Immunogenicity and Safety of GSK's FluLaval™ Quadrivalent Inactivated Influenza Vaccine in Children 6-35 Months of Age

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GSK Vaccines

Inactivated Influenza Vaccines for 6-35 Months of Age

Introduction

- Original inactivated influenza vaccines (IIVs) contained whole virus – they were given to children 6-35 months of age at a low dose to control reactogenicity[1-3]
- Most split or subunit IIVs are less reactogenic in young children but have variable immune responses [4-5]
- Fluzone™ is the sole IIV licensed in the US for children 6-35 months of age
  - Its approved dose is 7.5 µg HA per strain in 0.25 mL
  - No other IIV is approved in the US for this age group due either to lack of evidence supporting immunogenic non-inferiority to Fluzone™ or to unacceptable reactogenicity[6-7]
- In this development program, GSK used 0.5mL (15µg per strain) of FluLaval™ Quadrivalent*; this is double the dose of the comparator

* Manufactured in Ste Foy, Quebec

1.Wright PF, Thompson J, Vaughn WK, et al. J Infect Dis 1977;136:S731-41. 2. Gross PA, Ennis FA, Gaerlan PF, et al. J Infect Dis 1977;136:623-32.
3. Gross PA. J Infect Dis 1977;136:S616-25. 4. Englund JA, Walter EB,Gbadebo A, et al. Pediatrics 2006;118:e579-85. 5. Walter EB, Rajagopal S, Zhu Y, et al. Vaccine 2010;28:4376-83. 6. Li-Kim-Moy J, Booy R. Influenza Other Respir Viruses 2016;10:9-13. 7 Brady RC, Hu W, Houchin VG, et al. Vaccine 2014;32:7141-7.

FluLaval™ Quadrivalent

Product information

- FluLaval™ Quadrivalent (Q-QIV) received FDA approval in August 2013 for use in persons 3 years of age and older
  - Submitted sBLA to extend the indication to 6-35 months of age in Jan 2016
  - Expected FDA action date is Nov 26th 2016
- Dose: 0.5mL (same dose for all eligible, regardless of age)
  - Contains 15µg HA from each of the recommended A/H1N1, A/H3N2, B-Victoria and B-Yamagata strains
- Presentation: PFS and Multi-dose vial
- Proposed indication:

  FLULAVAL™ QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL™ QUADRIVALENT is approved for use in persons 6 months of age and older

FluLaval™ QIV Studies in the sBLA for 6-35 Months of Age

Safety was assessed in all subjects

Study /yr	Key Immunogenicity Objectives	Groups	N
003[1] 2010-2011	Assess immunogenicity in 6-35m open label arm	Q-QIV	301
013[2] 2012-2013	CBER's SCR criteria for each of the vaccine strains Superiority of B/Victoria strain present in Q-QIV vs Fluarix	Q-QIV Fluarix	299 302
021[3] 2013-2014	CBER's SCR criteria for each of the vaccine strains Superiority of B/Victoria strain present in Q-QIV vs Fluzone	Q-QIV Fluzone	158 156
022[4] 2014-2015	Immunogenic NI to Fluzone Quad: GMTs & SCR for all strains CBER SCR and SPR criteria for each of the vaccine strains	Q-QIV Fluzone-QIV	1,207 1,217
		Total Q- QIV exposed	1,965

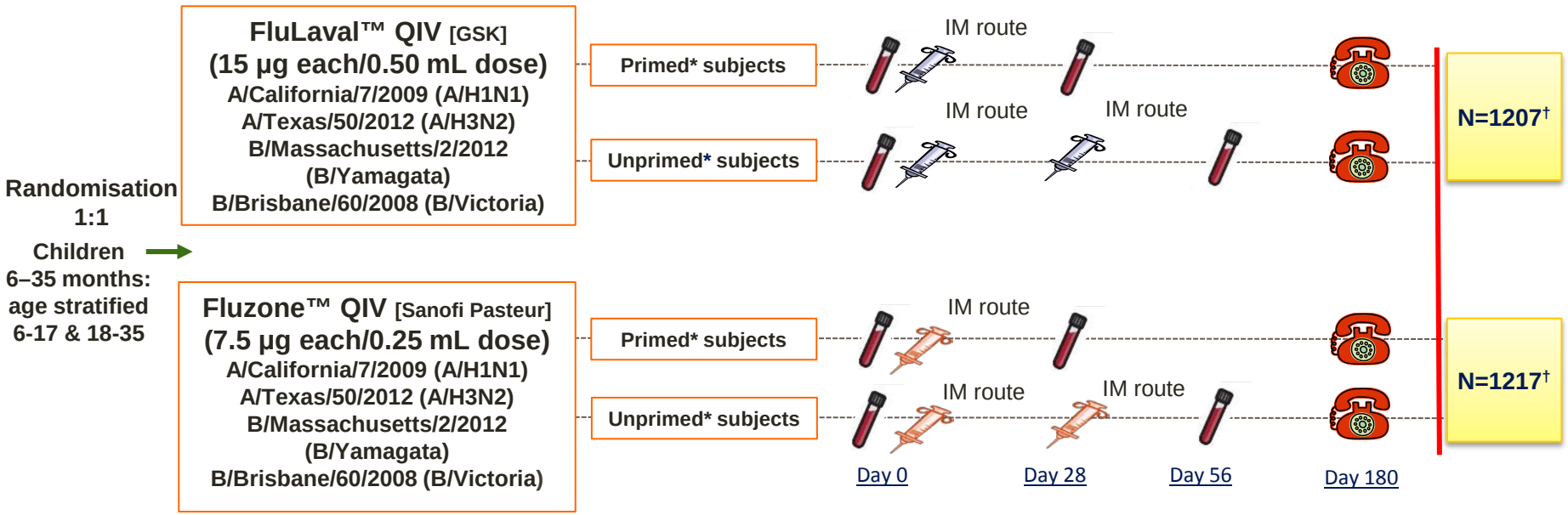
1.Langley JM, Martinez AC, Chatterjee A, et al. JID 2013;208:544-553; 2. Langley JM, Wang L, Aggarwal N, et al. J Pediatric Infect Dis Soc. 2015;4:242–251; 3. Wang L, Chandrasekaran V, Domachowske JB, et al. J Pediatric Infect Dis Soc. 2016;5:170-9; 4. Jain et al. Poster presented at the Pediatric Academic Society Annual Meeting, Baltimore, MD, April 30-May 3, 2016. Poster 3803.39

Q-QIV-022: Design of Pivotal Study

Children 6–35 months of age, N=2424 (TVC)

Phase III, observer-blind, 69 centres (USA, Mexico)

NCT02242643
Oct 2014 – Jun 2015



*Children were considered vaccine-primed if they had received two or more doses of seasonal influenza vaccine since July 1, 2010 or at least one dose of the 2013–14 seasonal influenza vaccine; all others were considered vaccine-unprimed

†Total vaccinated cohort

Fluzone™ QIV is a trademark of Sanofi-Pasteur

IM, intramuscular; QIV, Quadrivalent influenza vaccine;

Q-QIV-022: Protocol Objectives

- **Primary Objective**
  - Evaluate immunogenic non-inferiority of FluLaval™ QIV versus Fluzone™ QIV (in terms of GMTs and SCRs) approximately 28 days after completion of dosing in 6-35m old children
- **Secondary Objectives**
  - Evaluate immunogenicity of FluLaval™ QIV based on CBER's acceptance criteria for seroconversion and seroprotection
  - Describe safety and reactogenicity
    - Overall, 6-17m & 18-35m age strata, and in primed/unprimed population
  - Describe immunogenicity
    - Overall, 6-17m & 18-35m age strata, and in primed/unprimed population
  - Describe relative risk of fever for FluLaval™ QIV compared to Fluzone™ QIV within 2 days post-vaccination

