Outline of Presentation

• Review Comprehensive Investigation on 2010 Adverse Events in Southern Hemisphere
  – CSL 2010 SH Trivalent Influenza Vaccine (TIV)
    • purified, inactivated, split virion influenza vaccine

• Staged Clinical Development Program for Afluria
  – Peds 5 yrs to <9yrs modified TIV Safety Ph IV
  – Adult ≥18 yrs QIV Immunogenicity & Safety Ph III
  – Peds 5 yrs to <18 yrs QIV Immunogenicity & Safety Ph III
  – Peds 6m to 59m QIV Immunogenicity & Safety Ph III
Afluria®:

- Purified, inactivated, split virion influenza vaccine
- Manufactured at Parkville, Australia for >40 years
- Vaccine formulations:
  - thimerosal-free 0.5mL pre-filled syringe
  - thimerosal-containing 5mL multi-dose vial

- US Licensure:
  ≥18 years TIV: FDA approval in Nov 2007
  5 years to <18 years TIV: indication extended Dec 2011
  ≥18 years QIV: FDA approval in Aug 2016
    - 5 years to <18 years QIV: sBLA submitted to FDA
2010 Adverse Events in Southern Hemisphere

CSL 2010 SH TIV

• Increased reports of fever and febrile seizures, mainly in children aged <5 years compared to previous seasons
  – Occurring 4 to 24 hours after receiving CSL 2010 SH TIV
• Increased reports of fever also seen in children aged 5 yrs to <9 yrs

US Prescribing information

AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures

ACIP Recommendation (extract)

Other age-appropriate, licensed seasonal influenza vaccine formulation should be used in children aged 6 months through 8 years. If no other option is available for a child aged 5-8 years who has a medical condition that increases the risk for influenza complications, Afluria can be used; however, benefits and risks should be discussed with parents or caregivers.
Systematic and Comprehensive Investigation
Three Discrete Programs

1. Clinical Safety Review
   • Characterize the adverse events
   • Identify risk factors and at-risk populations

2. Manufacturing & Quality Review
   • Assessment of Safety and Manufacturing processes
   • Assessment of Quality (Purity and Potency)

3. Scientific Research Investigation
   • Explore potential indirect surrogate measures
     – *in vivo* and *in vitro* tests
   • Identify differences between manufacturers’ Flu vaccines
1. Clinical Safety Review

Unexpected Increase in Fever & Febrile Seizures in Southern Hemisphere in 2010

• Adverse Events (AE) occurred in Pediatric age ranges
  – The safety signal of fever and febrile seizures were highest in children younger than 5 years old
    » Febrile seizures typically occur in children between the ages of 6 months and up to 6 years due to the stage of hypothalamic development in young children

• Increased fever reports was also seen 5 years to <9 year olds
  – Due to the age-related nature of febrile seizures, no evidence was found in children >5 years of age with regard to febrile seizures following vaccination with the CSL 2010 SH TIV

Maraskovsky E et al. / Vaccine 30 (2012) 7400–7406
Rockman S et al. / Vaccine 32 (2014) 3861–3868
2. Review of Manufacturing Process

β-Propiolactone (BPL)  Sodium Tauro Deoxycholate (TDOC)
2. Manufacturing & Quality Review

Detailed review of all manufacturing aspects
- Starting at Seed---all the way to---Fill & Finish
  - including raw materials and processes;
- No deviation or change from previous seasonal formulation
- All batches met specification
  - No evidence of batch specific issues
- Laboratory testing
  - Ruled out chemical contamination
  - Ruled out bacterial contamination
  - Ruled out viral contamination
- No evidence of agglomeration as a contributing factor
2. Manufacturing & Quality Review

WHO recommended 3 new virus strains for inclusion in the 2010 influenza vaccines for the Southern Hemisphere (SH)
  – Complete strain change between 2009 and 2010

– TIV 2009 SH
  • A/Brisbane/59/2007 (H1N1) – Like
  • A/Uruguay/716/2007 (H3N2) – Like
  • B/Florida/4/2006 – Like

– TIV 2010 SH
  • A/California/7/2009 (H1N1) – Like
  • A/Perth/16/2009 (H3N2) – Like
  • B/Brisbane/60/2008 – Like
3. Scientific Research Investigation

