Afluria Quadrivalent (Afluria QIV)

Phase III, Randomized, Observer-Blind Comparator-Controlled Study, children 6 – 59 months

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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





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CLINICAL DEVELOPMENT PROGRAM BRIEF OVERVIEW

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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

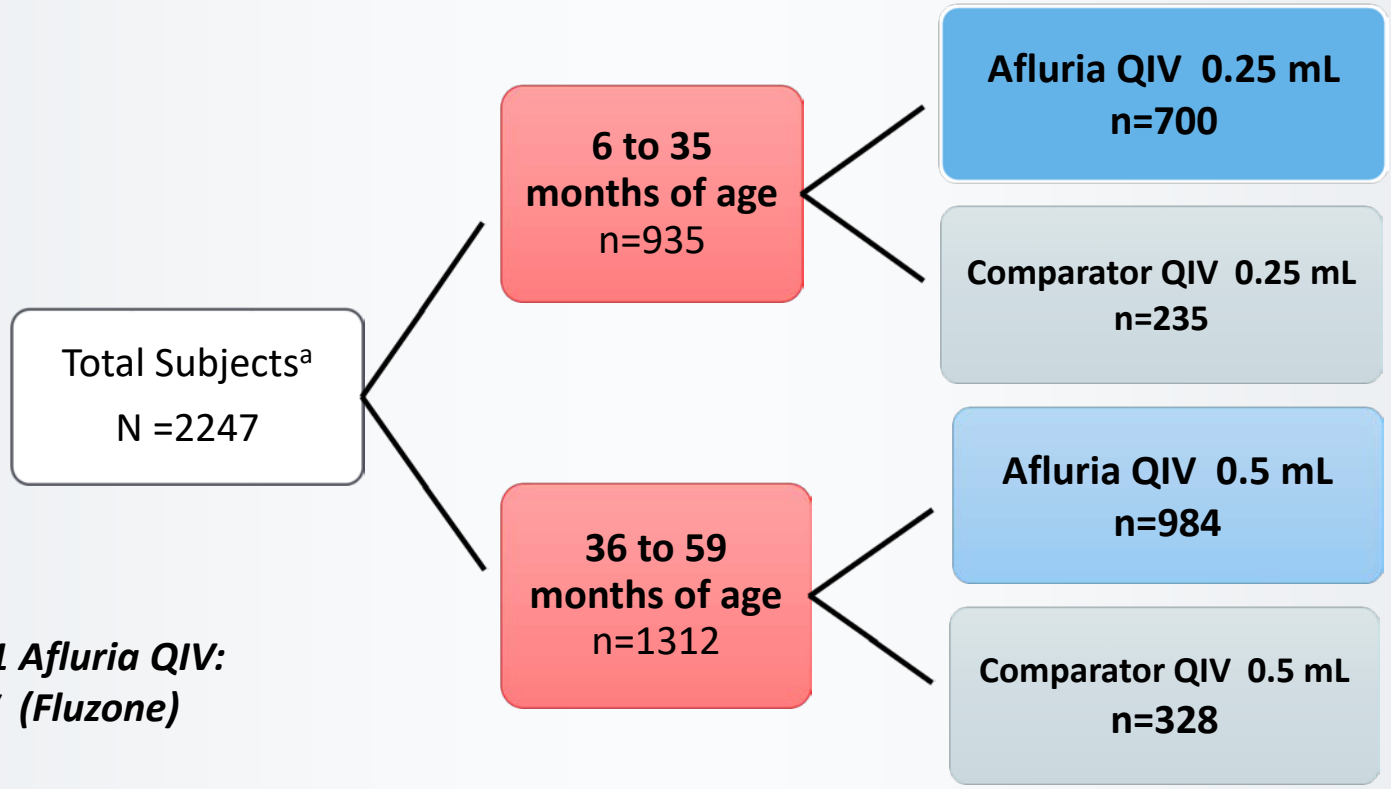
Afluria QIV Ped. (5 to <18 yrs)
Phase III, RCT
Immunogenicity and safety
FDA approval in Aug. 2017

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



[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

	6-59 months		6-35 months		36-59 months	
	Afluria QIV N=1684	**Comp QIV N=563**	Afluria QIV N=700	Comp QIV N=235	Afluria QIV N=984	Comp QIV N=328
Age, median, months	**38.0**	**39.0**	22.0	22.0	47.0	47.0
Sex, female	**48.7%**	**47.6%**	48.9%	43.4%	48.6%	50.6%
White	**71.6%**	**69.4%**	73.1%	74.0%	70.4%	66.2%
Black or Afr. Am.	**21.4%**	**21.8%**	20.9%	18.7%	21.8%	24.1%
Asian	**0.9%**	**1.8%**	0.9%	1.7%	0.9%	1.8%
Pre-vax temp, median (°F)	**97.25**	**97.40**	97.20	97.30	97.30	97.40
Indicated for 2 doses	**40.2%**	**38.7%**	61.1%	61.3%	25.3%	22.6%

AFLURIA QIV
IMMUNOGENICITY RESULTS SUMMARY

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Afluria QIV: Non-inferiority and Co-primary Endpoints

Non-inferior criteria are met if all eight (8) co-primary endpoints (2 endpoints, 4 strains) meet the following:

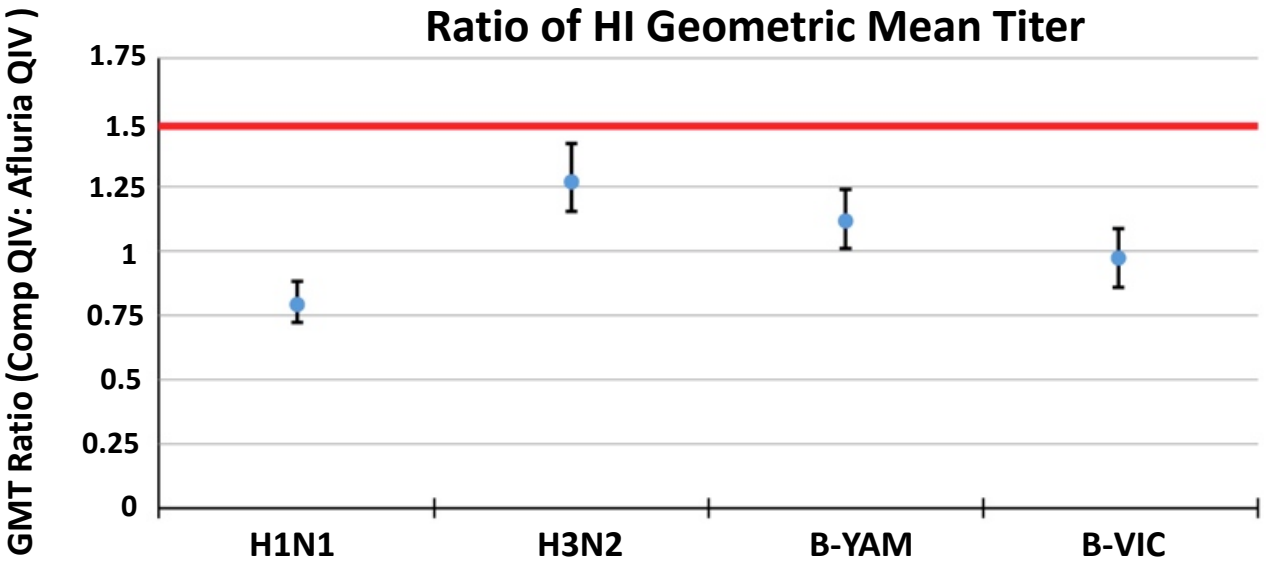
- **Geometric mean titer (GMT)**
  - upper bound of the 2-sided 95% CI of the **geometric mean titer ratios (Comp QIV/ Afluria QIV)** should ***not exceed 1.5***

