Afluria® Update

Comprehensive Investigation and Path Forward

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ACIP

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

Poland GA et al. / Vaccine 31S (2013) A1– A20
Maraskovsky E et al. / Vaccine 30 (2012) 7400– 7406

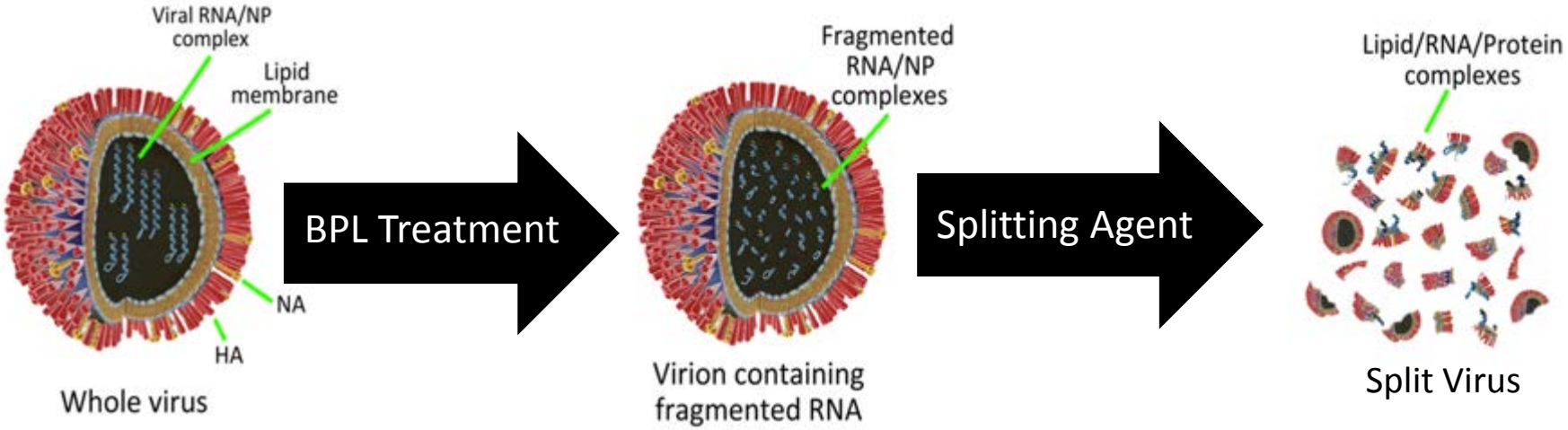
1. Clinical Safety Review

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-Propriolactone (BPL)

Sodium Tauro Deoxycholate (TDOC)

Poland GA et al. / Vaccine 31S (2013) A1– A20
Maraskovsky Vaccine 2014

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

Poland GA et al. / Vaccine 31S (2013) A1– A20

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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*

Maraskovsky E et al. / Vaccine 30 (2012) 7400– 7406

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

Rockman S et al. / Vaccine 32 (2014) 3861–3868

3. Scientific Research Investigation

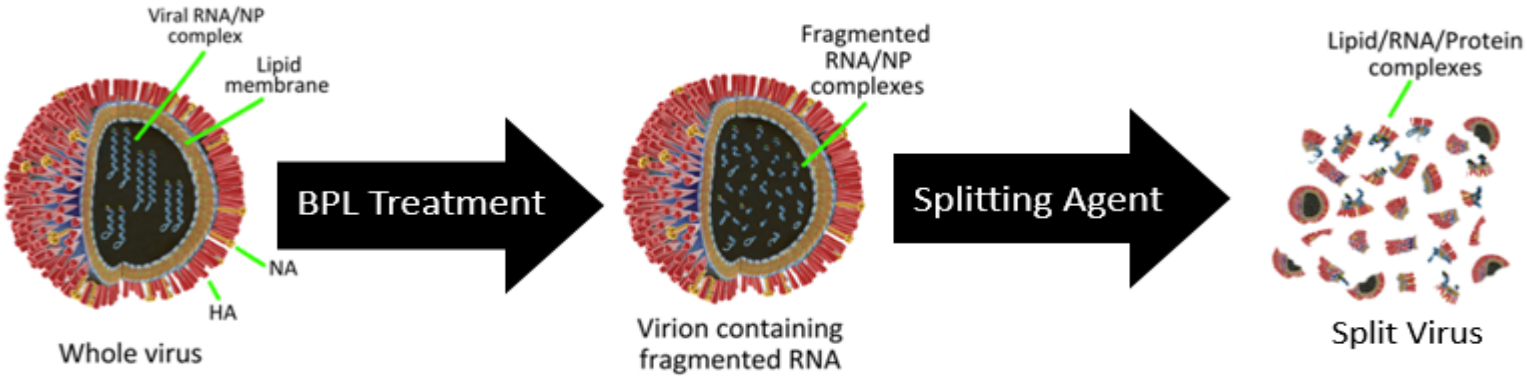
- *In vitro* models
  - CSL 2010 SH TIV stimulated the release of cytokines and chemokines in whole blood assays more robustly than previous CSL TIVs or other manufacturers' TIVs

