GlaxoSmithKline's Investigational Herpes Zoster Vaccine

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GSK - Philadelphia, PA

National Adult and Influenza Immunization Summit
May 10, 2016

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This presentation for an update on GSK's investigational herpes zoster vaccine was created at the request of Bruce Gellin, MD, MPH, Deputy Assistant Secretary for Health, Director National Vaccine Program, Office US Department of Health and Human Services; Carolyn Bridges, MD, Associate Director for Adult Immunizations, Immunization Services Division, Centers for Disease Control and Prevention and Litjen Tan, PhD, MS, Chief Strategy Officer, Immunization Action Coalition.

This is not a sales, marketing, or promotional presentation.

This is an overview of GSK's investigational herpes zoster vaccine. Because progression of investigational drugs is sometimes impacted by factors outside the complete control of GSK (for example: the pace of clinical study enrollment or regulatory review) outcomes may diverge from current expectations.

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Varicella Zoster Clinical Presentation: A Tale of Two Diseases[1,2]

Varicella or Chickenpox:

Occurs shortly after primary VZV infection; viremic spread via infected T-cells to skin causing diffuse cutaneous vesicular rash

CDC. Public Health Image Library. Image # 6121.
Available at: http://phil.cdc.gov/phil/. Accessed October 30, 2015

Herpes Zoster or Shingles:

Occurs when VZV reactivates from previously established latency in sensory ganglia; virus migrates back to skin along sensory nerves causing rash in dermatomal distribution

CDC. Prevention of Herpes Zoster. MMWR June 6, 2008, 57(05);1-30. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm. Accessed February 16, 2016

VZV = varicella zoster virus

1. CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. 2015.
2. CDC. http://www.cdc.gov/vaccines/vpd-vac/shingles/downloads/VZV_clinical_slideset_Jul2010.pdf. Accessed February 8, 2016

Complications of Herpes Zoster

- **Postherpetic Neuralgia (PHN)[1]**
  - Most common complication (~ 10%-18%)[2]
  - Duration of pain ≥ 90 days after rash onset (Mild to excruciating pain)
  - May persist weeks, months or occasionally years
  - Can disrupt sleep, mood, work, and activities of daily living and lead to social withdrawal and depression
  - Risk factors include age ≥ 50, severe pain before or after onset of rash, extensive rash, and trigeminal or ophthalmic distribution of rash
- **Herpes Zoster Ophthalmicus[1]**
  - ~15% of HZ cases
  - Untreated, > 50% develop acute ocular complications; can progress to chronic complications including reduced vision, even blindness
- **Neurologic/Neurovascular complications (VZV vasculopathy) [1]**
- **Visceral Complications[1]**
- **Dermatologic complications[1]**

HZ = herpes zoster; VZV = varicella zoster virus

1. CDC. http://www.cdc.gov/vaccines/vpd-vac/shingles/downloads/VZV_clinical_slideset_Jul2010.pdf. Accessed February 8, 2016
2. CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. 2015

Incidence of Herpes Zoster In the United States

1993–2013

Incidence of HZ in The US Population Stratified By Age Group[1]

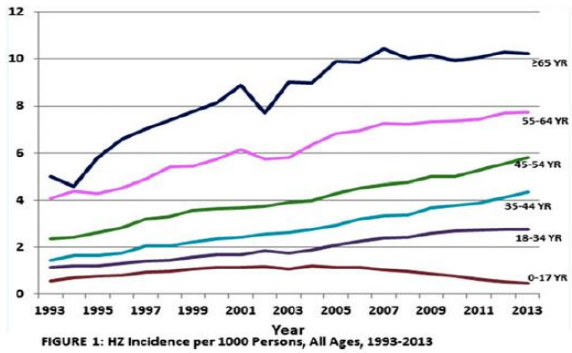


FIGURE 1: HZ Incidence per 1000 Persons, All Ages, 1993-2013

Medical claims data from MarketScan® Databases were obtained for 1993-2013. HZ identified based on first outpatient service with an HZ ICD-9 code (053.xx) and unadjusted incidence was calculated

U.S. Epidemiology

- ~1 million cases in the U.S. annually[2]
- Lifetime risk of zoster estimated to be 32%[2]
- 50% of persons living until age 85 years will develop zoster[2]
- Increasing age and immunosuppression are the most important risk factors[2]
- Estimated total direct annual healthcare cost of HZ is ~1.3 billion[3]

