GlaxoSmithKline’s Investigational Herpes Zoster Vaccine

Debora Rausch MD, MA
US Vaccines, Clinical and Medical Affairs
GSK - Philadelphia, PA

National Adult and Influenza Immunization Summit
May 10, 2016

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.
Varicella Zoster Clinical Presentation: A Tale of Two Diseases

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

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

Complications of Herpes Zoster

- **Postherpetic Neuralgia (PHN)**
  - Most common complication (~ 10%-18%)
  - 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**
  - ~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)**

- **Visceral Complications**

- **Dermatologic complications**
Incidence of Herpes Zoster In the United States
1993–2013

Incidence of HZ in The US Population Stratified By Age Group

U.S. Epidemiology

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

Incidence of HZ in The US Population Stratified By Age Group

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.

GSK’S Investigational Herpes Zoster Subunit (HZ/su) Vaccine Composition

Vaccine

Antigen Glycoprotein E (gE)

Specificity Of The Immune Response

Adjuvant System AS01

Enhances The Immune Response To Vaccine Antigen

**NOT FOR AFFIRMATIVE USE**
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

<table>
<thead>
<tr>
<th></th>
<th>ZOE-50¹ (Published in NEJM)</th>
<th>ZOE-70²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental design</strong></td>
<td>Randomised, observer-blind, placebo-controlled, multicentre multinational (North America, Europe, Latin America, Asia-Pacific)</td>
<td></td>
</tr>
<tr>
<td><strong>Key Exclusion Criteria:</strong></td>
<td>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 at least 4 years, or with conditions that might interfere with study evaluations</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Objectives</strong></td>
<td>HZ efficacy in persons ≥50 years of age</td>
<td>HZ efficacy in persons ≥70 years of age</td>
</tr>
<tr>
<td><strong>Primary Objectives in Pooled Analysis</strong></td>
<td>PHN efficacy in 70+</td>
<td>HZ efficacy in 70+</td>
</tr>
<tr>
<td><strong>Secondary &amp; Exploratory Objectives</strong></td>
<td>Safety and reactogenicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humoral and cellular* immunogenicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in reducing HZ-associated complications (other than PHN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in reducing HZ-related mortality and hospitalizations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in reducing PHN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in reducing HZ-associated pain (acute pain and duration of pain)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in reducing use of pain medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VE in improving QoL</td>
<td></td>
</tr>
<tr>
<td><strong>Age Ranges</strong></td>
<td>≥ 50 years of age</td>
<td>≥ 70 years of age</td>
</tr>
<tr>
<td></td>
<td>50-59, 60-69, 70-79, ≥80 years of age</td>
<td>70-79, ≥80 years of age</td>
</tr>
<tr>
<td><strong>Actual Enrolment</strong></td>
<td>16,160 Enrolled</td>
<td>14,816 Enrolled</td>
</tr>
<tr>
<td></td>
<td>15,411 Total Vaccine Cohort</td>
<td>13,900 Total Vaccine Cohort</td>
</tr>
</tbody>
</table>

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

¹ZOE-50 only
²Data on File. Study 113077. 2015. Available at: http://www.gsk- clinicalstudyregister.com
³Data on File. 2015N262105_00. 2015.

### ZOE-50: Vaccine Efficacy (VE): Overall and by Age Group

**Modified Total Vaccinated Cohort (mTVC)**

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Herpes Zoster Subunit Vaccine group</th>
<th>Placebo group</th>
<th>VE (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ cases</td>
<td>Rate of HZ (Number per 1000 Person-Years)</td>
<td>HZ cases</td>
</tr>
<tr>
<td>Overall (≥50)</td>
<td>6</td>
<td>0.3</td>
<td>210</td>
</tr>
<tr>
<td>50-59</td>
<td>3</td>
<td>0.3</td>
<td>87</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>≥70</td>
<td>1</td>
<td>0.2</td>
<td>48</td>
</tr>
<tr>
<td>≥60²</td>
<td>3</td>
<td>0.2</td>
<td>123</td>
</tr>
</tbody>
</table>

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)

