QIV-HD CLINICAL DEVELOPMENT AND PHASE 3 SAFETY AND IMMUNOGENICITY STUDY RESULTS

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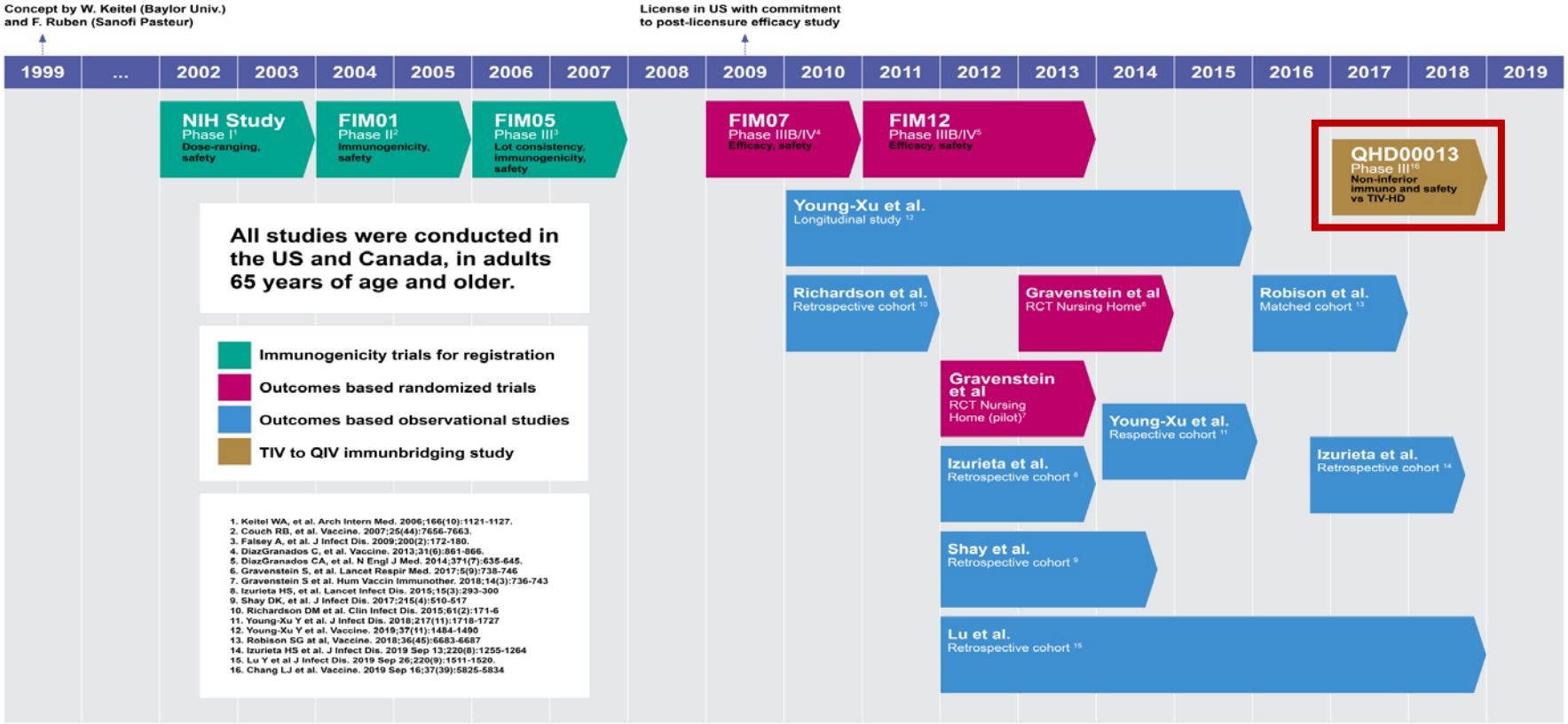
AGENDA

- **Introduction**
- **Phase III High-Dose Quadrivalent Vaccine Study**
  - Study design and results
- **Next Steps and Summary**
- **Questions**

Background on QIV-HD Vaccine Development

- **TIV-HD is a high dose, inactivated trivalent influenza vaccine that has been available in the US since 2010.**
  - 115 million doses sold since licensure
  - 2 out of 3 vaccinated adults 65+ years of age in the US received Fluzone HD vaccine during the 2018-2019 season (~22 million doses)
- **Two distinct B influenza lineages (Victoria and Yamagata) have co-circulated for over a decade, making it difficult to predict which will predominate the next season.**
- **QIV-HD has been developed to address the frequent influenza B strain mismatches by incorporating a strain from each B lineage.**
- **QHD00013 is a pivotal Phase III study which evaluated the safety and immunogenicity of QIV-HD as compared to TIV-HD.**

High Dose Studies Overview



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Meta-analysis and Systemic Review of TIV-HD Efficacy/Effectiveness versus SD Vaccine

Over 14 million adults received TIV-HD in the studies.