HZ = herpes zoster

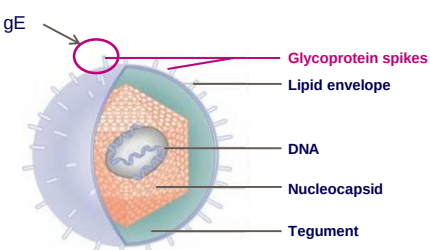
1. Harpaz R et al. Incidence of Pediatric and Adult Herpes Zoster in an Era of Varicella and Herpes Zoster Vaccines . IDWeek, October 7-11 2015, San Diego, CA. Poster 1052 Available at https://idsa.confex.com/idsa/2015/webprogram/Paper51175.html *Accessed February 19, 2016*
2. CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. 2015
3. Palmer L et al. Economic burden of herpes zoster by age group in immunocompetent patients in the United States. IDWeek 2014, Philadelphia, PA October 8-12, 2014. Poster 1046. Available at https://idsa.confex.com/idsa/2014/webprogram/Session6704.html. Accessed February 8, 2014

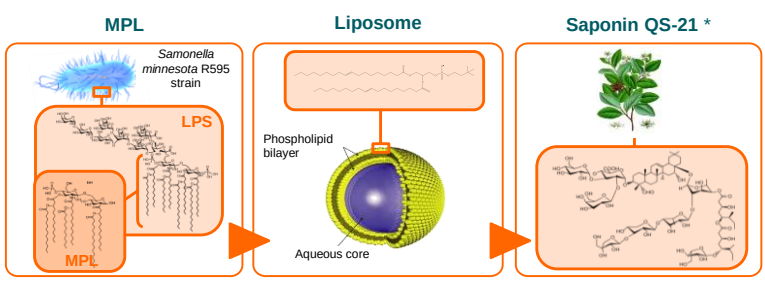
GSK'S Investigational Herpes Zoster Subunit (HZ/su) Vaccine Composition[1-4]

Vaccine

Antigen
Glycoprotein E (gE)
Specificity Of The Immune Response

Adjuvant System
AS01
Enhances The Immune Response To Vaccine Antigen





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

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

Herpes Zoster Subunit Vaccine Target Population and Clinical Development Program

The Herpes Zoster Subunit Vaccine Development Program Targets Two General Populations:*

- Adults ≥50 years of age
- Immunocompromised adults ≥18 years of age

HZ/su Clinical Development Program Aspirations:

- Vaccine efficacy in persons ≥50 years of age
- 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

HZ/su = herpes zoster subunit vaccine

* Indications may vary by country

ZOE-50 and ZOE-70: Brief review

Phase 3 efficacy studies conducted at the same sites

Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70

	ZOE-50[1] (Published in NEJM)	ZOE-70[2,3]
Experimental design	Randomised, observer-blind, placebo-controlled, multicentre multinational (North America, Europe, Latin America, Asia-Pacific)	
Key Exclusion Criteria:	Subjects that were immunocompromised, had a previous history of herpes zoster, were previously vaccinated against varicella or zoster, and patients whose survival was not considered to be a least 4 years, or with conditions that might interfere with study evaluations	
Primary Objectives	HZ efficacy in persons ≥50 years of age	HZ efficacy in persons ≥70 years of age
Primary Objectives in Pooled Analysis	PHN efficacy in 70+ HZ efficacy in 70+	
Secondary & Exploratory Objectives	– Safety and reactogenicity – Humoral and cellular* immunogenicity – VE in reducing HZ-associated complications (other than PHN) – VE in reducing HZ-related mortality and hospitalizations – VE in reducing PHN – VE in reducing HZ-associated pain (acute pain and duration of pain) – VE in reducing use of pain medications – VE in improving QoL	
Age Ranges	**≥ 50 years of age** 50-59, 60-69, 70-79, ≥80 years of age	**≥ 70 years of age** 70–79, ≥80 years of age
Actual Enrolment	16,160 Enrolled 15,411 Total Vaccine Cohort	14,816 Enrolled 13,900 Total Vaccine Cohort

HZ = herpes zoster; PHN = postherpetic neuralgia; Total vaccinated cohort = all vaccinated subjects for whom data related to efficacy end points was available; VE: = Vaccine Efficacy
*ZOE-50 only

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. Data on File. Study 113077. 2015. Available at: http://www.gsk-clinicalstudyregister.com/
3. Data on File. 2015N262105_00. 2015.

