Safety Summary of Investigational Vaccine: SHINGRIX* (HZ/su)

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*The name ‘Shingrix’ has not yet been approved for use by any regulatory authority

Today's Presentation

Agenda

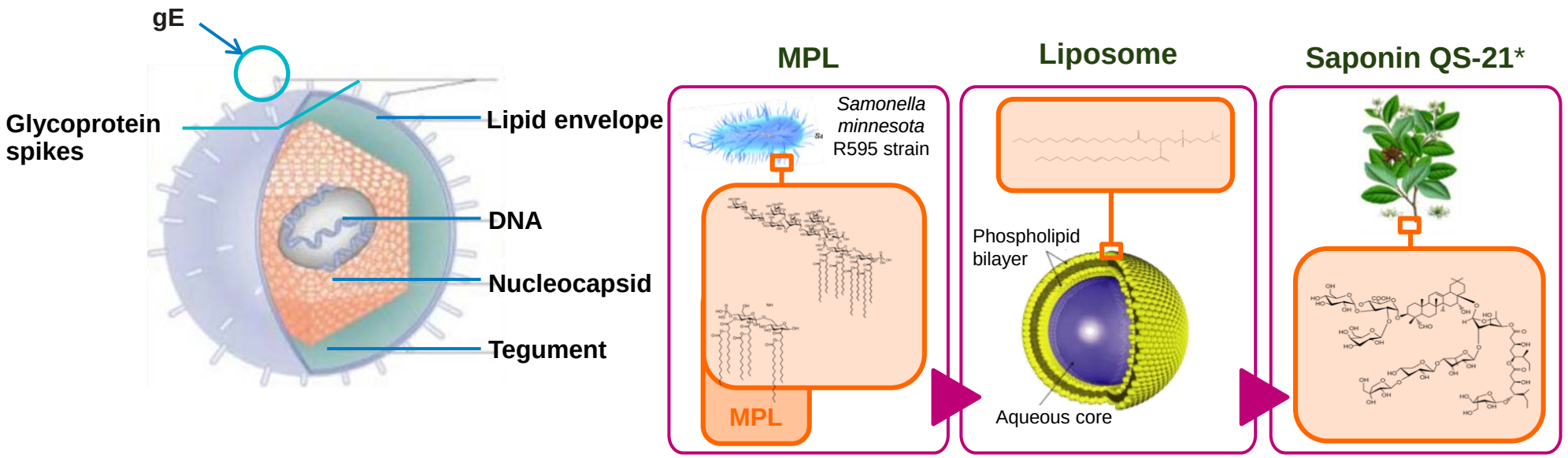
1. Vaccine Composition
2. Incidence of Solicited Local and Systemic Symptoms
3. Safety Analyses
4. Conclusions
5. Nine Year Immunogenicity Data

Vaccine Composition

Vaccine
Non-live

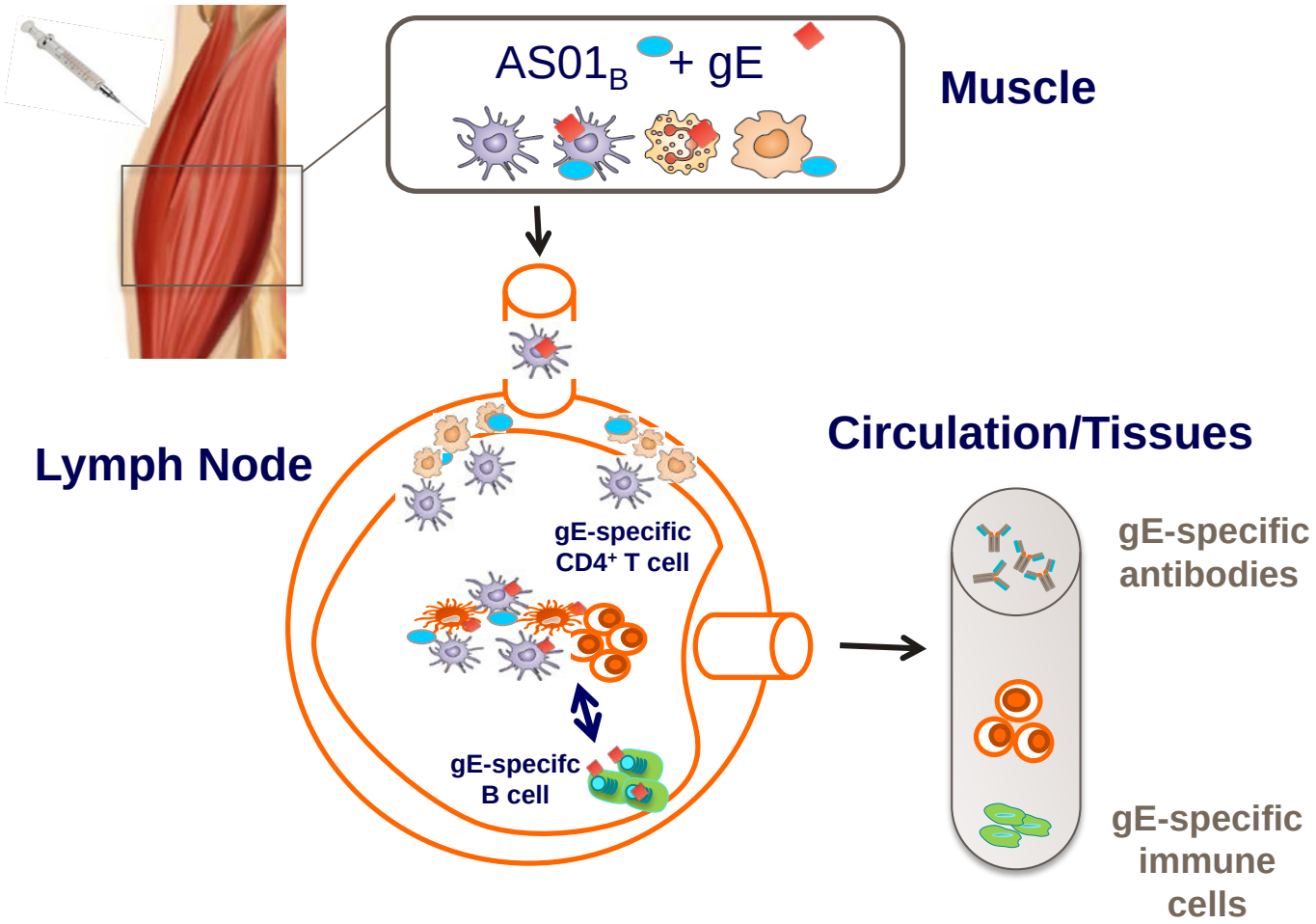
Antigen
Glycoprotein E (gE) - 50 µg

Adjuvant System
$AS01_B$ (MPL and QS-21*) - 50 µg each



* QS-21 (Quillaja saponaria Molina, fraction 21; licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

AS01 Helps to Restore Immunity Against VZV



- ✓ **AS01, similar to other adjuvants, induces a local and transient inflammatory response**
- ✓ **This transient inflammation, often associated with local or systemic symptoms, promotes a high and durable VZV-specific response[1,2]**

1. Didierlaurent et al, J. Immunol, 2014;. Didierlaurent et al, Exp Rev Vac, 2016.
2. Leroux-Roels G, et al.. Clin Immunol. 2016 May 25;169:16–27.