    - 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

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

Manufacturing Process



β-Propriolactone (BPL)

Sodium Tauro Deoxycholate (TDOC)

- 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

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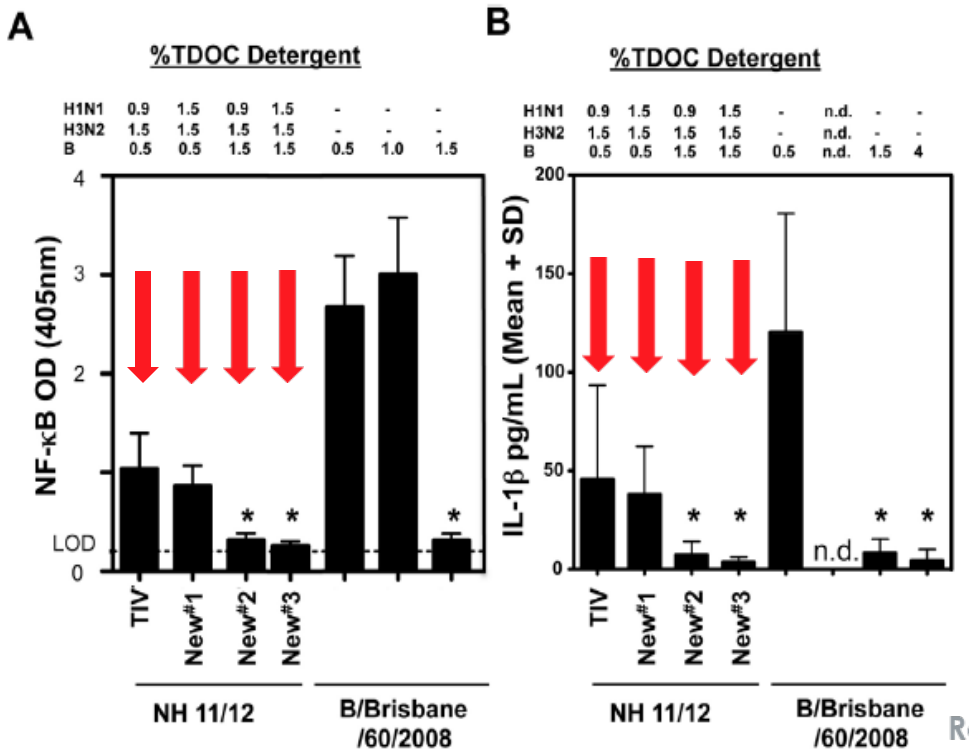
Rockman S et al. / Vaccine 32 (2014) 3861–3868; Rockman S et al. / Vaccine 32 (2014) 3869–3876

Effect of Varying TDOC levels on Cytokine Signaling

	%TDOC H1N1 A/California/07/2009	%TDOC H3N2 A/Victoria/210/2009	%TDOC B B/Brisbane/60/2008
Std TIV	0.9%	1.5%	0.5%
New #1	1.5% ↑	1.5% ↔	0.5% ↔
New #2	0.9% ↔	1.5% ↔	1.5% ↑
New #3	1.5% ↑	1.5% ↔	1.5% ↑



