ACIP Meeting

June 24, 2015

Fluzone® Intradermal Quadrivalent (Influenza Vaccine)

Corey Robertson, MD, MPH

Sanofi Pasteur

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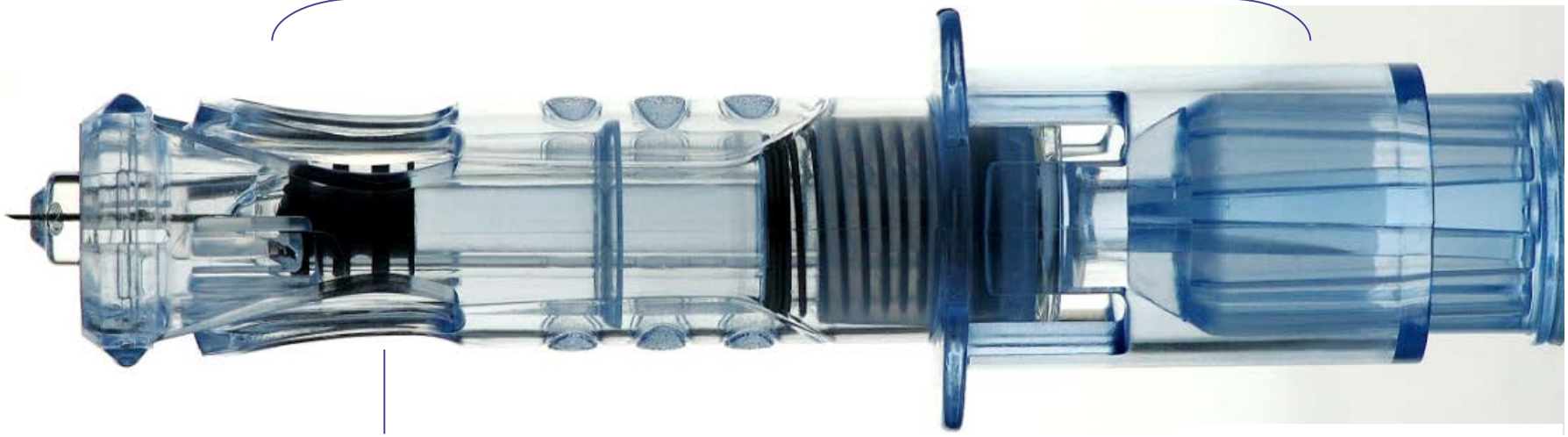
Microinjection: An Innovative Approach to Influenza Vaccine Administration[1,2]

Ready-to-use prefilled syringe

Requires no preparation or air purging



0.1 mL dose, 9mcg of hemagglutinin (HA) of each strain

Provides immunogenicity comparable to that associated with a higher amount of antigen injected intramuscularly[3]

References: **1.** Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? *Vaccine*. 2008;26(26):3197-3208. **2.** Fluzone Intradermal Quadrivalent vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2014. **3.** Fluzone Intradermal vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2014.

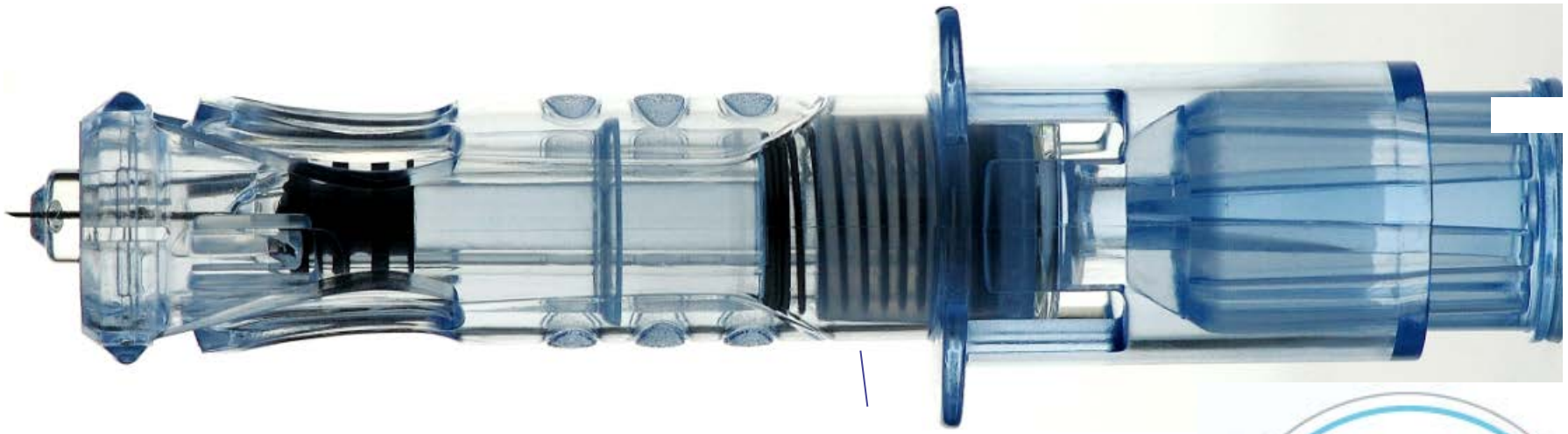
Microinjection: An Innovative Approach to Influenza Vaccine Administration[1,2]

1.5 mm, 30-gauge microneedle

Consistently delivers accurate dose of antigen directly into the dermis

References: **1.** Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? *Vaccine*. 2008;26(26):3197-3208. **2.** Fluzone Intradermal Quadrivalent vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2014.

Microinjection: An Innovative Approach to Influenza Vaccine Administration[1,2]



Integrated needle shield

Can be activated post-vaccination to cover needle

References: **1.** Lambert PH, Laurent PE. Intradermal vaccine delivery: will new delivery systems transform vaccine administration? *Vaccine*. 2008;26(26):3197-3208. **2.** Fluzone Intradermal Quadrivalent vaccine [Prescribing Information]. Swiftwater, PA: Sanofi Pasteur Inc.; 2014.