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

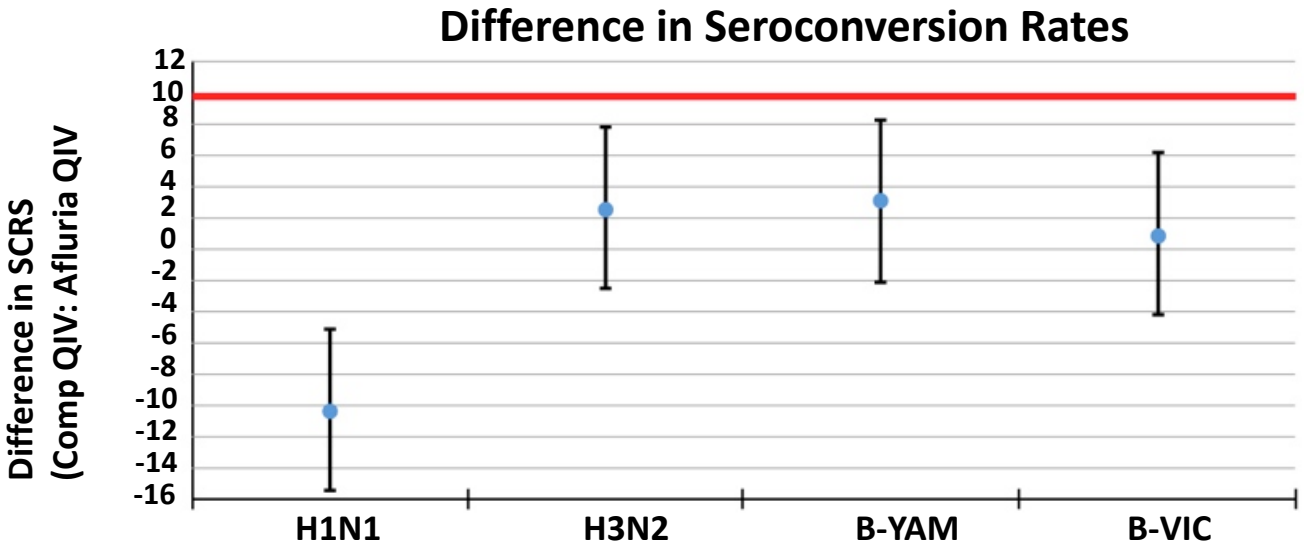
*SCR is defined as baseline seronegative subjects (<1:10) with a post-vaccination GMT ≥ 40 or baseline seropositive subjects (≥1:10) with a 4-fold increase

AFLURIA QIV: IMMUNOGENICITY RESULTS

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



Non-inferior if upper bound 95% CI is < 1.5



Non-inferior if upper bound 95% CI is ≤ 10%

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AFLURIA QIV SAFETY/TOLERABILITY RESULTS

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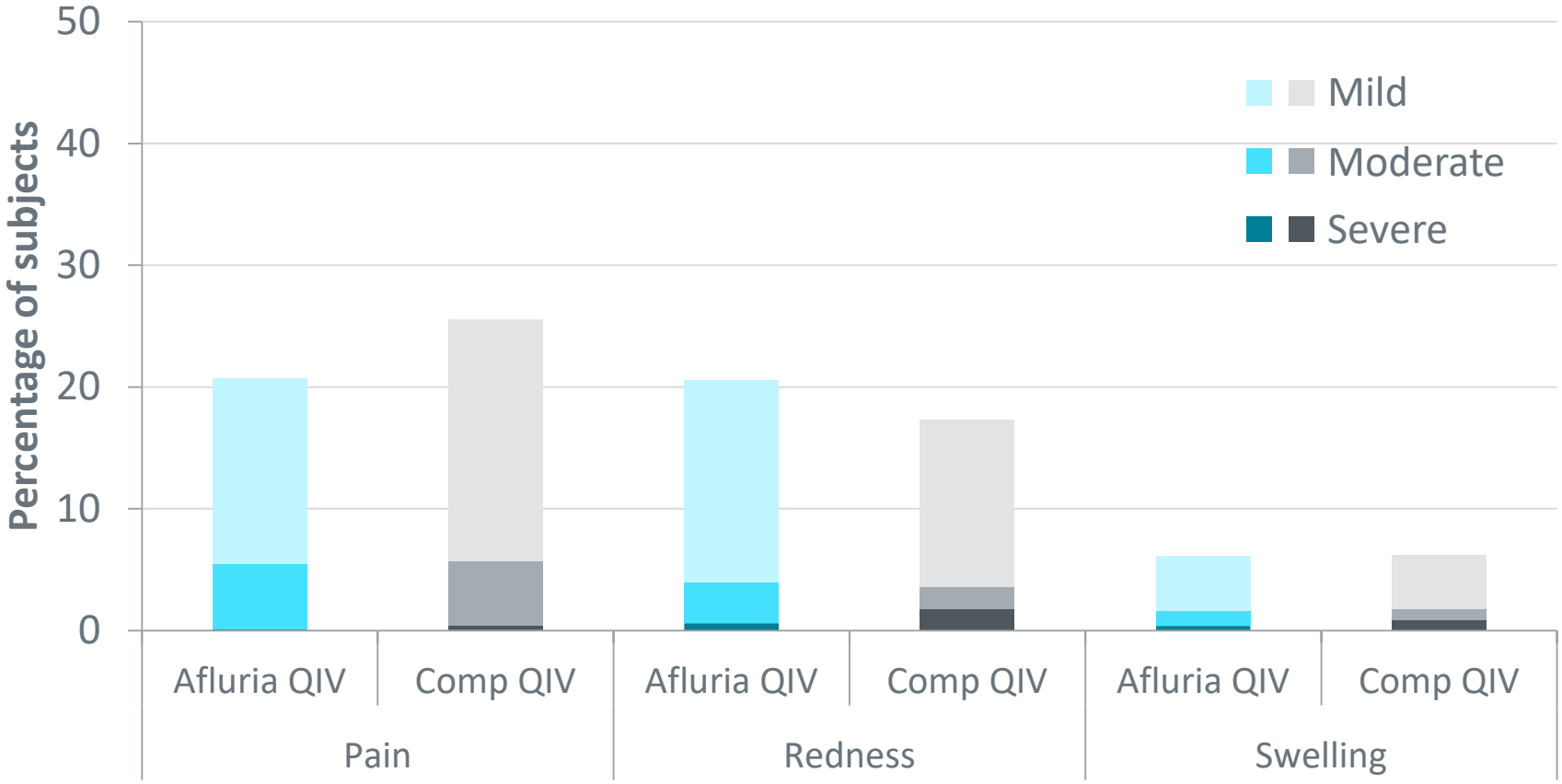
AFLURIA QIV: SOLICITED LOCAL ADVERSE REACTIONS

