# Investigational Herpes Zoster Adjuvanted Subunit (HZ/su) Vaccine: Efficacy in People 70 Years and Older

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# Epidemiology of Herpes Zoster (HZ) In the United States

**~1M**
cases in the U.S. annually[1]

**32%**
estimated lifetime risk of zoster[1]

**50%**
of persons living over age 85 years are likely to develop zoster[1]

The most important risk factors

**INCREASING AGE**

**IMMUNOSUPPRESSION**

Complications include

**PHN**

**herpes zoster opthalmicus**

**cranial nerve palsies**

1. CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. 2015

# Herpes Zoster Subunit Vaccine

*Target Population and Development Program*

## *Development Program Targets Two Populations*

**Adults ≥50 years of age**

**Immunocompromised adults ≥18 years of age**

## *Program Aspirations*

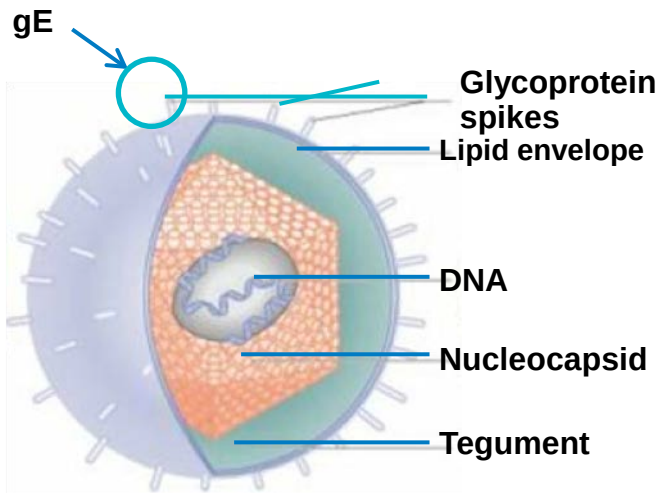
- High vaccine efficacy in persons ≥50 years of age
- High vaccine efficacy in the oldest persons (≥70 years of age)
- Safety and efficacy in all persons at increased risk for HZ including immunocompromised persons
- Prolonged duration of protection
- Ease of manufacture and reliability of supply

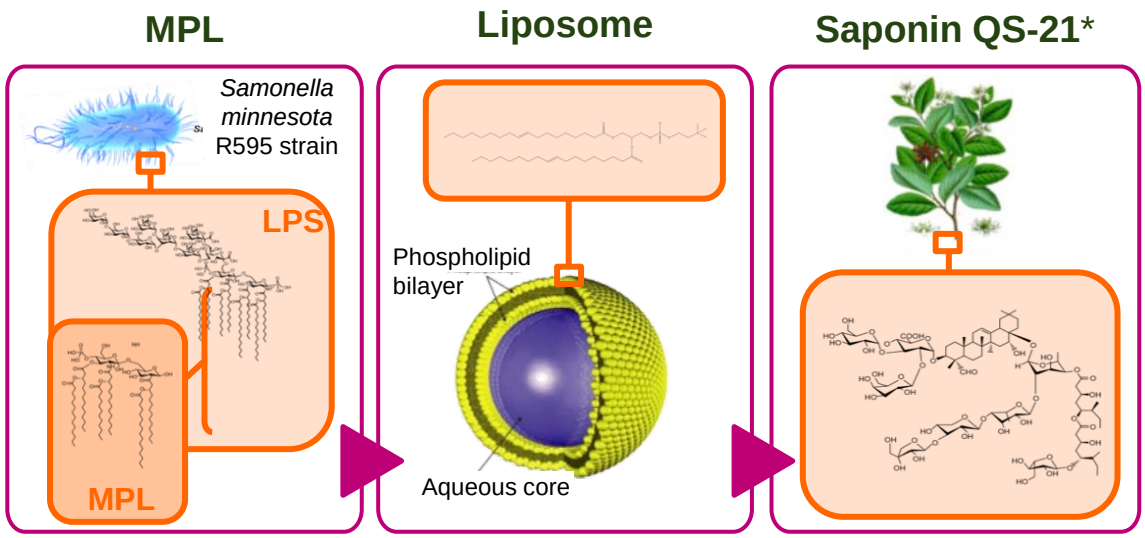
# GSK Herpes Subunit Candidate Vaccine Composition