Outcome	RCT and Observational Studies		RCT Studies only (4 trials)	
	rVE (95%CI)	p-value	rVE (95%CI)	p-value
Influenza-like Illness	**15.9%** (4.1% - 26.3%)	0.01	**24.1%** (10.0–36.1)	0.002
Influenza Hospitalization	**12.6%** (7.1% - 17.9%)	<0.001	Not assessed	
Pneumonia Hospitalization	**27.3%** (15.3% - 37.6%)	<0.001	**27.3%** (15.3–37.6)	<0.001
Pneumonia/Influenza Hospitalization	**13.4%** (7.3% - 19.2%)	<0.001	Not assessed	
Cardiorespiratory Hospitalization	**17.9%** (15.0% - 20.8%)	<0.001	**17.9%** (15.0% - 20.8%)	<0.001
All-cause Hospitalization	**8.4%** (5.7% - 11.0%)	<0.001	**11.9%** (2.0–20.7)	0.019

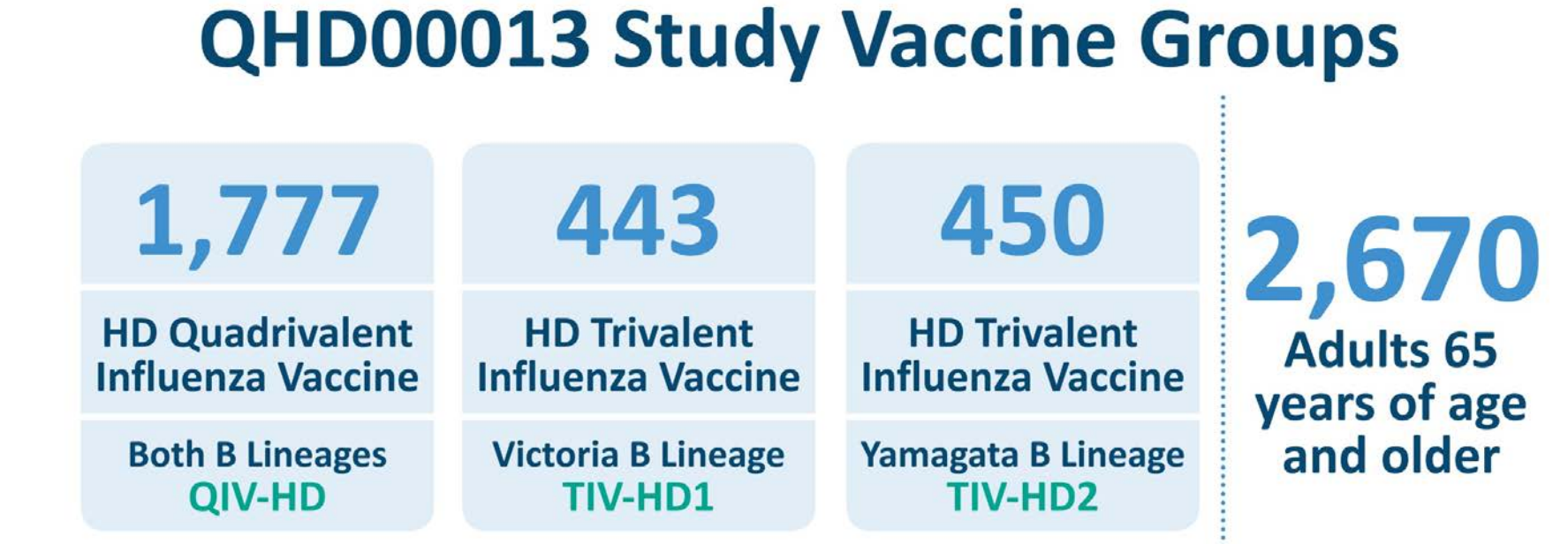
Lee et al. Meta-analysis and Systemic Review. Options X for the Control of Influenza. Aug 19, 2019.

Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine (QIV-HD) Administered by Intramuscular Route in Subjects Aged 65 Years and Older

Chang et al.

E-published ahead of print in *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

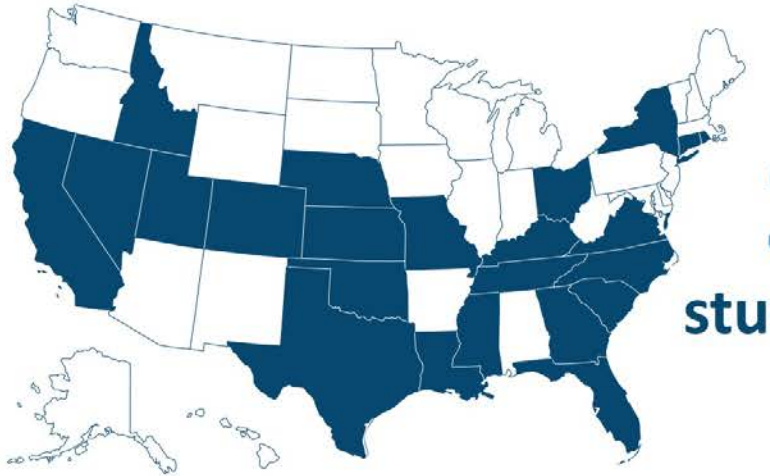
Phase III QHD00013 Overview



- Randomized, modified double-blind, active-controlled
- **Primary Objective:** to demonstrate non-inferior immunogenicity (based on HAI assay GMTs and seroconversion rates)

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

QHD00013 Study Overview



35
study sites

Northern Hemisphere Strains (2017-2018)

A/H1N1	Michigan/45/2015 X-275 pdm09
A/H3N2	Hong Kong/4801/2014(X-263B)
B/Victoria	Brisbane/60/2008
B/Yamagata	Phuket/3073/2013

First Visit First Subject **Sep 2017**

Last Contact Last Subject **Apr 2018**

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

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Demographics: Gender, Age, and Racial Origin

The randomized groups were balanced by age, gender, and racial origin.