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

Rockman S et al. / Vaccine 32 (2014) 3869–3874

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

Rockman S et al. / Vaccine 32 (2014) 3869–3876

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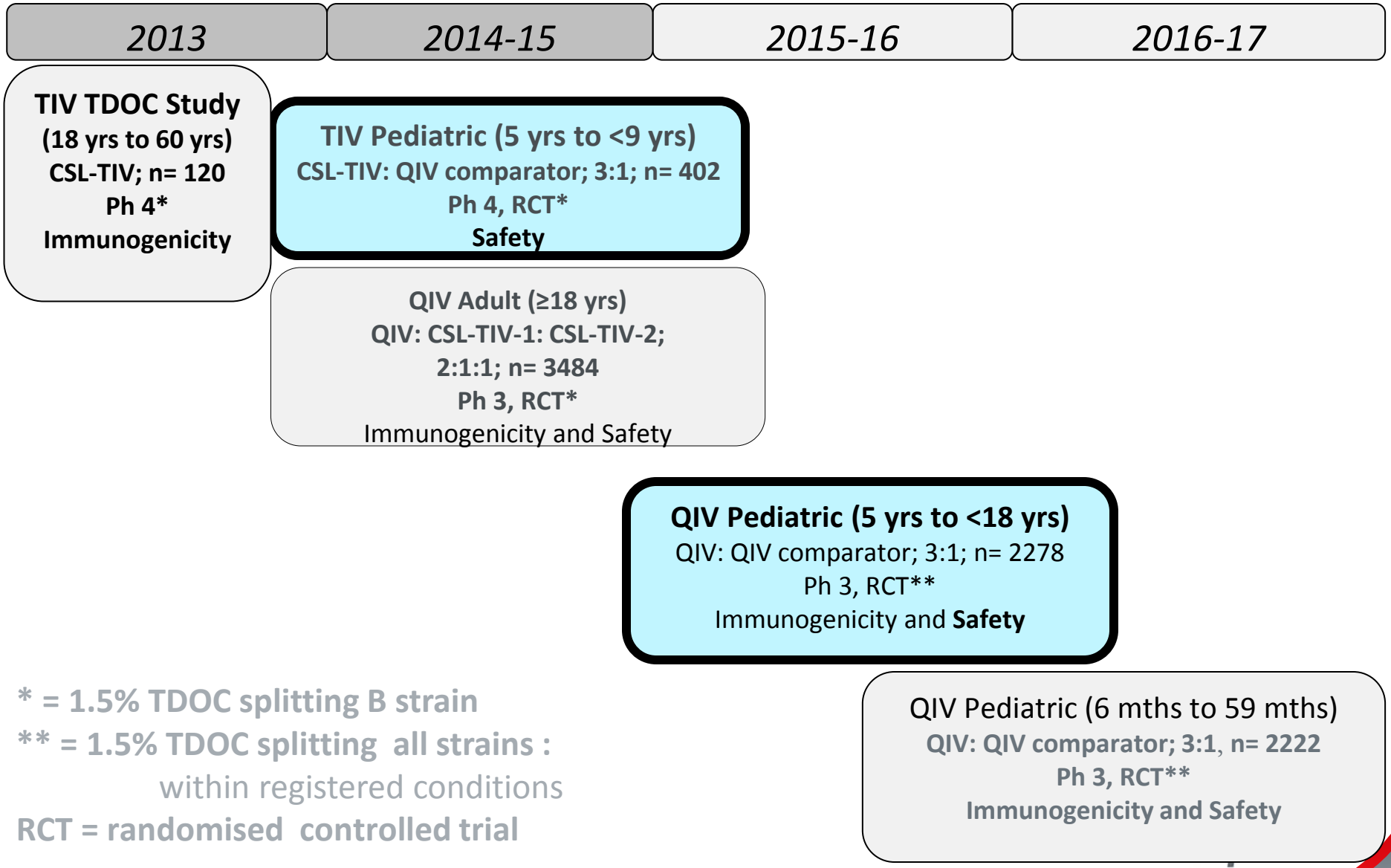
Afluria Staged Clinical Development Plan



* = 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

TIV-10-69 Study; https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000175-27/results

