Immunogenicity and Safety of Shingrix in Adults Previously Vaccinated With a Live-Attenuated Herpes Zoster Vaccine (Zoster-048 Study)

ACIP – June 21, 2017

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Global Medical Affairs Lead, Zoster
GSK
Today’s Presentation

ZOE-50 Efficacy
June 2015

ZOE-70 Efficacy
Oct 2016

HZ/su Safety
Feb 2017

Revaccination with HZ/su (Zoster-048)
June 2017

HZ/su, herpes zoster subunit vaccine; ZOE, zoster efficacy trials.
Agenda

1. Context and Rationale
2. Objectives and Study Design (Zoster-048)
3. Results (Zoster-048)
4. Summary
HZ/su Vaccine Composition

Context and rationale

Vaccine
Non-live

Antigen
Glycoprotein E (gE) - 50 µg

Adjuvant System
AS01B (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). HZ/su, Herpes zoster subunit vaccine; MPL, monophosphoryl lipid A.

QS-21
Glycoprotein spikes (gE)
Lipid envelope
DNA
Nucleocapsid
Tegument

MPL
Saponin QS-21
S. minnesota R595 strain
Phospholipid bilayer
Aqueous core
Live-attenuated zoster vaccine (ZVL) has been licensed since 2006 and is recommended by ACIP for the prevention of HZ in immunocompetent adults ≥60 years of age.

Approximately 31% of US adults ≥60 years of age have been vaccinated for HZ.

Vaccination with ZVL as the current standard offers protection against HZ (VE=51% in adults ≥60 years of age) and this protection wanes over time.

The Zoster-048 study was designed to generate immunogenicity and safety data in persons who received ZVL at least 5 years prior, to help inform immunization policy decision-making.

HZ, herpes zoster; VE, vaccine efficacy; ZVL, live-attenuated zoster vaccine (Zostavax®).

2. 2016 Zostavax PI.
Objectives and Study Design

Zoster-048
## Brief Overview of Zoster-048

*Prospective, group-matched, non-randomized trial*

<table>
<thead>
<tr>
<th>Experimental design</th>
<th>Previous ZVL</th>
<th>No Previous ZVL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase III, prospective, group-matched, non-randomized, open label, multicenter study in US</td>
<td></td>
</tr>
<tr>
<td>HZ vaccination history</td>
<td>ZVL ≥5 years prior</td>
<td>No previous HZ vaccine</td>
</tr>
<tr>
<td>Age range</td>
<td>≥65 years of age</td>
<td></td>
</tr>
</tbody>
</table>

### Co-primary objectives
- Compare anti-gE antibody concentrations 1 month post-dose 2 (non-inferiority)\(^a\)
- Safety and reactogenicity up to 1 month post dose 2

### Secondary objectives
- Humoral immune response and cell-mediated immunity at baseline, 1 month post-dose 1, and 1 and 12 months post-dose 2
- Safety up to 12 months post-dose 2 (ongoing)

\(^a\)Non-inferiority: upper limit of two-sided 95% CI of adjusted geometric mean concentration ratio (No Previous ZVL over Previous ZVL 1 month post-dose 2) is below 1.5 for anti-gE antibodies.

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Previous ZVL, received live-attenuated zoster vaccine (Zostavax\(^\circledR\)) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax\(^\circledR\)). CI, confidence internal; gE, glycoprotein E; HZ, herpes zoster.
Zoster-048 Study Design

Prospsective, group-matched, non-randomized trial

**Zoster-048 Study Design**

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**Screening visit**
- Eligibility, ZVL history, matching variables

**Previous ZVL (n=215)**
- Visit 1: Month 0
- Visit 2: Month 1
- Visit 3: Month 2
- Visit 4: Month 3
- Monthly contacts
- Visit 5: Month 14

**No Previous ZVL (n=215)**
- HZ/su vaccination
- Blood sampling for HI and CMI

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Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier;
No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®).
HZ/su, Herpes zoster subunit vaccine; HI, humoral immune response; CMI, cell-mediated immunity.
According to Protocol (ATP) Cohort

- 213 received dose 2; completed active phase (month 3)
- 212 received dose 2; completed active phase (month 3)
Results