(N= number of evaluable subjects)	QIV-HD (N= 1680)	TIV-HD1 (N= 423)	TIV-HD2 (N= 430)	Overall (N= 2533)
Males	703 (41.8%)	172 (40.7%)	191 (44.5%)	1066 (42.1%)
Females	977 (58.2%)	251 (59.3%)	239 (55.6%)	1467 (57.9%)
Mean age (years)	72.9	72.8	73.2	73.0
Percentage of subjects ≥75 yrs of age	35.4%	33.3%	38.1%	35.5%
Caucasian	91.2%	89.8%	89.5%	90.7%

Total subjects based on the Per-Protocol Analysis Dataset (PPAS) in this table.
5.1% attrition rate seen in the study.

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

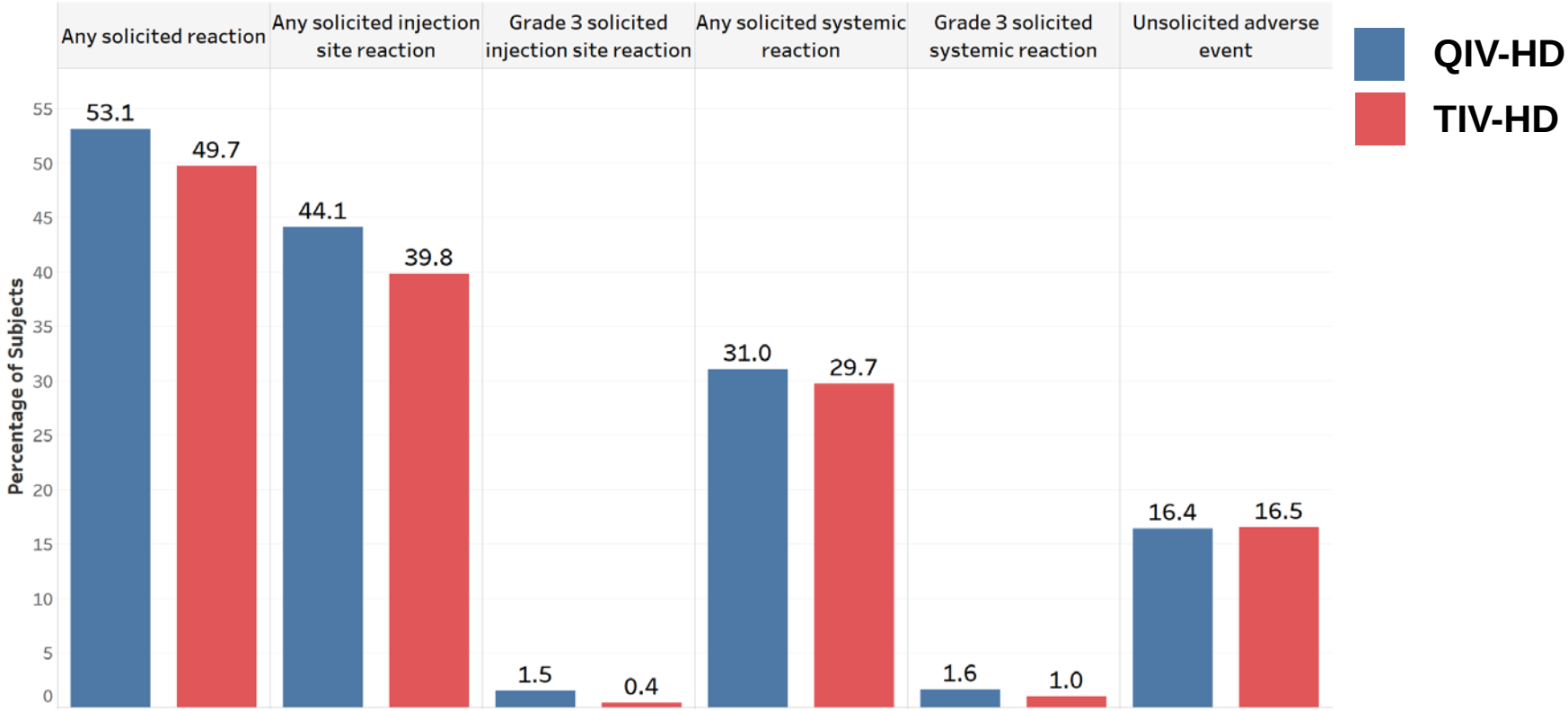
QHD00013 Safety Overview

No related deaths or related AE of special interest in all study groups.