QID01: Study Design

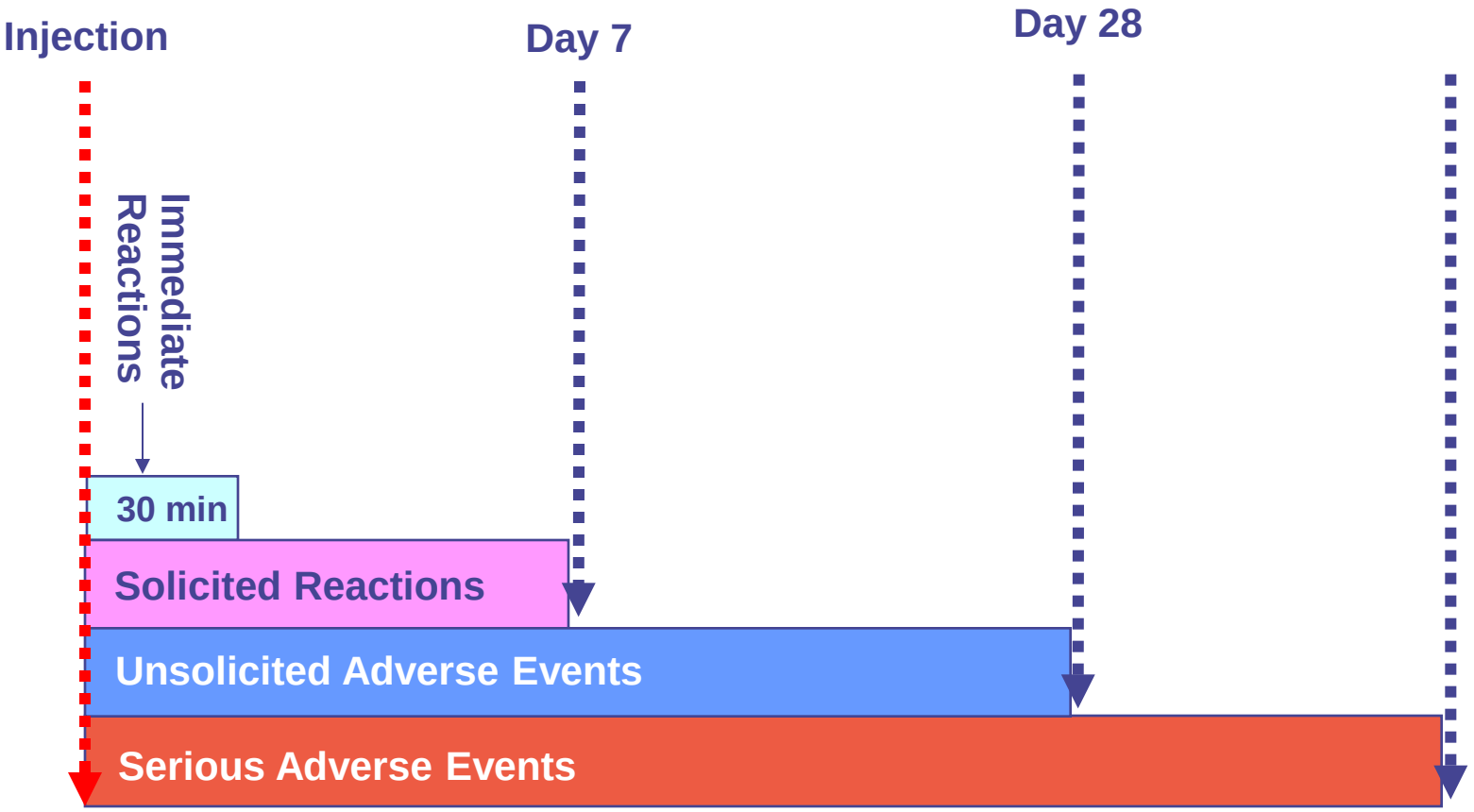
- Randomized, double-blind, active-controlled, multi-center trial conducted in US
- 3360 adults 18–64 years of age were randomly assigned to receive 1 of 3 study vaccines

IIV4-ID N=1676	IIV3-ID(1) N=837	IIV3-ID(2) N=847
A/Brisbane/59/2007(H1N1)	A/Brisbane/59/2007(H1N1)	A/Brisbane/59/2007(H1N1)
A/Uruguay/716/2007(H3N2)	A/Uruguay/716/2007(H3N2)	A/Uruguay/716/2007(H3N2)
B/Texas/6/2011 (Yamagata)	B/Texas/6/2011 (Yamagata)	
B/Brisbane/60/2008 (Victoria)		B/Brisbane/60/2008 (Victoria)

- Each vaccine contained 9 mcg HA per strain
- Each subject received a 0.1 mL intradermal dose of study vaccine on Day 0

IIV4-ID: Fluzone Intradermal Quadrivalent vaccine
IIV3-ID(1): Licensed 2012-2013 Fluzone Intradermal vaccine
IIV3-ID(2): Investigational trivalent intradermal influenza vaccine

QID01: Safety Data Collection



Safety data were collected for:

- **1672 IIV4-ID recipients**
- **1683 IIV3-ID recipients**

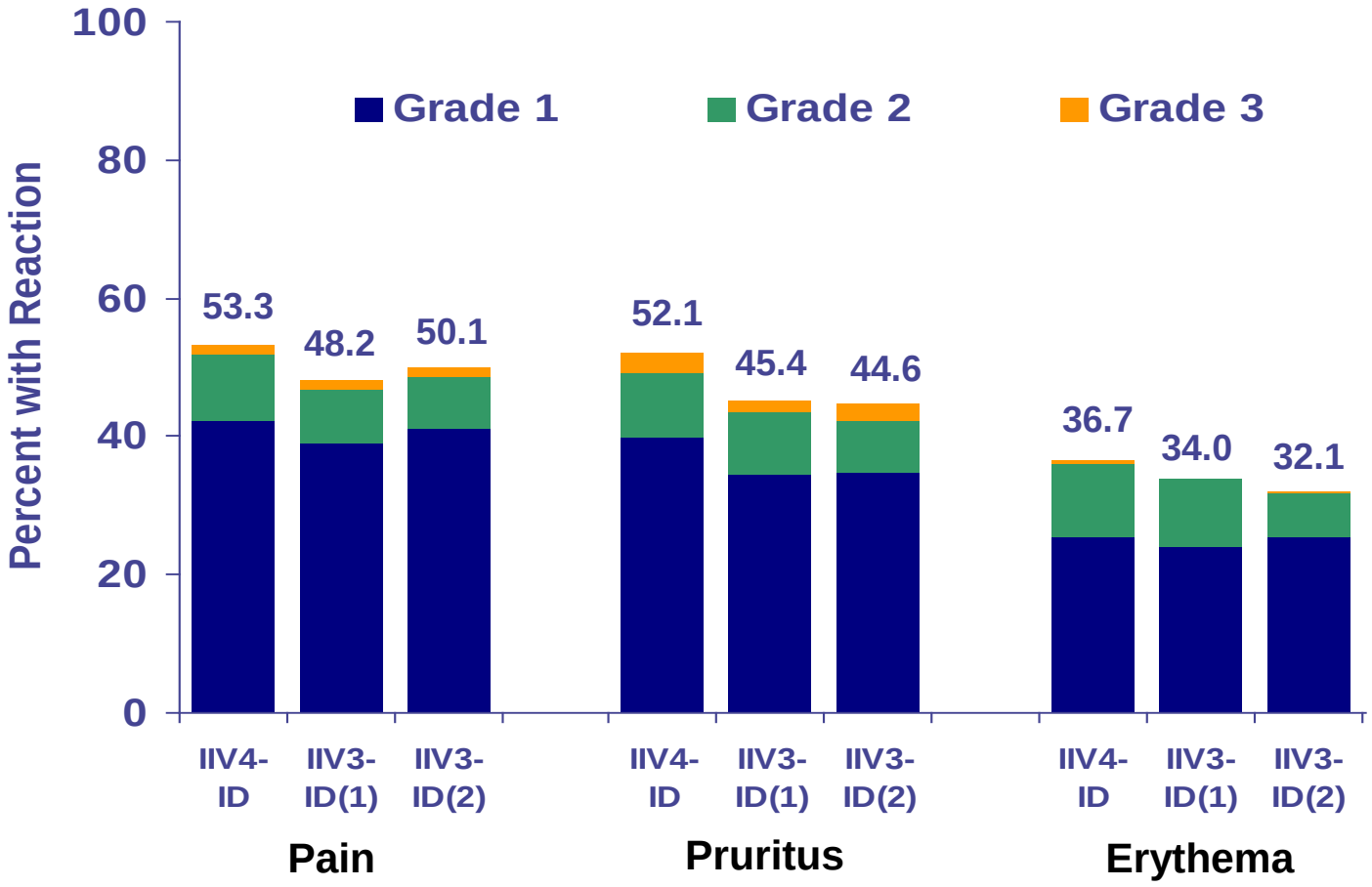
QID01: Immunogenicity Evaluation

- **Blood specimens collected pre-vaccination and 28-35 days post-vaccination from a random 2/3 subset of subjects**
- **Standardized HAI antibody assays performed by persons blinded to vaccine assignment**
- **Endpoints**
  - **HAI GMTs**
  - **% subjects with 4-fold rise in HAI titers pre- to post-vaccination[a]**
  - **% subjects with post-vaccination HAI titers ≥ 1:40**

[a]4-fold rise defined as either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a four-fold increase in post-vaccination titer