Clinical Experience with AS01 Covers a Wide Range of Populations and Antigens in Over 43,000 Subjects

All of these investigational products have shown to have a favorable benefit/risk profile

Disease/Pathogen	Antigen (Adjuvant)	Groups Studied	Exposure (No. of Subjects)
Herpes zoster (shingles)/ Varicella zoster virus	gE ($AS01_{B/E}$)	Adult/Older Adult	>28,000
Malaria/ Plasmodium falciparum	RTS,S ($AS01_{E}$)	Infant/Toddler	>12,000
AIDS/ Human immunodeficiency virus	F4c0 gp120/NefTat ($AS01_{B/E}$)	Child/Adult	>3,000
Tuberculosis/ Mycobacterium tuberculosis	M72 ($AS01_{B/E}$)	Child/ Adolescent/Adult	
Hepatitis B/Hepatitis B virus	HBsAg ($AS01_{B/E}$)	Adult	
Anogenital cancer/ Human papillomavirus	HPV-16/18/33/58 ($AS01_{B/E}$)	Adolescent/Adult	

$AS01_B$ is an Adjuvant System containing MPL, QS-21 and liposome (50 g MPL and 50 µg QS-21)

$AS01_E$ is an Adjuvant System containing MPL, QS-21 and liposome (25 g MPL and 25 µg QS-21)

Safety Data from pivotal ZOE trials comprises Main Safety Pooling

Main Safety Pooling (comparative) Includes:	HZ/su	Placebo
	n	n
ZOE-50 (≥50)	7,695	7,710
ZOE-70 (≥70)	6,950	6,950
TOTAL	14,645	14,660

- ✓ The main safety pooling analysis comprises the safety data from the two pivotal ZOE-50 and ZOE-70 studies, which have a similar study design and were performed simultaneously.
- ✓ A comparative analysis performed on HZ/su group vs. the placebo group (saline), including all safety endpoints: local and systemic reactions, SAEs and potential immune-mediated diseases (pIMDs)

Overview of Data Collection for Safety Reporting

Solicited Local/Systemic Symptoms*

7 Days

7 Days

Unsolicited AEs

30 Days

30 Days

SAEs Collection

Up to 12 Months Post-Dose 2

Related SAEs*, any fatal SAEs, pIMDs

Entire Study Period

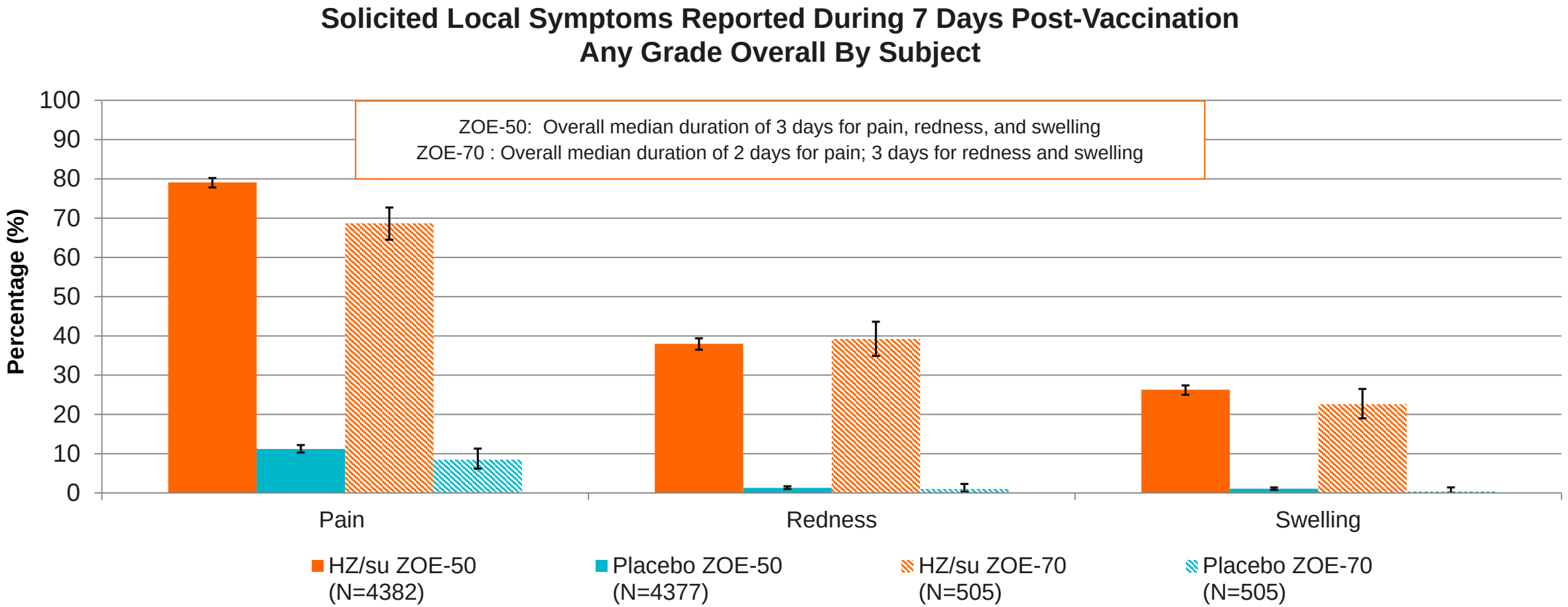
Mean follow-up: 4.1 years

*Related to investigational vaccine, study participation or GSK concomitant medication/vaccine

Incidence of Solicited Local and Systemic Symptoms

ZOE-50 and ZOE-70

Reactogenicity Subgroups[1,2]

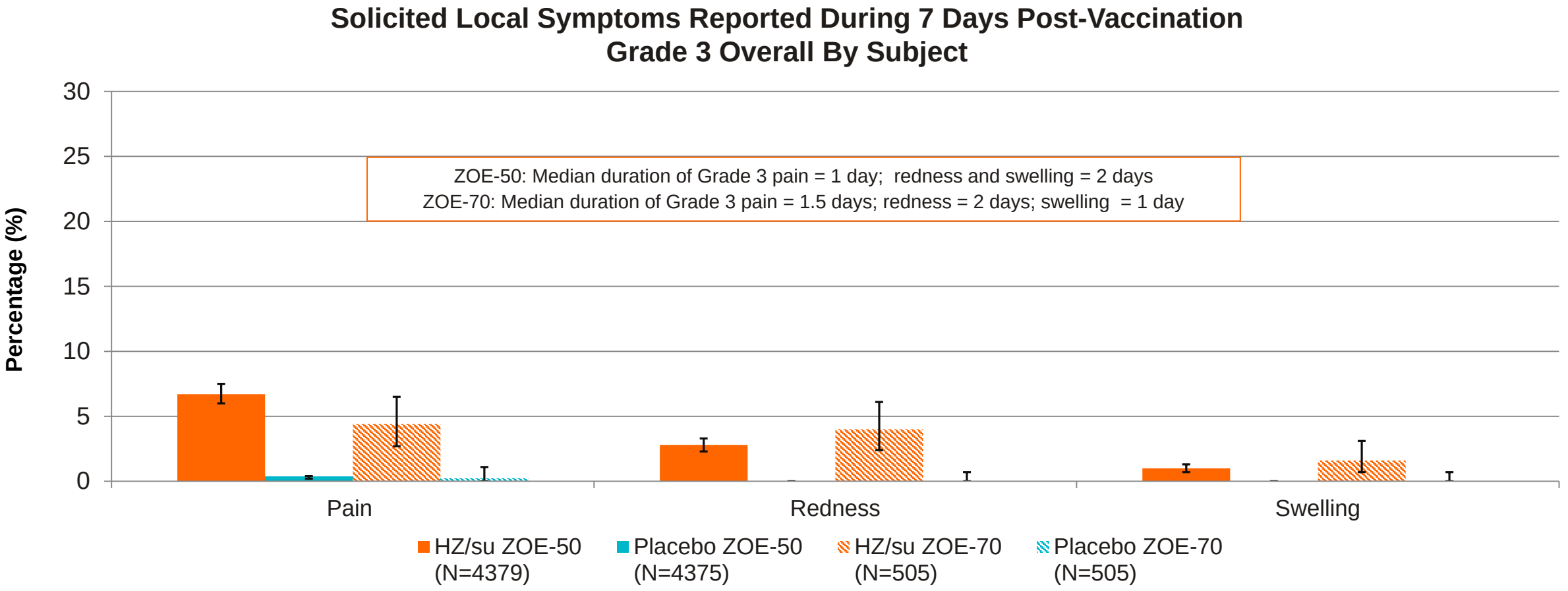


N= Number of subjects with at least one documented dose
%= Percentage of subjects reporting the symptom at least once when the intensity is maximum