GMT: Geometric Mean Titer; SCR: Seroconversion rate; CBER: Center for Biologics Evaluation and Research

Jain et al. Poster presented at the Pediatric Academic Society Annual Meeting, Baltimore, MD, April 30-May 3, 2016. Poster 3803.39

Q-QIV-022: Subject Demographics

Total Vaccinated Cohort

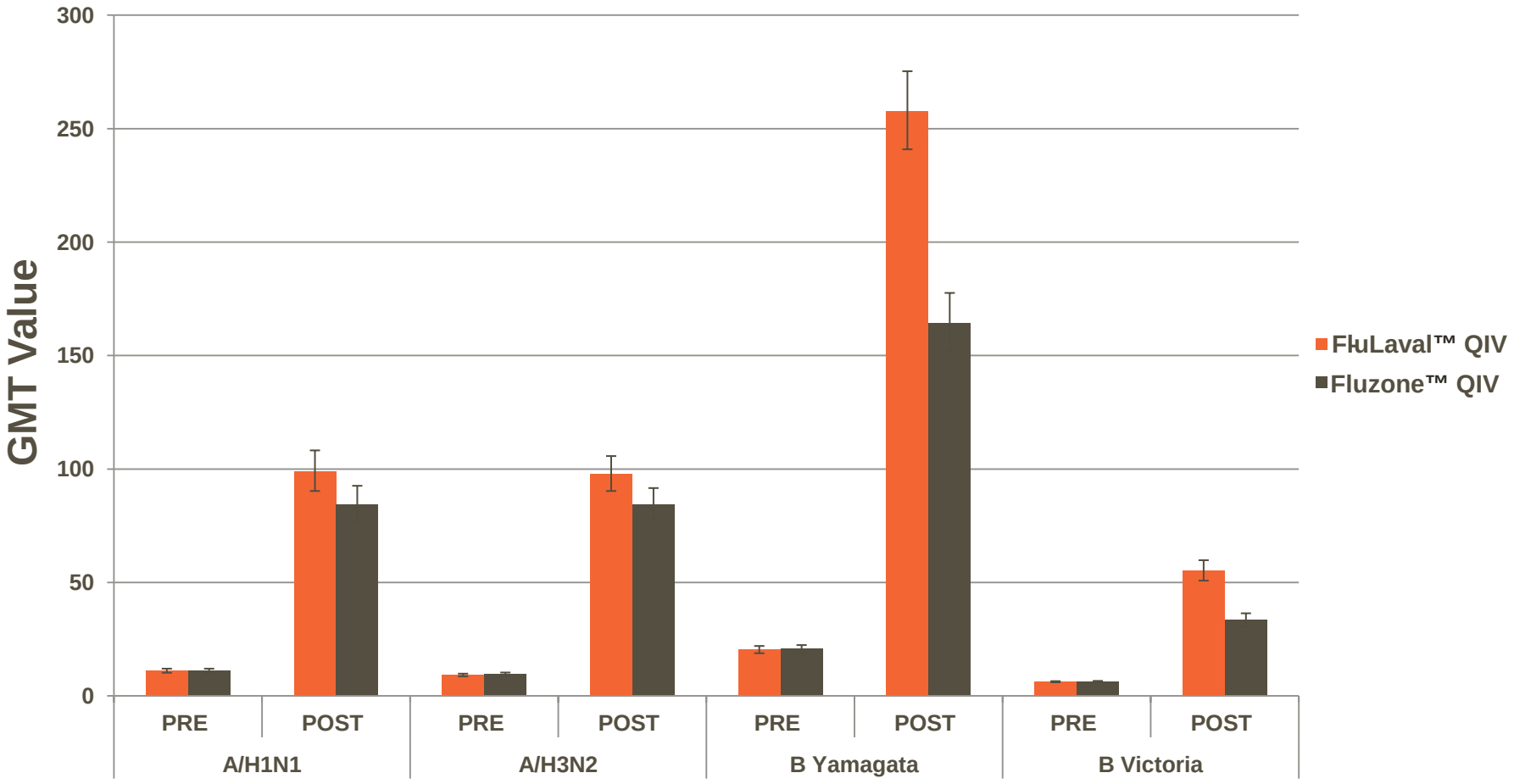
		FluLaval™ QIV		Fluzone™ QIV		Total	
		N = 1207		N = 1217		N = 2424	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (months) at dose 1	Mean	19.4	-	19.5	-	19.5	-
	SD	8.7	-	8.9	-	8.8	-
	Median	19.0	-	19.0	-	19.0	-
	Minimum	6	-	6	-	6	-
	Maximum	35	-	36*	-	36	-
Gender	Female	547	45.3	582	47.8	1129	46.6
	Male	660	54.7	635	52.2	1295	53.4
Ethnicity	American hispanic or latino	305	25.3	302	24.8	607	25.0
	Not American hispanic or latino	902	74.7	915	75.2	1817	75.0
Vaccination Status	Primed	657	54.4	657	54.0	1314	54.2
	Unprimed	550	45.6	560	46.0	1110	45.8

Demographics were similar between the study groups

GSK Data on file: Clinical Study Report for Study 201234 (FLU-Q-QIV-022)

Q-QIV-022: Geometric Mean Titer (GMT)

6–35 months
N=2041 (ATP)



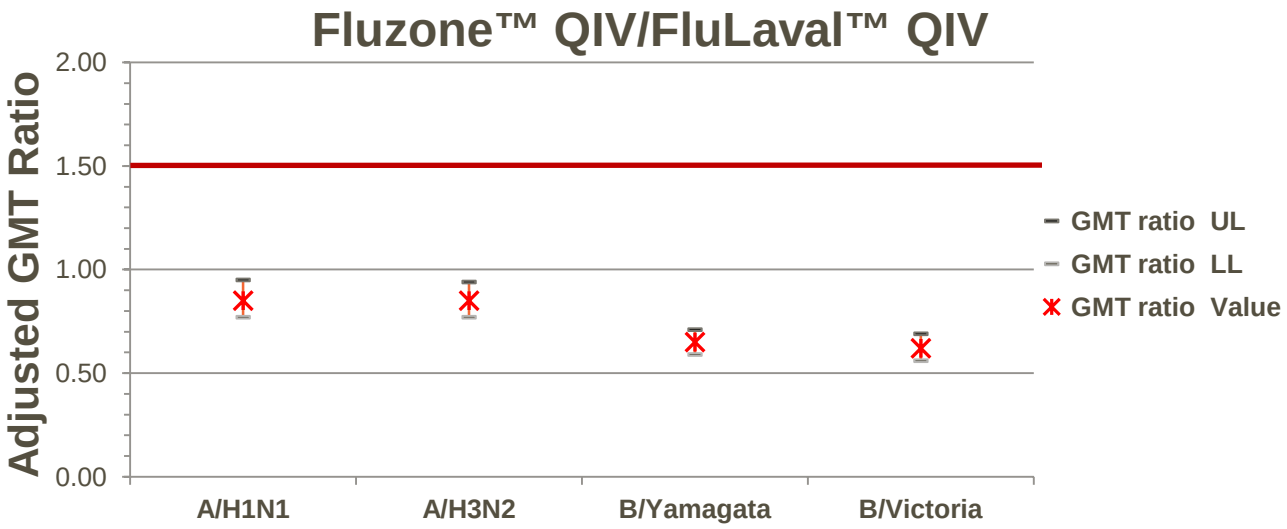
ATP: According to protocol.