6 – 35 MONTHS AGE GROUP, AFTER ANY VACCINATION



- Solicited local adverse reactions were similar between groups
- Most reactions were mild or moderate

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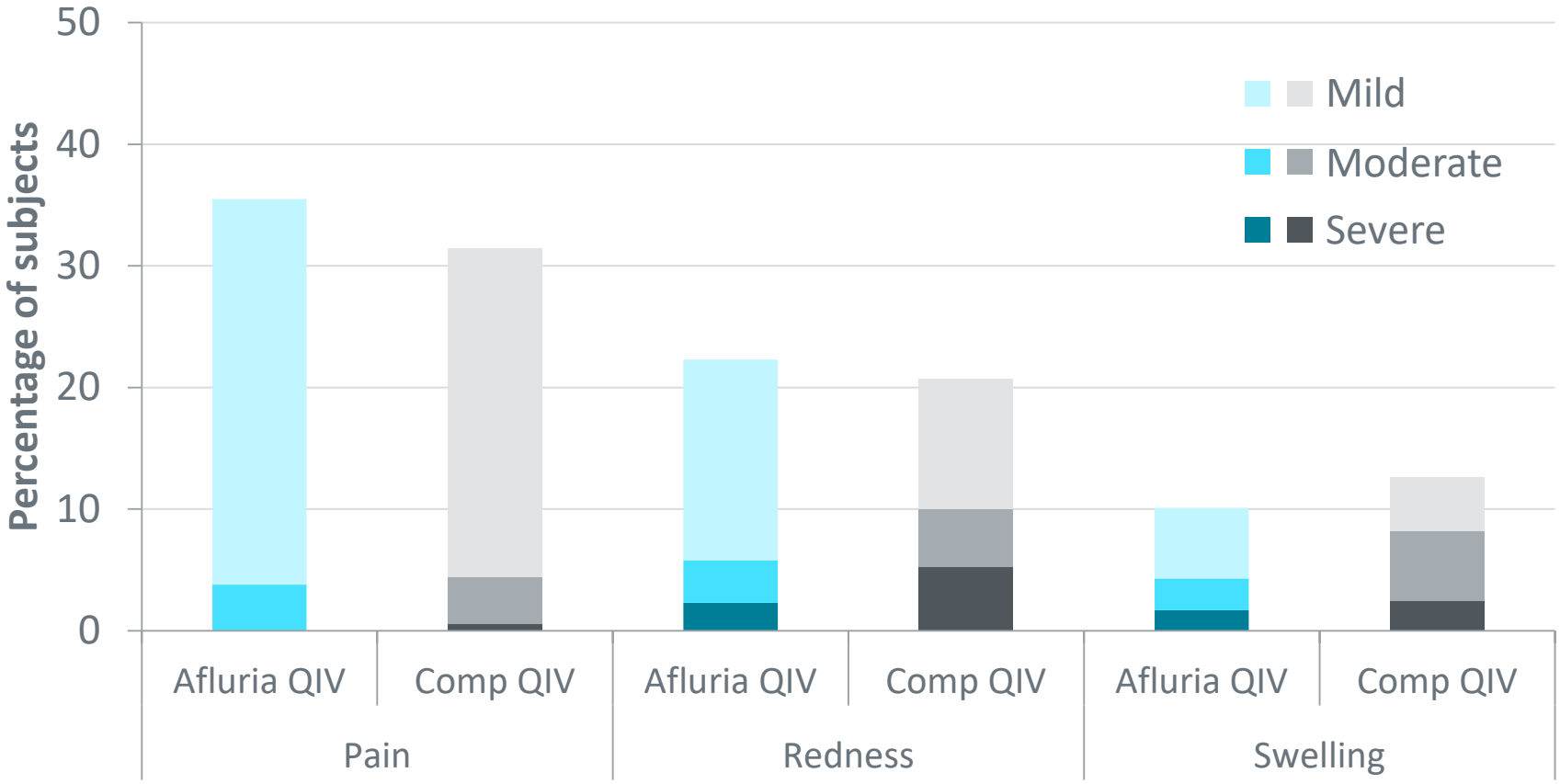
AFLURIA QIV: SOLICITED LOCAL ADVERSE REACTIONS

36 – 59 MONTHS AGE GROUP, AFTER ANY VACCINATION



- Solicited local adverse reactions similar between groups
- Most reactions mild or moderate for both vaccines