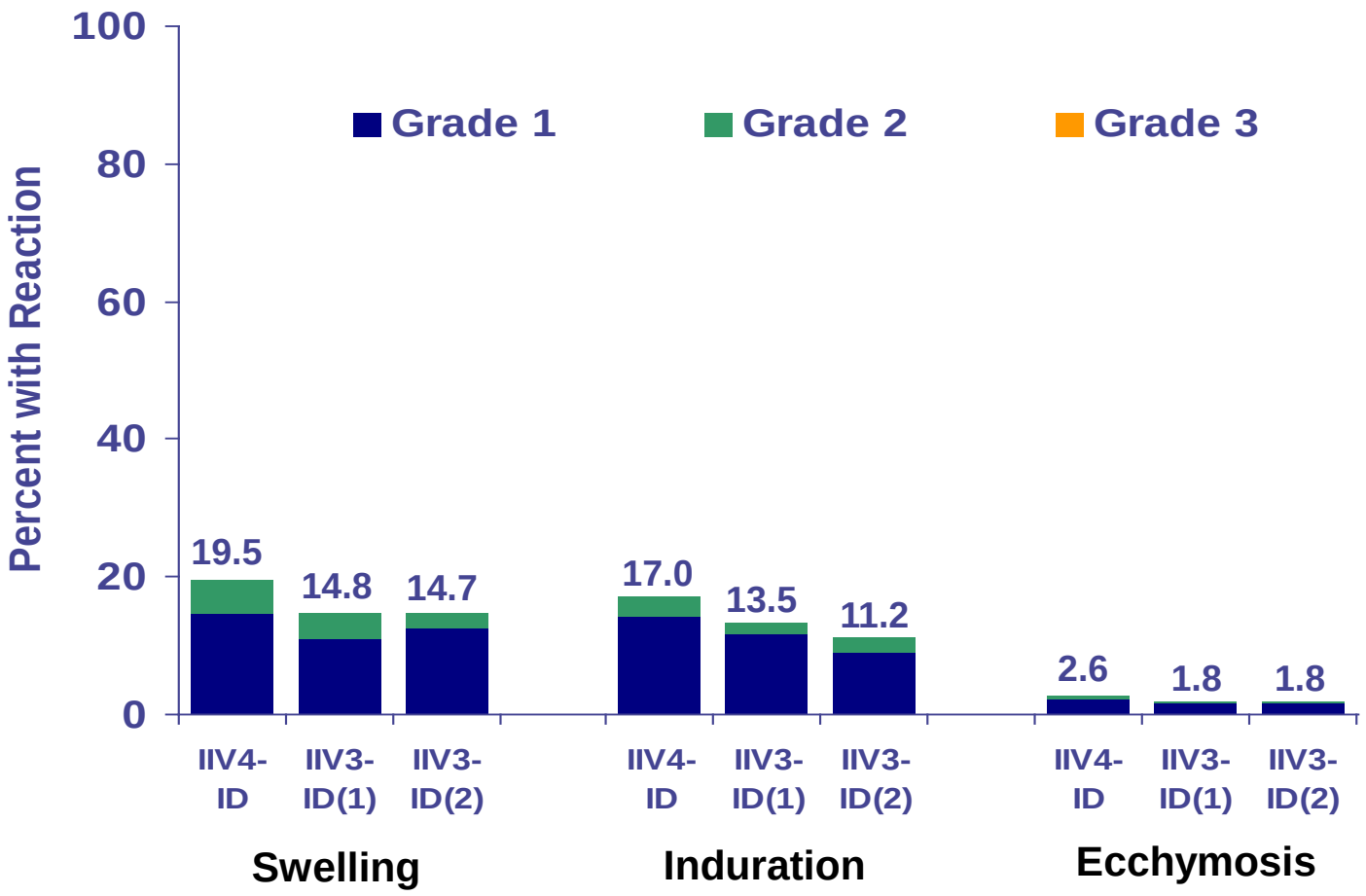
QID01: Safety Results

QID01: Solicited Injection-Site Reactions, Days 0-7 Post-vaccination



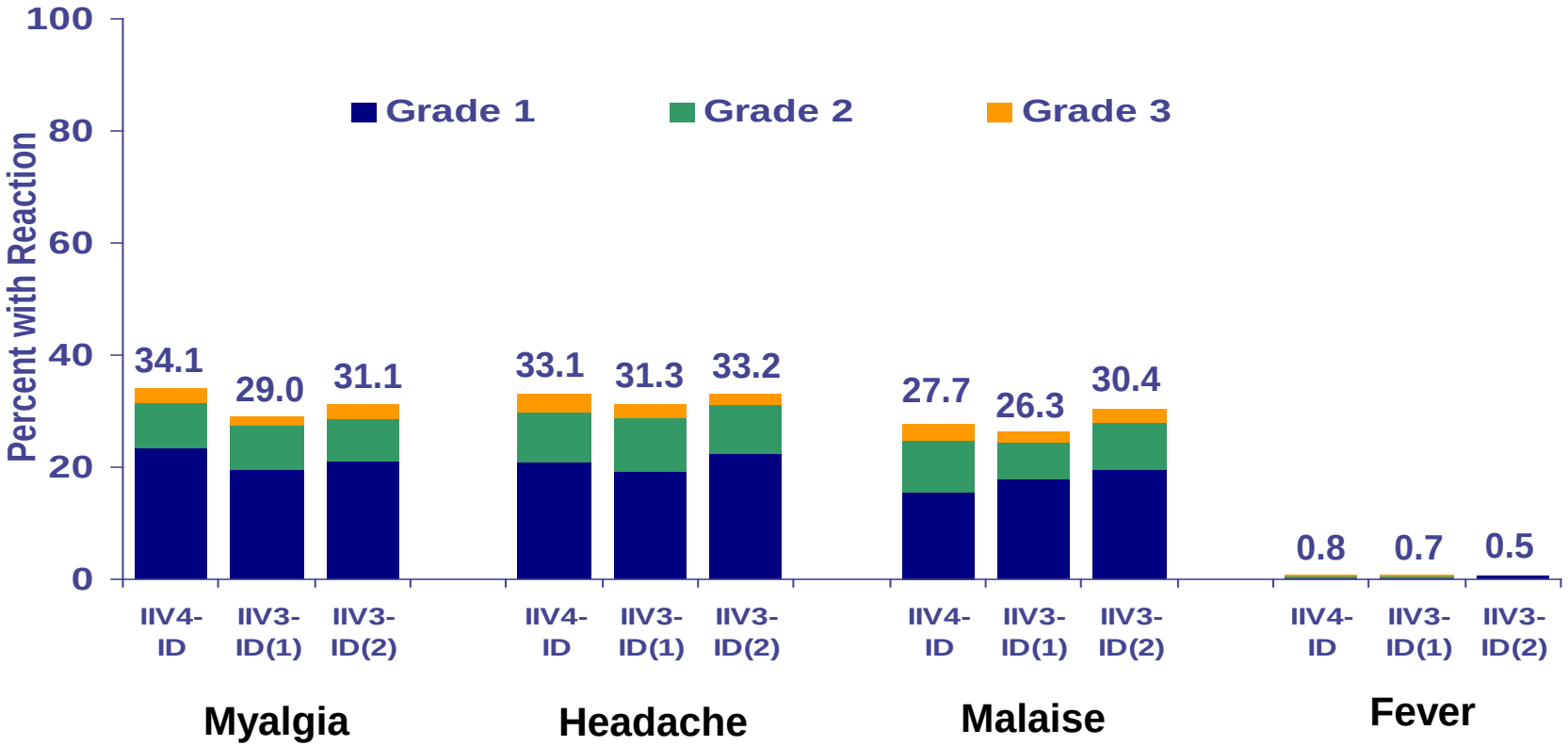
Pain and pruritus: Grade I: no interference with activity; Grade II: some interference with activity; Grade III: prevents daily activity.
Erythema: Grade I: ≥2.5 to ≤5 cm; Grade II: >5 to ≤10 cm; Grade III: >10 cm.

QID01: Solicited Injection-Site Reactions, Days 0-7 Post-vaccination (2)



Grade I: ≥2.5 to ≤5 cm; Grade II: >5 to ≤10 cm; Grade III: >10 cm.

QID01: Solicited Systemic Reactions, Days 0-7 Post-vaccination



Grade I: no interference with activity; Grade II: some interference with activity; Grade III: prevents daily activity.
Fever: Grade I: ≥100.4ºF to ≤101.1ºF; Grade II: >101.1ºF to ≤102.0ºF; Grade III: >102.0ºF.

QID01: Unsolicited Adverse Events (AEs) and Serious Adverse Events (SAEs)

	IIV4-ID (N=1672)		IIV3-ID(1) (N=837)		IIV3-ID(2) (N=846)	
Subjects experiencing at least one:	**n**	**%**	**n**	**%**	**n**	**%**
Within 28 days after any vaccine injection						
Immediate unsolicited AE	7	**0.4**	2	**0.2**	4	**0.5**
Immediate unsolicited adverse reaction (AR)	6	**0.4**	2	**0.2**	3	**0.4**
Unsolicited AE	386	**22.8**	170	**20.3**	215	**25.4**
Unsolicited AR	76	**4.5**	22	**2.6**	37	**4.4**
SAE	6	**0.4**	2	**0.2**	3	**0.4**
Death	0	**0.0**	0	**0.0**	0	**0.0**
AE of special interest (AESI)[a]	0	**0.0**	0	**0.0**	0	**0.0**
During the entire trial						
SAE	20	**1.2**	14	**1.7**	11	**1.3**
Death	1[b]	**<0.1**	0	**0.0**	0	**0.0**

[a]AESIs included new onset of Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

[b]A 60-year-old male subject died due to acute coronary myocardial infarction 177 days after receipt of IIV4-ID. The subject had risk factors for heart disease (hypertension and hyperlipidemia); this death was considered not related to the vaccine.