Subject experiencing at least one	QIV-HD (N= 1777)	TIV-HD pooled (N= 893)
Immediate unsolicited AE	5 (0.3%)	2 (0.2%)
AE leading to study discontinuation	1/1777 (<0.1%)	2/893 (0.2%)
SAE (within 28 days)	19/1777 (1.1%)	12/893 (1.3%)
SAE (entire study)	80/1777 (4.5%)	48/893 (5.4%)
Fatal	3/1777 (0.2%)	2/893 (0.2%)
AE of special interest	1/1777 (<0.1%)	2/893 (0.2%)

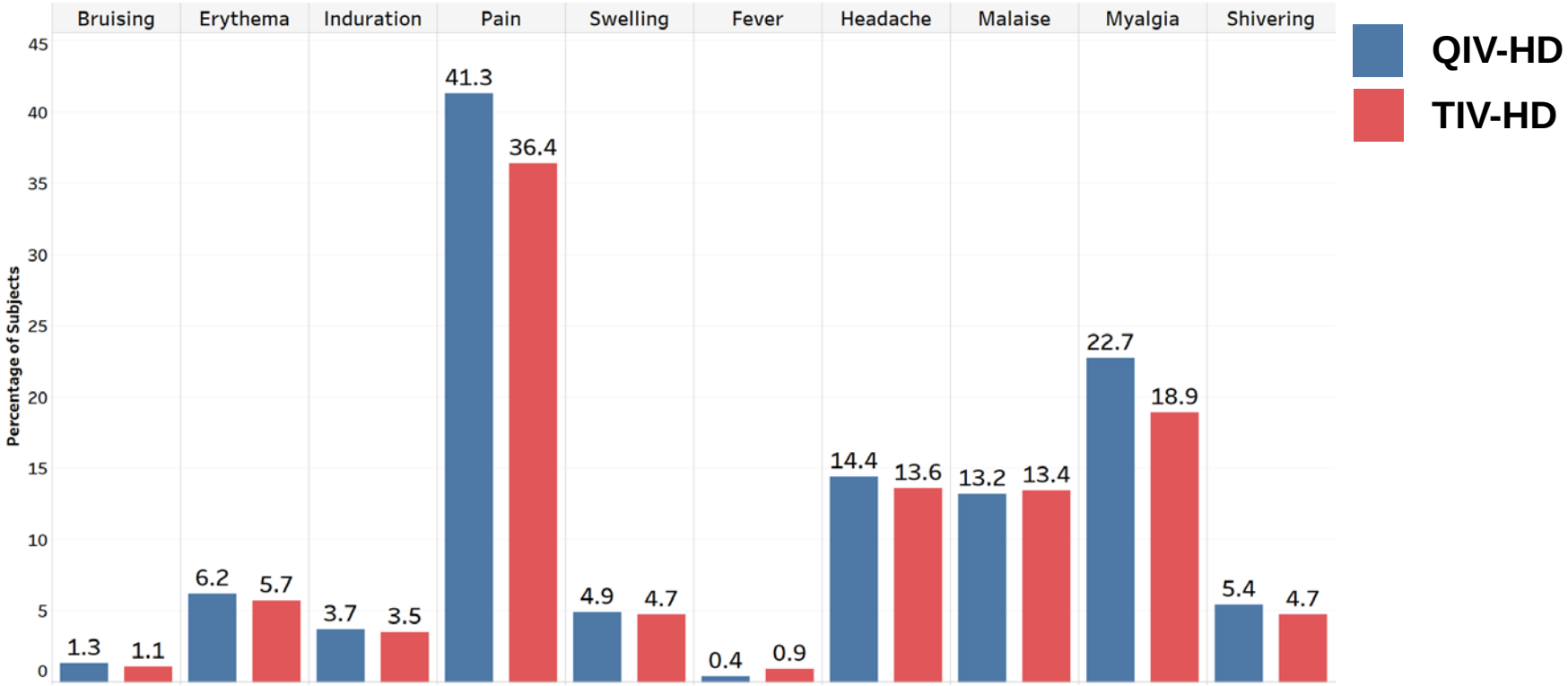
Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

Solicited Reactions Overview



Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

Solicited Reactions: Local and Systemic



Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

QHD00013: Summary of Safety Results

- **While higher percentages for some solicited reactions were observed for QIV-HD, the overall reactogenicity profile was comparable to TIV-HD.**
  - QIV-HD and TIV-HD study groups showed similar rates of unsolicited events, AEs leading to study discontinuation, SAEs, fatal SAEs, and AEs of special interest.
- **One related SAE: a subject reporting small fiber neuropathy diagnosed 42 days after QIV-HD vaccination with other concomitant etiologies (vitamin B12 deficiency and recent viral illness)**
  - Our (the Sponsor) assessment was unrelated to study vaccine given the other more likely etiologies and symptom improvement with vitamin B12 supplementation