1. Lal H, Cunningham A, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. NEJM 2015;372:2087-96.
2. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age and Older. NEJM 2016;375:1019-32

ZOE-50 and ZOE-70

Reactogenicity Subgroups[1,2]



Grade 3 = Redness and swelling at the injection site were scored as grade 3 for those more than 100 mm. All other symptoms were scored as 3 for preventing normal activity

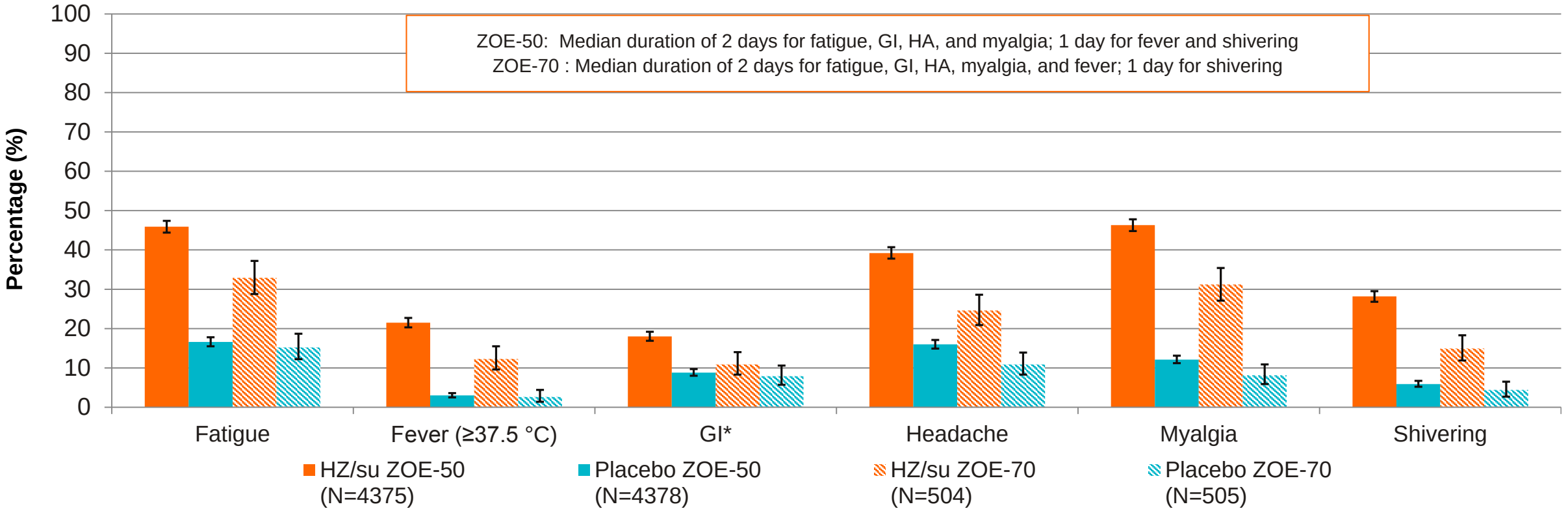
N= Number of subjects with at least one documented dose
%= Percentage of subjects reporting the symptom at least once when the intensity is maximum

1. Data on File. Study 113077. 2016 Available at: http://www.gsk-clinicalstudyregister.com/
2. Data on File. Study 110390. 2016. Available at: http://www.gsk-clinicalstudyregister.com/

ZOE-50 and ZOE-70

Reactogenicity Subgroups[1,2]

Solicited Systemic Symptoms Reported During 7 Days Post-Vaccination
Any Grade Overall By Subject



***Gastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain**

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%= Percentage of subjects reporting the symptom at least once when the intensity is maximum

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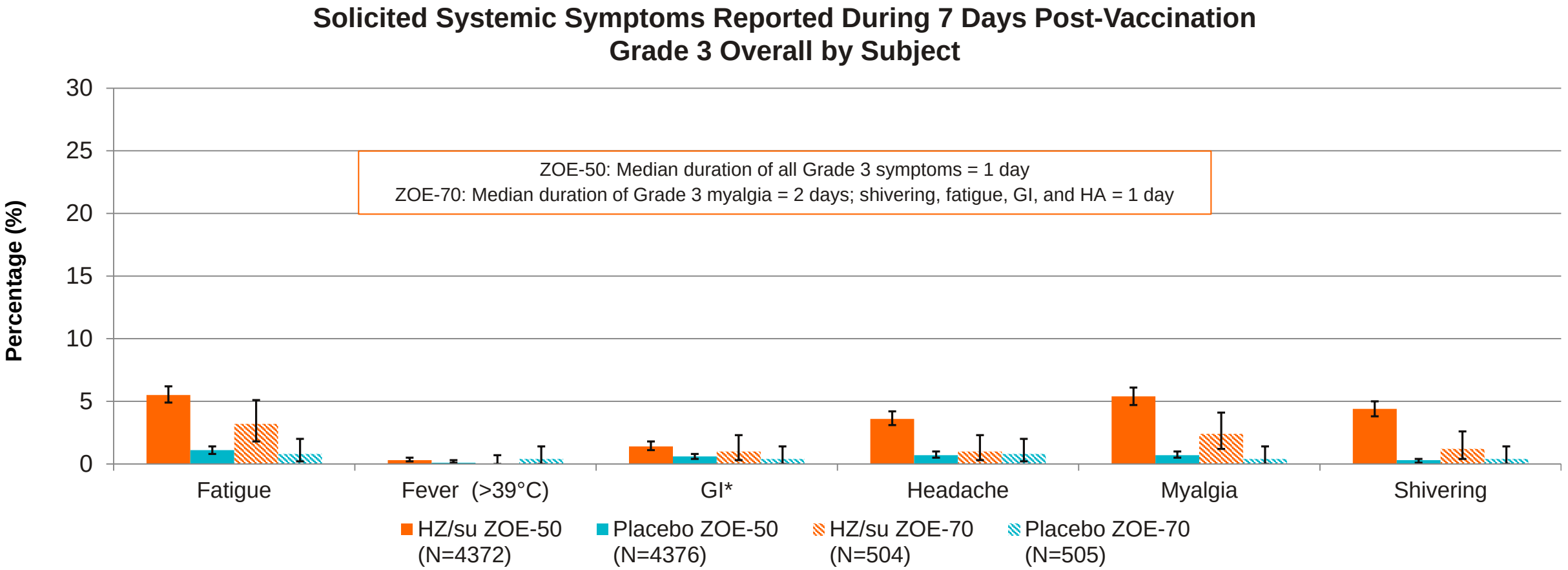
ZOE-50 and ZOE-70

Reactogenicity Subgroups[1,2]