**Vaccine**
Non-live

**Antigen**
Glycoprotein E (gE) - 50 µg

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



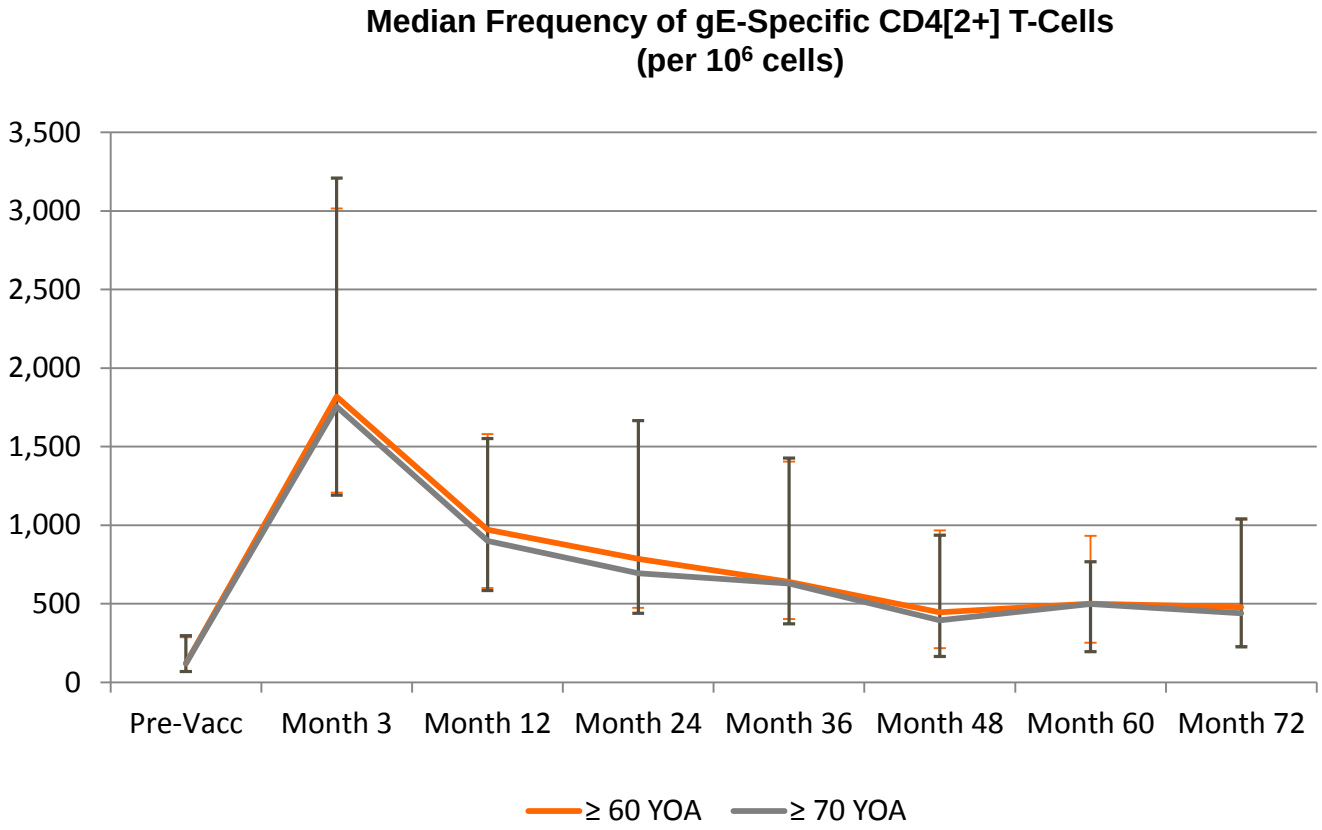

*QS-21: Stimulon® adjuvant licensed from Antigenics Inc, a wholly owned subsidiary of Agenus Inc.

Dendouga *et al. Vaccine* 2012;30:3126–35; Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam: Elsevier; 2011; chapter 4: p89–113; Dendouga *et al. Vaccine* 2012;30:3126–35; Grunewald et al. Science 2003;302:1396–8; Mata-Haro et al. Science 2007;316:1628–32

# Conclusions from Early Phase Studies

*Including Duration of Immune Response*

- Two doses of HZ/su induced gE-specific CD4+ T cell and humoral immune responses in adults ≥60 years of age
- Immune responses to HZ/su were well-preserved with age including in adults ≥70 years of age
- In older adults, immune responses to HZ/su remained above baseline for at least 6 years following vaccination (Mean Age = 72.8)




**Geometric Mean Frequency of CD4⁺ T cells expressing ≥2 activation markers (from among IFN-γ, IL-2, TNF-α or CD40L) as quantitated by flow cytometry following intracellular cytokine staining**


Chilbek R, Pauksens K, Rombo L, et al. Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults 2015; http://dx.doi.org/10.1016/j.vaccine.2015.09.073

# HZ/su Development Program

*Pivotal Phase 3 Efficacy Studies*

| Study | Population | Objectives | Status |
|---|---|---|---|
| **006 (ZOE-50)** **(Presented to ACIP-June 2015)** | Adults (≥50) | HZ efficacy, safety, immunogenicity and reactogenicity | Completed - *Lal H. NEJM 2015;372:2087-96* |
| **022 (ZOE-70)** | Adults (≥70) | HZ efficacy, safety; immunogenicity and reactogenicity<br>PHN efficacy (pooled 006/022 analysis) | Completed - *Cunningham AL. NEJM 2016;375:1019-1032* |
| **002** | Adults (≥18)<br>aHSCT* | HZ efficacy, safety, immunogenicity and reactogenicity | Ongoing |