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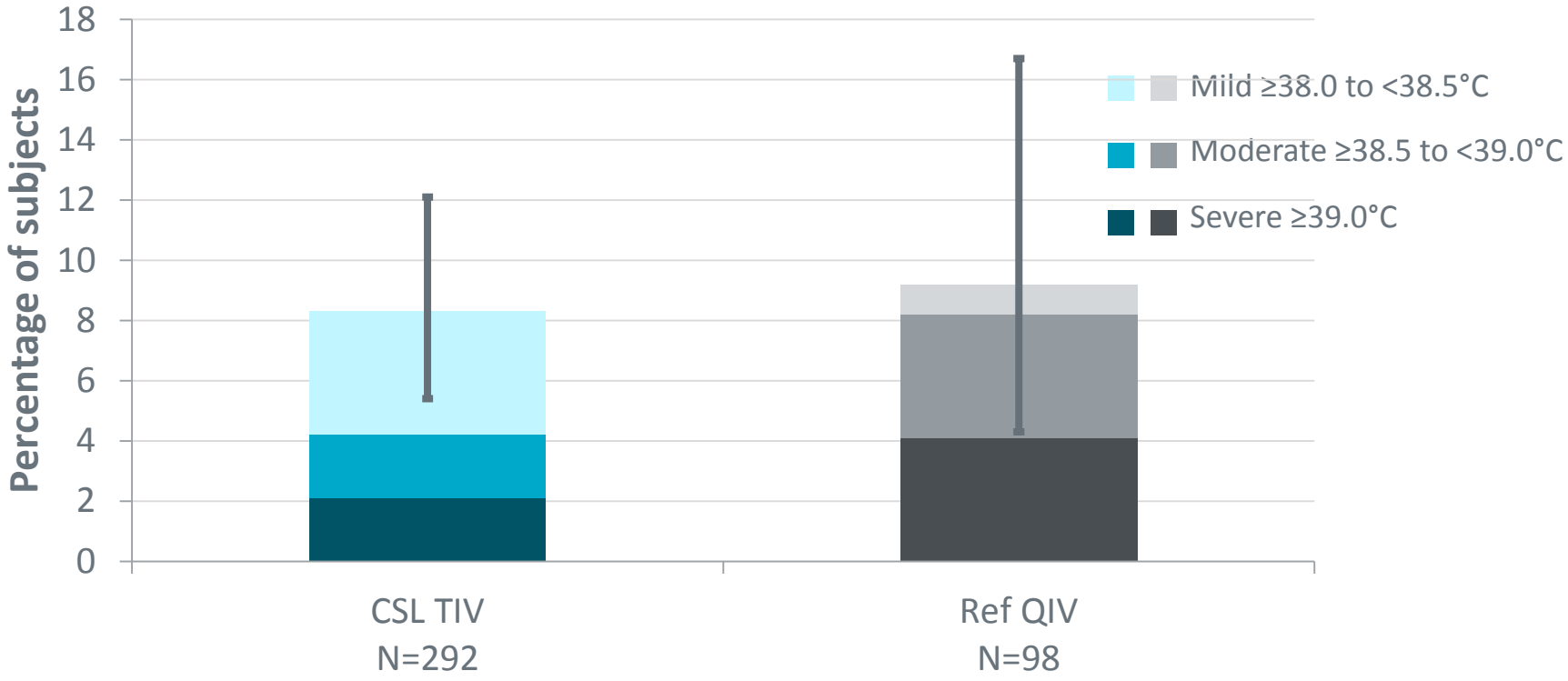
Phase 4 Study: Modified TIV
Fever rates post vaccination in children aged 5 years to <9 years

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)**

TIV-10-69 Study (NH 2014/15)