Jain et al. Poster presented at the Pediatric Academic Society Annual Meeting, Baltimore, MD, April 30-May 3, 2016. Poster 3803.39

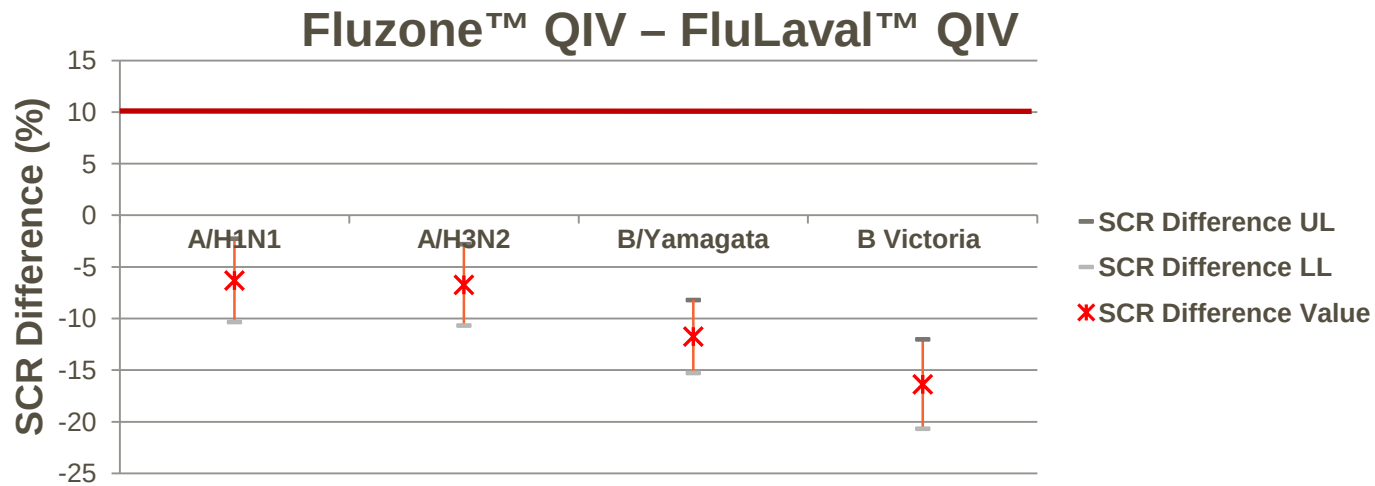
Q-QIV-022: Primary Confirmatory Objective Met

Immunogenic NI for Adjusted GMT ratio and SCR Difference

6–35 months
N=2041 (ATP)



Success criterion:
UL of 95% CI for GMT Ratio ≤ 1.5 for each strain



Success criterion:
UL of 95% CI for difference in SCR ≤ 10% for each strain

NI: Non-inferiority; CI: Confidence interval; UL: Upper limit; LL: Lower limit

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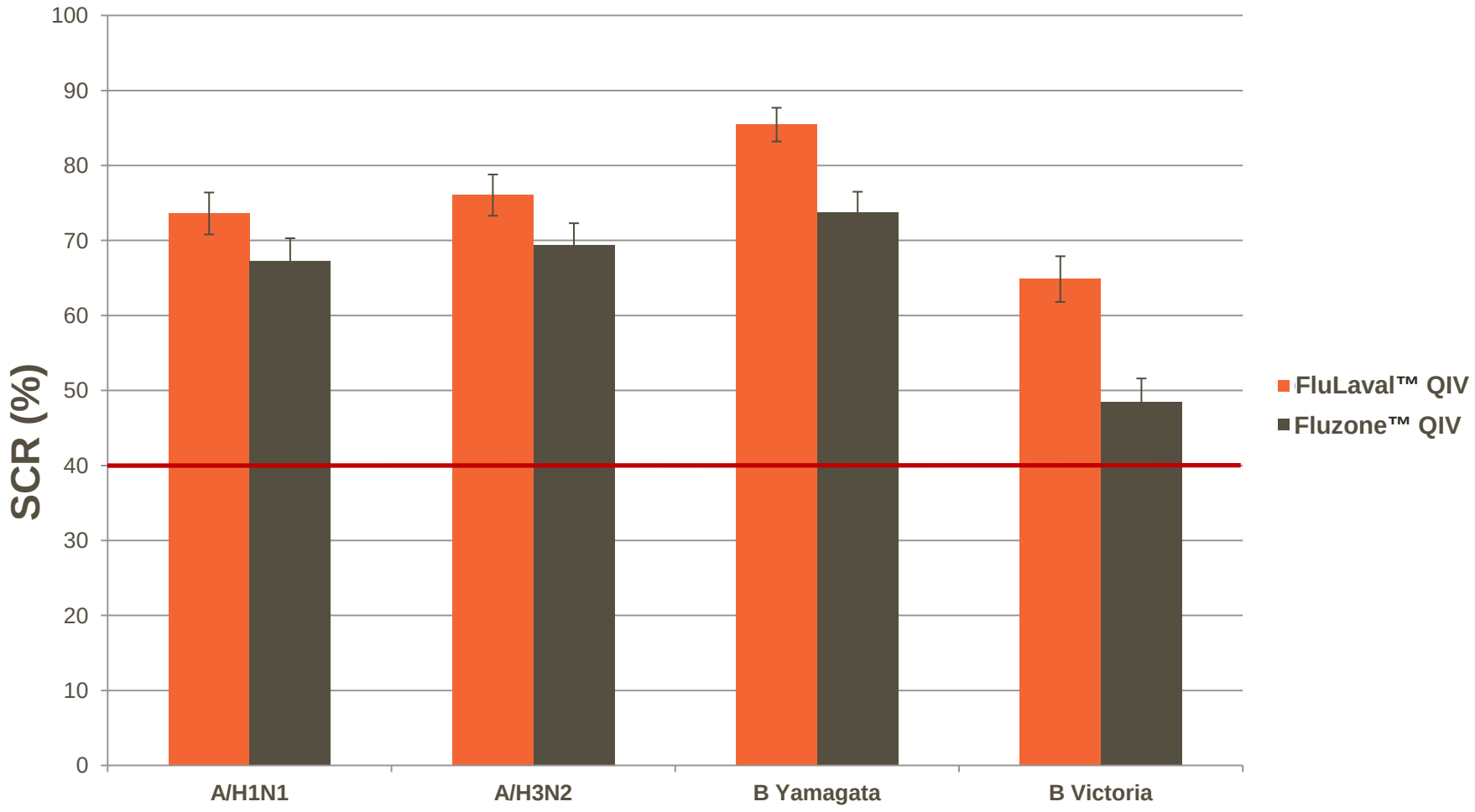
Q-QIV-022: Seroconversion Rate (SCR)

6–35 months
N=2041 (ATP)



