Herpes Zoster Adjuvanted Subunit (HZ/su) Vaccine: Development program and Phase 3 results

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Zoster Vaccine Development Program:
Target populations and vaccine design

The herpes zoster adjuvanted subunit vaccine (HZ/su) development program targets two general populations:

- Older adults ≥50 yoa
- Immunocompromised adults ≥18 yoa

HZ/su was specifically designed to elicit strong cellular and humoral immune responses against VZV in these high-risk populations:

- **Vaccine antigen:** ***Varicella-zoster virus (VZV) glycoprotein E (gE)***
  - Abundantly expressed in the virion envelope and membranes of VZV-infected cells
  - Prominent target of VZV-specific cellular and humoral immune responses

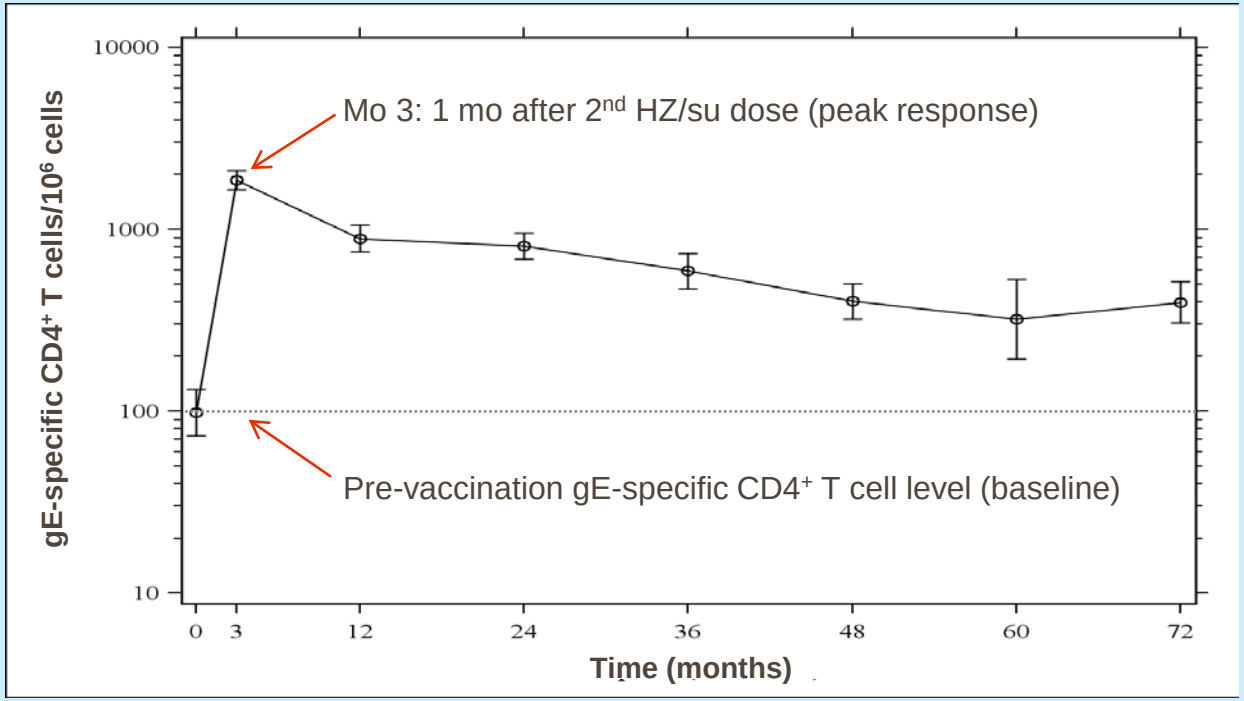
- **Vaccine adjuvant:** ***Adjuvant System 01_B ($AS01_B$)***
  - The GSK proprietary AS01 adjuvant system is a liposome based adjuvant and contains 2 immunostimulants: QS-21* and MPL (monophsophoryl lipid A)
  - Designed to enhance both cellular and humoral immune responses to subunit antigens
  - Shown to induce robust gE-specific $CD4^+$ T cell and humoral immune responses in mice