- **In vivo models**
  - No suitable in vivo animal model for febrile seizures
  - None of the TIVs tested, including the CSL 2010 SH TIV, induced symptoms consistent with febrile seizures in any of the *in vivo* models examined

- **In vitro models**
  - Published literature suggested that increased cytokine levels were observed after febrile seizures
  - Thus cytokine/chemokine models were explored as correlates of *in vivo* pyrogenicity
  - Mapping these cytokines/chemokines *in vitro* may act as an indirect surrogate measure of the reactogenic potential of the TIVs
3. Scientific Research Investigation

• *In vitro* models
  – CSL 2010 SH TIV stimulated the release of cytokines and chemokines in whole blood assays more robustly than previous CSL TIVs or other manufacturers’ TIVs

• The difference between the CSL 2010 SH TIV and other TIVs suggested that the manufacturing process may have played a role

• The difference between the CSL 2010 SH TIV and previous CSL TIVs suggested that the new influenza strains may have played a role
– CSL manufacturing process resulted in more residual lipid and RNA components with the CSL 2010 SH TIV than other licensed flu vaccines
– Lab studies failed to demonstrate an inflammatory signal with RNA alone in the *in vitro* assays
– Further studies showed the lipid-mediated delivery of fragmented viral RNA induced a stronger than expected signal
– These findings suggested that the residual lipid content inversely correlated with the concentration of TDOC
Effect of Varying TDOC levels on Cytokine Signaling

<table>
<thead>
<tr>
<th>%TDOC</th>
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<th>%TDOC</th>
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</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>H3N2</td>
<td>B</td>
</tr>
<tr>
<td>Std TIV</td>
<td>0.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>New #1</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>New #2</td>
<td>0.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>New #3</td>
<td>1.5%</td>
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</table>

Increasing TDOC for both H1N1 /California/07/2009 and B/Brisbane/60/2008 resulted in the greatest attenuation of the inflammatory signal.
Summary of Comprehensive Scientific Investigation

– *In vitro* models demonstrated that lipids and degraded RNA fragments “preserved by the standard TDOC manufacturing process” as well as the 3 new strains were the contributing factors of the CSL 2010 SH TIV pediatric AE profile

– The investigation demonstrated that increasing levels of TDOC attenuated the pro-inflammatory signals *in vitro*

– These conclusions led to the staged approach to a new Clinical Development Program for Afluria
Afluria Staged Clinical Development Plan

2013

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

2014-15

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

QIV Adult (≥18 yrs)
QIV: CSL-TIV-1: CSL-TIV-2;
2:1:1; n= 3484
Ph 3, RCT*
Immunogenicity and Safety

2015-16

QIV Pediatric (5 yrs to <18 yrs)
QIV: QIV comparator; 3:1; n= 2278
Ph 3, RCT**
Immunogenicity and Safety

2016-17

QIV Pediatric (6 mths to 59 mths)
QIV: QIV comparator; 3:1, n= 2222
Ph 3, RCT**
Immunogenicity and Safety

* = 1.5% TDOC splitting B strain
** = 1.5% TDOC splitting all strains:
within registered conditions
RCT = randomised controlled trial
Pediatric Phase 4 Safety Study 5 years to <9 years
Modified* Trivalent Influenza Vaccine

• Exploratory study to examine febrile events
  – Phase IV trial with B strain split at 1.5% TDOC
  – Subjects (n= 402) (5 years to <9 years) in 2014/15 NH influenza season to evaluate safety and tolerability
  – Results to Inform QIV Pediatric clinical development program
  – Results to use as an indirect comparison with historical data and comparator QIV

*within registered conditions
H3N2 at 1.5% TDOC and H1N1 at 0.9% TDOC

Phase 4 Study: Modified TIV
Fever rates post vaccination in children aged 5 years to <9 years

Previous TIV: B strain split at 0.6% TDOC, H3N2 at 1.5% TDOC, H1N1 at 0.9% TDOC
Study TIV: B strain split at 1.5% TDOC, H3N2 at 1.5% TDOC and H1N1 at 0.9% TDOC (within registered conditions)