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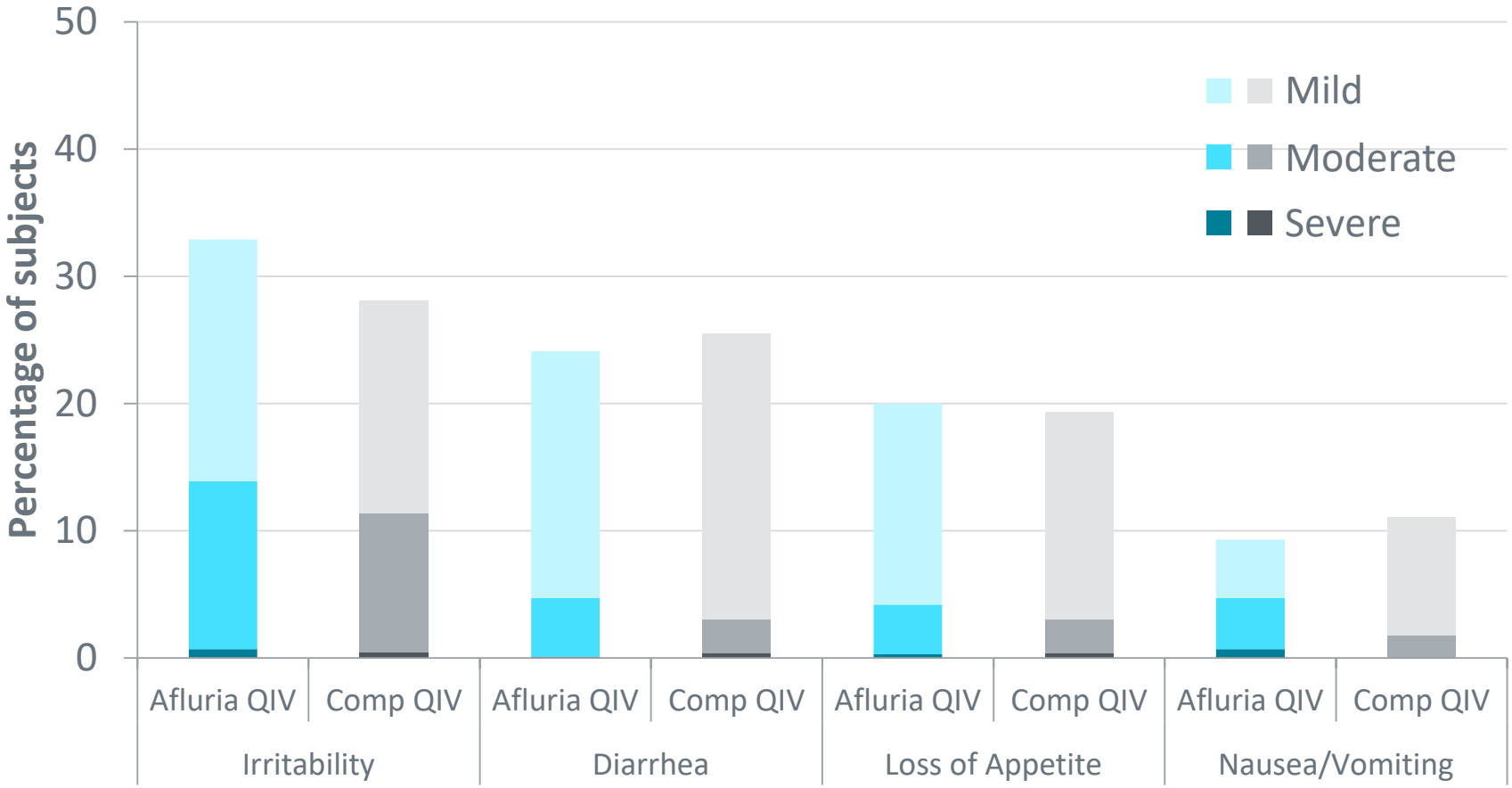
AFLURIA QIV: SOLICITED SYSTEMIC ADVERSE EVENTS

6 – 35 MONTHS AGE GROUP, AFTER ANY VACCINATION



- Solicited systemic adverse events similar between groups; most events mild or moderate in intensity

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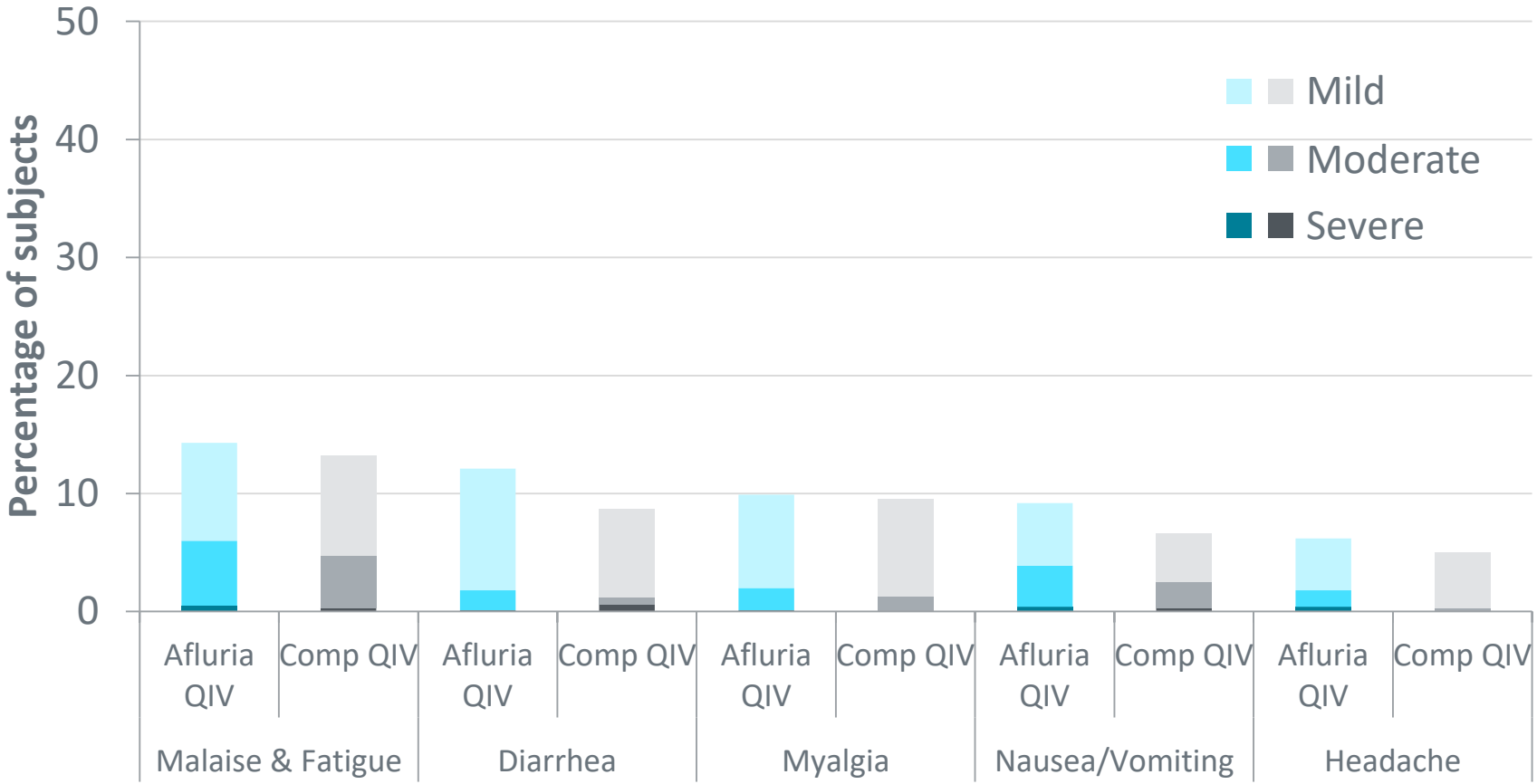
AFLURIA QIV: SOLICITED SYSTEMIC ADVERSE EVENTS