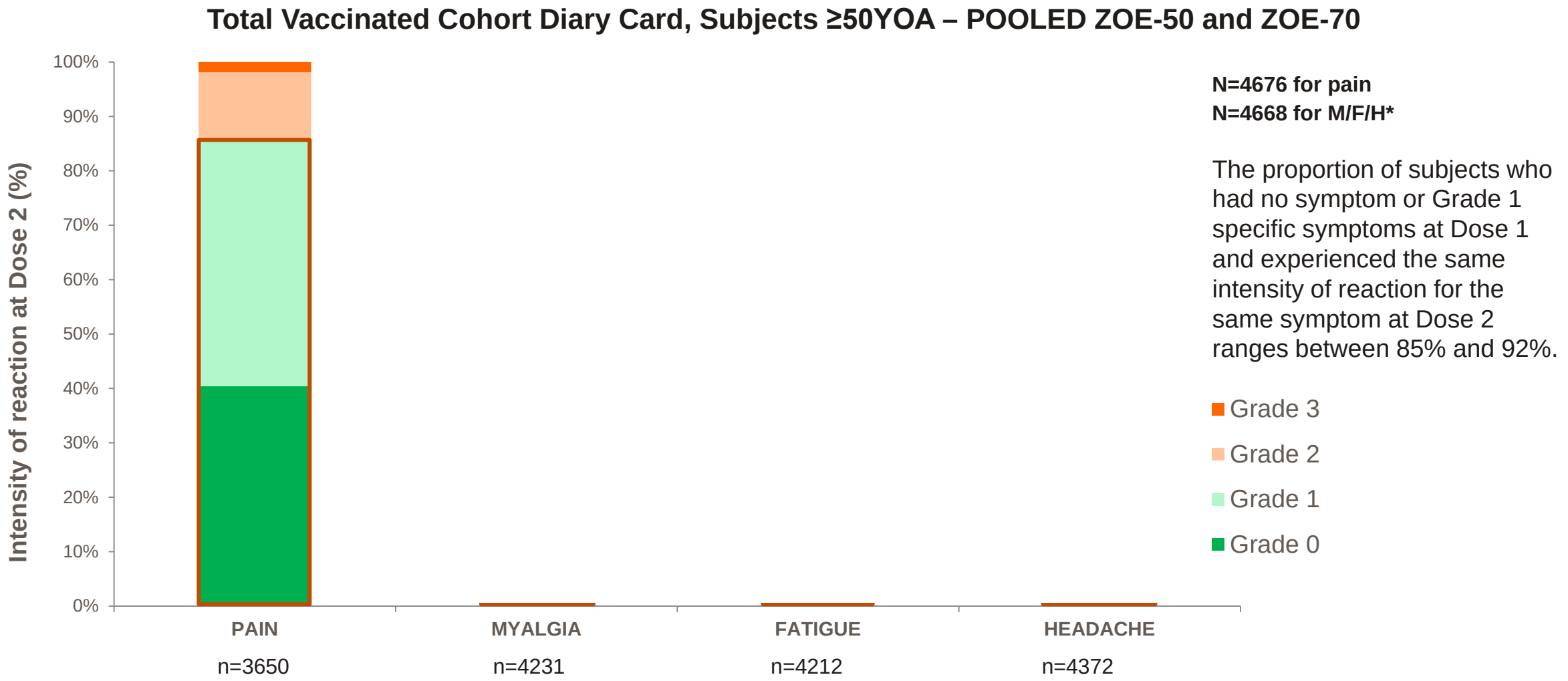


Grade 3 = Temperature was scored as grade 3 for more than 39°C. (The preferred route for recording temperature was oral). All other symptoms were scored as 3 for preventing normal activity *Gastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain

N= Number of subjects with at least one documented dose
%= Percentage of subjects reporting the symptom at least once when the intensity is maximum

1. Data on File. Study 113077. 2016 Available at: http://www.gsk-clinicalstudyregister.com/
2. Data on File. Study 110390. 2016. Available at: http://www.gsk-clinicalstudyregister.com/

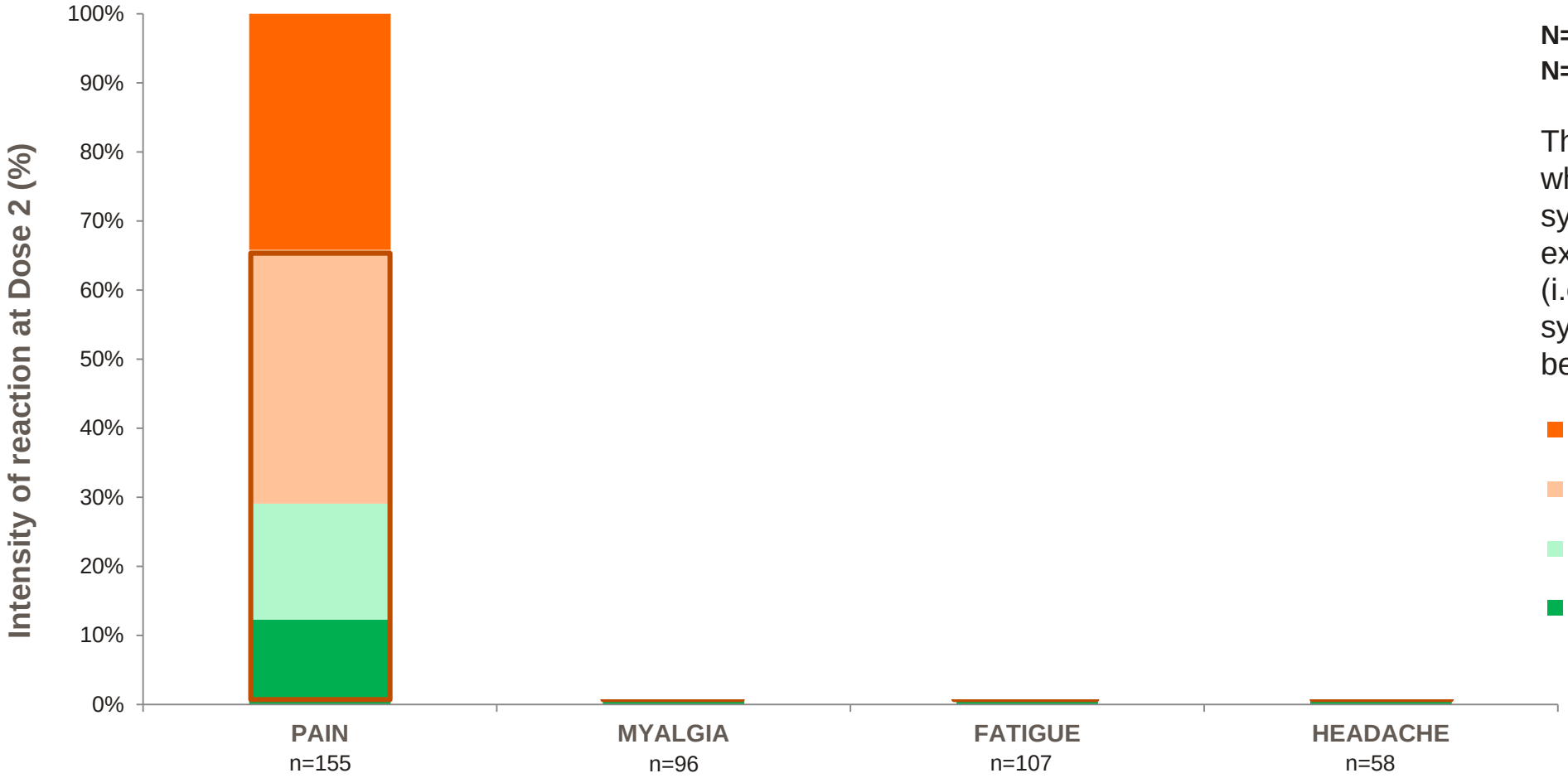
Similar Intensity of Reaction at Dose 2 for Subjects with Grade 0 or 1 Reaction at Dose 1



Note: The analysis was performed for the most frequently reported symptoms (pain, myalgia, fatigue and headache) for the subjects with 7-day diary card reporting available for both doses received.
N= Number of subjects with documented doses for both administered HZ/su doses for the symptom considered
n= Number of subjects with reporting for the symptom at dose 1 and dose 2, presenting a grade 0 or grade 1 at dose 1
*M/F/H=Myalgia/Fatigue/Headache

Lower Intensity of Reaction at Dose 2 for Subjects with Grade 3 Reaction at Dose 1

Total Vaccinated Cohort Diary Card, Subjects ≥50YOA – POOLED ZOE-50 and ZOE-70



N=4676 for pain
N=4668 for M/F/H*

The proportion of subjects who had a Grade 3 specific symptom at Dose 1 and experienced a lower intensity (i.e.≤ Grade 2) for the same symptom at Dose 2 ranges between 66% and 76%.