Zoster-048; Active phase month 3 data
# Summary of Demographic Characteristics

## Total vaccinated cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameters or Categories</th>
<th>Previous ZVL n=215</th>
<th>No Previous ZVL n=215</th>
<th>Total N=430</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Value or n</td>
<td>%</td>
<td>Value or n</td>
</tr>
<tr>
<td>Age (years) at vaccination dose 1</td>
<td>Mean</td>
<td>71.1 - 70.8 - 70.9</td>
<td>-</td>
<td>70.8 - 4.6 - 4.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.5 - 4.6 - 4.6</td>
<td>-</td>
<td>4.6 - 4.6 - 4.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>70.0 - 70.0 - 70.0</td>
<td>-</td>
<td>70.0 - 70.0 - 70.0</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>65 - 65 - 65</td>
<td>-</td>
<td>65 - 65 - 65</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>87 - 87 - 87</td>
<td>-</td>
<td>85 - 85 - 85</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>109  100  50.7</td>
<td>-</td>
<td>111  100  51.6</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>106  100  49.3</td>
<td>-</td>
<td>104  100  48.4</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td>White—Caucasian / European Heritage</td>
<td>215 100 100</td>
<td>-</td>
<td>215 100 100</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0 0 0.0</td>
<td>-</td>
<td>0 0 0.0</td>
</tr>
<tr>
<td>Time (years) since previous ZVL vaccination</td>
<td>Mean</td>
<td>6.7 - - - -</td>
<td>-</td>
<td>- - - -</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.11 - - - -</td>
<td>-</td>
<td>- - - -</td>
</tr>
</tbody>
</table>

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier;
No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®).
SD, standard deviation.
### Adjusted ratios of No Previous ZVL over Previous ZVL anti-gE antibody ELISA GMCs at one month post-dose 2 (ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th></th>
<th>Previous ZVL</th>
<th>No Previous ZVL</th>
<th>Adjusted GMC ratio (No Previous ZVL/ Previous ZVL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>204</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td>Value</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td>204</td>
</tr>
<tr>
<td>Adjusted GMC</td>
<td>48589.4</td>
<td>50522.9</td>
<td>1.04</td>
</tr>
<tr>
<td>95% CI</td>
<td>42649.4</td>
<td>44347.4</td>
<td>0.92</td>
</tr>
<tr>
<td>55356.6</td>
<td>57558.4</td>
<td></td>
<td>1.17</td>
</tr>
</tbody>
</table>

Adjusted ratios of No Previous ZVL over Previous ZVL anti-gE antibody ELISA GMCs at one month post-dose 2 (ATP cohort for immunogenicity)

UL of 95% CI < 1.5

Non-inferiority is reached
Month 3 Humoral Immune Responses Similar Between Groups and Consistent With ZOE Trials

Geometric mean concentrations of anti-gE antibody

**Zoster-048**
(mean: 70.9 years of age)

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccination (M0)</th>
<th>Post-dose 1 (M1)</th>
<th>Post-dose 2 (M3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ZVL</td>
<td>1784</td>
<td>29959</td>
<td>49327</td>
</tr>
<tr>
<td>No Previous ZVL</td>
<td>1409</td>
<td>25234</td>
<td>51619</td>
</tr>
</tbody>
</table>

**ZOE-50/70 pooled**
(mean: ~75 years of age)

<table>
<thead>
<tr>
<th></th>
<th>Pre-vaccination (M0)</th>
<th>Post-dose 2 (M3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ZVL</td>
<td>1453</td>
<td>49692</td>
</tr>
<tr>
<td>No Previous ZVL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). gE, glycoprotein E; GMC, geometric mean concentration; M, month; ZOE-50/70, zoster efficacy trials.
Month 3 Cellular Immune Responses Similar Between Groups and Consistent With ZOE-50 Trial

gE-specific $\text{CD4}^+[2+]$ frequencies

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). CD4$^+[2+]$, CD4+ T-cells secreting at least two activation markers (IFN-$\gamma$, IL-2, TNF-$\alpha$, CD40L); gE, glycoprotein E; M, month; Q1, Quartile 1=25th percentile; Q3, Quartile 3=75th percentile; ZOE-50, zoster efficacy trial ≥50 years of age.
Overview of Safety Reporting

Zoster-048 study ongoing; 3-month analysis

- AE, adverse event; pIMD, potential Immune-Mediated Disease; SAE, serious adverse event.