36 – 59 MONTHS AGE GROUP, AFTER ANY VACCINATION



- Solicited systemic adverse events similar between groups
- Most events mild or moderate in intensity

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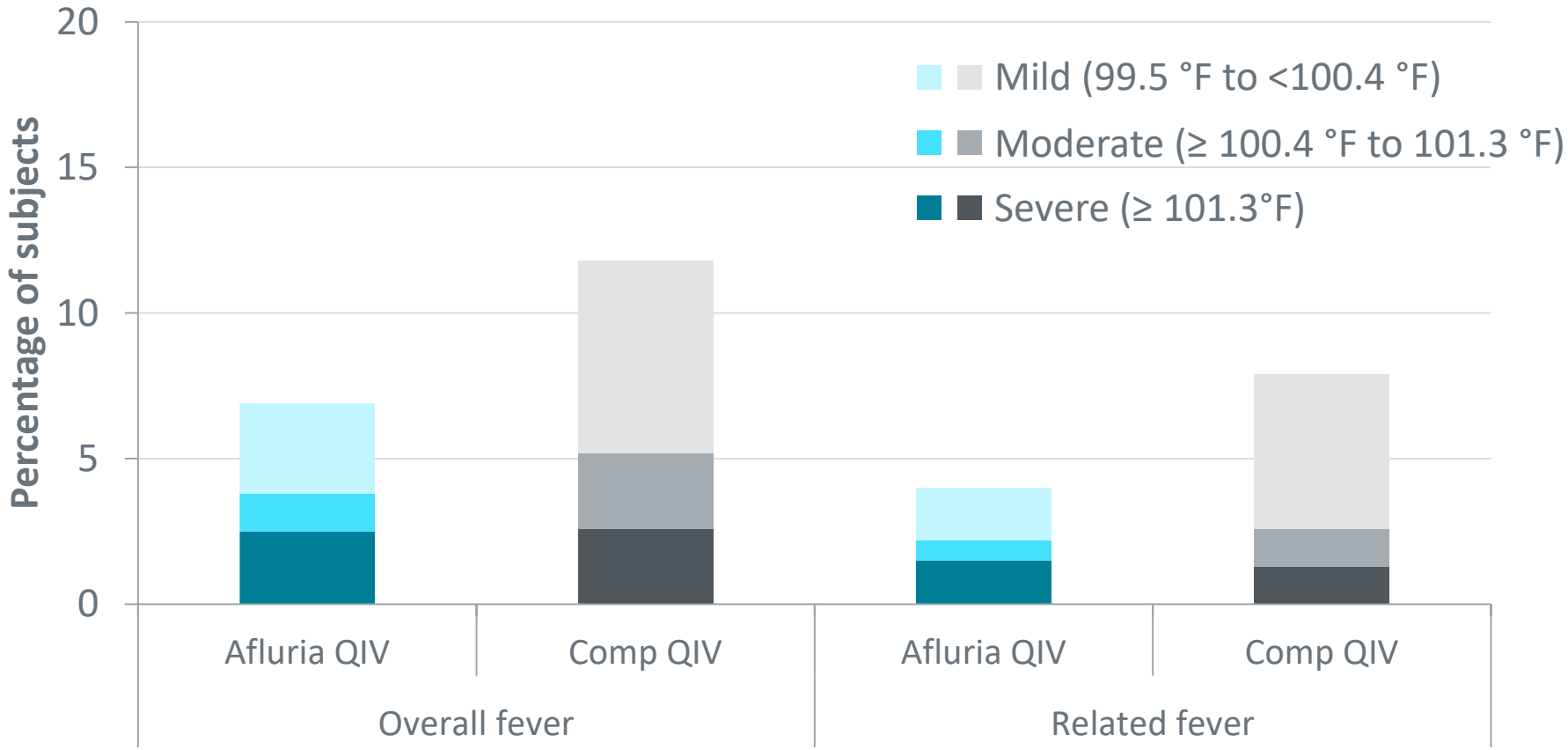
AFLURIA QIV: SUMMARY OF FEVER EVENTS