- CSL TIV fever rate similar to Reference QIV
  - CSL TIV: 8.2% (95% CI: 5.3, 12.0), Reference QIV: 9.2% (95% CI: 4.3, 16.7)
Comparison with Historical Fever Rates
5 years to <9 years age group

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Fever Rate</th>
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<tbody>
<tr>
<td>Historical TIV</td>
<td></td>
</tr>
<tr>
<td>CSL NHF0405</td>
<td>0%</td>
</tr>
<tr>
<td>CSL USF0629</td>
<td>2%</td>
</tr>
<tr>
<td>CSL USF0736</td>
<td>4%</td>
</tr>
<tr>
<td>CSL TIV Pooled*</td>
<td>6%</td>
</tr>
<tr>
<td>CSL USF1069</td>
<td>8%</td>
</tr>
<tr>
<td>Fluzone USF1069</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
Comparison with Historical Severe Fever Rates
5 years to <9 years age group

Severe fever intensity ≥ 39.0°C

*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
Conclusions: Modified TIV Study and next steps

CSL TIV fever rates observed in the study were similar to comparator QIV vaccine in children 5 yrs to <9 yrs

– Afluria QIV clinical development program incorporated the increased TDOC concentration for splitting all strains

– Staged approach for QIV program:
  • Phase III Study ≥18 years (FDA Approved)
  • Phase III Study 5 years to <18 years (Submitted)
  • Phase III Study 6 months to 59 months (Ongoing)

Phase III Trials are Immunogenicity and Safety
Afluria Peds QIV: Key Immunogenicity Findings
5 years to <18 years

All 8 co-primary endpoints met

- Afluria QIV demonstrated non-inferior immunogenicity for all strains to the comparator QIV (Fluarix QIV) in children 5 years to <18 years of age

- Descriptive secondary immunogenicity endpoints overall, and by age subgroups (5 yrs to <9 yrs, and 9 yrs to <18 yrs inclusive) were robust and consistent with expectations for these age groups, and similar with the comparator QIV
Afluria QIV 5 yrs to <18 yrs: Fever rates following vaccination

**Previous TIV:** B strain split at 0.6% TDOC, H3N2 at 1.5% TDOC, H1N1 at 0.9% TDOC

**Study 10-69 TIV:** B strain split at 1.5% TDOC, H3N2 at 1.5% TDOC and H1N1 at 0.9% TDOC

**QIV 13-02** with all strains split at 1.5% TDOC (within registered conditions)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Afluria QIV</th>
<th>Comp QIV</th>
<th>Afluria QIV</th>
<th>Comp QIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 8 yrs</td>
<td>N = 829</td>
<td>N = 274</td>
<td>N = 792</td>
<td>N = 261</td>
</tr>
<tr>
<td>9 - 17 yrs</td>
<td></td>
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**Afluria QIV fever rate similar to comparator QIV in both age groups**

- **5 yrs to <9 yrs:** 4.5% (95% CI: 3.2, 6.1) vs 3.6% (95% CI: 1.8, 6.6)
- **9 yrs to <18 yrs:** 2.1% (95% CI: 1.3, 3.4) vs 0.8% (95% CI: 0.1, 2.7)
Comparison with Historical Fever Rates

5 years to <9 years age group

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<td>8%</td>
</tr>
<tr>
<td>Fluzone USF0736</td>
<td>10%</td>
</tr>
<tr>
<td>Fluzone USF1069</td>
<td>12%</td>
</tr>
<tr>
<td>Fluarix QIV1302</td>
<td>14%</td>
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<tr>
<td>Afluria QIV</td>
<td>16%</td>
</tr>
</tbody>
</table>

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Comparison with Historical Severe Fever Rates
5 years to <9 years age group

Historical TIV
↑ TDOC TIV (B Strain)
Comparator TIV/QIV
↑ TDOC QIV (All Strains)

*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
Severe fever intensity ≥ 39.0°C
Summary of Afluria (TIV & QIV) Safety in 5 years to <18 years

• Acceptable Safety Profile in TIV & QIV
  – Fever rates (5 years to <9 years) similar to comparator
  – Fever rates (5 years to <9 years) less than historical vaccines

• Both Afluria TIV & QIV will be offered in the U.S. during the 2017-2018 Influenza season
THANK YOU