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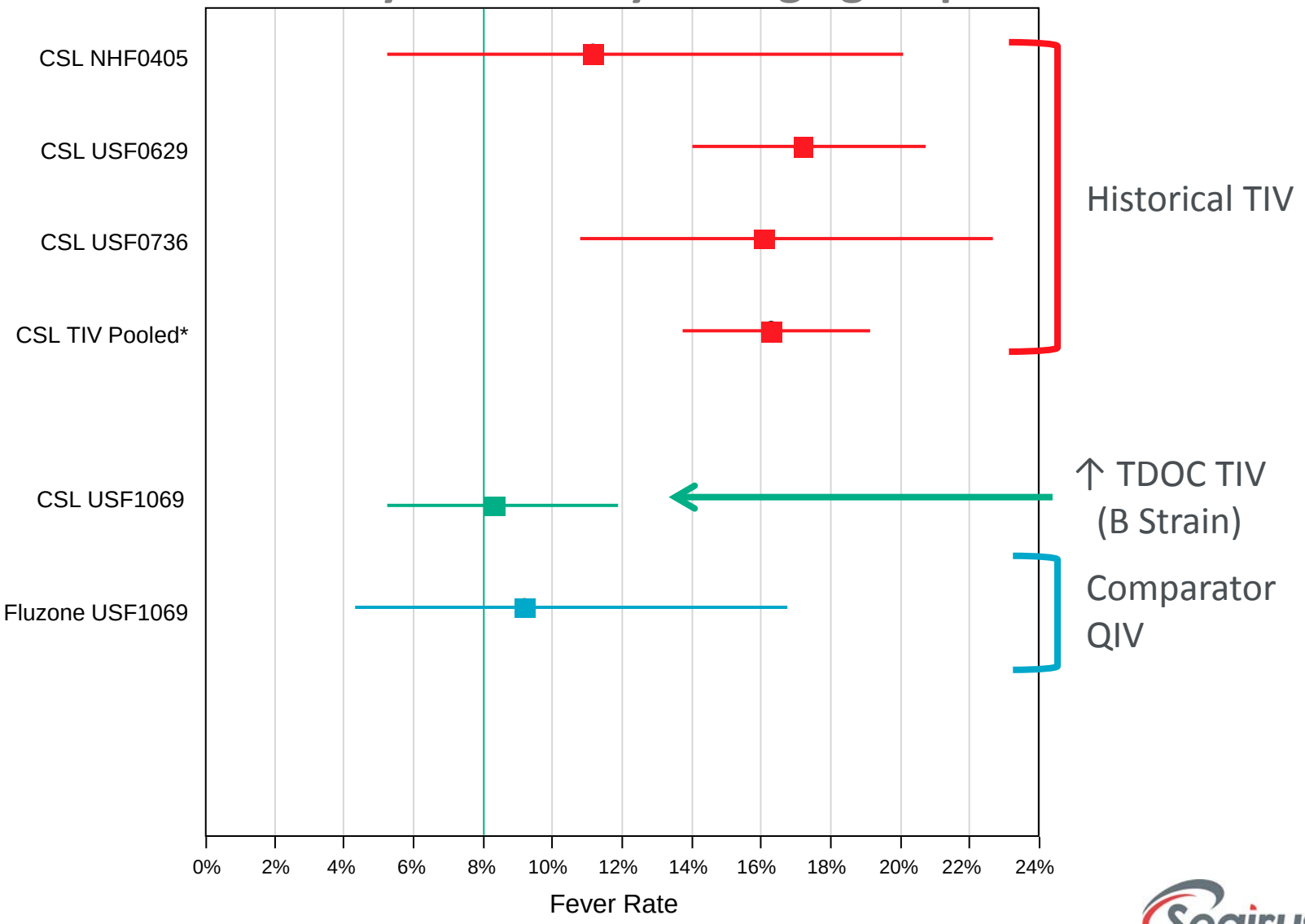
Comparison with Historical Fever Rates

5 years to <9 years age group