Note: The analysis was performed for the most frequently reported symptoms (pain, myalgia, fatigue and headache) for the subjects with 7-day diary card reporting available for both doses received.
N= Number of subjects with documented doses for both administered HZ/su doses for the symptom considered
n= Number of subjects with reporting for the symptom at dose 1 and dose 2, presenting a grade 3 at dose 1
*M/F/H=Myalgia/Fatigue/Headache

ZOE-50 and ZOE-70 Second Dose Compliance

Total Vaccinated Cohort

ZOE-50

Total number of doses received	HZ/su N = 7698		Placebo N = 7713	
	n	%	n	%
1	337	4.4	277	3.6
2	7361	**95.6**	7436	**96.4**
Any	7698	100	7713	100

ZOE-70

Total number of doses received	HZ/su N = 6950		Placebo N = 6950	
	n	%	n	%
1	392	5.6	305	4.4
2	6558	**94.4**	6645	**95.6**
Any	6950	100	6950	100

HZ/su = Herpes zoster subunit vaccine

1. Lal H, Cunningham A, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. NEJM 2015;372:2087-96.
2. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age and Older. NEJM 2016;375:1019-32

Dose 2 Compliance Among Subjects With Dose 1 Grade 3 Reactions

91.4%

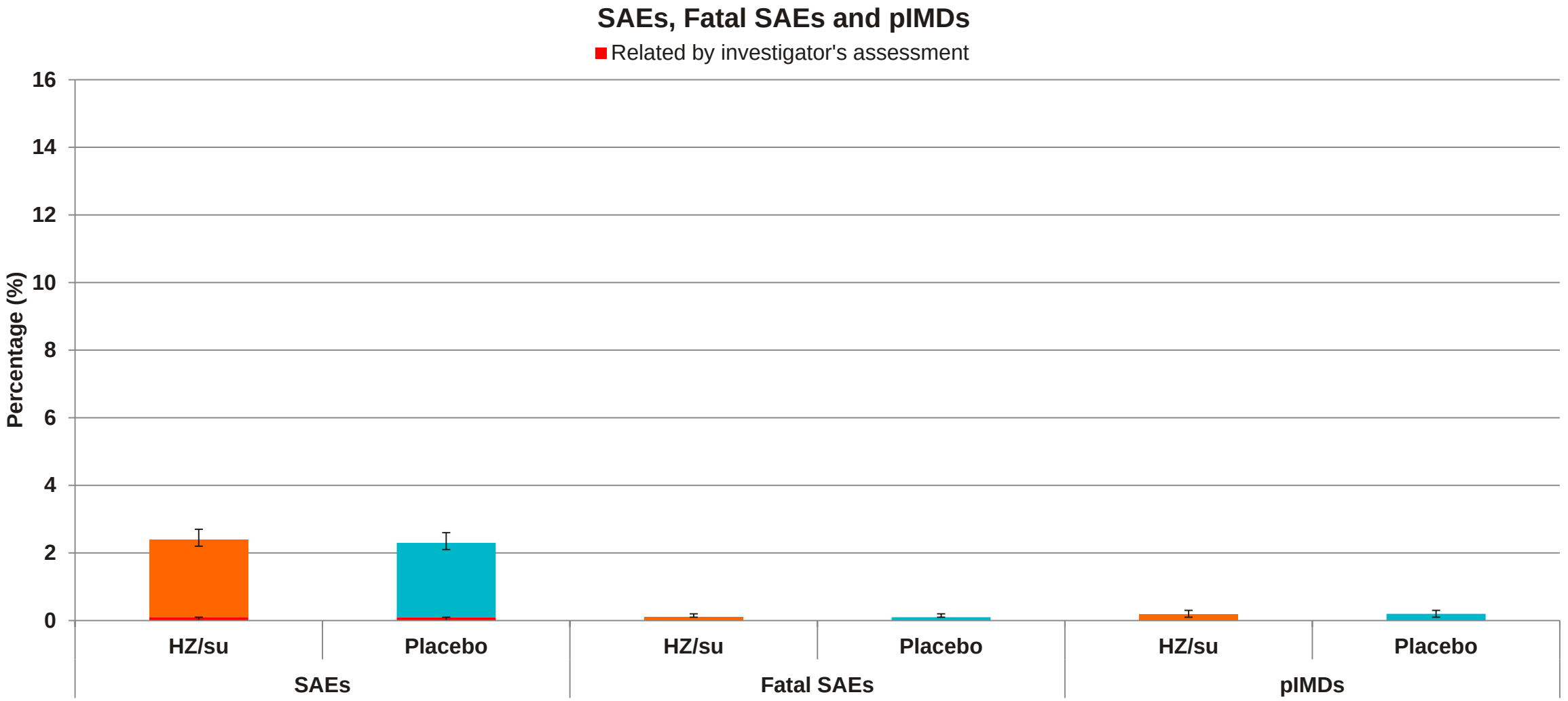
Of the 268 subjects who experienced a first-dose Grade 3 local reaction, 23 received Dose 1 only and 245 received both Dose 1 and Dose 2.

89.2%

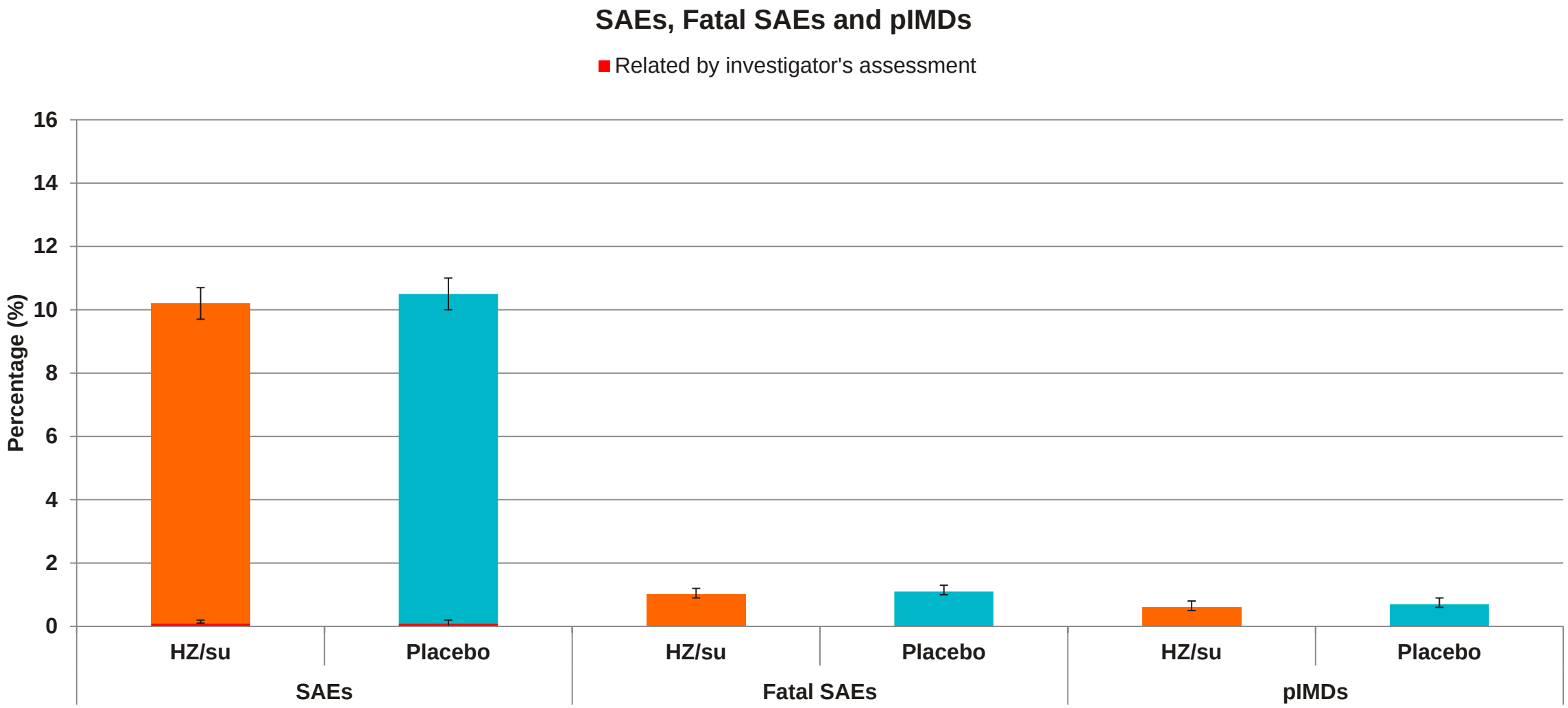
Of the 251 subjects who experienced a first-dose Grade 3 systemic reaction, 27 received Dose 1 only and 224 received both Dose 1 and Dose 2.