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

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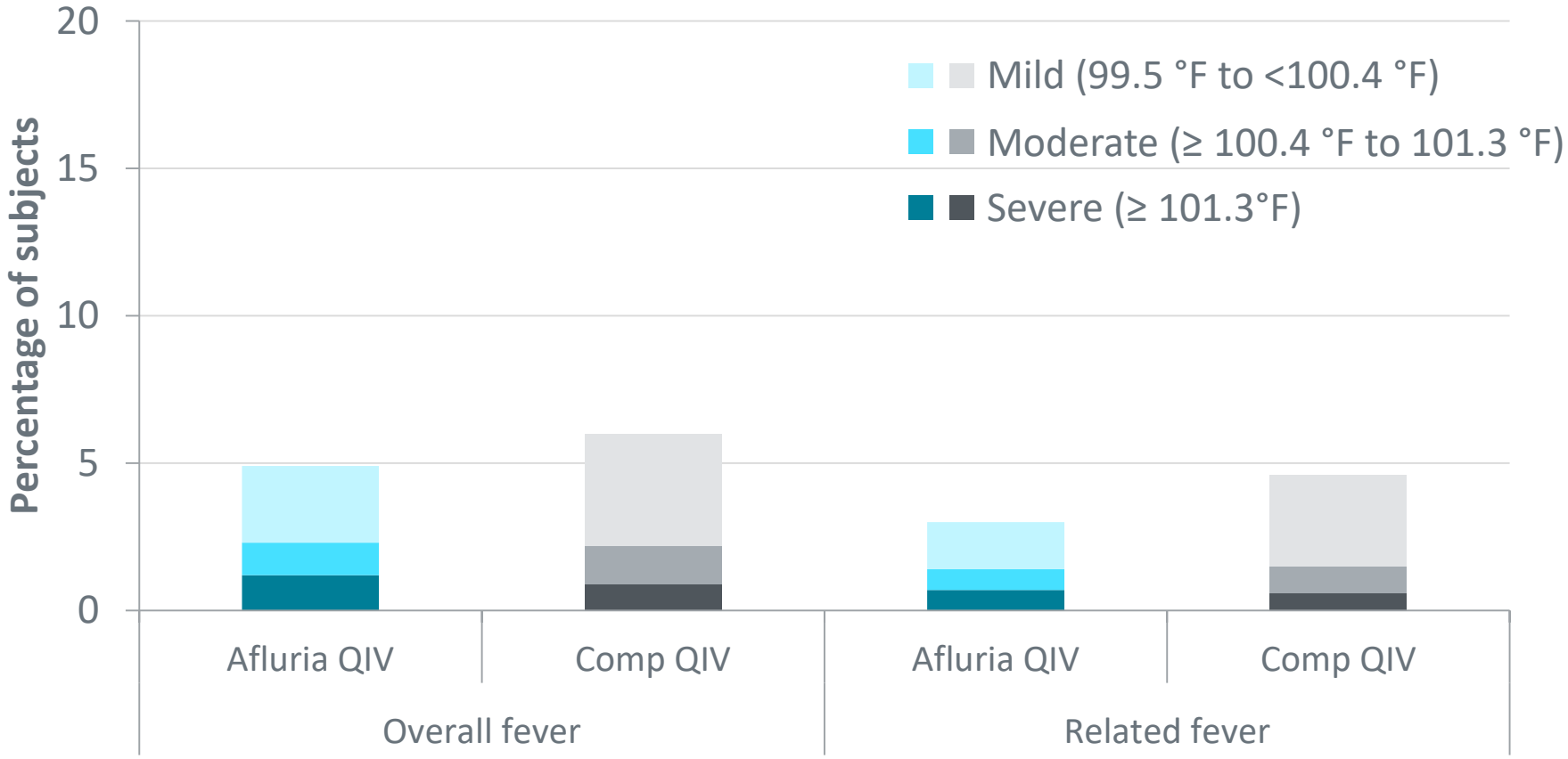
AFLURIA QIV: SUMMARY OF FEVER EVENTS

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

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AFLURIA QIV: SAFETY SUMMARY

	Afluria QIV N = 1684 (full analysis set)		Comparator QIV N = 563 (full analysis set)	
Subjects	*6 – 35 mon*	*36 – 59 mon*	*6 – 35 mon*	*36 – 59 mon*
Safety population	**694**	**979**	**233**	**326**
Solicited safety pop	**669**	**949**	**227**	**318**
Deaths	**0**	**0**	**0**	**0**
Discont. due to AE	**0**	**0**	**0**	**0**
SAEs to Day 28*	**4 (0.6%)**	**0**	**0**	**0**
SAEs to End of Study*	**11 (1.6%)**	**0**	**2 (0.9%)**	**1 (0.3%)**
AESIs to Day 28	**0**	**0**	**0**	**0**
AESIs to End of Study*	**2 (0.3%)**	**0**	**0**	**0**
Cellulitis-like reactions	**0**	**0**	**0**	**1**

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

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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 ≥ 101.3°F / 38.5°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

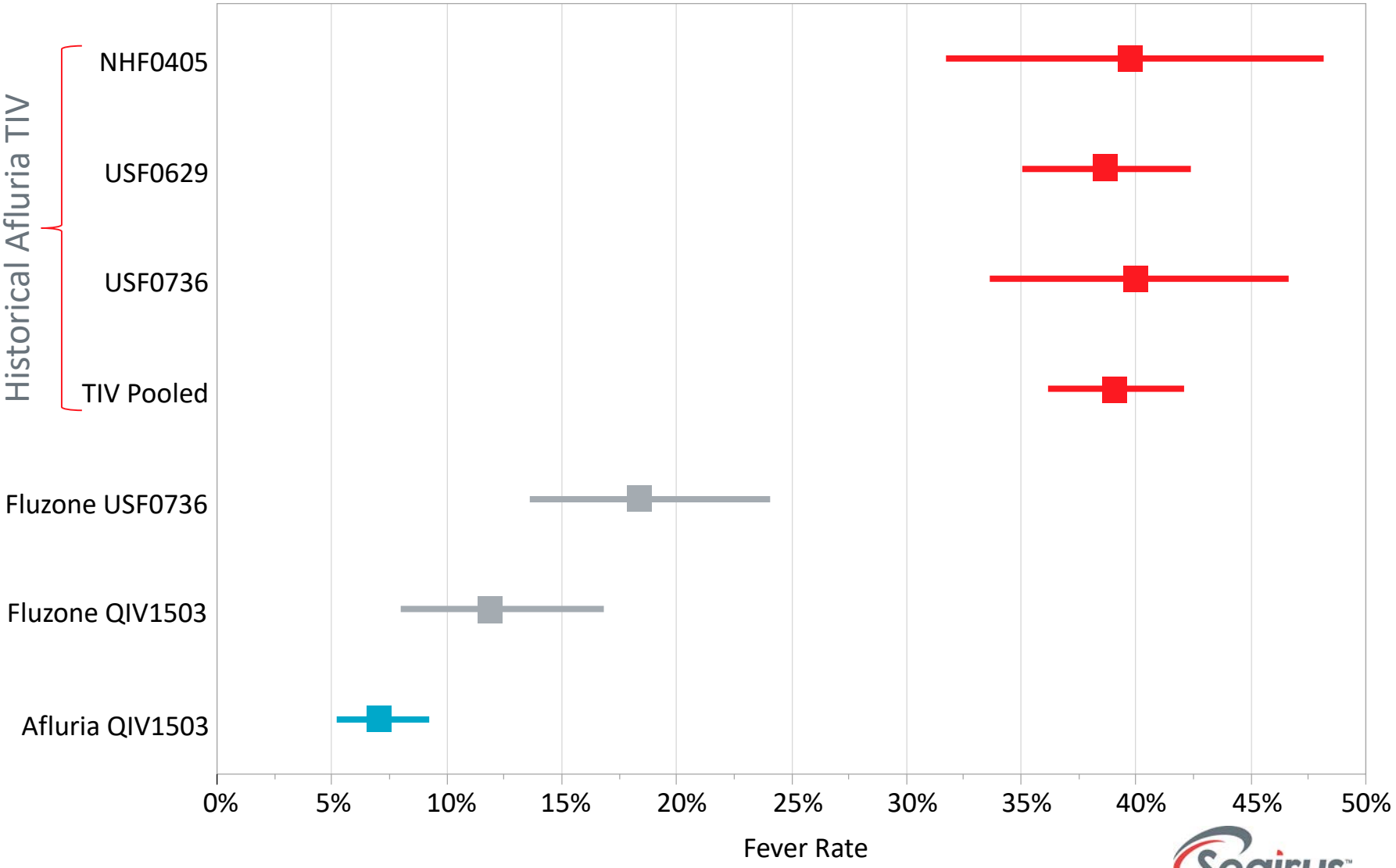
- ≥ 5% of subjects experience a cellulitis-like reaction (concurrent severe pain, redness, and swelling)
- ≥ 5% of subjects experience a related severe (≥ 38.5°C / 101.3°F) fever