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

Summary of Phase 1 and 2 Clinical Trial Results

- Two doses of HZ/su induced robust gE-specific CD4⁺ T cell and humoral immune responses in adults ≥50 yoa
- Immune responses to HZ/su were well-preserved with subject age including in adults ≥70 yoa
- In older adults, immune responses to HZ/su remained above baseline for 6 years following vaccination
- In autologous stem cell transplant recipients and HIV-infected adults, two doses of HZ/su induced immune responses comparable to those in older adults

HZ/su-induced CD4 T cell response in older adults*[1]



gE-specific CD4⁺ T cell response levels:

- Mo 3 (peak: 1 mo >2nd HZ/su dose): 19-fold over baseline
- Month 72: 4.0-fold over baseline

* GMF 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

[1] Lal, et al., IDWeek 2014

HZ/su Development Program: Pivotal Efficacy Studies

Study	Population	Objectives	Status
Pivotal efficacy studies			
006 (ZOE-50)	Adults ≥50 yoa	HZ efficacy, safety	Ongoing; *Efficacy and safety analyses complete*
022 (ZOE-70)	Adults ≥70 yoa	HZ efficacy, safety; PHN efficacy (pooled 006/022 analysis)	Ongoing
002	Adult ≥18 yoa; aHSCT*	HZ efficacy, safety	Ongoing

* aHCST = autologous hematopoietic stem cell transplant

The efficacy and safety results of ZOE-50 will be presented today

HZ/su Development Program: Supporting Studies

Study	Population	Objectives	Status
Co-administration studies			
004	≥50 yoa	Influenza vaccine (quadrivalent)	Ongoing
035	≥50 yoa	Pneumococcal vaccine (PPV-23)	Ongoing
042	≥50 yoa	Tdap vaccine	Ongoing
Other older adult studies			
007	≥50 yoa	Lot-lot consistency	Ongoing
026	≥50 yoa	Schedule comparison	Completed
033	≥50 yoa with history of HZ	Safety/immunogenicity	Completed
048	≥65 yoa; prior Zostavax™ recipients	Safety/immunogenicity	Planned
Other studies in immunocompromised populations (≥18 yoa)			
028	≥18 yoa; solid organ malignancy	Safety, immunogenicity	Ongoing
039	≥18 yoa; hematological malignancy	Safety, immunogenicity	Ongoing
041	≥18 yoa; renal transplant	Safety, immunogenicity	Ongoing

ZOE-50 Objectives

- **Primary objective**
  - **To evaluate overall vaccine efficacy (VE) in reducing HZ risk compared to placebo in adults ≥50 years**

- **Analyzed secondary objectives**
  - **To determine vaccine efficacy in reducing HZ risk compared to placebo in each age stratum (50-59, 60-69, and 70+ years)**
  - **To evaluate HZ/su safety and reactogenicity**

- Secondary protocol-specified objectives to be analyzed upon completion of ZOE-50 and ZOE-70 studies:
  - VE in reducing PHN
  - VE in reducing HZ-associated complications (other than PHN)
  - VE in reducing HZ-related mortality and hospitalizations
  - VE in reducing HZ-associated pain (acute pain and duration of pain)
  - VE in reducing use of pain medications
  - VE in improving QoL
  - Humoral and cellular immunogenicity

ZOE-50 Design

- **Design** Randomized, observer-blind, placebo-controlled study
- **Location** 18 countries: Asia/Australia, Europe, Latin America, North America
- **Population:**
  - Inclusion: Adults ≥50 years of age stratified by age (50–59, 60–69 and 70+ years)
  - Exclusions: History of HZ, previous vaccination against VZV or HZ, immunocompromising conditions
- **Study groups** (randomized 1:1)
  - HZ/su
  - Placebo (saline solution)
- **Intervention:** 2 doses of HZ/su or placebo by IM injection at 2-month intervals
- **Contacts:**
  - Visits Months 0 and 2 (vaccination), 3, 14, 26, 38
  - Contacts Monthly phone calls (for collection of safety data and suspected HZ cases)