Success criterion: LL of 95% CI for SCR ≥ 40% for each strain

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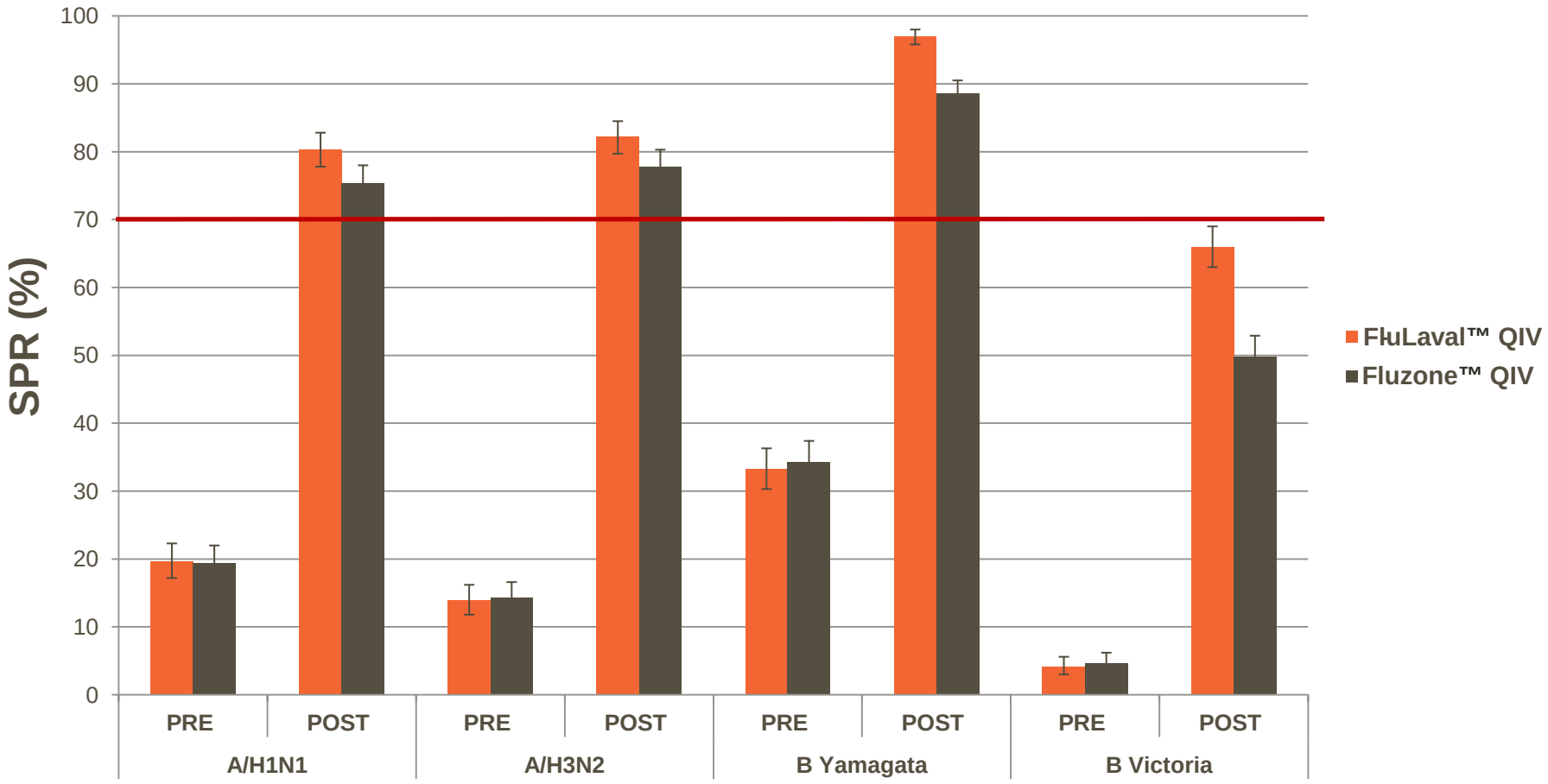
Q-QIV-022: Seroprotection Rate (SPR)

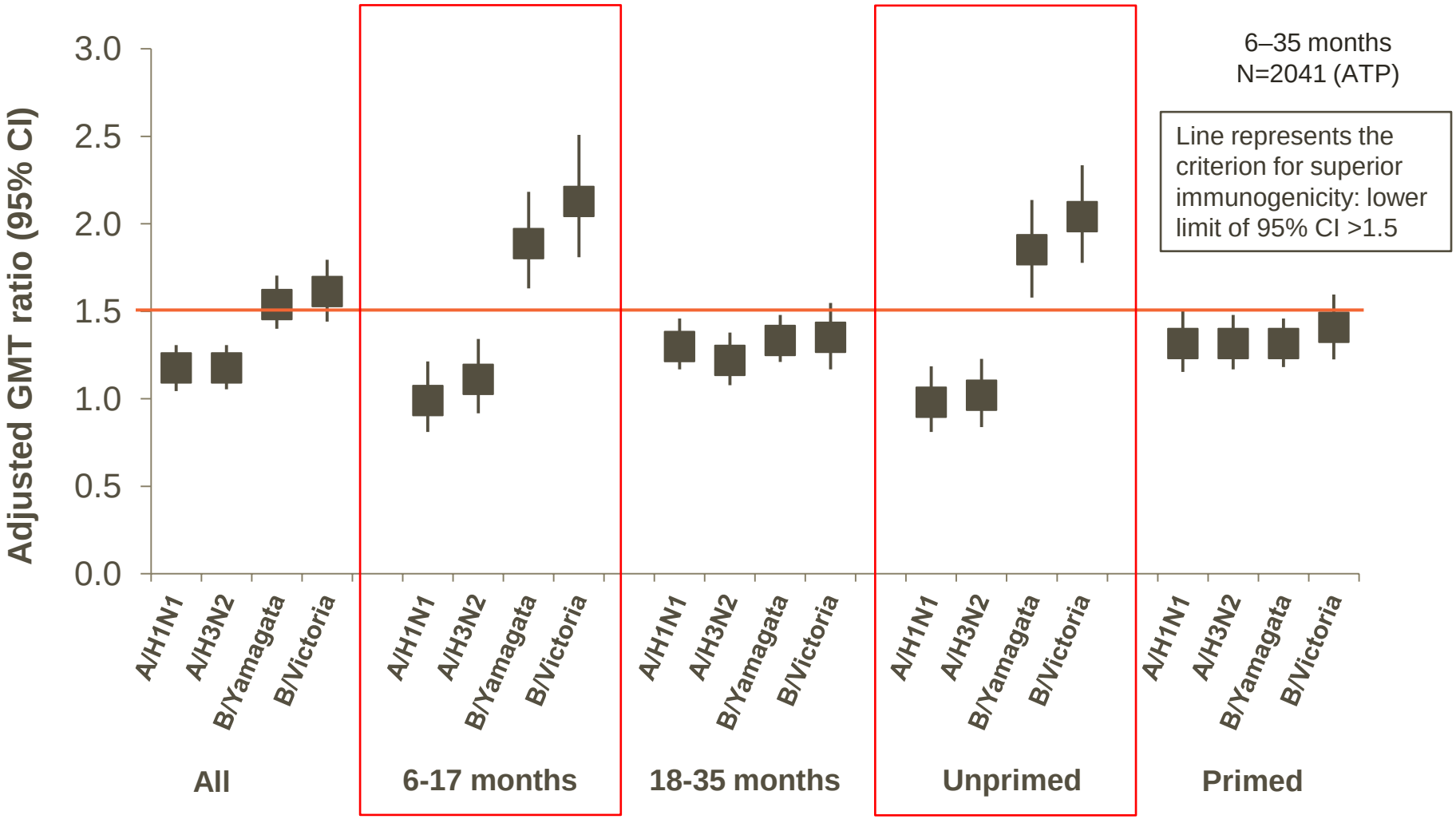
6–35 months
N=2041 (ATP)