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

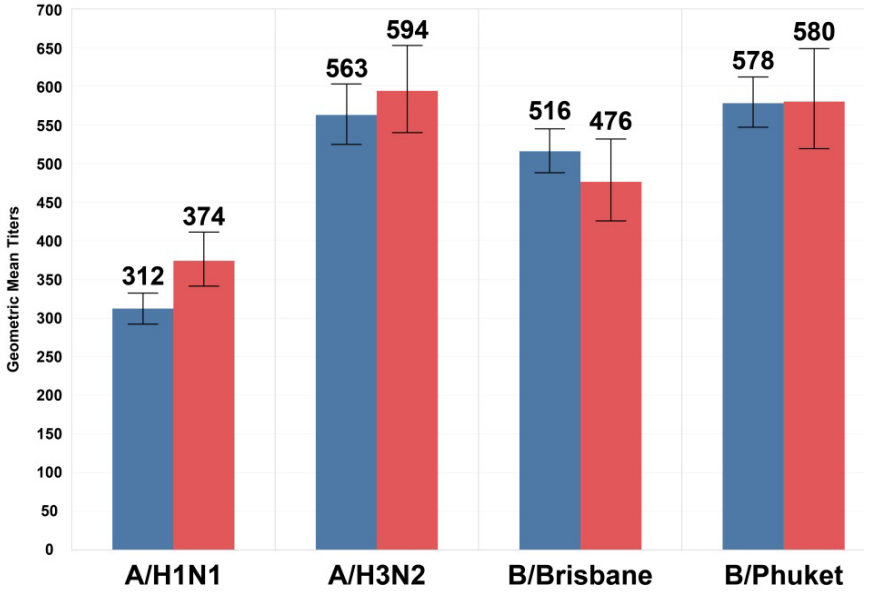
GMTs: QIV-HD versus TIV-HD

QIV-HD induced **non-inferior antibody responses (GMTs)** compared to TIV-HD against all 4 vaccine strains 28 days post-vaccination.

QIV-HD

TIV-HD†

†TIV-HD GMTs pooled for the A/H1N1 and A/H3N2 comparison. TIV-HD1 (contains B Brisbane but not B Phuket) or TIV-HD2 (contains B Phuket but not B Brisbane) GMTs for the matching B strain used for the B strain comparisons.



	A/H1N1	A/H3N2	B/Brisbane	B/Phuket
Ratio of GMT	0.83	0.95	1.08	1.00
Lower bound of the CI*	0.744	0.842	0.958	0.881

***Lower bound of the confidence interval (CI) should be >0.667 for non-inferiority to be reached.**

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

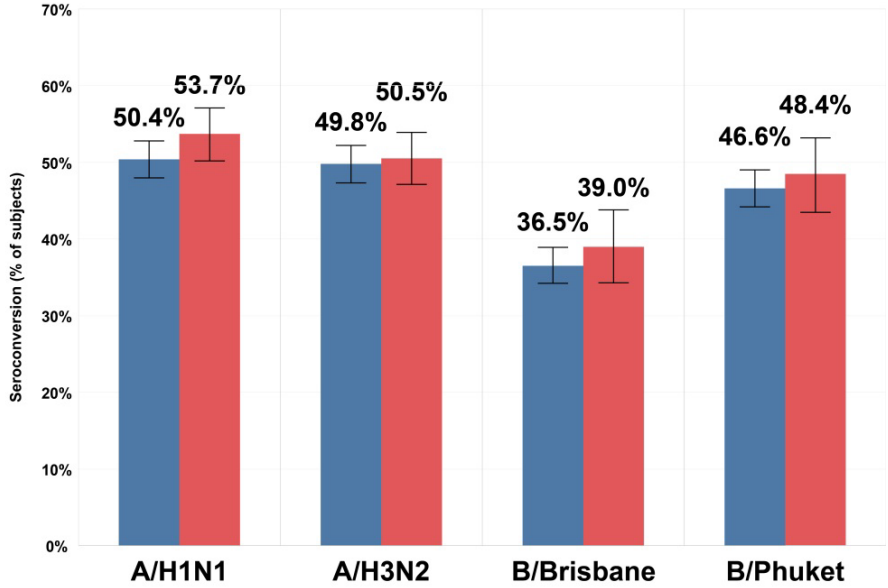
Seroconversion: QIV-HD versus TIV-HD

QIV-HD induced **non-inferior seroconversion rates** compared to TIV-HD against all 4 vaccine strains 28 days post-vaccination.

QIV-HD

TIV-HD†

†TIV-HD seroconversion rates pooled for the A/H1N1 and A/H3N2 comparison. TIV-HD1 (contains B Brisbane but not B Phuket) or TIV-HD2 (contains B Phuket but not B Brisbane) seroconversion rates for the matching B strain used for the B strain comparisons against QIV-HD.



	A/H1N1	A/H3N2	B/Brisbane	B/Phuket
Difference in Seroconversion (QIV-HD minus TIV-HD)	**-3.27%**	**-0.71%**	**-2.41%**	**-1.75%**
Lower bound of the CI*	**-7.37%**	**-4.83%**	**-7.66%**	**-7.04%**

***Lower bound of the confidence interval (CI) should be >-10% for non-inferiority to be reached.**

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

Secondary Endpoint: Superiority for Alternate B Strain

QIV-HD induced an immune response superior to that induced by the TIV-HD that did not contain the corresponding B strain.

