIV
- Severe related fevers similar between 2 vaccine groups; overall related fever 4% for Afluria QIV vs. 7.9% in comparator QIV

CSLCT-Afluria QIV-15-03
**AFLURIA QIV: SUMMARY OF FEVER EVENTS**

**36 – 59 MONTHS AGE GROUP, AFTER ANY VACCINATION**

- Afluria QIV overall any fever rate (4.8%) similar to comparator QIV (6.0%)
- Severe related fevers similar between 2 vaccine groups; overall related fever 3.1% for Afluria QIV vs. 4.7% in comparator QIV
# Afluria QIV: Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Afluria QIV N = 1684 (full analysis set)</th>
<th>Comparator QIV N = 563 (full analysis set)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>6 – 35 mon</td>
<td>36 – 59 mon</td>
</tr>
<tr>
<td><strong>Safety population</strong></td>
<td>694</td>
<td>979</td>
</tr>
<tr>
<td><strong>Solicited safety pop</strong></td>
<td>669</td>
<td>949</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Discont. due to AE</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>SAEs to Day 28</strong></td>
<td>4 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>SAEs to End of Study</strong></td>
<td>11 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>AESIs to Day 28</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>AESIs to End of Study</strong></td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cellulitis-like reactions</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAE = Serious Adverse Event; AESI = Adverse Event of Special Interest  
* = all events unrelated to study vaccine  
† Interim DL= Interim Database Lock
OVERALL CONCLUSIONS

• Afluria QIV demonstrated noninferior immunogenicity to a US-licensed Comparator QIV

• Safety and Tolerability of Afluria QIV is similar to Comparator QIV in children <60 months
  – Overall any fever (≥ 99.5 °F) rate for Afluria QIV was 7.2% and 11.9% for comparator QIV
  – No febrile convulsion during the first 7 days
  – Severe related fever are similar between the two groups in both age groups

• Afluria QIV was FDA approved in Oct. 2018 for children <60 months of age based on this Phase 3 study
SUPPLEMENTARY SLIDES
AFLURIA QIV-15-03: HALTING RULE CRITERIA

Enrolment will be halted for DSMB review if, during 7 days after vaccination, any of the following occur:
• One or more subjects experience a SUSAR
• One or more subjects experience a related SAE that is life threatening or causes death
• One or more subjects experience a serious febrile AE (SAE associated with fever of \( \geq 101.3\, ^\circ \text{F} / 38.5\, ^\circ \text{C}, \) axillary)
• One or more subjects experience a severe
  – Allergic reaction
  – Injection site ulceration, abscess, or necrosis

If either of the following occur in either age strata:
• \( \geq 5\% \) of subjects experience a cellulitis-like reaction (concurrent severe pain, redness, and swelling)
• \( \geq 5\% \) of subjects experience a related severe (\( \geq 38.5\, ^\circ \text{C} \) / 101.3\, ^\circ \text{F}) fever

DSMB chair notified of any SAE occurring within 7 days after vaccination.

No study halts occurred for CSLCT-QIV-15-03

CSLCT-Afluria QIV-15-03
DSMB = Data Safety Monitoring Board
COMPARISON WITH HISTORICAL FEVER RATES
6 TO 35 MONTHS AGE GROUP

Historical Afluria TIV

- NHF0405
- USF0629
- USF0736
- TIV Pooled

Fluzone USF0736
Fluzone QIV1503
Afluria QIV1503

Fever Rate

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%

CSLCT-Afluria QIV-15-03
COMPARISON WITH HISTORICAL SEVERE FEVER RATES
6 TO 35 MONTHS AGE GROUP

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%
Severe Fever Rate

NHF0405
USF0629
USF0736
TIV Pooled
Fluzone USF0736
Fluzone QIV1503
Afluria QIV1503

CSLCT-Afluria QIV-15-03
COMPARISON WITH HISTORICAL FEVER RATES
36 TO 59 MONTHS AGE GROUP

Fever Rate

Historical Afluria TIV
NHF0405
USF0629
USF0736
TIV Pooled
Fluzone USF0736
Fluzone QIV1503
Afluria QIV1503

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%

Fever Rate

CSLCT-Afluria QIV-15-03
COMPARISON WITH HISTORICAL SEVERE FEVER RATES
36 TO 59 MONTHS AGE GROUP
Concomitant Use with other Childhood Vaccines

• Concomitant vaccinations were an exclusion criteria for the purpose of evaluating the safety of Afluria QIV without confounders that may impact the reactogenicity
  – Inadvertent concomitant vaccinations were varicella, MMR, polio, pneumococcal, DTAP, HiB, HepA and HepB.
  – However, these were taken > 7 days after study vaccine and therefore no conclusions can be drawn with respect to reactogenicity

• Overall fever rate for Afluria QIV (7.2%) was significantly lower than Fluzone QIV (11.9%).