* aHCST = autologous hematopoietic stem cell transplant

**The efficacy, safety and reactogenicity results of ZOE-70 and pooled ZOE-50/ZOE-70 will be presented today**

# ZOE-50 and ZOE-70

*Brief Overview*

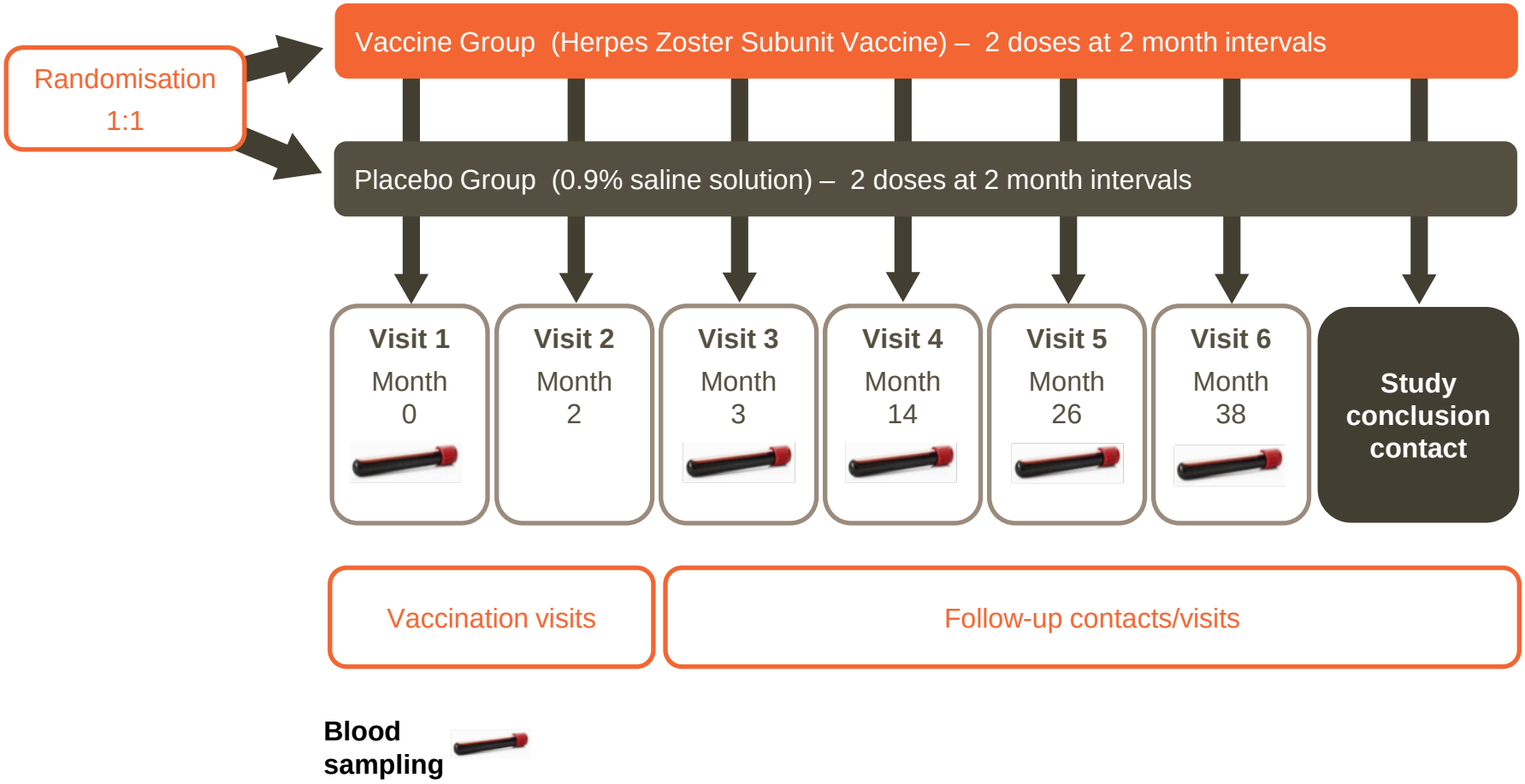
| Study design & Objectives | ZOE-50[1] (Zoster-006) | ZOE-70[2] (Zoster-022) |
|---|---|---|
| Experimental design | Randomised, Observer-blind, Placebo-controlled, Multicenter<br>Multinational (North America, Europe, Latin America, Asia-Pacific) | |
| Primary objectives | **HZ efficacy in persons ≥50 YOA** | **HZ efficacy in persons ≥70 YOA** |
| Primary objectives in pooled analysis | PHN efficacy in 70+<br>HZ efficacy in 70+ | |
| Age ranges | **≥ 50 YOA** | **≥ 70 YOA** |
| Actual enrollment | **16,160 Enrolled** | **14,816 Enrolled** |

**Efficacy studies conducted at the same sites.**
**Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70.**


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. *NEJM* 2016;375:1019-1032

# ZOE-50/ZOE-70

*Study Design Overview*[1,2]





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. *NEJM* 2016;375:1019-1032

# ZOE-50

*Vaccine Efficacy Overall & by Age Group*[1]

## Modified Total Vaccinated Cohort (mTVC)*

| Age range (years) | HZ/su VACCINE GROUP N = 7344 HZ cases | HZ/su VACCINE GROUP N = 7344 Rate of HZ (Number per 1000 Person-Years) | PLACEBO GROUP N = 7415 HZ cases | PLACEBO GROUP N = 7415 Rate of HZ (Number per 1000 Person-Years) | VE (95% CI)† |
|---|---|---|---|---|---|
| **Overall (≥50)** | **6** | **0.3** | **210** | **9.1** | **97.2** (93.7-99.0) |
| **50-59** | 3 | 0.3 | 87 | 7.8 | **96.6** (89.6-99.3) |
| **60-69** | 2 | 0.3 | 75 | 10.8 | **97.4** (90.1-99.7) |
| **≥70** | 1 | 0.2 | 48 | 9.4 | **97.9** (87.9-100) |
| **≥60**[2] | 3 | 0.2 | 123 | 10.2 | **97.6** (92.8-99.6) |

**†*P*-value for all efficacy comparisons with placebo <0.001**

Primary Objective

Secondary Objective

*Excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2


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. CDC. Advisory Committee on Immunization Practices. June 2015 Meeting; http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2015-06/zoster-03-heineman.pdf

# ZOE-70

*Study Objectives*

## ZOE-70

**Primary Objective**

Evaluate vaccine efficacy (VE) in the prevention of HZ.

**Key Secondary Objectives**

- Evaluate VE in the prevention of PHN.
- Evaluate vaccine safety and reactogenicity.

## ZOE-70/ZOE-50 Pooled Analysis

**Primary Objectives**

- Evaluate VE in the prevention of PHN in subjects ≥70 YOA across both phase III studies.
- Evaluate VE in the prevention of HZ in subjects ≥70 YOA across both phase III studies.