Solicited Local/Systemic Symptoms

<table>
<thead>
<tr>
<th>Interval</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Month 3 Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Days</td>
<td>Month 0</td>
<td>Month 2</td>
<td>Analysis</td>
</tr>
</tbody>
</table>

Unsolicited AEs

<table>
<thead>
<tr>
<th>Interval</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Month 3 Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days</td>
<td>Month 0</td>
<td>Month 2</td>
<td>Analysis</td>
</tr>
</tbody>
</table>

SAEs, pIMDs

<table>
<thead>
<tr>
<th>Interval</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Month 3 Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Study Period</td>
<td></td>
<td></td>
<td>Analysis</td>
</tr>
</tbody>
</table>
Safety Reporting up to 30 Days Post-Last Vaccination

Total vaccinated cohort

Percentage of subjects reporting an event from first vaccination up to 30 days post-last vaccination

No pIMDs or related SAEs were reported from first vaccination up to 30 days post last vaccination

According to the investigator AE is considered as potentially related to HZ/su vaccination.

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). AE, adverse event; HZ/su, herpes zoster subunit vaccine; pIMD, potential Immune-Mediated disease; SAE, serious adverse event.
Solicited Local Symptoms Within 7 Days Post-Vaccination

*Any grade overall by subject in total vaccinated cohort*

- Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier;
- No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®).

Median duration of pain=2 days; redness and swelling=2–3 days

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Previous ZVL</th>
<th>No Previous ZVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Redness</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Swelling</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Solicited Local Symptoms Within 7 Days Post-Vaccination

**Grade 3 overall by subject in total vaccinated cohort**

<table>
<thead>
<tr>
<th></th>
<th>Previous ZVL</th>
<th>No Previous ZVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Redness</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Swelling</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Median duration of grade 3 pain, redness and swelling: 1 day

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Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier;
No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®).

Redness/swelling at the injection site scored as grade 3 for those >100 mm. Pain was scored as grade 3 if preventing normal activity.
Solicited Systemic Symptoms Within 7 Days Post Vaccination

*Any grade* overall by subject in total vaccinated cohort

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- Solicited Systemic Symptoms Within 7 Days Post Vaccination
- Any grade overall by subject in total vaccinated cohort
- Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). 
- GI: Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
- Temperature: Preferred route for recording temperature was oral.

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Median duration of GI, headache, shivering and temperature = 1 day; fatigue = 1–2 days and myalgia = 2 days

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**%**

- **Fatigue**
  - Previous ZVL: 50%
  - No Previous ZVL: 40%
- **GI**
  - Previous ZVL: 20%
  - No Previous ZVL: 10%
- **Headache**
  - Previous ZVL: 30%
  - No Previous ZVL: 20%
- **Myalgia**
  - Previous ZVL: 40%
  - No Previous ZVL: 30%
- **Shivering**
  - Previous ZVL: 10%
  - No Previous ZVL: 10%
- **Temperature**
  - Previous ZVL: 10%
  - No Previous ZVL: 10%

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Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain. °C (preferred route for recording temperature was oral).
Solicited Systemic Symptoms Within 7 Days Post-Vaccination

**Grade 3 overall by subject in total vaccinated cohort**

Previous ZVL, received live-attenuated zoster vaccine (Zostavax®) ≥5 years earlier; No Previous ZVL, never received live-attenuated zoster vaccine (Zostavax®). aGastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain. bScored as grade 3 ≥39°C (preferred route for recording temperature was oral). All other symptoms were scored as 3 for preventing normal activity.

Median duration of grade 3 fatigue, headache, myalgia, and shivering=1 day; GI=1−1.5 days

- Fatigue
- GI
- Headache
- Myalgia
- Shivering
- Temperature

Previous ZVL: Previous ZVL
No Previous ZVL: No Previous ZVL
Summary

Zoster-048: Active phase month 3 data
Shingrix (adjuvanted herpes zoster subunit vaccine) induced a strong immune response (humoral and cellular), consistent with ZOE trials, regardless of previous vaccination with ZVL (live-attenuated herpes zoster vaccine).

No apparent safety differences observed between study groups within 30 days post dose 2 of Shingrix.

Solicited local and systemic symptoms were similar between study groups.
Summary of Shingrix Clinical Data

ZOE-50, ZOE-70, and Zoster-048

June 2015: >90% efficacy with Shingrix in all age groups (50 to >80 years of age)

Oct 2016: No significant decline in efficacy during follow-up period (~4 years)

Feb 2017: Well characterized safety profile

Solicited symptoms were more common in the HZ/su group versus placebo (saline)

Most were transient and mild-to-moderate intensity

June 2017: Similar immunogenicity, safety, and reactogenicity with or without previous ZVL vaccination

Immune response maintained for at least 9 years

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*Large safety database (>14,645 subjects) available to evaluate safety of HZ/su candidate vaccine (gE + AS01B) with more than 60,000 person years of active follow up.*
Thank You