Non-inferiority of IIV4-ID vs. IIV3-ID: All Grade 2 or Grade 3 Solicited Systemic Reactions Combined

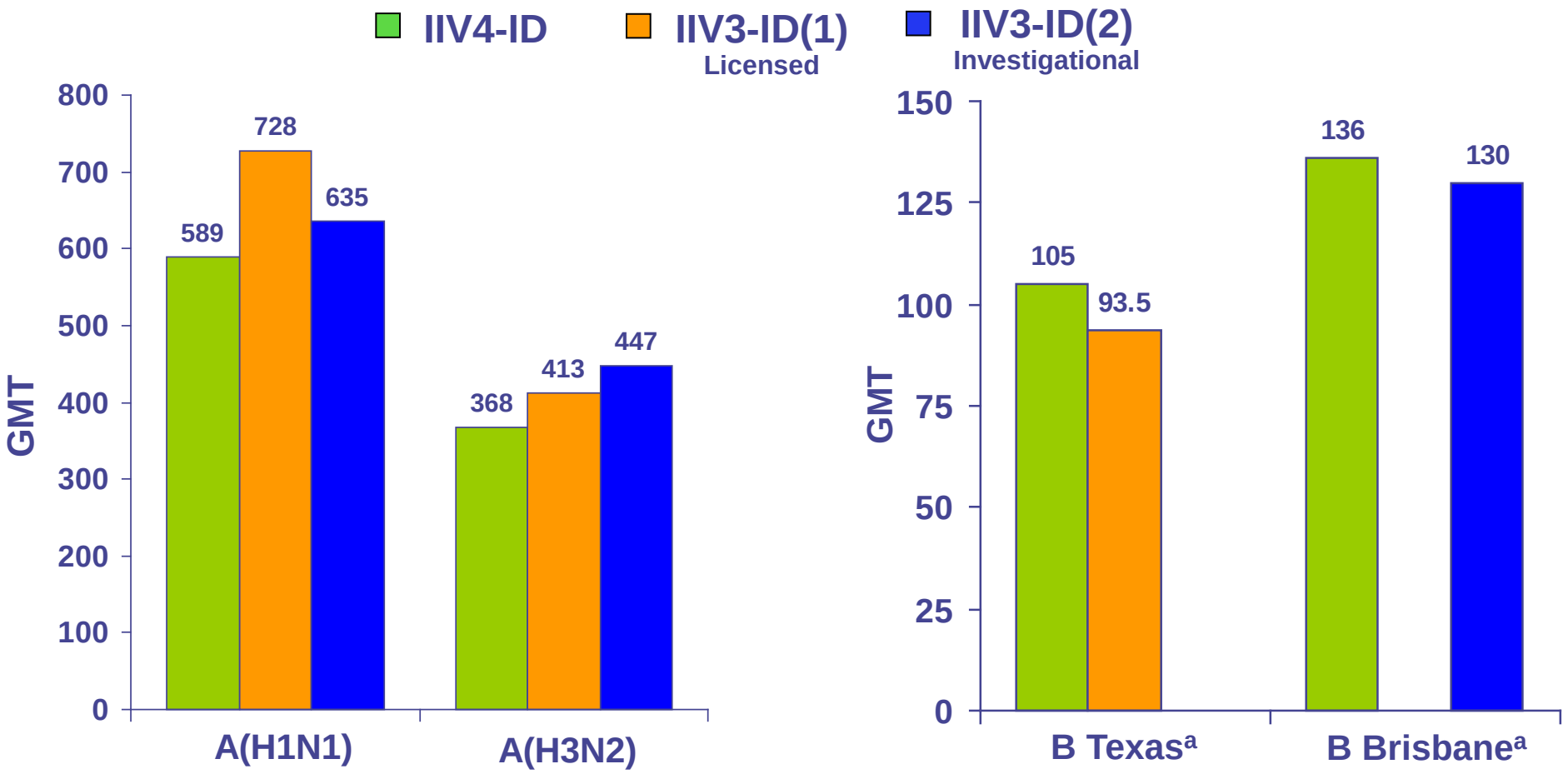
	IIV4-ID (N=1672)			IIV3-ID Pooled (N=1683)			Ratio of proportions IIV4-ID / IIV3-ID pooled	95% CI for ratio	Non-inferiority (upper confidence level of ratio<3)
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**-**	**-**	**-**
Grade 2 or 3 Solicited Systemic Reaction	**351/1656**	**21.2**	**(19.2; 23.2)**	**335/1658**	**20.2**	**(18.3; 22.2)**	**1.05**	**(0.92; 1.20)**	**Yes**

Non-inferiority of IIV4-ID vs. IIV3-ID: All Grade 3 Solicited Injection-Site Reactions Combined

	IIV4-ID (N=1672)			IIV3-ID Pooled (N=1683)			Ratio of proportions IIV4-ID / IIV3-ID pooled	95% CI for ratio	Non-inferiority (upper confidence level of ratio <3)
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**-**	**-**	**-**
All Grade 3 solicited injection-site reactions combined	**66/1656**	**4.0**	**(3.1; 5.0)**	**51/1658**	**3.1**	**(2.3; 4.0)**	**1.30**	**(0.90; 1.86)**	**Yes**

QID01: Immunogenicity Results

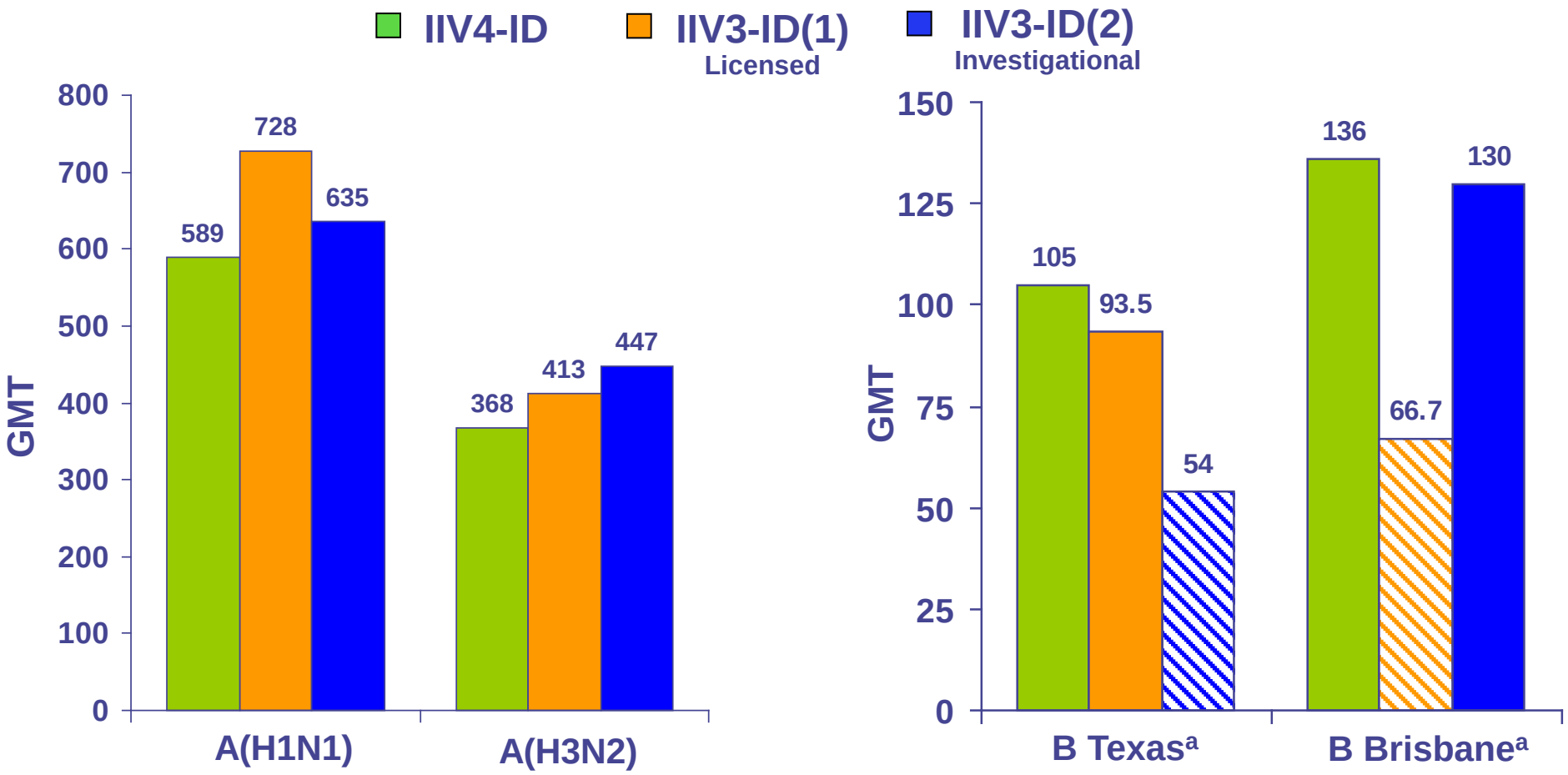
QID01: Geometric Mean Titers (GMTs), 28 Days Post-vaccination