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-70 Results

*Study Cohorts*

| Population | HZ/su | Placebo |
|---|---|---|
| **Total vaccinated cohort (TVC): All subjects receiving at least 1 dose**<br>- N = 13,900; mean follow-up time = 4.0 years<br>- Primary cohort for safety analyses | 6,950 | 6,950 |
| **Modified total vaccinated cohort (mTVC): Excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2**<br>- N = 13,163; mean follow-up time = 3.7 years<br>- Primary cohort for efficacy analyses | 6,541 | 6,622 |
| **Diary card cohort**<br>- Subset of TVC; N = 1,025<br>- Cohort for reactogenicity analyses | 512 | 513 |

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-70

*Results – Demography*

## TVC – Total Vaccinated Cohort

| Characteristics | ZOE-70 HZ/su N=6950 | ZOE-70 Placebo N=6950 |
|---|---|---|
| **Age** (mean age at dose 1, years ± SD) | 75.6 ± 4.7 | 75.6 ± 4.7 |
| **Age, years (%)** | | |
| 70-79 | 78 | 78 |
| ≥ 80 | 22 | 22 |
| **Gender (%)** | | |
| Female | 54 | 55 |
| Male | 46 | 45 |
| **Region (%)** | | |
| Australasia | 19 | 19 |
| Europe | 54 | 54 |
| Latin America | 8 | 8 |
| North America | 19 | 19 |
| **Race (%)** | | |
| White | 77 | 77 |
| Black | 1 | 1 |
| Asian | 18 | 18 |
| Other | 4 | 5 |

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-70

*Vaccine Efficacy Against HZ Overall & by Age Group*

## Modified Total Vaccinated Cohort (mTVC)

| Age range (years) | HZ/su VACCINE GROUP N = 6541 HZ cases | HZ/su VACCINE GROUP N = 6541 Rate of HZ (Number per 1000 Person-Years) | PLACEBO GROUP N = 6622 HZ cases | PLACEBO GROUP N = 6622 Rate of HZ (Number per 1000 Person-Years) | VE (95% CI)† |
|---|---|---|---|---|---|
| **Overall (≥70)** | **23** | **0.9** | **223** | **9.2** | **89.8** (84.2-93.7) |
| **70-79** | 17 | 0.9 | 169 | 8.8 | **90.0** (83.5-94.4) |
| **≥80** | 6 | 1.2 | 54 | 11.0 | **89.1** (74.6-96.2) |

†*P*-value for all efficacy comparisons with placebo <0.001

Primary Objective

Secondary Objective

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults ≥70 years of age. NEJM 2016;375:1019-1032

# Pooled ZOE-70 and ZOE-50

*Vaccine Efficacy Against HZ Over 70 Years of Age*

## Modified Total Vaccinated Cohort (mTVC)

| Age range (years) | HZ/su VACCINE GROUP N = 8250 HZ cases | HZ/su VACCINE GROUP N = 8250 Rate of HZ (Number per 1000 Person-Years) | PLACEBO GROUP N = 8346 HZ cases | PLACEBO GROUP N = 8346 Rate of HZ (Number per 1000 Person-Years) | VE (95% CI) † |
|---|---|---|---|---|---|
| **Overall (≥70)** | **25** | **0.8** | **284** | **9.3** | **91.3** (86.8-94.5) |
| **70-79** | 19 | 0.8 | 216 | 8.9 | **91.3** (86.0-94.9) |
| **≥80** | 6 | 1.0 | 68 | 11.1 | **91.4** (80.2-97.0) |

†***P*-value for all efficacy comparisons with placebo <0.001**

Primary Objective

Secondary Objective

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults ≥70 years of age. *NEJM* 2016;375:1019-1032

# Pooled ZOE-70 and ZOE-50

*Vaccine Efficacy by Year Post-Vaccination*

## Modified Total Vaccinated Cohort (mTVC)

| Time post-vaccination* | HZ/su VACCINE GROUP N=8250 HZ cases | HZ/su VACCINE GROUP N=8250 Rate of HZ (Number per 1000 Person-Years) | PLACEBO GROUP N=8346 HZ cases | PLACEBO GROUP N=8346 Rate of HZ (Number per 1000 Person-Years) | VE (95% CI)† |
|---|---|---|---|---|---|
| **Year 1** | 2 | 0.2 | 83 | 10.1 | **97.6** (90.9-99.8) |
| **Year 2** | 7 | 0.9 | 87 | 11.1 | **92.0** (82.8-96.9) |
| **Year 3** | 9 | 1.2 | 58 | 7.7 | **84.7** (69.0-93.4) |
| **Year 4** | 7 | 1.0 | 56 | 8.2 | **87.9** (73.3-95.4) |

Secondary Objective

†***P*-value for all efficacy comparisons with placebo <0.001**

*Year 1: from 30 days to 395 days after the second vaccination. Year 2: from >395 days to 760 days after the second vaccination. Year 3: from >760 days to 1,125 days after the second vaccination. Year 4: from >1,125 days after the second vaccination to the last contact date.