Success criterion: LL of 95% CI for SPR ≥ 70% for each strain

Q-QIV-022: *Post-Hoc* Superiority Analysis

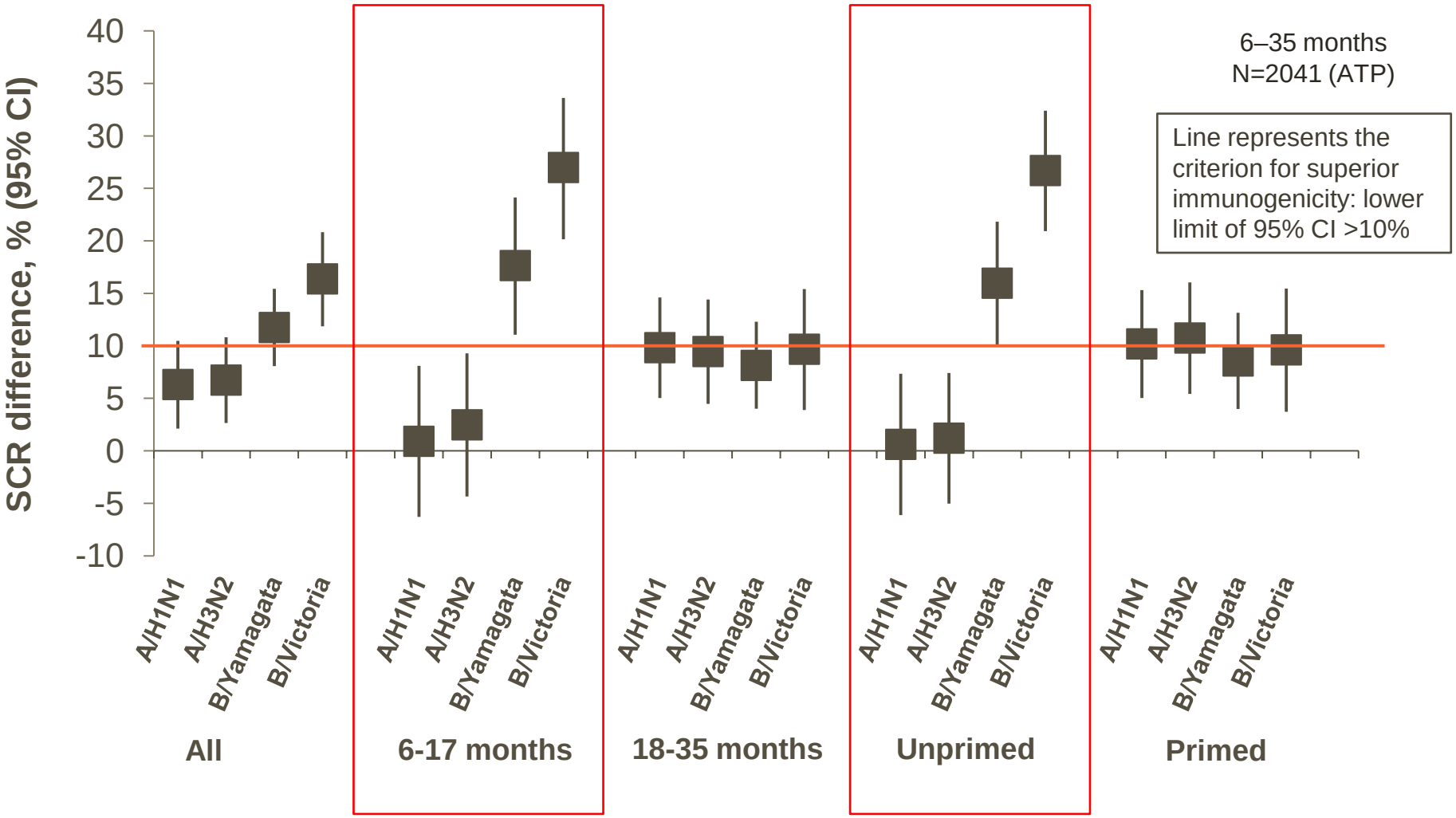
Adjusted GMT ratio (FluLaval™ QIV/Fluzone™ QIV)
Overall & age/priming subgroups



Q-QIV-022: *Post-Hoc* Superiority Analysis

SCR difference (FluLaval™ QIV - Fluzone™ QIV)

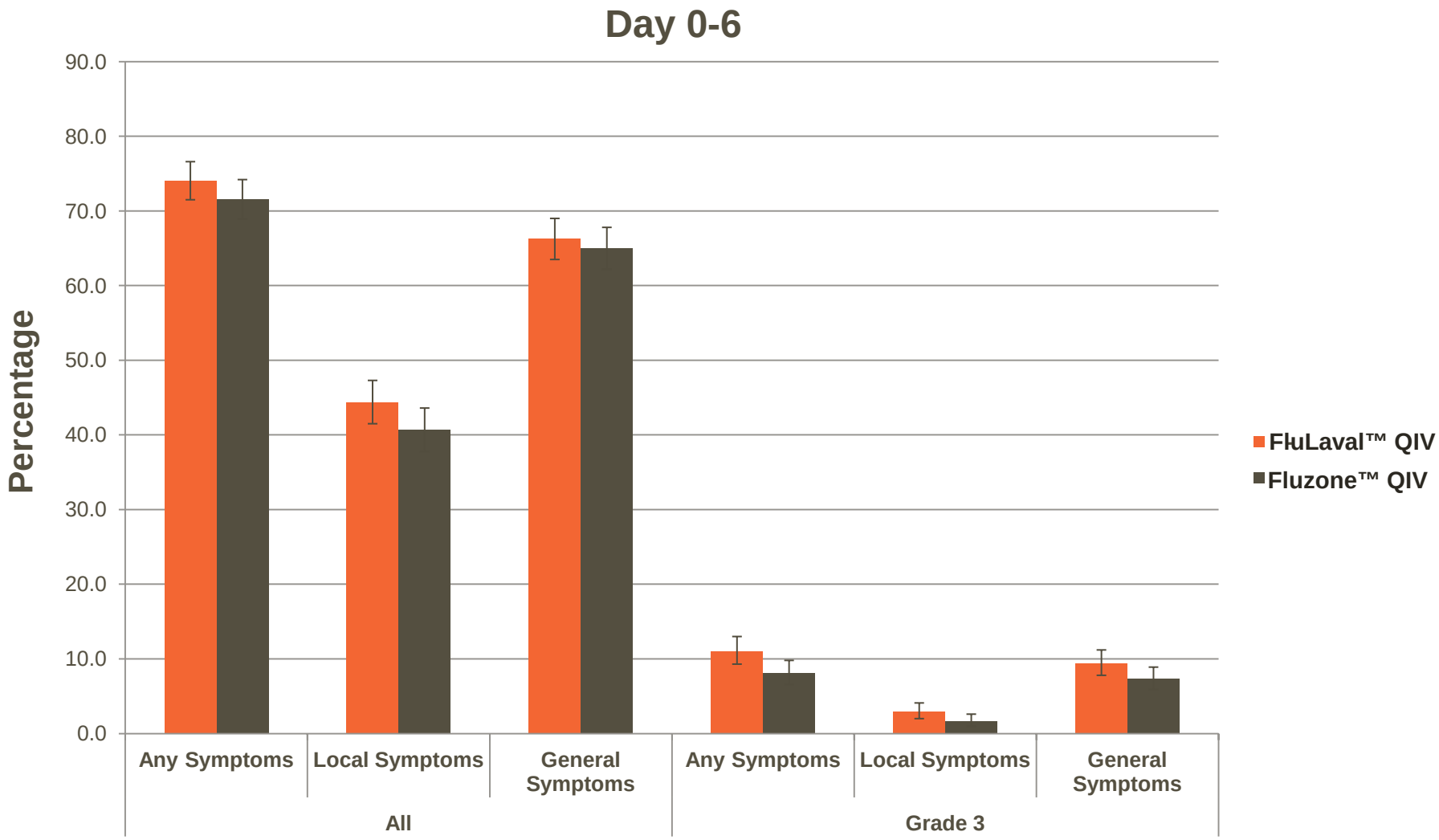
Overall & age/priming subgroups



Q-QIV-022: Summary of Solicited Adverse Events

Incidence rates per subject

6–35 months
N=2424 (TVC)