IIV3-ID(1) contained B/Texas (Yamagata lineage); IIV3-ID(2) contained B Brisbane (Victoria lineage); IIV4-ID contained both.

[a] Striped bar represents strain not contained in each respective vaccine.

QID01: Geometric Mean Titers (GMTs), 28 Days Post-vaccination



IIV3-ID(1) contained B/Texas (Yamagata lineage); IIV3-ID(2) contained B Brisbane (Victoria lineage); IIV4-ID contained both.

[a] Striped bar represents strain not contained in each respective vaccine.

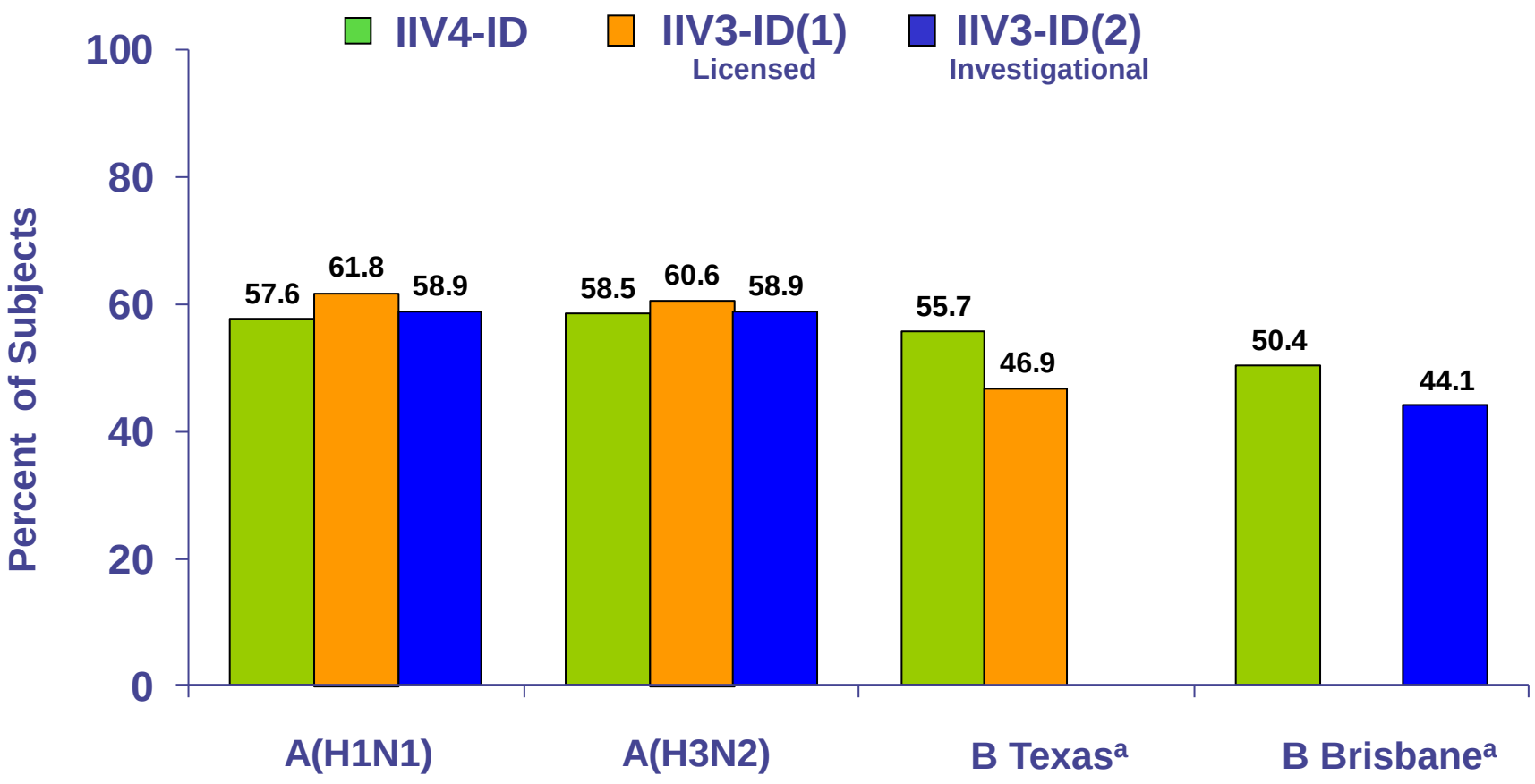
QID01: Comparison of Geometric Mean Titers (GMTs), IIV4-ID vs. IIV3-ID

Strain	IIV4-ID GMT (N=1041)	IIV3-ID(1) GMT (N=539)	IIV3-ID(2) GMT (N=539)	GMT Ratio (95% CI)	Statistical Comparison[a]
A/H1N1	589	680 (pooled)		0.866 (0.777; 0.966)	Noninferior
A/H3N2	368	430 (pooled)		0.857 (0.770; 0.955)	Noninferior
B/Texas	105	93.5	–	1.13 (1.02, 1.25)	Noninferior
B/Brisbane	136	–	130	1.05 (0.939, 1.16)	Noninferior
B/Texas	105	–	54.0	1.95 (1.75; 2.17)	Superior
B/Brisbane	136	66.7	–	2.04 (1.84; 2.27)	Superior

Noninferiority: lower bound of 95% CI of GMT ratio > 0.667.
Superiority: lower bound of 95% CI of GMT ratio > 1.5.