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults ≥70 years of age. *NEJM* 2016;375:1019-1032

# Pooled ZOE-70 and ZOE-50

*Vaccine Efficacy Against Postherpetic Neuralgia Overall & by Age Group*

## Modified Total Vaccinated Cohort (mTVC)

| Age range (years) | HZ/su VACCINE GROUP N=13881 PHN cases | HZ/su VACCINE GROUP N=13881 Rate of PHN (Number per 1000 Person-Years) | PLACEBO GROUP N=14035 PHN cases | PLACEBO GROUP N=14035 Rate of PHN (Number per 1000 Person-Years) | VE (95% CI) |
|---|---|---|---|---|---|
| ≥70 | 4 | 0.1 | 36 | 1.2 | **88.8*** (68.7-97.1) |
| ≥50 | 4 | 0.1 | 46 | 0.9 | **91.2*** (75.9-97.7) |
| ≥60 | 4 | 0.1 | 38 | 1.0 | **89.4*** (70.5-97.3) |
| 70-79 | 2 | 0.1 | 29 | 1.2 | **93.0*** (72.4-99.2) |
| ≥80 | 2 | 0.3 | 7 | 1.1 | **71.2†** (-51.6-97.1) |

***P <0.001; †P = 0.1844 (the number of cases in the placebo group were not sufficient in ≥ 80 year group)**

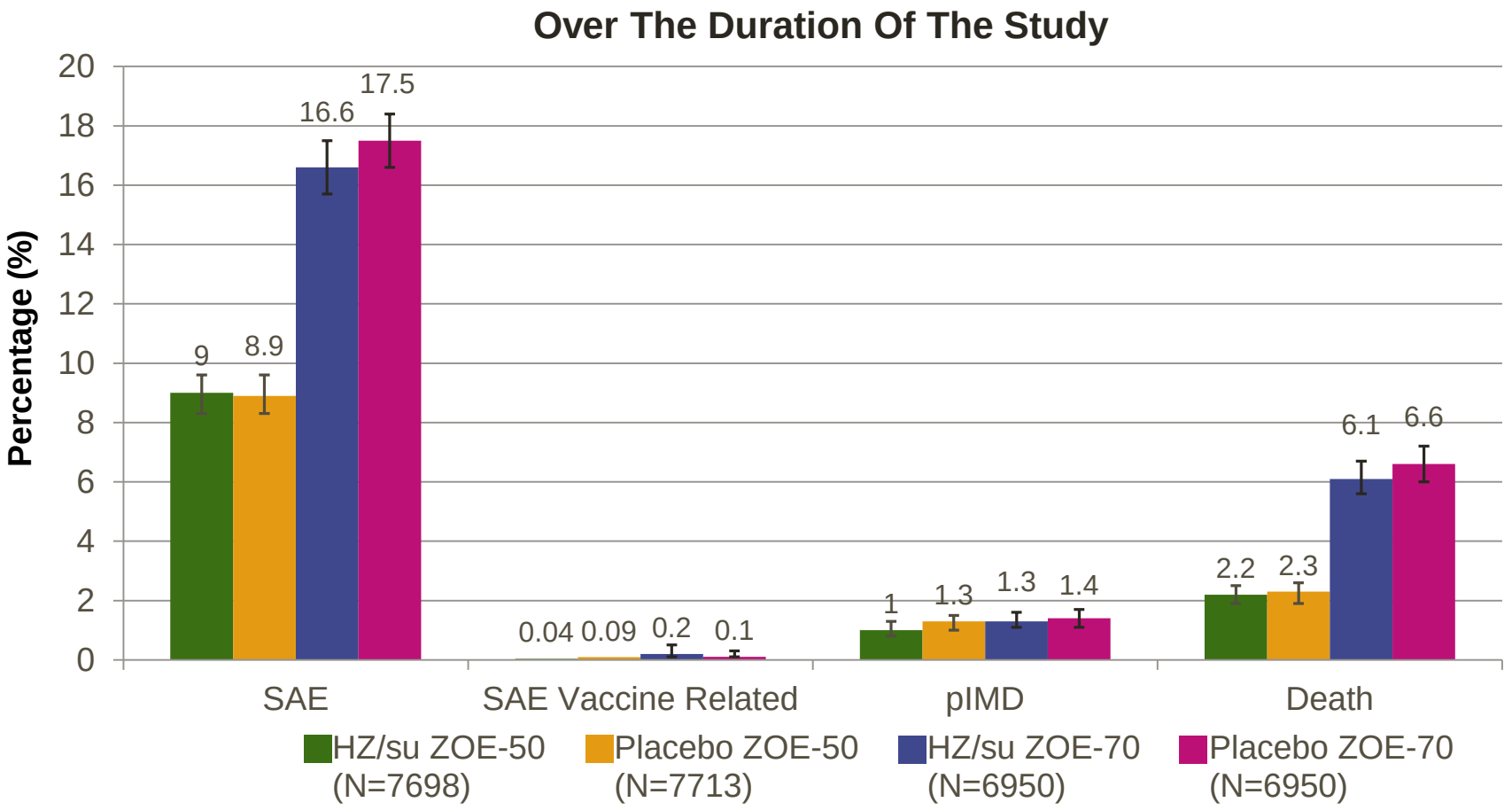
Primary Objective

Secondary Objective

Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults ≥70 years of age. *NEJM* 2016;375:1019-1032