*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000175-27/results

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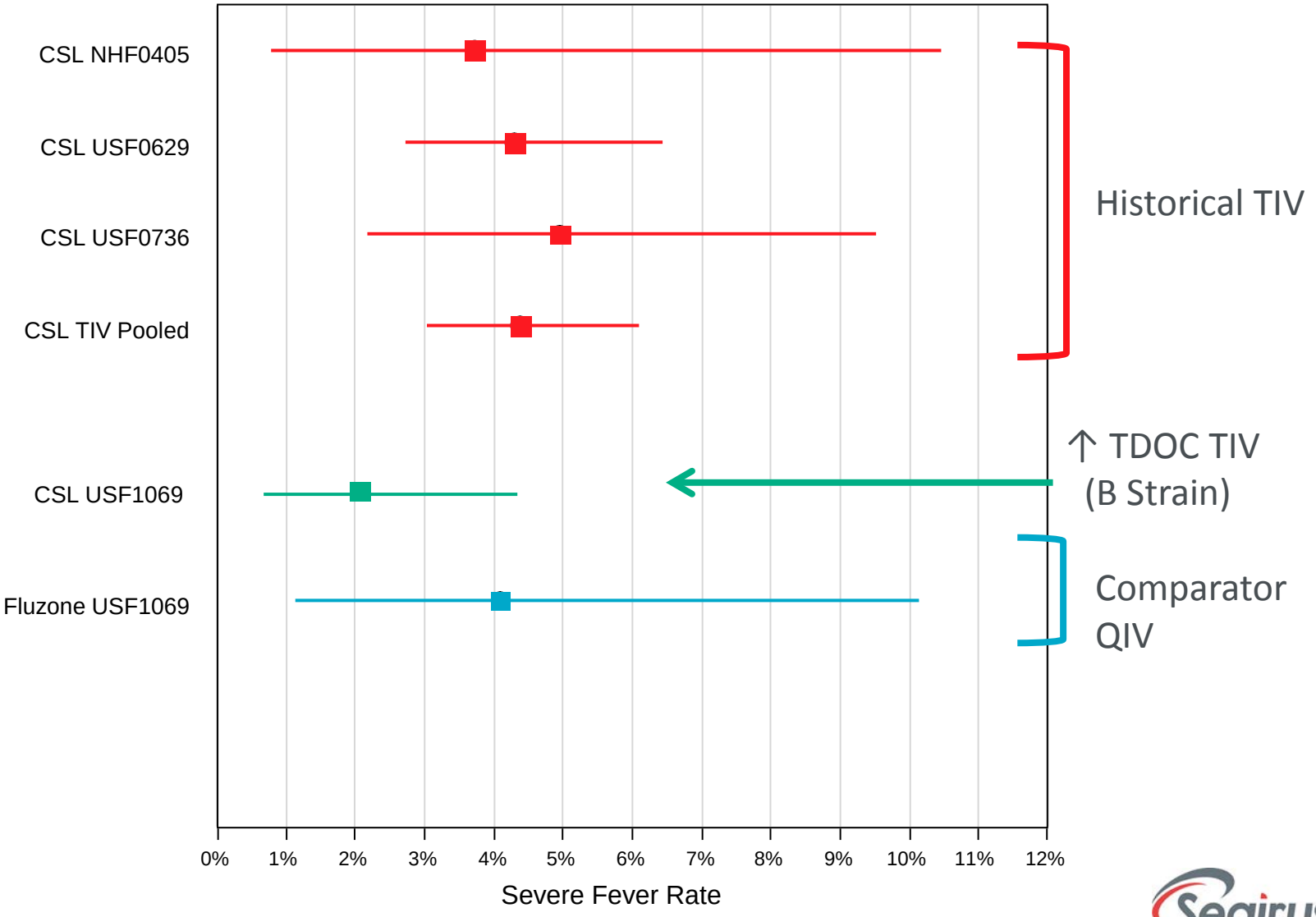
Comparison with Historical Severe Fever Rates