TVC: Total Vaccinated Cohort

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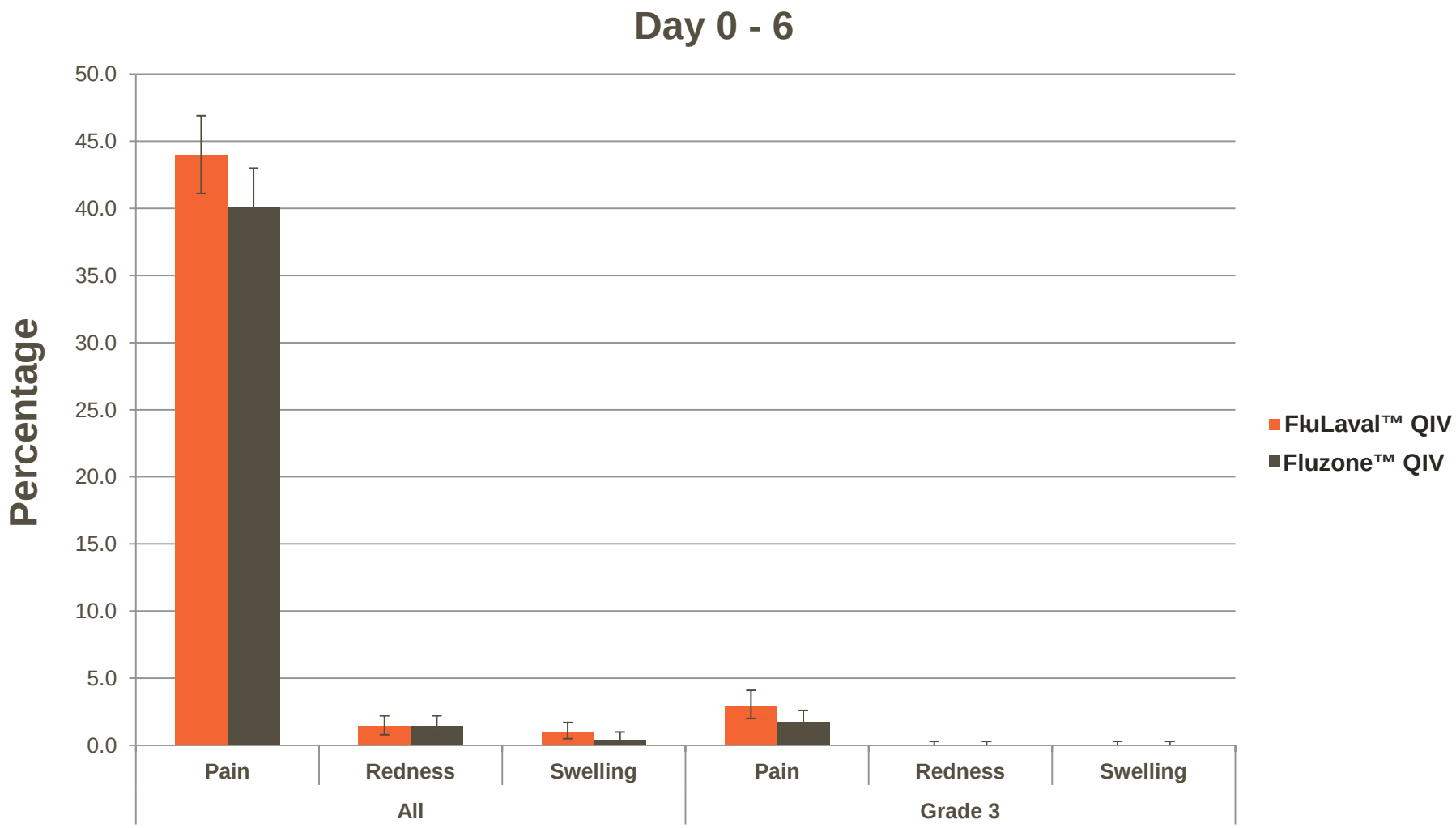
Q-QIV-022: Solicited Injection Site Adverse Events

All and Grade 3, per subject

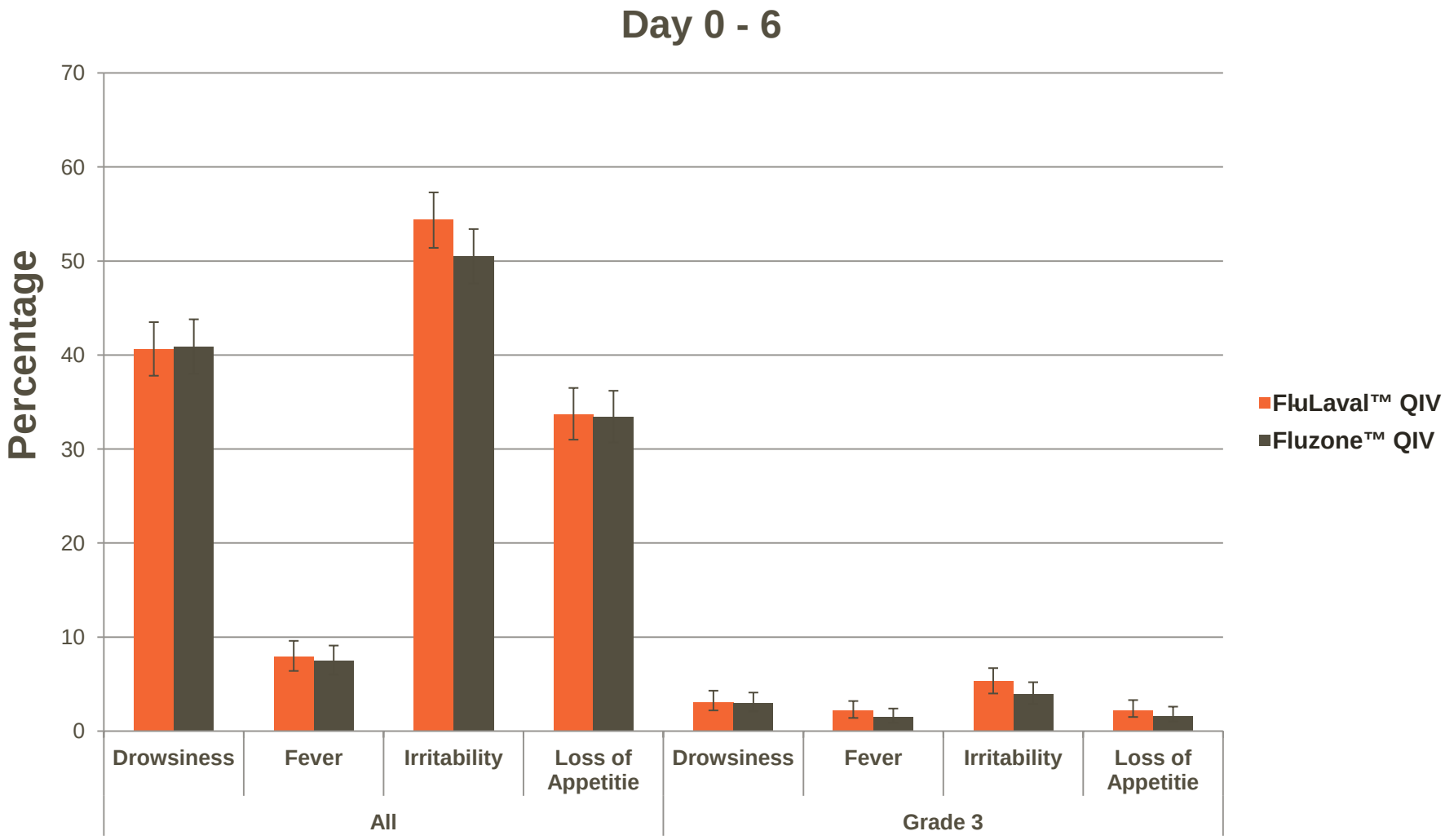
6–35 months
N=2424 (TVC)