# ZOE-50[1] and ZOE-70[2]

*Safety – Total Vaccinated Cohort*




**pIMDs = potential immune mediated diseases**

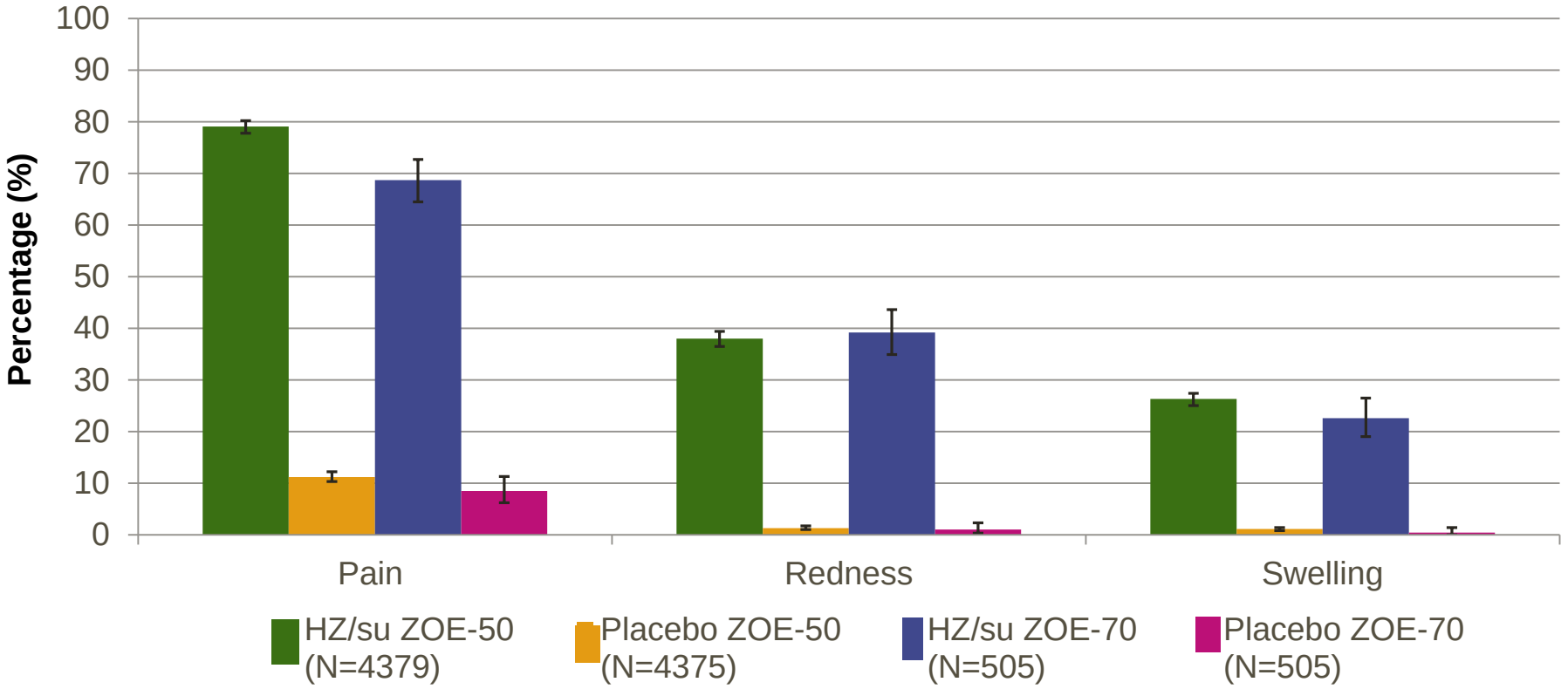
**ZOE-50: Duration: mean = 4.1 years**
**ZOE-70: Duration: mean = 4.0 years**


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]