HZ Case Confirmation

Subjects educated to recognize a suspected case of HZ, which is defined as:

New unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis

Visit study site within 48 hrs → PI evaluation → HZ not suspected by investigator → 

PI evaluation → HZ suspected

HZ suspected → F/u until pain free for 4 weeks
Pain assessed by Zoster Brief Pain Inventory (ZBPI)

HZ suspected → Lesion samples for PCR + Digital photo of rash → **HZ confirmed by Q-PCR** → If PCR indeterminate, final case adjudication by the HZAC*

* HZAC: HZ Adjudication Committee

ZOE-50 Results – Study cohorts

Characteristics	HZ/su	Placebo
Total vaccinated cohort (TVC): All subjects receiving at least 1 dose - N = 15,411; mean follow-up time = 3.5 years - Primary cohort for safety analyses	**7698**	**7713**
Modified total vaccinated cohort (mTVC): Excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2 - N = 14,759; mean follow-up time = 3.2 years - Primary cohort for efficacy analyses	**7344**	**7415**
Diary card cohort (reactogenicity analyses) - Subset of TVC; N = 8926 - Cohort for reactogenicity analysis	**4460**	**4466**

ZOE-50 Results – Demography

Characteristics (TVC)	HZ/su	Placebo	Total
Age (mean age at dose 1, years ± SD)	62.4 ± 9.0	62.3 ± 9.0	62.3 ± 9.0
Sex (%)			
Female	61.2	61.1	61.2
Male	38.8	38.9	38.8
Race (%)			
White	71.9	71.8	71.8
Black	1.8	1.7	1.8
Asian	19.0	19.1	19.1
Other	7.3	7.5	7.4
Region (%)			
Asia/Australia	21.3	21.3	21.3
Europe	51.2	51.2	51.2
Latin America	10.0	10.1	10.1
North America	17.4	17.4	17.4

ZOE-50: VE Overall and by Age Group

mTVC

Age range (years)	HZ/su group		Placebo group		VE (95% CI)*
	HZ cases	Incidence (per 1000 person-yrs)	HZ cases	Incidence (per 1000 person-yrs)	
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	3	0.2	123	10.2	**97.6** (92.8-99.6)

* p-value for all comparisons <0.0001

VE = % vaccine efficacy (Poisson method); CI, confidence interval
p-value = Two sided exact p-value conditional to number of cases

ZOE-50: Durability of VE

mTVC

ZOE-50 remains blinded at the subject level because the study is ongoing. Therefore, to avoid unblinding, VE by year has not been communicated to the study team.