Q-QIV-022: Solicited General Adverse Events

All vs Grade 3, per subject

6–35 months
N=2424 (TVC)



Q-QIV-022: Incidence of Unsolicited Adverse Events

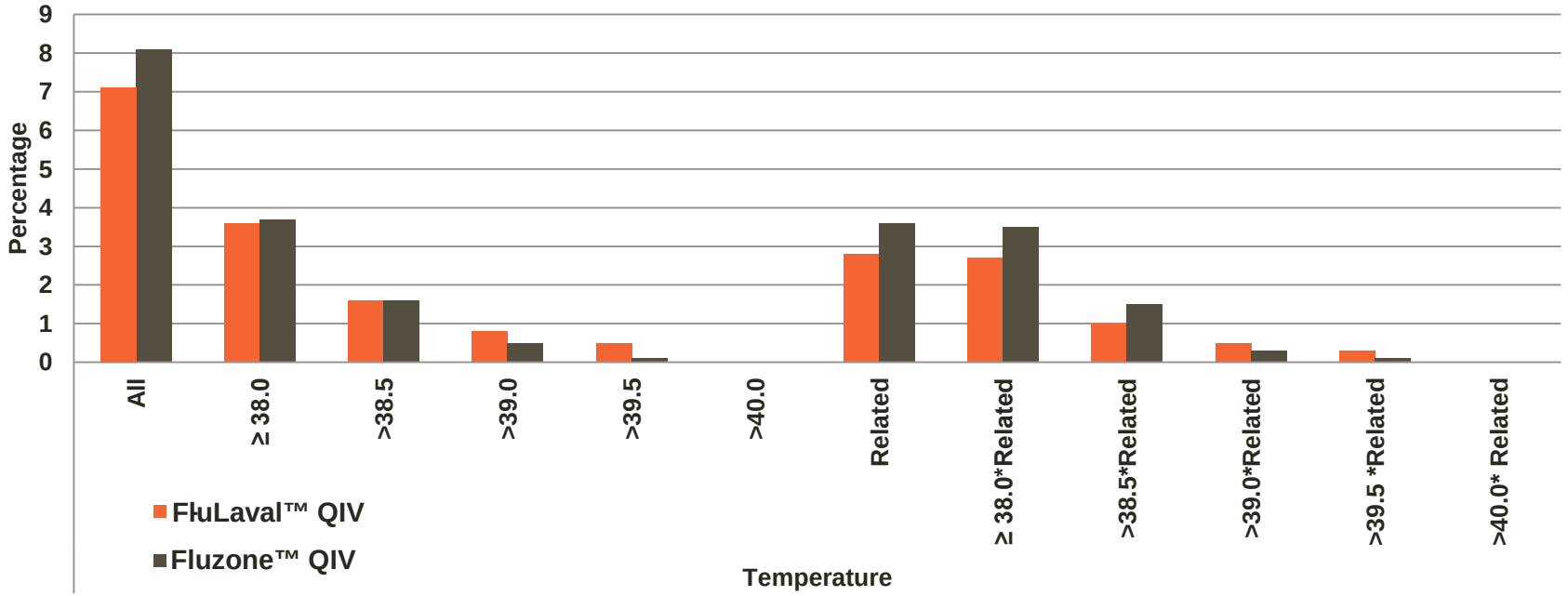
6–35 months
N=2424 (TVC)

	FluLaval™ QIV	Fluzone™ QIV
[follow up period]	N = 1207	N = 1217
Any unsolicited AEs, n (%) [28 days after vaccination]	549 (45.5%)	537 (44.1%)
Medically attended AEs, n (%) [entire study]	727 (60.2%)	719 (59.1%)
Potential immune mediated disease, n (%) [entire study]	1 (0.1%)	1 (0.1%)
Any SAEs, n (%) [n related] [entire study]	22 (1.8%) [0]	21 (1.7%) [0]

Q-QIV-022: Relative Risk of Fever

Day 0-1 post-vaccination

6–35 months
N=2424 (TVC)



§	All	≥ 38.0	>38.5	>39.0	>39.5	>40.0	Related	≥ 38.0 *Related	>38.5 *Related	>39.0 *Related	>39.5 *Related	>40.0 *Related
FluLaval™ QIV	7.1	3.6	1.6	0.8	0.5	0.0	2.8	2.7	1.0	0.5	0.3	0.0
Fluzone™ QIV	8.1	3.7	1.6	0.5	0.1	0.0	3.6	3.5	1.5	0.3	0.1	0.0
Relative Risk	0.88	0.97	0.99	1.49	5.96	INF	0.78	0.77	0.70	1.49	2.98	INF
P-Value	0.4261	0.9777	1.0000	0.6156	0.1244		0.3422	0.3296	0.4484	0.7614	0.6296	

* Related = determined by the investigator to have reasonable possibility of being related to vaccination

§ Relative risk = Q-QIV/F-QIV

GSK Data on file: Clinical Study Report for Study 201234 (FLU-Q-QIV-022)

Q-QIV-022: Conclusions

- ✓ Primary objective was met: Immunogenic non-inferiority of FluLaval™ QIV to Fluzone™ QIV was demonstrated for all four strains in terms of GMTs and SCR
  - ✓ FluLaval QIV met CBER's SCR and SPR acceptance criterion for all strains, except the SPR for B/Victoria
- ✓ In *post-hoc* analysis, FluLaval™ QIV was immunogenically superior to Fluzone™ QIV for B strains in 6-17 month age group and all 6-35 month old unprimed children
- ✓ FluLaval™ QIV and Fluzone™ QIV have a similar reactogenicity and safety profile
  - ✓ Both were generally well tolerated; there was no new safety signal
  - ✓ There was no risk of increased fever (≥38°C) with FluLaval™ QIV compared to Fluzone™ QIV during 2-days after vaccination

The use of 0.5mL dose (15µg per strain) FluLaval™ QIV in children 6 months-35 months of age simplifies influenza vaccination by allowing the same vaccine dose to be used for all eligible individuals, and may improve protection against influenza B relative to Fluzone™ QIV (0.25mL dose) in some young children