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

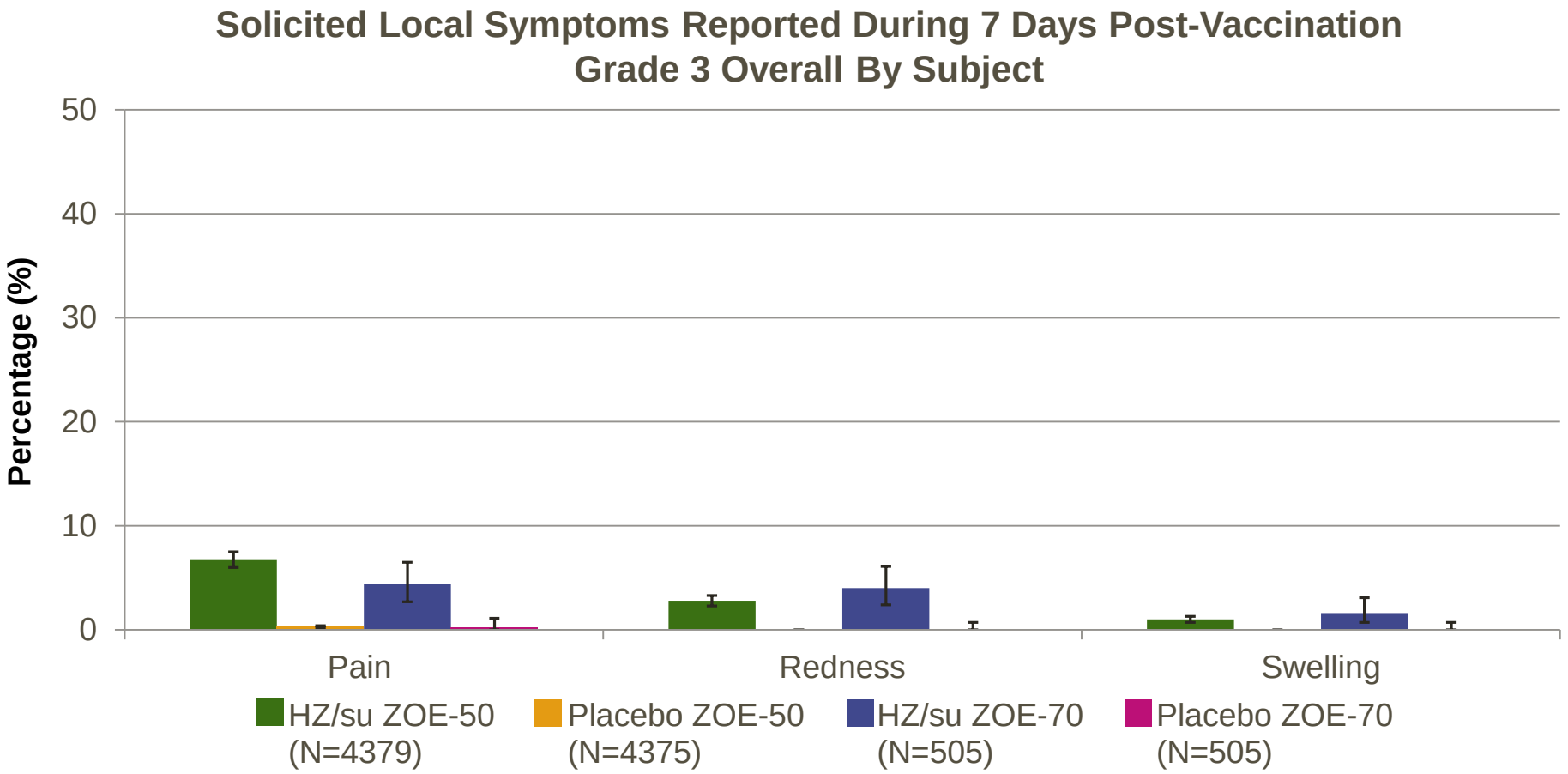



**ZOE-50: Overall median duration of 3 days for pain, redness, and swelling**
**ZOE-70 : Overall median duration of 2 days for pain; 3 days for redness and swelling**


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**

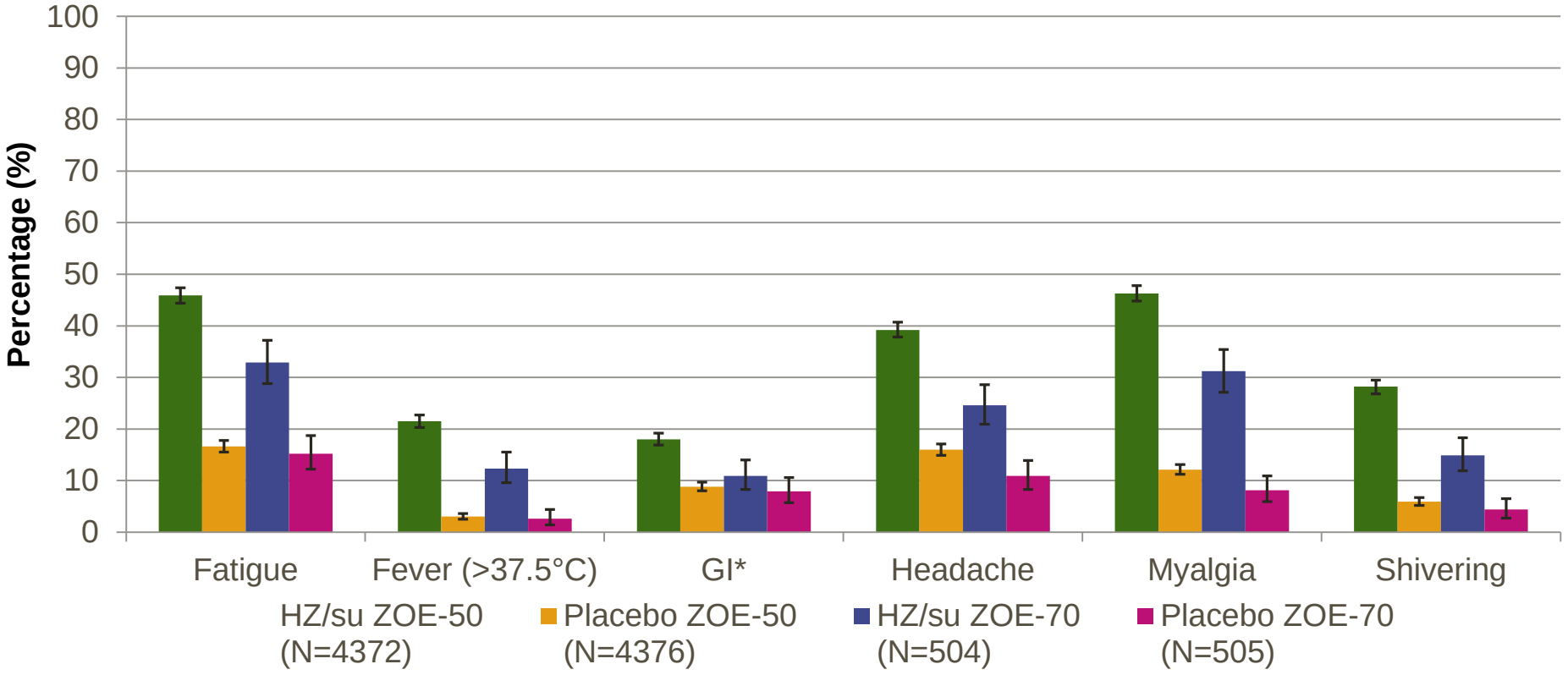
**ZOE-50: Median duration of Grade 3 pain = 1 day ; redness and swelling = 2 days**
**ZOE-70: Median duration of Grade 3 pain = 1.5 days; redness = 2 days; swelling = 1 day**