5 years to <9 years age group



*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
Severe fever intensity ≥ 39.0°C

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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

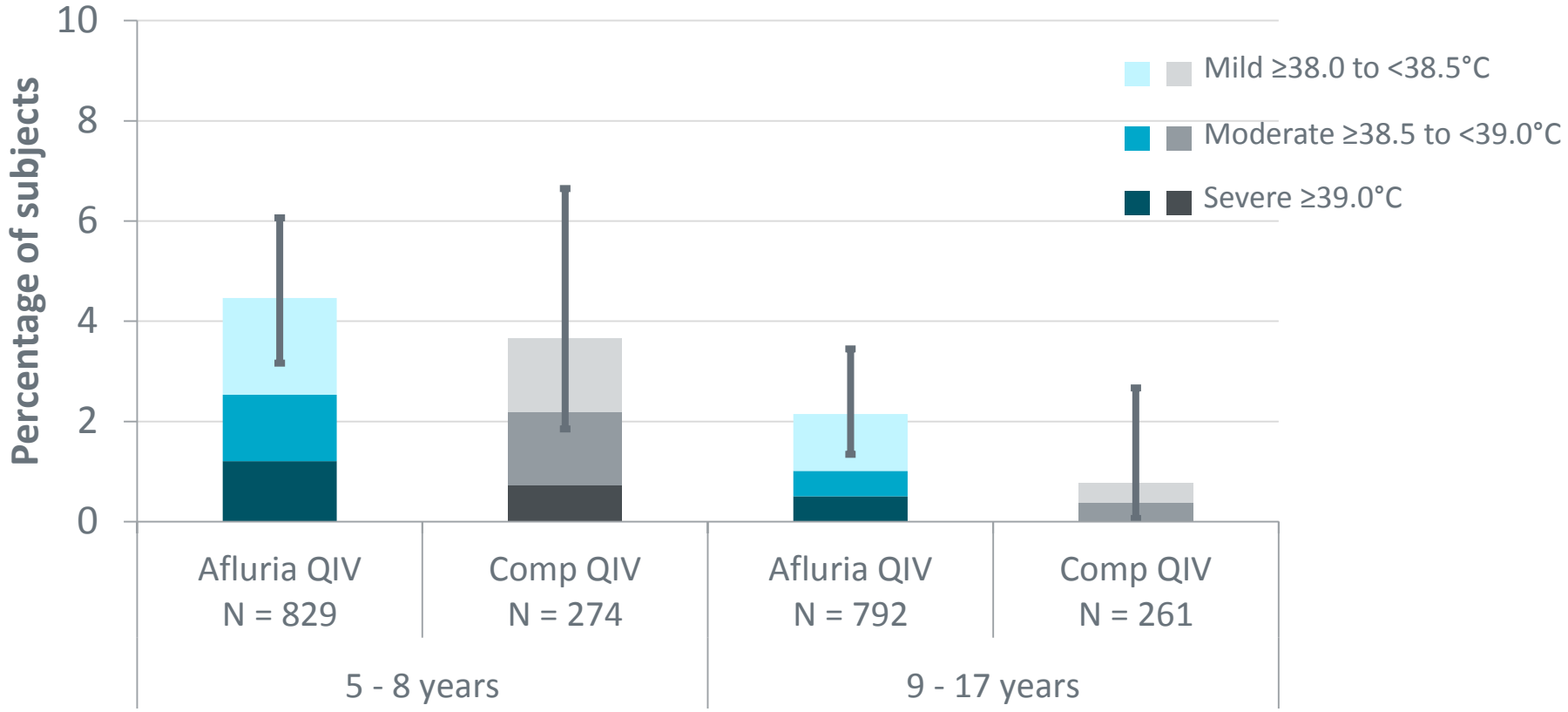
All 8 co-primary endpoints met

- 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)



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)

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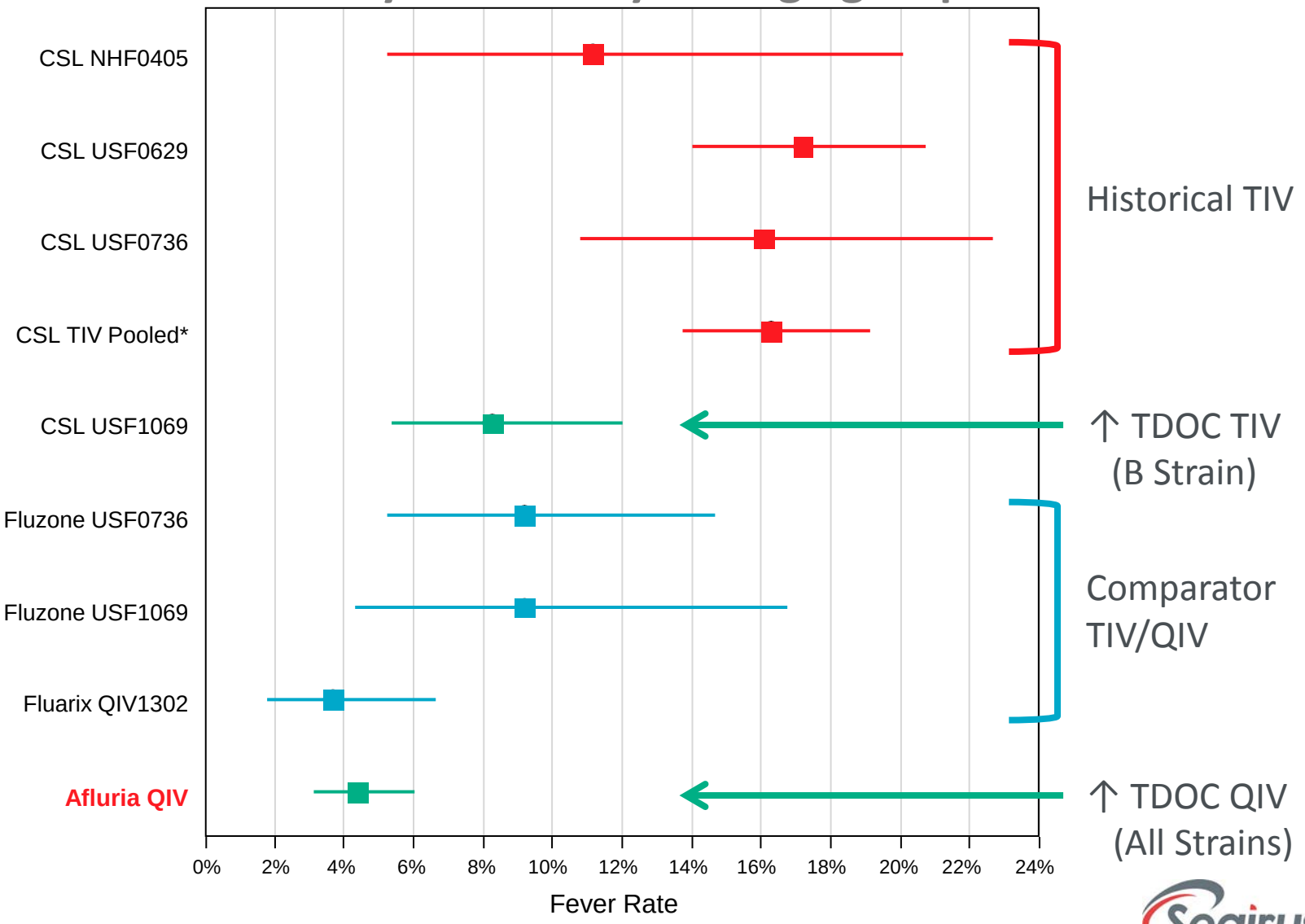
Comparison with Historical Fever Rates