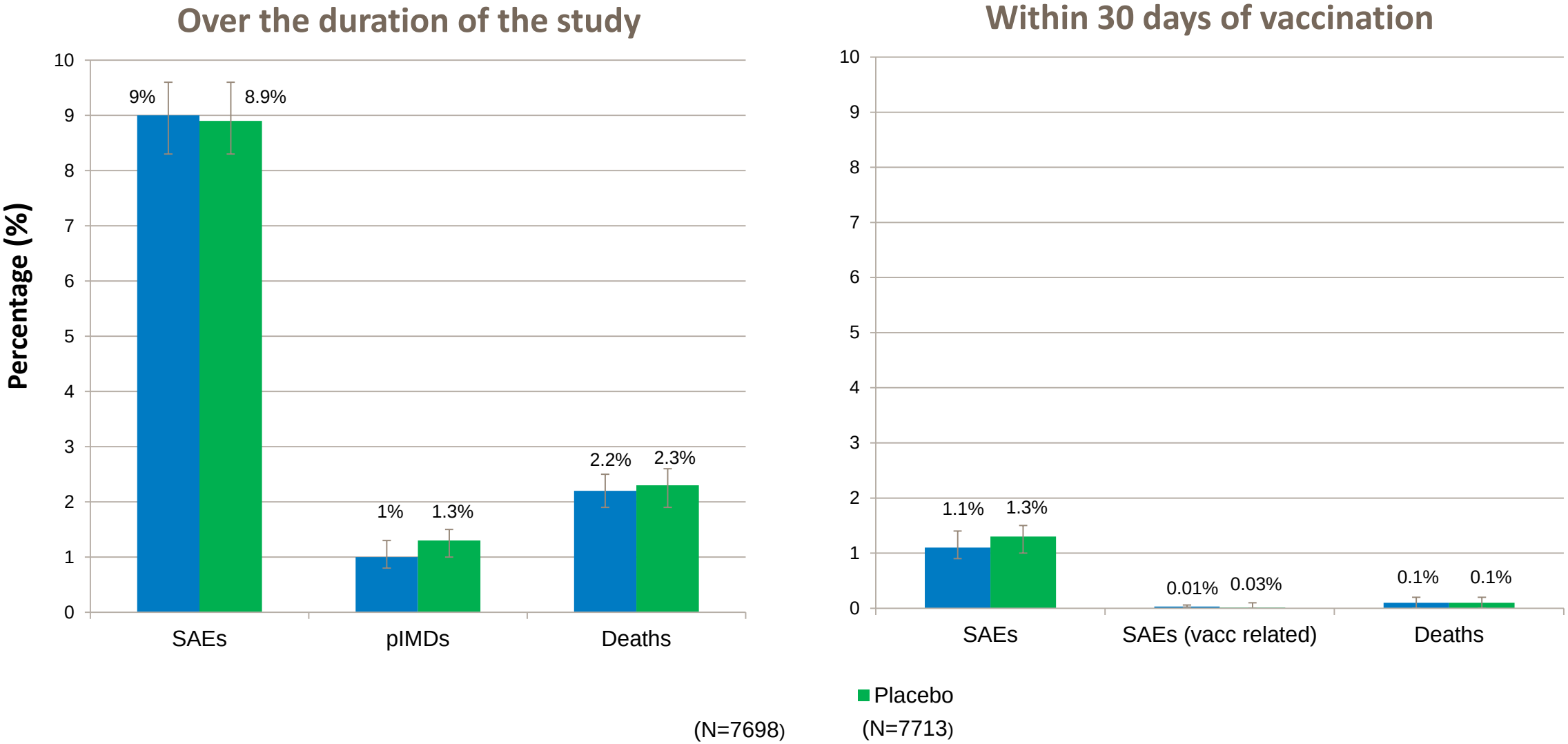
However, no apparent waning of efficacy by year during years 1-4

Time post-vaccination	Pooled HZ/su and placebo groups		VE *
	HZ cases	Incidence (per 1000 person-yrs)	
Year 1	63	4.3	>90%
Year 2	70	4.9	>90%
Year 3	64	4.7	>90%
Year 4	19	4.7	>90%