GMT	QIV-HD	TIV-HD	GMT ratio (QIV-HD/TIV-HD)	Lower Bound of the CI*
B/Brisbane	516	253	2.04	1.805
B/Phuket	578	282	2.05	1.806

Seroconversion	QIV-HD	TIV-HD	Difference in SC (QIV-HD—TIV-HD)	Lower Bound of the CI*
B/Brisbane	36.5%	15.2%	21.36%	17.01%
B/Phuket	46.6%	17.6%	29.04%	24.45%

***Lower bound of the confidence interval (CI) should be >1.5 for superiority to be reached with respect to GMT and >10% for superiority to be reached with respect to seroconversion.**

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

Overall Key Study Results

- **Safety Results**
  - **No safety issues** were observed with QIV-HD in adults 65 years of age and older.
    - Safety profiles between QIV-HD and TIV-HD were similar.
- **Immunogenicity Results**
  - **Primary Objective Met**: QIV-HD was **non-inferior** to TIV-HD by GMTs and seroconversion rates for all 4 strains.
  - **Secondary Objective Met**: QIV-HD induced an immune response **superior** to that induced by the TIV-HD that did not contain the corresponding B strain.

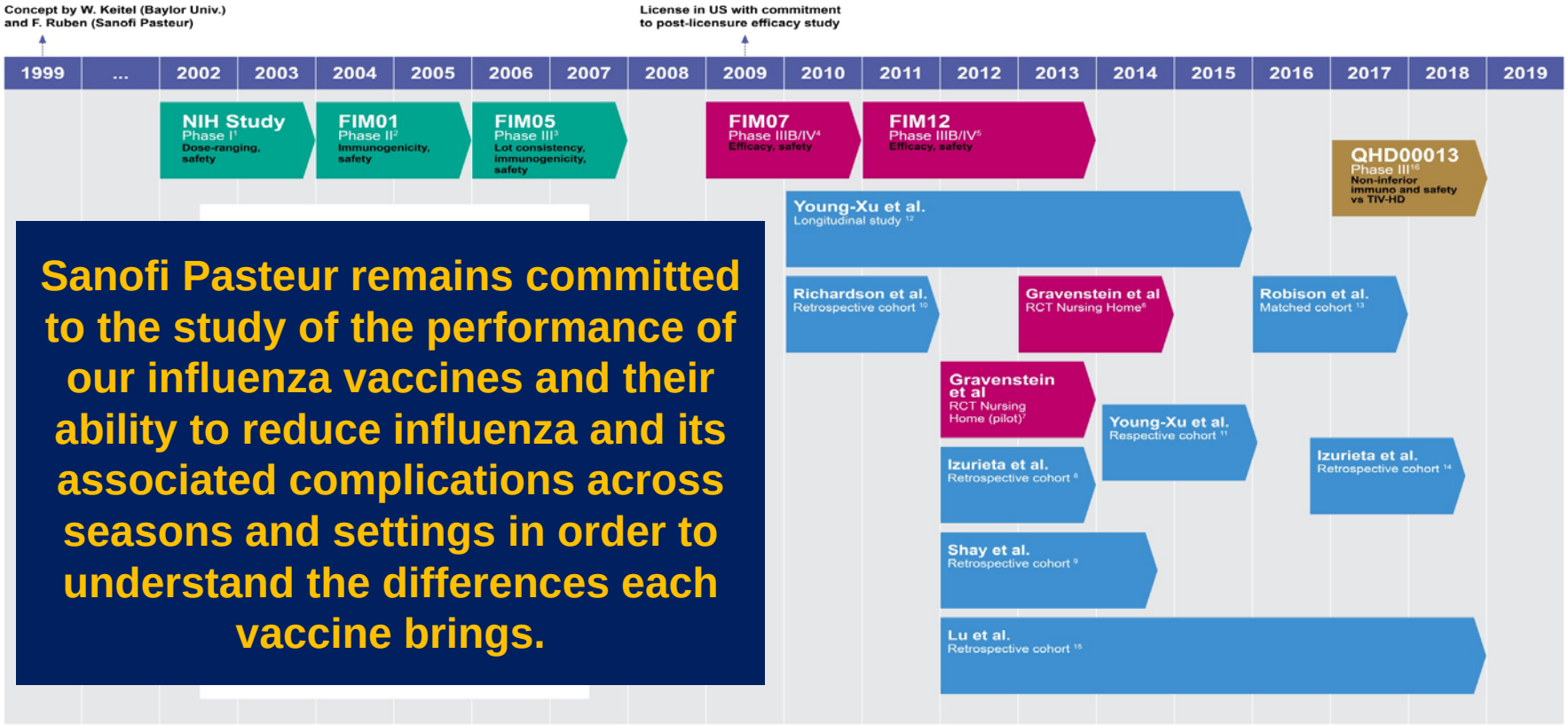
The study results demonstrated that addition of a second influenza B strain in QIV-HD did not impact the safety or immunogenicity of the other 3 strains in subjects 65 years of age and older.