Safety Analyses

Overview of SAEs, Fatal SAEs and pIMDs During 30 Days Post Last Vaccination



Overview of SAEs, Fatal SAEs and pIMDs within 1 Year Post Last Vaccination



Most Frequent SAEs within 1 Year Post Last Vaccination

SAE (Preferred Term)	HZ/su N = 14,645		Placebo N = 14,660	
	n*	%	n	%
At least one symptom	1482	10.1	1525	10.4
Pneumonia	83	0.6	66	0.5
Atrial fibrillation	55	0.4	58	0.4
Myocardial infarction	40	0.3	42	0.3
Cerebrovascular accident	39	0.3	27	0.2
Coronary artery disease	37	0.3	38	0.3

(≥0.3% of HZ/su recipients)

Overview of Fatal SAEs by Time Period

	HZ/su N=14,645		Placebo n=14,660	
	n	%	n	%
Subjects with fatal SAEs reported within 30 days post vacc.	17	0.1	21	0.1
Subjects with related fatal SAEs reported within 30 days post vacc.	0	0.0	0	0.0
Subjects with fatal SAEs reported within 365 days post vacc.	153	1.0	168	1.1
Subjects with related fatal SAEs reported within 365 days post vacc.	1*	0.0	0	0.0
Subjects with fatal SAEs reported during whole post vacc. period	634	4.3	680	4.6

As per investigator assesment

Most Frequent Fatal SAEs During the Whole Post-Vaccination Period Overall and by Age Strata

Fatal SAE (Preferred Term)	HZ/su N = 14,645		Placebo N = 14,660	
	n*	%	n	%
At least one symptom	634	4.3	680	4.6
Cardiac failure	42	0.3	53	0.4
Pneumonia	39	0.3	47	0.3
Myocardial infarction	39	0.3	39	0.3
Cardiac arrest	29	0.2	23	0.2
Death	28	0.2	44	0.3
Lung neoplasm malignant	27	0.2	13	0.1

(≥0.2% of HZ/su recipients)

By Age Strata during the Whole Post-Vaccination Period

	50-69 YOA				≥70YOA			
	HZ/su (N=5,887)		Placebo (N=5,887)		HZ/su (N= 8,758)		Placebo (N=8,773)	
	n	%	n	%	n	%	n	%
Fatal SAEs reported during the whole post vacc. period	95	1.6	100	1.7	539	6.2	580	6.6

Overview of Potential Immune Mediated Diseases (pIMDs) by Time Period

	HZ/su N = 14,645		Placebo N = 14,660	
	n*	%	n	%
Subjects with pIMDs reported within 30 days post vacc.	30	0.2	30	0.2
Subjects with pIMDs reported within 365 days post vacc.	90	0.6	105	0.7
Subjects with pIMDs reported during the whole study period	179	1.2	202	1.4
Subjects with related* pIMDs reported during whole study period	16	0.1	18	0.1

**As per investigator assesment*

Most Frequent pIMDs During the Entire Study Period

pIMD (Preferred Term)	HZ/su N = 14,645		Placebo N = 14,660	
	n*	%	n	%
	179	1.2	202	1.4
Polymyalgia rheumatica	32	0.2	29	0.2
Rheumatoid arthritis	20	0.1	26	0.2
Psoriasis	15	0.1	18	0.1
Autoimmune thyroiditis	13	0.1	10	0.1

**Only ≥8 cases in HZ/su group are shown*

Conclusions

Conclusions on Local and Systemic Solicited Symptoms

- Local and systemic solicited symptoms were higher in the HZ/su versus placebo (saline) group
- Majority of symptoms were mild to moderate intensity and of short duration
- It was observed that subjects with Grade 3 reaction at Dose 1 were likely to experience a lower grade reaction at Dose 2 for the same symptom
- Compliance for the second dose was 95% overall, and ≥ 89% even among subjects who had Grade 3 reaction at Dose 1

General Safety Conclusions

- Large safety database (>14,645 subjects) was available to evaluate the safety of HZ/su candidate vaccine (gE + $AS01_B$) with more than 60,000+ person years of active follow up
- Safety data from the HZ/su clinical program has not raised any safety concern
- Overall incidence of SAEs, deaths and potential immune-mediated diseases was similar between vaccine and placebo groups
- Based on the data available, the current Benefit/Risk profile of HZ/su is favorable

Nine-year Immunogenicity (persistence) Data

Long term (Year 9) Immunogenicity and Safety Study

Study Design

- Zoster-060 is an extension to a Phase II immunogenicity and safety study (Zoster 003)
- Subjects in the original study, received 2 doses of HZ/su, at a 2 month interval
- Zoster-060 included 70 subjects for evaluation of immune response at year 9 post vaccination
- Endpoints assessed included antigen-specific humoral and cell-mediated immune response