* LL of the 95% CI for all >30%

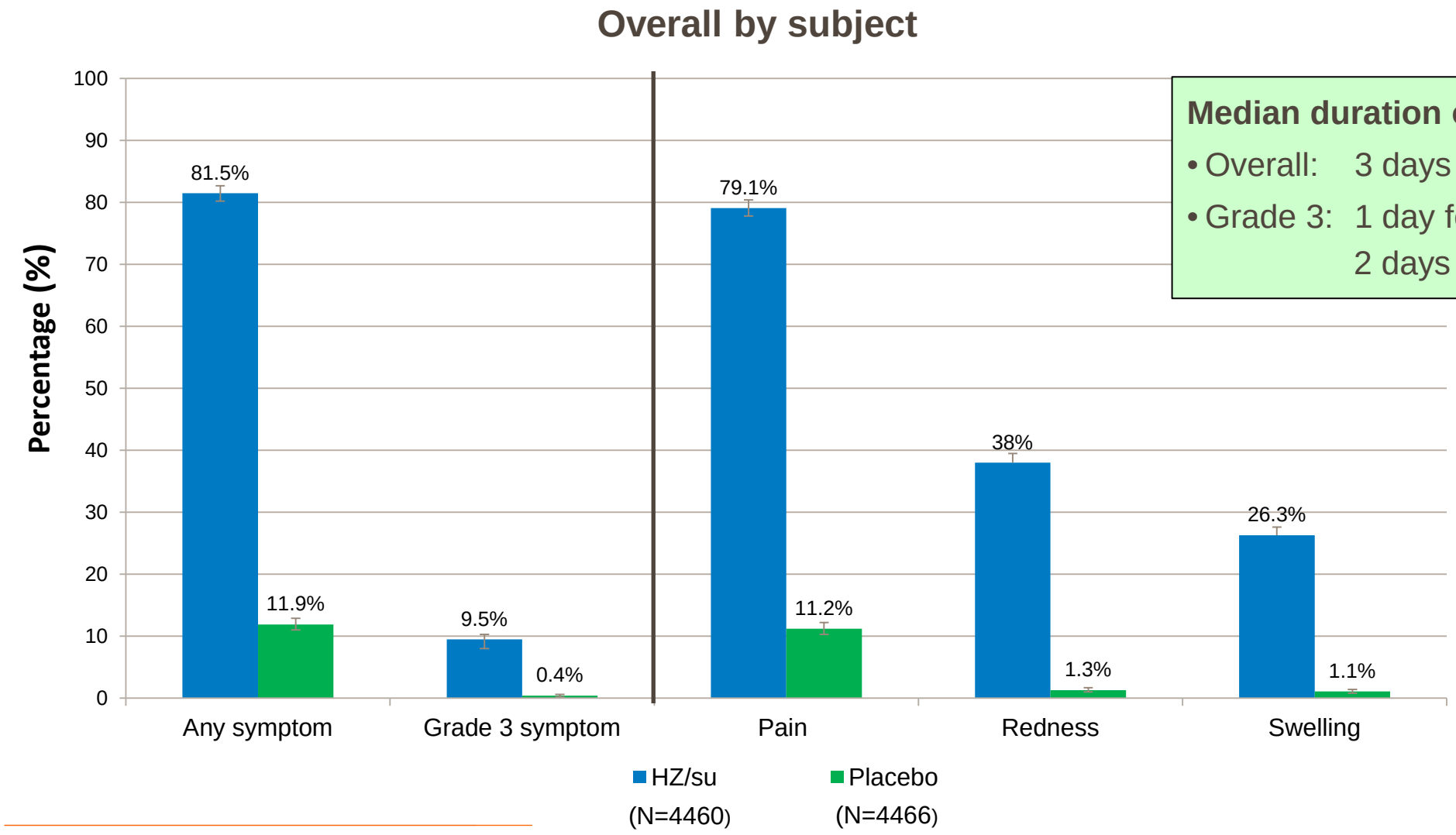
VE = % vaccine efficacy (Poisson method); CI, confidence interval