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

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

DSMB = Data Safety Monitoring Board

Comparison with Historical Fever Rates
6 to 35 months age group



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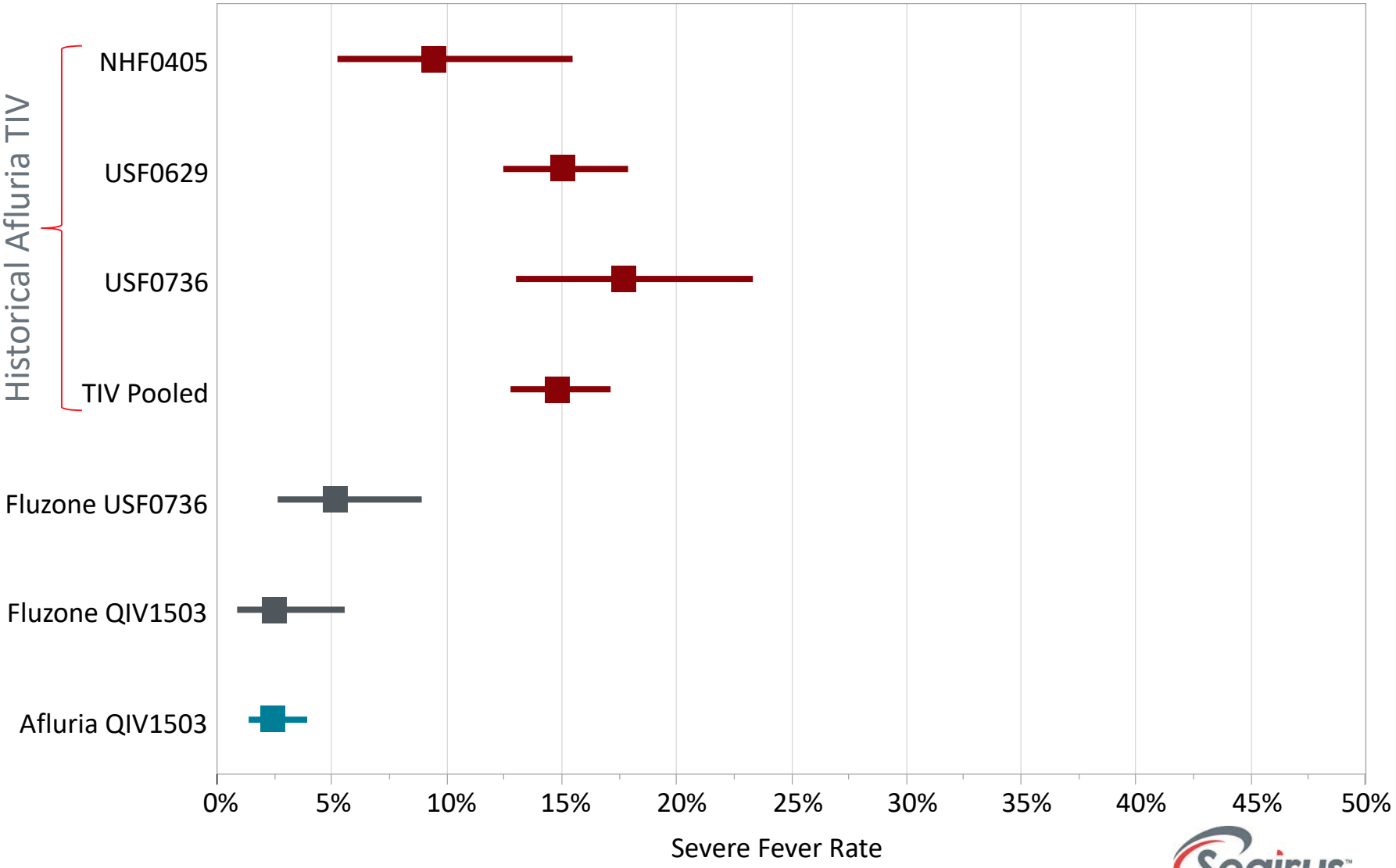
Comparison with Historical Severe Fever Rates
6 to 35 months age group