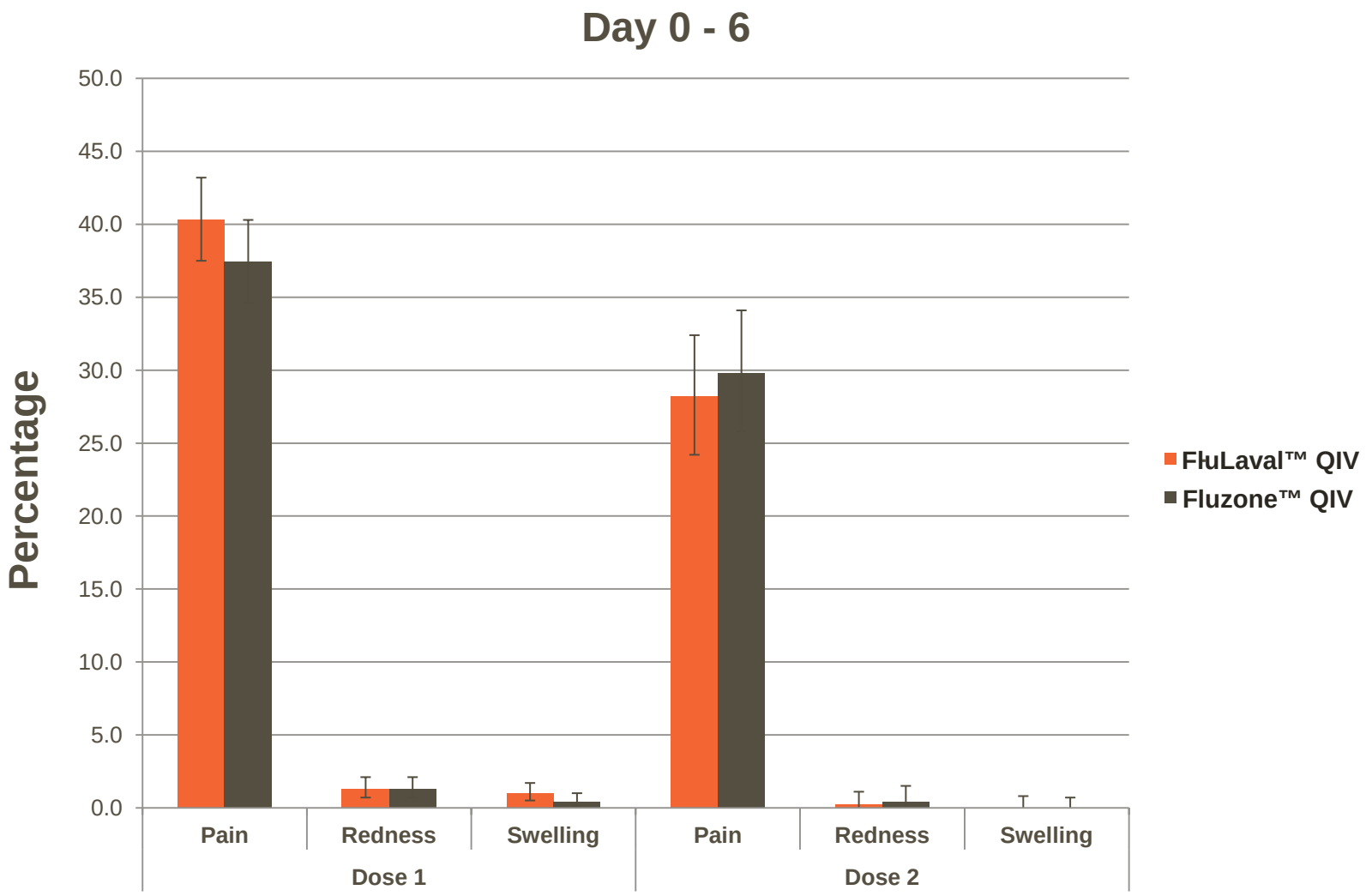
Back Up Slides

Supporting Data

Q-QIV-022: Solicited Injection Site Adverse Events

Dose 1 vs dose 2

6–35 months
N=2424 (TVC)

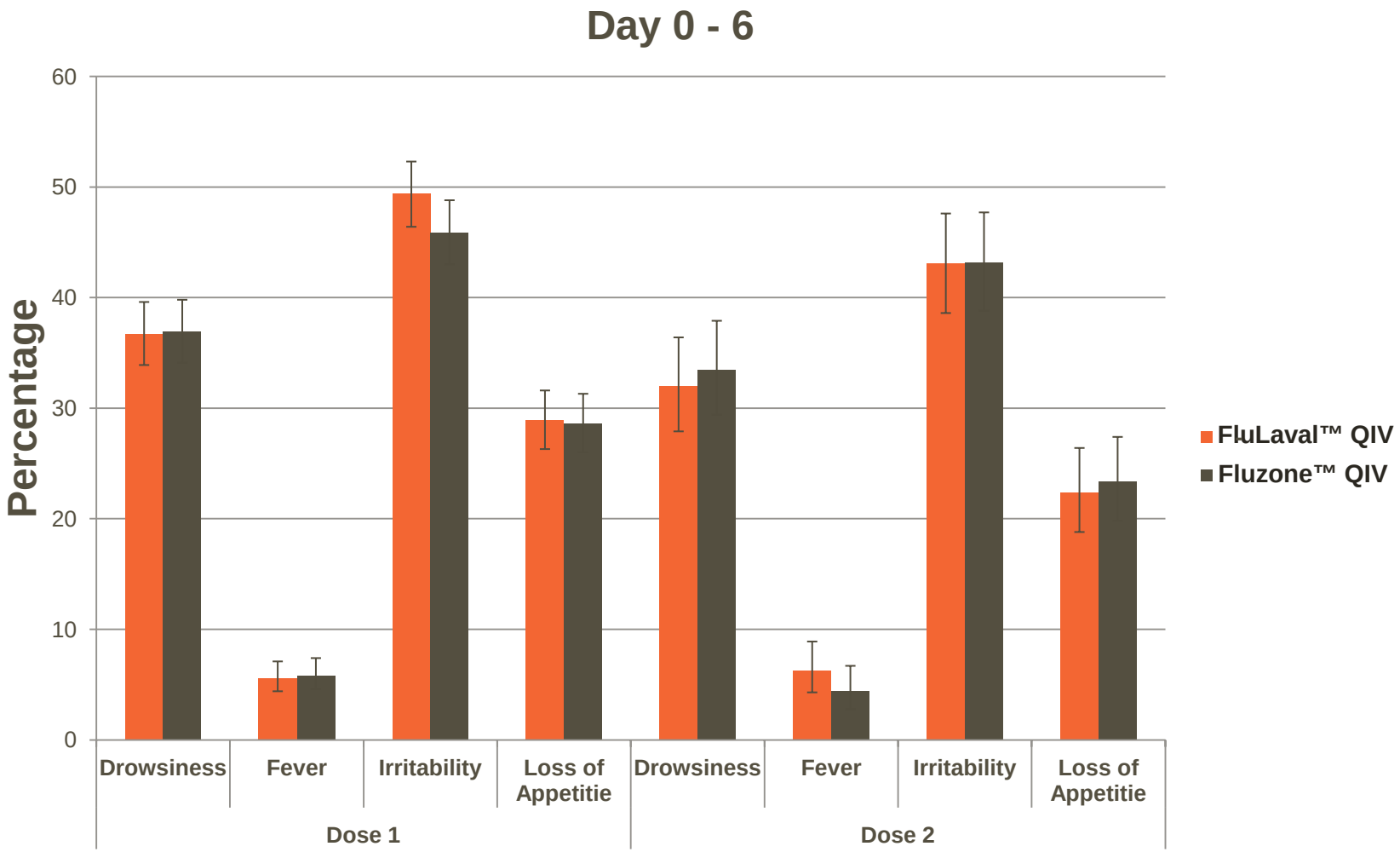


GSK Data on file: Clinical Study Report for Study 201234 (FLU-Q-QIV-022)

Q-QIV-022: Solicited General Adverse Events

Dose 1 vs dose 2

6–35 months
N=2424 (TVC)



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