ZOE-50 Safety



ZOE-50 Reactogenicity

Solicited local symptoms reported during the 7 days post-vaccination

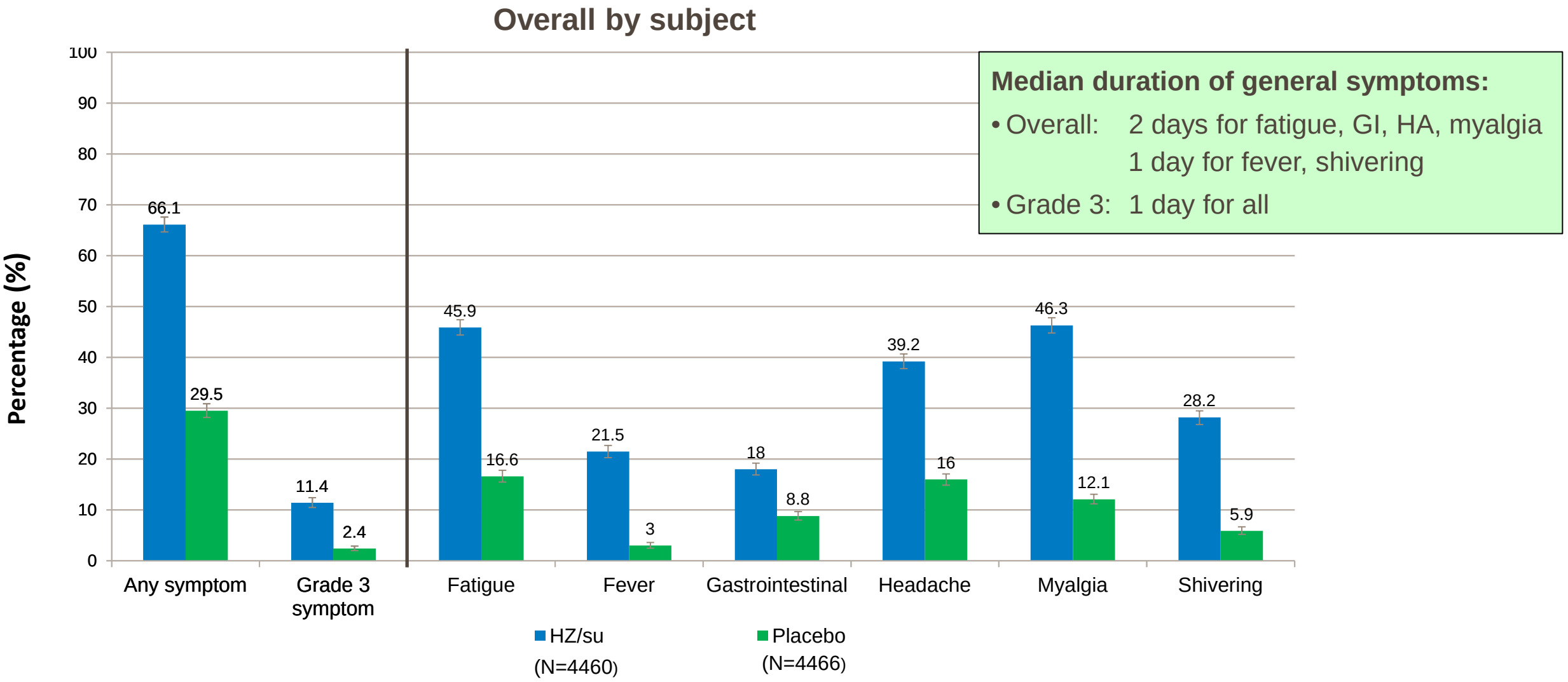


Median duration of local symptoms:

- Overall: 3 days
- Grade 3: 1 day for pain
  2 days for redness and swelling

ZOE-50 Reactogenicity

Solicited general symptoms reported during the 7 days post-vaccination



Median duration of general symptoms:

- Overall: 2 days for fatigue, GI, HA, myalgia
  1 day for fever, shivering
- Grade 3: 1 day for all

Upcoming Results and Next Steps

Results of ongoing studies

- **ZOE-70 and ZOE-50/ZOE-70 pooled analyses**
  - VE against HZ in people ≥70 yoa
  - VE against PHN, HZ-associated pain, etc.; HZ/su impact on QoL; immunogenicity
- **HZ/su efficacy in autologous stem cell transplant recipients**
- **Coadministration studies, safety/immunogenicity in immunocompromised populations, etc.**

Duration of protection and immune persistence

- **10 year post-vaccination follow-up of ZOE-50 and ZOE-70 HZ/su recipients**
- **10-year post-vaccination follow-up of HZ/su recipients from the Zoster-024 phase 2 study (6 years to date) for vaccine-specific CMI and humoral immunity**

Boostability

- **Safety/immunogenicity of additional doses of HZ/su (1 or 2 doses) ~5 and 10 years after the 2nd dose in the original series** (planned)

Reactogenicity

- **Assessment of impact of HZ/su reactogenicity on QoL/normal daily activities** (planned)

ZOE-50 Results Summary

- HZ/su efficacy was 97.2% for the prevention of HZ in adults ≥50 years
- HZ/su efficacy appeared to be age-independent and fully preserved in people ≥70 years
- HZ/su efficacy did not wane during the study period
- No imbalance in the incidence of safety endpoints (serious adverse events, potential autoimmune diseases, deaths) were observed between the HZ/su and placebo groups
- Local and systemic reactions to HZ/su are common in the first 7 days after vaccination; the large majority are mild-moderate intensity and of short duration