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



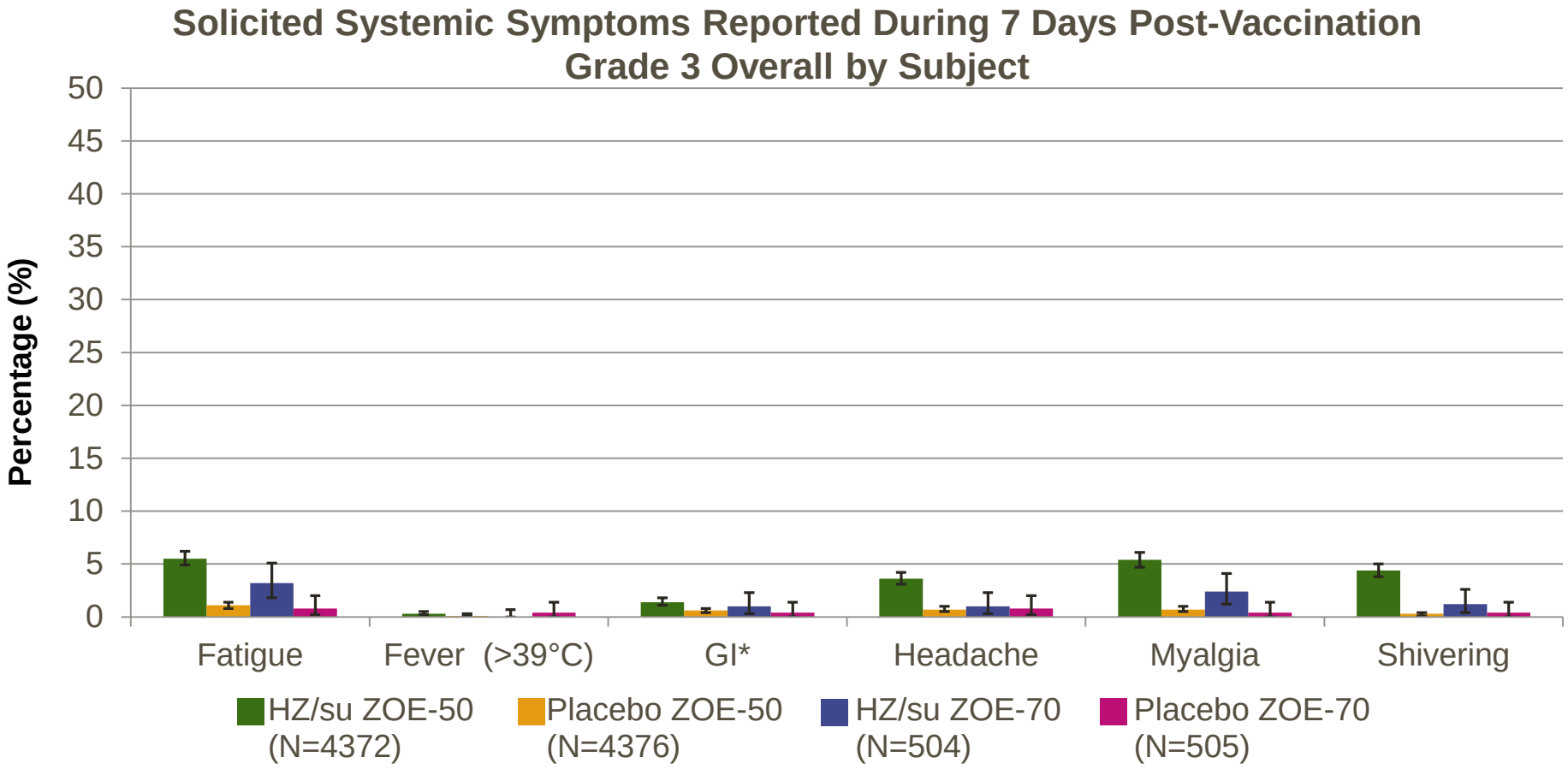

***Gastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain**

**ZOE-50: Median duration of 2 days for fatigue, GI, HA, and myalgia; 1 day for fever and shivering**
**ZOE-70 : Median duration of 2 days for fatigue, GI, HA, myalgia, and fever; 1 day for shivering**


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 = 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**

**ZOE-50: Median duration of all Grade 3 symptoms = 1 day**
**ZOE-70: Median duration of Grade 3 myalgia = 2 days; shivering, fatigue, GI, and HA = 1 day**


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

*Vaccination Compliance*

## Total Vaccinated Cohort

### ZOE-50

| Total number of doses received | HZ/su N = 7698 | | Placebo N = 7698 | |
|---|---|---|---|---|
| | 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

# ZOE-70 and ZOE-50/ZOE-70

## *Safety/Reactogenicity*

- No imbalance in the incidence of safety endpoints (serious adverse events, potential autoimmune diseases, deaths) were observed between the HZ/su and placebo groups
- Adverse events and safety endpoints were as expected in this patient population
- Local and systemic reactions to HZ/su were common in the first 7 days after vaccination; the large majority were of mild-moderate intensity and of short duration

# ZOE-70 and ZOE-50/ZOE-70

## *Efficacy*

- ZOE-70 Vaccine efficacy in adults 70 years and older was >90% for the prevention of HZ ; these results are consistent with the previous 97% vaccine efficacy in this age group from ZOE-50 trial.
- In the pooled analyses, vaccine efficacy for the prevention of herpes zoster in adults 80 years and older was 91%
- HZ/su vaccine efficacy (87.9%) remained high in year 4 after vaccination.
- HZ/su exhibited similarly high vaccine efficacy (89%) in the prevention of PHN in individuals 70 years and older.

# Next Steps

## *Upcoming Evidence Generation*

**Revaccination:** Immunogenicity, safety and reactogenicity in individuals with history of Zostavax™ immunization

**Co-administration:** Immunogenicity, safety and reactogenicity with quadrivalent influenza, PPSV23, and Tdap

**Duration of protection:** Efficacy, safety, and immunogenicity persistence post-vaccination follow-up of ZOE-50/ZOE-70 subjects

# Next Steps

## *Regulatory Submissions*

- GSK plans to submit BLA for CBER review of candidate HZ/su vaccine before the end of 2016

**Planned Indication:** Prevention of herpes zoster in adults greater than 50 years of age

*GSK believes HZ/su has the real potential to improve the prevention of shingles and could shed light on the way future vaccines are developed to overcome the challenge of decreasing immunity in older adults and the elderly.*