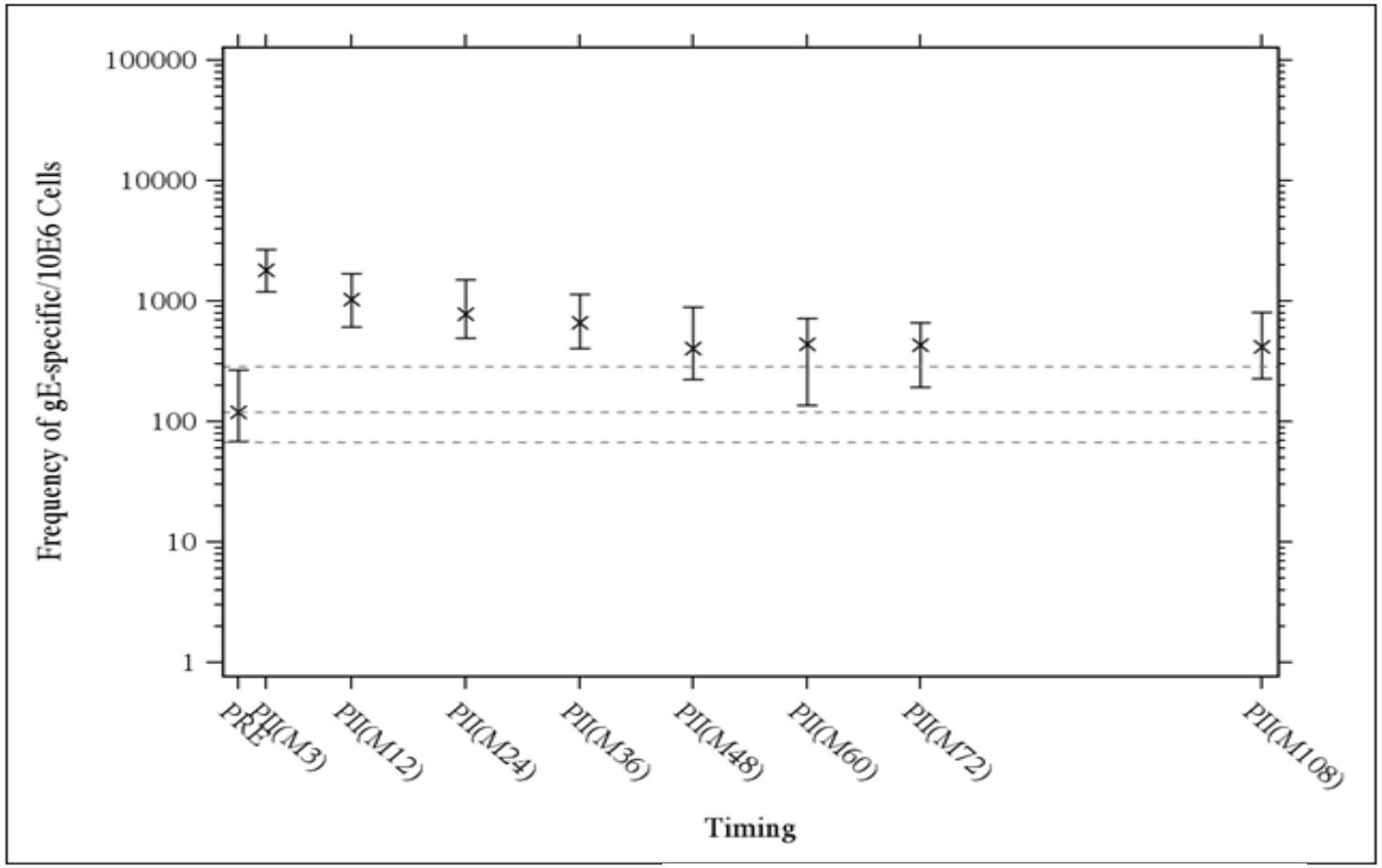
Demography Results

Summary of Demographic Characteristics (ATP cohort for immunogenicity Y9)

Characteristics	Parameters or Categories	HZ/su N = 70	
		Value or n	%
Age (Years) at Vaccination Dose: 1	Mean	72.3	-
	Minimum	61	-
	Maximum	81	-
Gender	Female	43	61.4
	Male	27	38.6
Ethnicity	Not American Hispanic or Latino	70	100
Geographic Ancestry	White – Caucasian / European Heritage	70	100

Sustained Cellular Immune Response (Overall)

Plot of frequency of gE-specific CD4(2+) T-cell/10E6 quartiles at Month 0, 3, 12, 24, 36, 48, 60, 72 and 108 in subjects vaccinated with HZ/su (ATP cohort for immunogenicity Y9)



Q3 (75th percentile

Median (50th percentile)

Q1 (25th percentile)

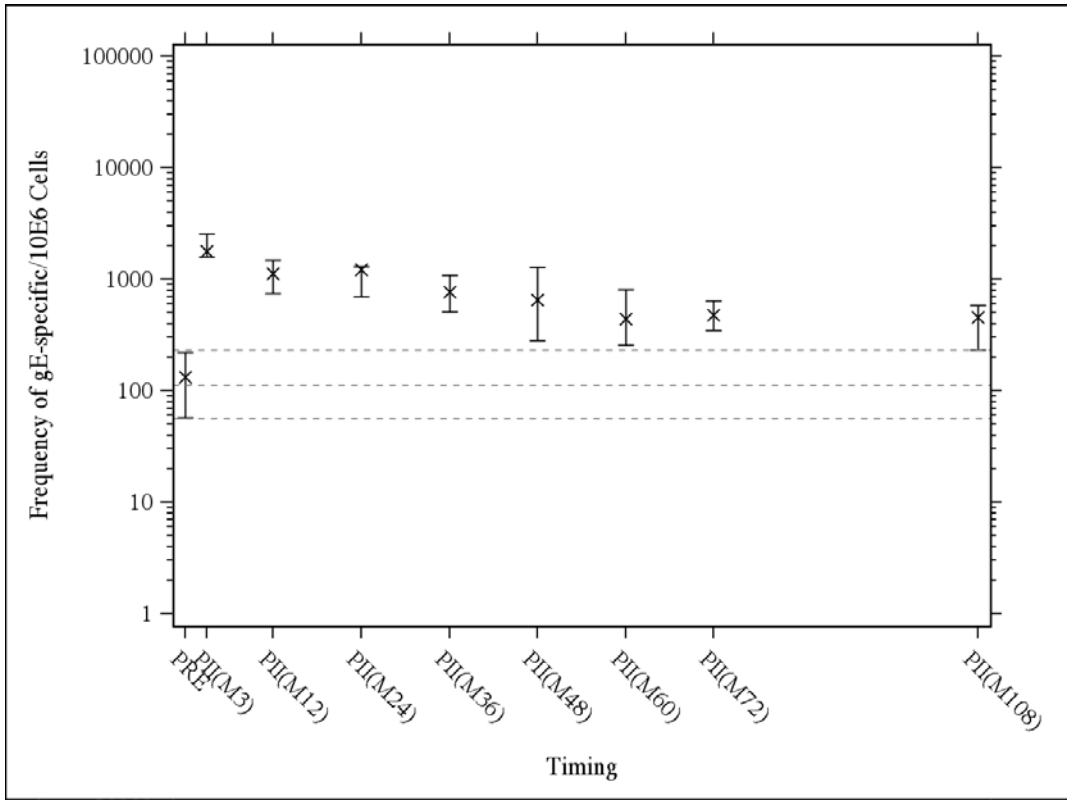
Fold increase over pre-vaccination

Timing	Median
PII(M3)	12.5
PII(M12)	8.0
PII(M24)	6.3
PII(M36)	5.4
PII(M48)	3.4
PII(M60)	3.0
PII(M72)	3.4
PII(M108)	3.4

Sustained Cellular Immune Response (Per Age)

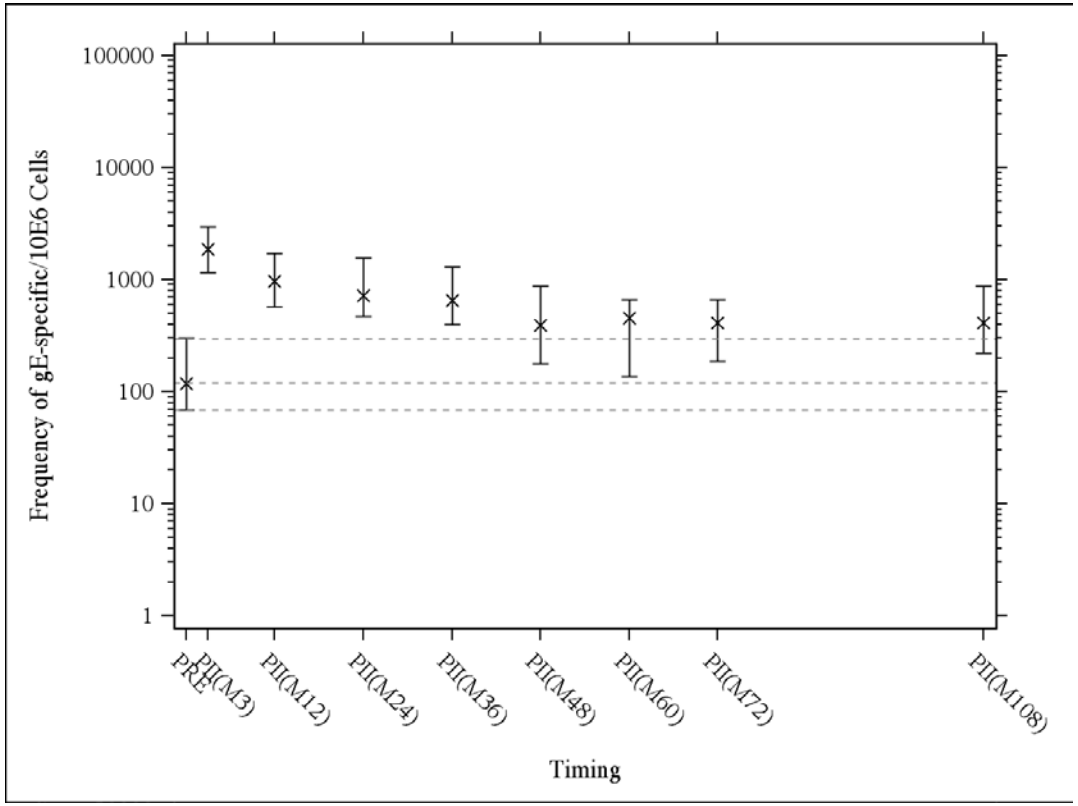
Plot of frequency of gE-specific CD4(2+) T-cells/10E6 quartiles at Month 0, 3, 12, 24, 36, 48, 60, 72 and 108 by age strata