[a]All comparisons are based on data from the Per-Protocol Analysis Set.

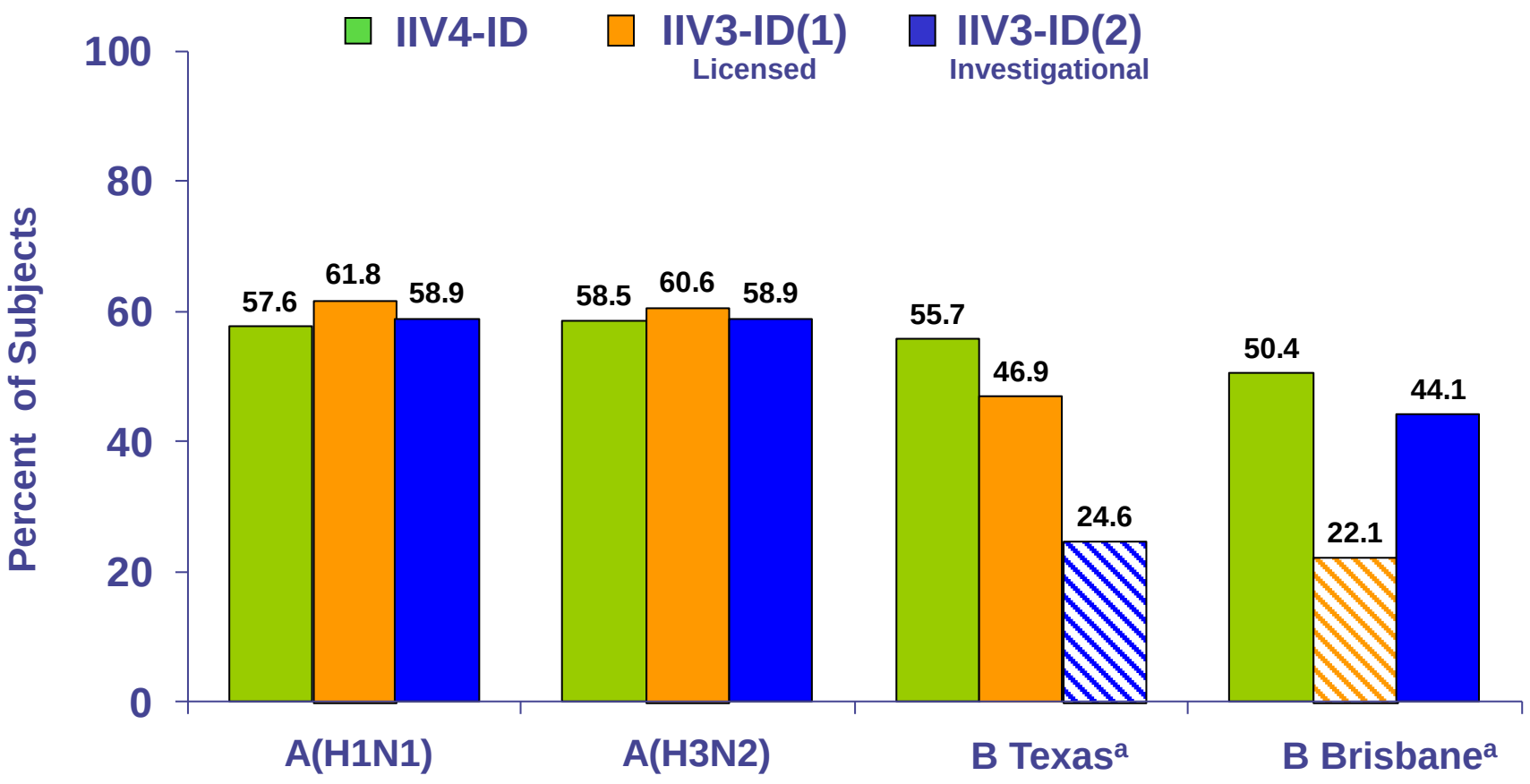
QID01: Seroconversion Rates, 28 Days Post-vaccination



IIV3-ID(1) contained B/Texas (Yamagata lineage); IIV3-ID(2) contained B/Brisbane (Victoria lineage); IIV4-ID contained both.

[a] Striped bar represents strain not contained in each respective vaccine.

QID01: Seroconversion Rates, 28 Days Post-vaccination



IIV3-ID(1) contained B/Texas (Yamagata lineage); IIV3-ID(2) contained B/Brisbane (Victoria lineage); IIV4-ID contained both.

[a] Striped bar represents strain not contained in each respective vaccine.

QID01: Comparison of Seroconversion (SC) Rates, IIV4-ID vs. IIV3-ID

Strain	IIV4-ID SC Rate (%) (N=1041)	IIV3-ID(1) SC Rate (%) (N=539)	IIV3-ID(2) SC Rate (%) (N=539)	SC Rate Difference (%) (95% CI)	Statistical Comparison[a]
A/H1N1	57.6	60.4 (pooled)		-2.72 (-6.90; 1.47)	Noninferior
A/H3N2	58.5	59.8 (pooled)		-1.30 (-5.48; 2.89)	Noninferior
B/Texas	55.7	46.9	–	8.78 (3.58; 13.9)	Noninferior
B/Brisbane	50.4	–	44.1	6.34 (1.13; 11.5)	Noninferior
B/Texas	55.7	–	24.6	31.1 (26.3; 35.7)	Superior
B/Brisbane	50.4	22.1	–	28.3 (23.5; 32.8)	Superior

Noninferiority: lower bound of 95% CI of SC rate difference > -10%.
Superiority: lower bound of 95% CI of SC rate difference > 10%.
[a]All comparisons are based on data from the Per-Protocol Analysis Set

Summary

- **Fluzone Intradermal Quadrivalent vaccine was as immunogenic and as safe as trivalent intradermal vaccine in a healthy adult population**

- **With inclusion of a second B strain, Fluzone Intradermal Quadrivalent vaccine reduces the risk of B-strain mismatch and can help improve protection against influenza**

Important Safety Information for Fluzone Intradermal Quadrivalent Vaccine

Indication

Fluzone Intradermal Quadrivalent vaccine is indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone intradermal Quadrivalent vaccine is approved for use in persons 18 through 64 years of age.