1. P-value for all comparisons <0.001

---

### ZOE-50: Durability of VE

**Modified Total Vaccinated Cohort**

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

<table>
<thead>
<tr>
<th>Time post-vaccination</th>
<th>Pooled Herpes Zoster Subunit Vaccine Group and Placebo Groups</th>
<th>VE *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ cases</td>
<td>Rate of HZ (Number per 1000 Person-Years)</td>
</tr>
<tr>
<td>Year 1</td>
<td>63</td>
<td>4.3</td>
</tr>
<tr>
<td>Year 2</td>
<td>70</td>
<td>4.9</td>
</tr>
<tr>
<td>Year 3</td>
<td>64</td>
<td>4.7</td>
</tr>
<tr>
<td>Year 4</td>
<td>19</td>
<td>4.7</td>
</tr>
</tbody>
</table>

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%

---

**ZOE-50: Safety**

*Total Vaccinated Cohort*

**Over the Duration of the Study**

Incidence of These Adverse Events Between Placebo and Herpes Zoster Subunit Vaccine were Similar

**Within 30 Days of Vaccination**

SAEs

<table>
<thead>
<tr>
<th>SAEs</th>
<th>pIMDs</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Herpes Zoster Subunit Vaccine**

(N=7698)

**Placebo**

(N=7713)

SAEs (vacc related)

| 0.03 | 0.01 | 0.1   |

**SAEs**

**Deaths**

---

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


---

**ZOE-50: Reactogenicity**

*Reactogenicity Subgroup*¹

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade 3</th>
<th>Pain</th>
<th>Redness</th>
<th>Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes Zoster Subunit Vaccine (N=4460)</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>Placebo (N=4466)</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>38</td>
</tr>
</tbody>
</table>

**Median duration of local symptoms**:¹ ³

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

**Median duration of general symptoms**:¹ ³

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

---


---

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.
ZOE-70: Top Line Results\textsuperscript{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 $\geq$70 years of age compared to placebo = \textbf{89.79\%} 
  \hspace{5mm} (95\% Confidence Interval [CI], 84.29\%-93.66\%; $P < 0.0001$)
- VE for prevention of PHN in adults $\geq$70 years of age compared to placebo = \textbf{88.78\%} 
  \hspace{5mm} (95\% CI, 68.7\%-97.1\%; $P < 0.0001$)
- VE for the prevention of PHN compared to placebo in adults $\geq$50 years of age compared to placebo = \textbf{91.22\%} 
  \hspace{5mm} (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)

---


---

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Objectives</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-administration studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>004</td>
<td>$\geq$50 yoa</td>
<td>Influenza vaccine (quadrivalent)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>035</td>
<td>$\geq$50 yoa</td>
<td>Pneumococcal vaccine (PPV-23)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>042</td>
<td>$\geq$50 yoa</td>
<td>Tdap vaccine</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Other older adult studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>007</td>
<td>$\geq$50 yoa</td>
<td>Lot-lot consistency</td>
<td>Ongoing</td>
</tr>
<tr>
<td>026</td>
<td>$\geq$50 yoa</td>
<td>Schedule comparison</td>
<td>Ongoing</td>
</tr>
<tr>
<td>033</td>
<td>$\geq$50 yoa with history of HZ</td>
<td>Safety/immunogenicity</td>
<td>Completed</td>
</tr>
<tr>
<td>048</td>
<td>$\geq$65 yoa; prior Zostavax\textsuperscript{TM} recipients</td>
<td>Safety/immunogenicity</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Other studies in immunocompromised populations ($\geq$18 yoa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>002</td>
<td>$\geq$18 yoa; autologous HCT recipients</td>
<td>Efficacy, safety, immunogenicity</td>
<td>Ongoing</td>
</tr>
<tr>
<td>028</td>
<td>$\geq$18 yoa; solid tumor malignancy</td>
<td>Safety, immunogenicity</td>
<td>Ongoing</td>
</tr>
<tr>
<td>039</td>
<td>$\geq$18 yoa; hematological malignancy</td>
<td>Safety, immunogenicity</td>
<td>Ongoing</td>
</tr>
<tr>
<td>041</td>
<td>$\geq$18 yoa; renal transplant</td>
<td>Safety, immunogenicity</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

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