ZOE-50: Vaccine Efficacy (VE): Overall and by Age Group[1]

Modified Total Vaccinated Cohort (mTVC)

Age range (years)	Herpes Zoster Subunit Vaccine group		Placebo group		VE (95% CI)*
	HZ cases	Rate of HZ (Number per 1000 Person-Years)	HZ cases	Rate of HZ (Number per 1000 Person-Years)	
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)

CI = confidence interval; HZ = herpes zoster; mTVC = all subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose (n=7344 vaccine, n=7415 placebo); *P*-value = Two sided exact *P*-value conditional to number of cases; VE = % vaccine efficacy (Poisson method)
**P*-value for all comparisons <0.001

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-50: Durability of VE[1,2]

Modified Total Vaccinated Cohort

No apparent waning of VE by year during years 1-4

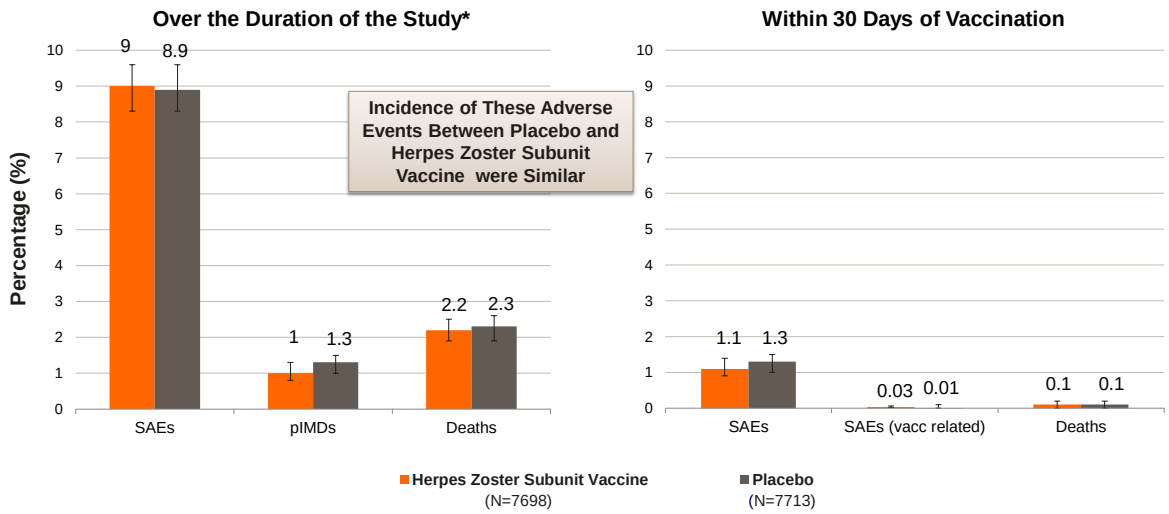
Time post-vaccination	Pooled Herpes Zoster Subunit Vaccine Group and Placebo Groups		VE *
	HZ cases	Rate of HZ (Number per 1000 Person-Years)	
Year 1	63	4.3	>90%
Year 2	70	4.9	>90%
Year 3	64	4.7	>90%
Year 4	19	4.7	>90%

mTVC = all subjects randomized in the study who received a second dose of the vaccine and did not develop a confirmed case of HZ within one month after the second dose (n=7344 vaccine, n=7415 placebo); VE = % vaccine efficacy (Poisson method)
* LL of the 95% CI for all >30%

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-50: Safety

Total Vaccinated Cohort



SAE = serious adverse events; Total Vaccinated Cohort = subjects with at least one administered dose; pIMDs = potential immune mediated diseases

* Duration: mean = 4.1 years, median = 4.4 years

Lal H, Cunningham A, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. NEJM 2015;372:2087-96.