Chang L-J, et al. *Vaccine* (Aug 2019): https://doi.org/10.1016/j.vaccine.2019.08.016

QIV-HD Next Steps

- **CBER action date: November 4, 2019**
- **Assuming licensure:**
  - **HCPs will be able to pre-order QIV-HD in Q1 2020**
  - **TIV-HD will be entirely replaced by QIV-HD for the 2020-2021 season**

Sanofi Pasteur's **High Dose** Influenza Vaccine



Sanofi Pasteur remains committed to the study of the performance of our influenza vaccines and their ability to reduce influenza and its associated complications across seasons and settings in order to understand the differences each vaccine brings.

BACK UP

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QHD00013: Race and Ethnicity

(N= number of evaluable subjects)	QIV-HD (N=1680)	TIV-HD1 (N=423)	TIV-HD2 (N=430)	Overall (N=2533)
Racial origin: n (%)				
American Indian or Alaska Native	9 (0.5)	2 (0.5)	3 (0.7)	14 (0.6)
Asian	12 (0.7)	2 (0.5)	3 (0.7)	17 (0.7)
Black or African American	114 (6.8)	36 (8.5)	32 (7.4)	182 (7.2)
Native Hawaiian or other Pacific Islander	3 (0.2)	1 (0.2)	1 (0.2)	5 (0.2)
White	1532 (**91.2**)	380 (**89.8**)	385 (**89.5**)	2297 (**90.7**)
Multiple	6 (0.4)	1 (0.2)	2 (0.5)	9 (0.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	4 (0.2)	1 (0.2)	4 (0.9)	9 (0.4)
Ethnicity				
Hispanic or Latino	47 (2.8)	9 (2.1)	13 (3.0)	69 (2.7)
Not Hispanic or Latino	1630 (97.0)	413 (97.6)	415 (96.5)	2458 (97.0)
Unknown	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)
Not reported	3 (0.2)	1 (0.2)	1 (0.2)	5 (0.2)

QHD00013: Solicited Reactions

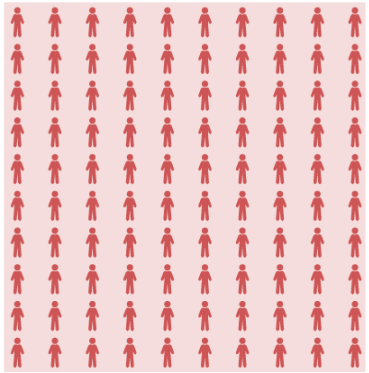
Most frequently reported reactions: injection site pain and myalgia

Solicited reactions within 7 days after vaccine injection (Safety Analysis Set)

	QIV-HD (N=1777)			TIV-HD1 (N=443)			TIV-HD2 (N=450)			TIV-HD Pooled (N=893)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	938/1768	53.1	(50.7 ; 55.4)	235/440	53.4	(48.6 ; 58.1)	207/449	46.1	(41.4 ; 50.8)	442/889	49.7	(46.4 ; 53.1)
Injection site reaction	779/1768	44.1	(41.7 ; 46.4)	189/440	43.0	(38.3 ; 47.7)	165/449	36.7	(32.3 ; 41.4)	354/889	39.8	(36.6 ; 43.1)
Bruising	23/1765	1.3	(0.8 ; 1.9)	6/439	1.4	(0.5 ; 3.0)	4/448	0.9	(0.2 ; 2.3)	10/887	1.1	(0.5 ; 2.1)
Erythema	110/1768	6.2	(5.1 ; 7.5)	30/440	6.8	(4.6 ; 9.6)	21/449	4.7	(2.9 ; 7.1)	51/889	5.7	(4.3 ; 7.5)
Induration	66/1766	3.7	(2.9 ; 4.7)	17/439	3.9	(2.3 ; 6.1)	14/448	3.1	(1.7 ; 5.2)	31/887	3.5	(2.4 ; 4.9)
Pain	731/1768	41.3	(39.0 ; 43.7)	172/440	39.1	(34.5 ; 43.8)	152/449	33.9	(29.5 ; 38.4)	324/889	36.4	(33.3 ; 39.7)
Swelling	86/1766	4.9	(3.9 ; 6.0)	23/439	5.2	(3.3 ; 7.8)	19/448	4.2	(2.6 ; 6.5)	42/887	4.7	(3.4 ; 6.3)
Systemic reaction	548/1768	31.0	(28.8 ; 33.2)	132/440	30.0	(25.8 ; 34.5)	132/449	29.4	(25.2 ; 33.9)	264/889	29.7	(26.7 ; 32.8)
Fever	7/1761	0.4	(0.2 ; 0.8)	3/437	0.7	(0.1 ; 2.0)	5/448	1.1	(0.4 ; 2.6)	8/885	0.9	(0.4 ; 1.8)
Headache	254/1768	14.4	(12.8 ; 16.1)	63/440	14.3	(11.2 ; 17.9)	58/449	12.9	(10.0 ; 16.4)	121/889	13.6	(11.4 ; 16.0)
Malaise	233/1768	13.2	(11.6 ; 14.8)	52/440	11.8	(9.0 ; 15.2)	67/449	14.9	(11.8 ; 18.6)	119/889	13.4	(11.2 ; 15.8)
Myalgia	402/1768	22.7	(20.8 ; 24.8)	80/440	18.2	(14.7 ; 22.1)	88/449	19.6	(16.0 ; 23.6)	168/889	18.9	(16.4 ; 21.6)
Shivering	95/1768	5.4	(4.4 ; 6.5)	20/440	4.5	(2.8 ; 6.9)	22/449	4.9	(3.1 ; 7.3)	42/889	4.7	(3.4 ; 6.3)