Important Safety Information for Fluzone Intradermal Quadrivalent Vaccine (2)

Safety Information

The most common local reactions to Fluzone Intradermal Quadrivalent vaccine include pruritus, erythema, swelling, and induration at the injection site. Such reactions occurred more frequently with trivalent Fluzone Intradermal vaccine than with trivalent Fluzone vaccine. Other adverse reactions to Fluzone Intradermal Quadrivalent vaccine include pain at the injection site; myalgia, headache, myalgia, and malaise. Adverse reactions other than those listed above may occur.

Fluzone Intradermal Quadrivalent vaccine should not be administered to anyone with a known hypersensitivity (eg, anaphylaxis) to any vaccine component, including egg protein, or to a previous dose of any influenza vaccine.

Important Safety Information for Fluzone Intradermal Quadrivalent Vaccine (3)

Safety Information (*cont*)

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Intradermal Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks. Vaccination with Fluzone Intradermal Quadrivalent vaccine may not protect all individuals.

Before administering Fluzone Intradermal Quadrivalent vaccine, please see full Prescribing Information.

Thank You

Back Up

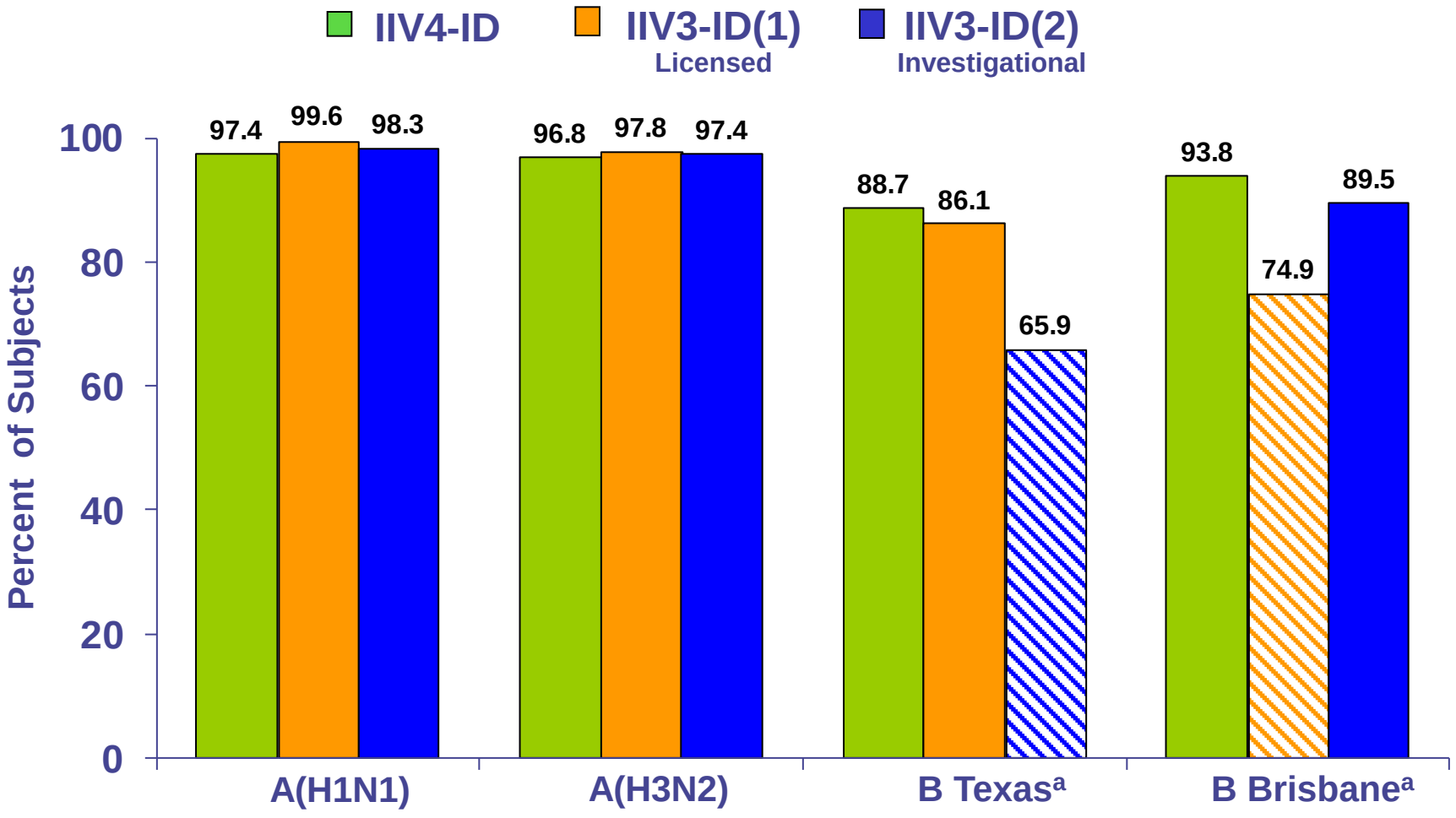
QID01: Primary Trial Objective

- **To demonstrate that IIV4-ID induces an immune response that is non-inferior to responses induced by IIV3-ID(1) and IIV3-ID(2) as assessed by hemagglutination inhibition (HAI) geometric mean titers (GMTs) and seroconversion rates**

QID01: Additional Trial Objectives

- **To demonstrate that each B strain in IIV4-ID induces an immune response that is superior to the response induced by the IIV3-ID that does not contain the corresponding B strain as assessed by HAI GMTs and seroconversion rates**
- **To describe:**
  - **Rates of post-vaccination seroprotection induced by IIV4-ID and IIV3-ID**
  - **Post-vaccination immunogenicity for selected secondary endpoints**
  - **Safety profiles of IIV4-ID and IIV3-ID**
    - **Non-inferiority of IIV4-ID compared to IIV3-ID in terms of all Grade 2 or Grade 3 solicited systemic reactions combined**
    - **Non-inferiority of IIV4-ID compared to IIV3-ID in terms of all Grade 3 solicited injection-site reactions combined**

QID01: Seroprotection Rates, 28 Days Post-vaccination



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[a] Striped bar represents strain not contained in each respective vaccine.

Manufacturing and Licensing Timeline

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Fluzone Intradermal Quadrivalent Vaccine: Timeline of Key Milestones