11

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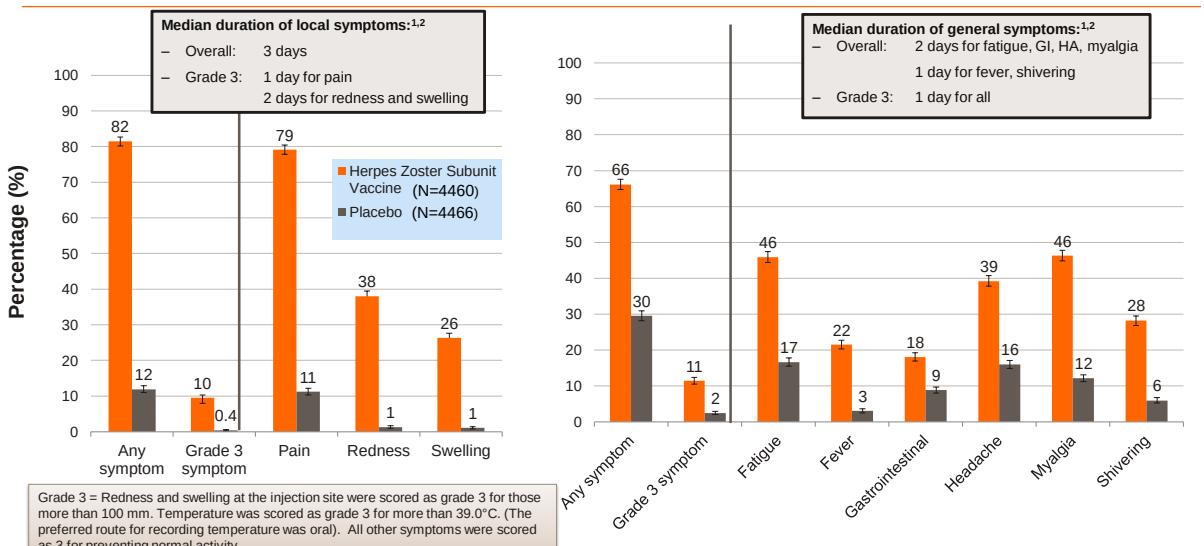
ZOE-50: Reactogenicity

Reactogenicity Subgroup[1]

Solicited Local And General Symptoms Reported During the 7 Days Post-vaccination - Overall by Subject



Grade 3 = Redness and swelling at the injection site were scored as grade 3 for those more than 100 mm. Temperature was scored as grade 3 for more than 39.0°C. (The preferred route for recording temperature was oral). All other symptoms were scored as 3 for preventing normal activity

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. Vesikari T. et al. Reactogenicity of an adjuvanted herpes subunit vaccine in older adults: Results of phase III ZOE-50 trial.Poster 1230. IDWeek Oct 7-11 2015, San Diego CA

12

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ZOE-70: Top Line Results[1,2,3]

The results of ZOE-70 and end of study ZOE-50/ZOE 70 pre-specified pooled analysis:

- Vaccine efficacy (VE) for prevention of HZ in adults ≥70 years of age compared to placebo = 89.79%
  - (95% Confidence Interval [CI], 84.29%-93.66%; *P* <0.0001)
- VE for prevention of PHN in adults ≥70 years of age compared to placebo = 88.78%
  - (95% CI, 68.7%-97.1%; *P* <0.0001)
- VE for the prevention of PHN compared to placebo in adults ≥50 years of age compared to placebo = 91.22%
  - (95% CI, 75.95%-97.70%, *P* <0.0001)

The safety profile of HZ/su in older adults is from more than 16,000 adults who received the vaccine in phase I, II and III clinical trials (including ZOE-50 and ZOE-70)

Most common adverse events seen 7 days after vaccination include local symptoms (pain, redness, swelling at the injection site) and systemic symptoms (muscle pain, fatigue and headache)

1. Data on File. Study 113077. 2015. Available at: http://www.gsk-clinicalstudyregister.com/
2. Data on File. 2015N262105_00. 2015.
3. Lal H, Cunningham A, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. NEJM 2015;372:2087-96

Herpes Zoster Subunit Vaccine 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	Ongoing
033	≥50 yoa with history of HZ	Safety/immunogenicity	Completed
048	≥65 yoa; prior Zostavax™ recipients	Safety/immunogenicity	Enrolling
Other studies in immunocompromised populations (≥18 yoa)			
002	≥18 yoa; autologous HCT recipients	Efficacy, safety, immunogenicity	Ongoing
028	≥18 yoa; solid tumor malignancy	Safety, immunogenicity	Ongoing
039	≥18 yoa; hematological malignancy	Safety, immunogenicity	Ongoing
041	≥18 yoa; renal transplant	Safety, immunogenicity	Ongoing

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

Pearls Of Wisdom

- Estimated 1 million cases of herpes zoster each year in the U.S.
- Increasing age and immunosuppression are the most important risk factors
- Adjuvants are being utilized in vaccines to direct the immune response to target antigen
- In clinical trials GSK's investigational zoster vaccine composed of glycoprotein E antigen and the AS01 adjuvant provided a high level of protection against HZ and PHN for all adults, including people 70 and older

HZ = herpes zoster; PHN = postherpetic neuralgia