In 60-69 YOA subjects*



60-69YOA: N~13
≥ 70 YOA: N~55

In ≥ 70 YOA subjects*

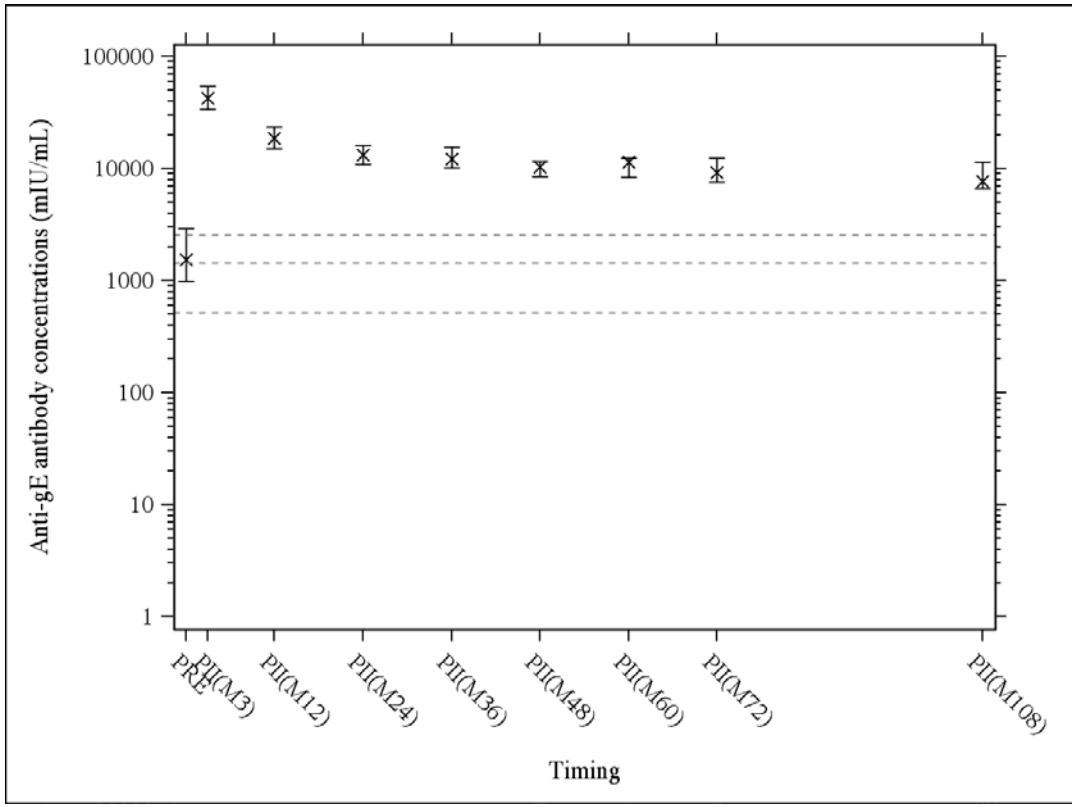


*age at which subject was first vaccinated

Sustained Humoral Immune Response (Per Age)

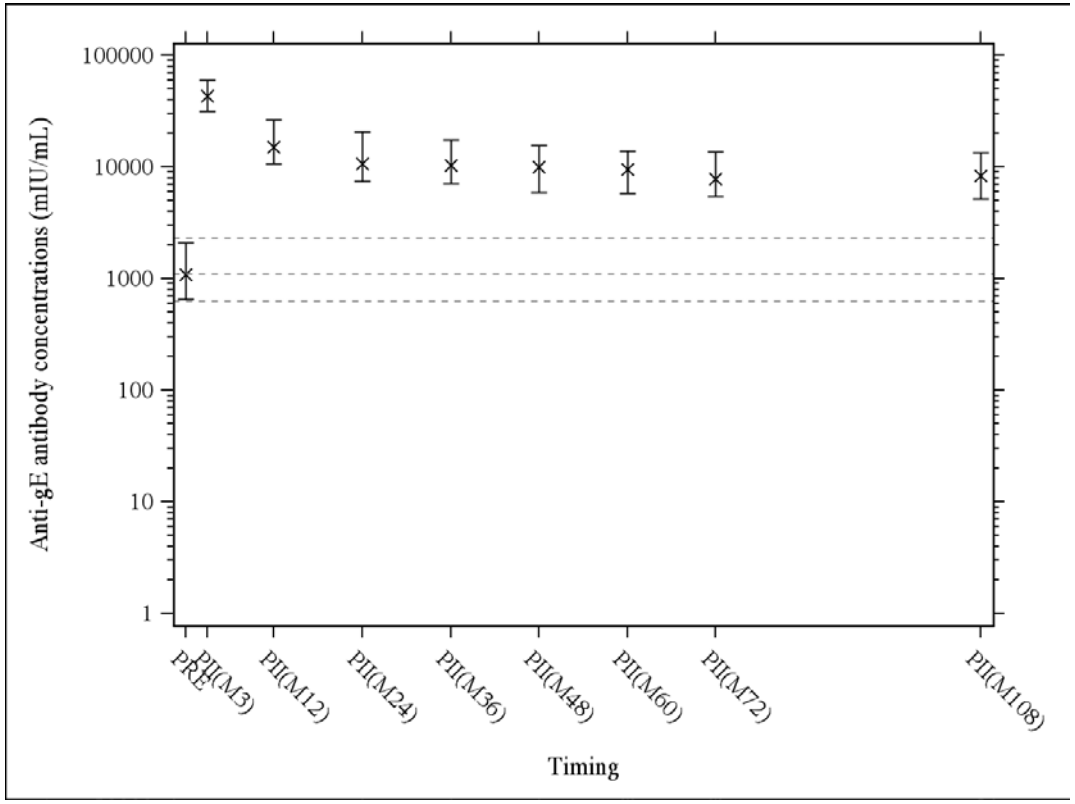
Plot of anti-gE antibody concentrations (mIU/ml) titres quartiles at Month 0, 3, 12, 24, 36, 48, 60, 72 and 108 by age strata

In 60-69 YOA subjects*



60-69 YOA: N~13
≥ 70 YOA: N~55

In ≥ 70 YOA subjects*



*age at which subject was first vaccinated

Conclusion: Sustained Immune Response at Year Nine

- Nine years post vaccination, immune responses to HZ/su were above baseline values (median 3.4-fold increase) in healthy older adults
- Stable, persistent immune responses were observed between Yr 4 and Yr 9
- Immune responses maintained in the oldest age cohort (≥ 70 yrs)
- Additional year 10 data will be available 1Q 2018

Overall Summary: Shingrix (HZ/su)

- Well characterized safety profile, no concerns to date
- Local and systemic reactions (the majority mild to moderate intensity and of short duration) higher among HZ/su recipients than placebo
- $AS01_B$ contributes to robust immunogenicity, persisting through 9 years post vaccination
- Vaccine Efficacy (>90%) independent of age and extending at least 4 years post-vaccination