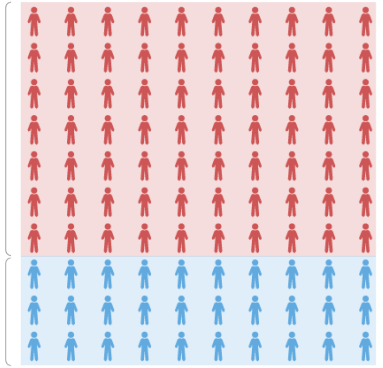
Visual Example: Relative Efficacy Translates to Absolute Efficacy

100 influenza cases in adults 65 years of age if no one is vaccinated



Vaccinate with SD

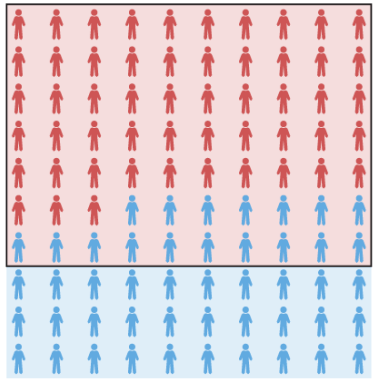
70 out of 100 cases would still develop influenza despite standard dose (SD) influenza vaccination



30% absolute efficacy

30 out of 100 cases prevented by SD influenza vaccination

Vaccinate with HD



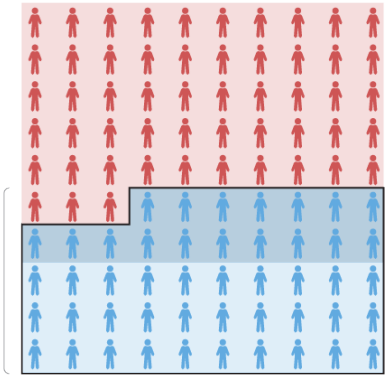
24% relative efficacy

If everyone was vaccinated with TIV-HD instead of a SD influenza vaccine, 17 cases out of 70 would be prevented

=

47% absolute efficacy

30 + 17 = 47 cases out of 100 averted



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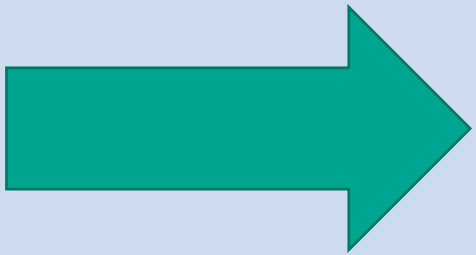
How 24% Relative Efficacy Translates to Absolute Efficacy

Absolute Efficacy of SD vaccine	Relative Efficacy of HD vaccine	Absolute Efficacy of HD vaccine
10%	**24%** relative efficacy 	32%
20%		39%
30%		47%
40%		54%
50%		62%
60%		70%
70%		77%
80%		85%

Efficacy Results of HD vs SD Fluzone Vaccine in a Randomized Clinical Trial

Compared to standard-dose (SD), the benefit of high-dose (HD) was demonstrated across age groups, influenza types, comorbidities, and frailty-associated conditions in 32,000 community-dwelling seniors

PRIMARY ENDPOINT	Similar to Vaccine Strains[1]	Year 1[3]	Year 2[3]
24.2% **more efficacious*** HD (N=228) vs. SD (N=301) *(95% CI: 9.7; 36.5)*	**35.4%** *(95% CI: 12.5; 52.5)*	**45.3%** *(95% CI: 6.9; 68.6)*	**20.7%** *(95% CI: 4.4; 34.3)*
	65-74 Years of Age[2]	75+ Years of Age[2]	
	19.7% *(95% CI: 0.4; 35.4)*	**32.4%** *(95% CI: 8.1; 50.6)*	
Demonstrated SUPERIOR EFFICACY against primary endpoint compared to IIV3-SD[1]	≥1 High-Risk Comorbidity[2]	1 Frailty-Associated Condition[2]	
	22.1% *(95% CI: 3.9; 37.0)*	**27.5%** *(95% CI: 0.4; 47.4)*	

against laboratory-confirmed influenza illness caused by **any virus type or subtype in adults 65 years of age and older*

References: [1,2]DiazGranados CA et al. N Engl J Med 2014;371(7):635-645.
[3]DiazGranados CA et al. 2015 Vaccine;33(36):4565-4571.

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