5 years to <9 years age group



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Leong J, et al. file:///C:/Users/SU000044/Downloads/POSTER77_761.pdf

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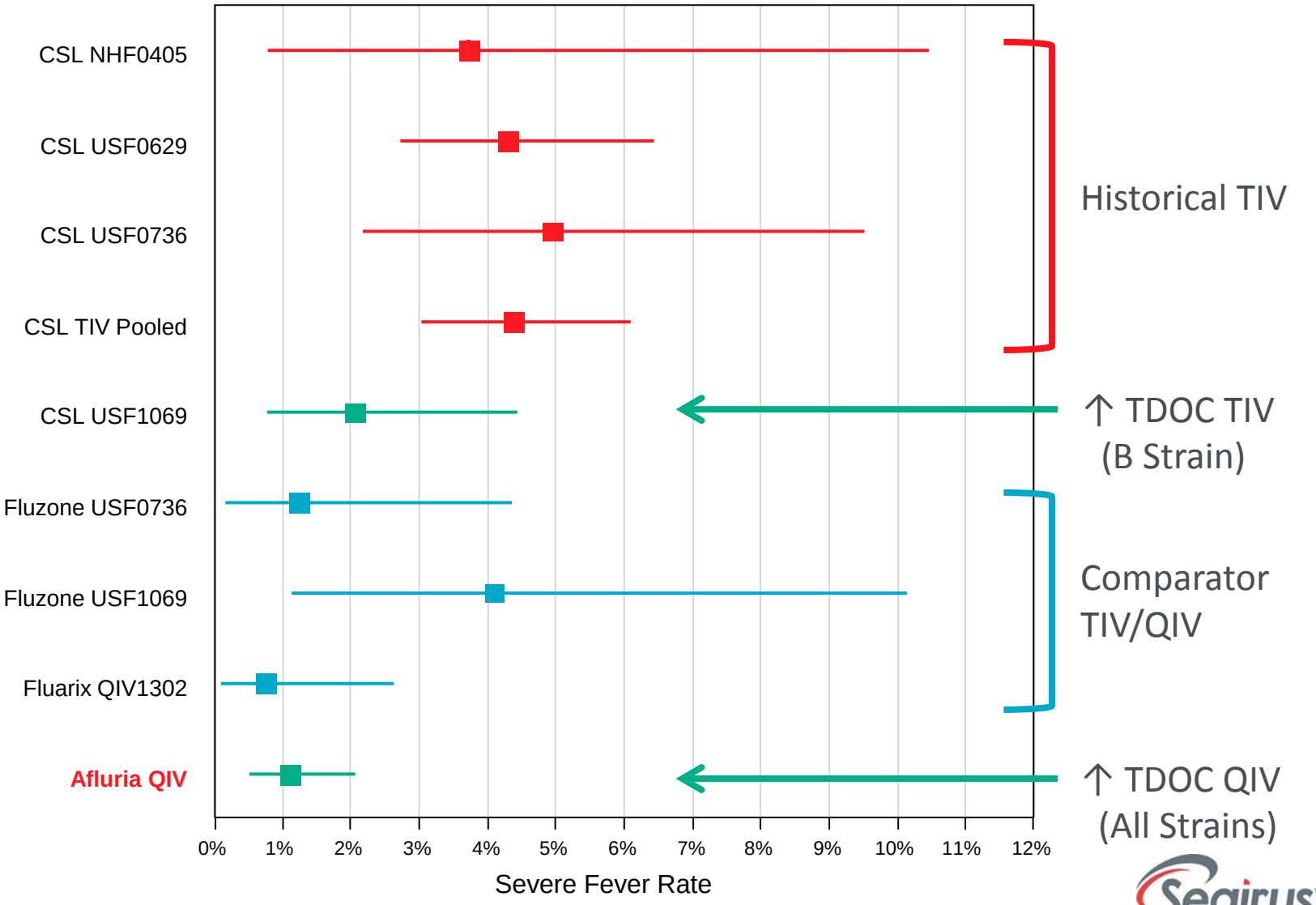
Comparison with Historical Severe Fever Rates

5 years to <9 years age group



*Pooled estimate includes studies CSLCT-NHF-04-05, CSLCT-USF-10-69, and CSLCT-USF-07-36
Severe fever intensity ≥ 39.0°C

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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

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THANK YOU