CSLCT-Afluria QIV-15-03

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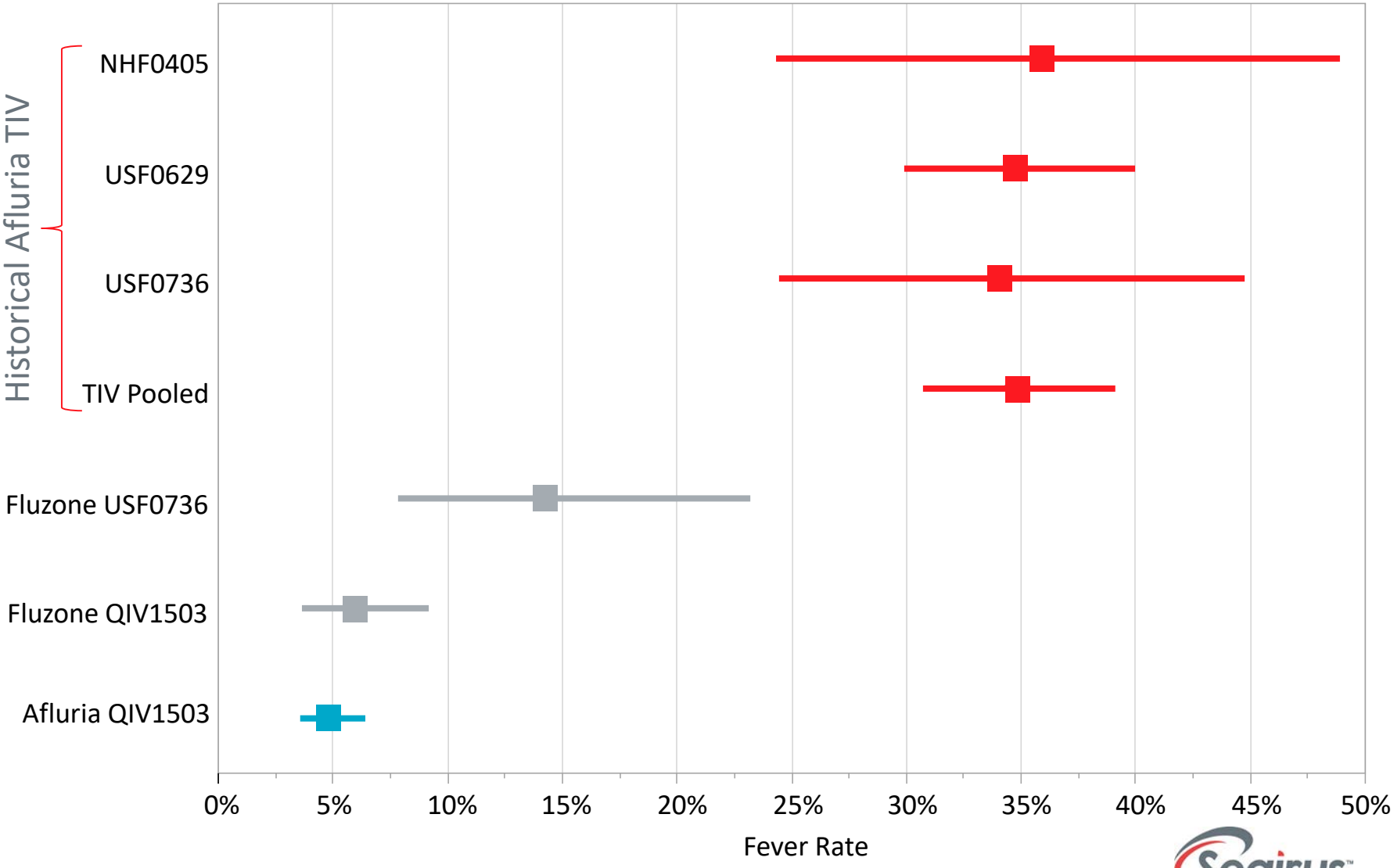
Comparison with Historical Fever Rates
36 to 59 months age group



CSLCT-Afluria QIV-15-03

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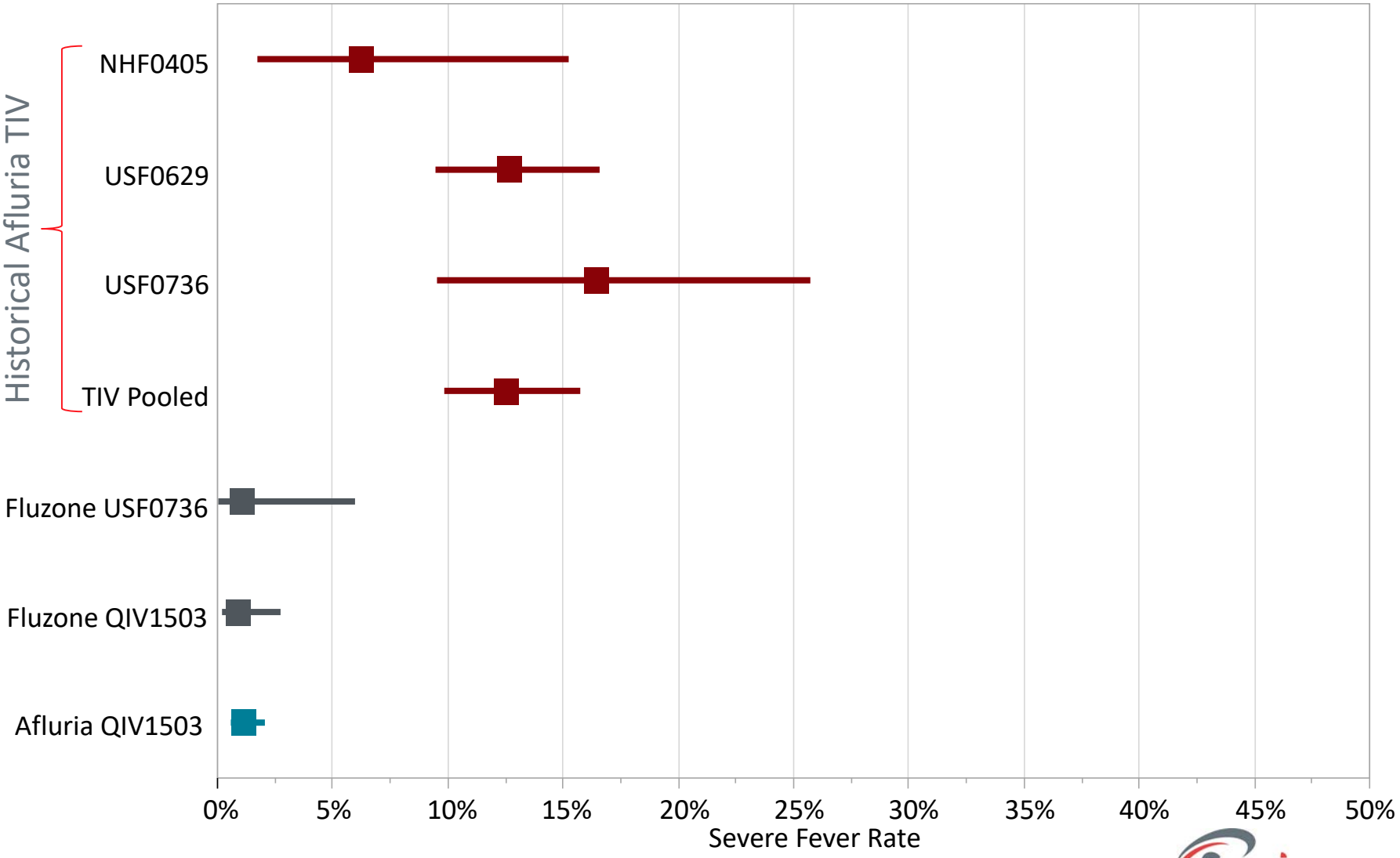
Comparison with Historical Severe Fever Rates
36 to 59 months age group



CSLCT-Afluria QIV-15-03

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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%).