LONG-TERM IMMUNOLOGICAL PERSISTENCE OF THE ADJUVANTED RECOMBINANT ZOSTER VACCINE: CLINICAL DATA AND MATHEMATICAL MODELING

Adriana Bastidas,1,a Grégory Catteau,2 Stéphanie Volpe,1 Tomas Mrkvan,1 Adaora Enemuo,3 Jan Smetana,4 Tino Schwarz,5 Lars Rombo,6 Karlis Pauksens,7 Estelle Berengier,2 Caroline Hervé,1 Lidia Oostvogels,1,b Anne Schuind3

1GSK, Wavre, Belgium; 2GSK, Rixensart, Belgium; 3GSK, Rockville, MD, USA; 4Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic; 5Klinikum Wuerzburg Mitte, Standort Juliussspital, Wuerzburg, Germany; 6Dept of Infectious Diseases, Uppsala University, Eskilstuna, Sweden; 7Dept of Infectious Diseases, Uppsala University Hospital, Uppsala, Sweden;
Current affiliations: aMithra Pharmaceuticals, Flemalle, Belgium; bCureVac AG, Tübingen, Germany

Abstract no: 678379 / presentation nb: 2905

IDWeek, 2–6 October 2019, Washington, DC, USA
Disclosures

- GlaxoSmithKline Biologicals SA was the funding source and involved in all the stages of the study conduct and analysis and the development of this presentation.
- Anne Schuind is an employee of the GSK Group of Companies and holds shares/stock options as part of her remuneration.
- Shingrix is a registered trademark of the GSK group of companies.

Acknowledgements

- We thank all the participants included in this trial, the investigators, study nurses, other staff members and GSK study team for contributing to this study.
- Medical writing/editorial support and publication coordination were provided by Ioana Anamaria Sima and Sander Hulsmans (Modis c/o GSK).
Background and aims

- Herpes zoster (HZ) results from reactivation of latent varicella-zoster virus (VZV) and occurs most frequently in older adults\(^1,2\)
- The adjuvanted recombinant zoster vaccine (RZV, Shingrix, GSK) has been licensed for the prevention of HZ in adults ≥50 years of age (YOA) since 2017
  - Composition of RZV: VZV gE+AS01\(_B\)\(^3\)
- The 2-dose schedule RZV has demonstrated ≥90% efficacy against HZ across all age strata (50–59, 60–69 and 70+)\(^4\) that is sustained over 4 years of follow-up
- In adults ≥60 YOA robust immune responses were elicited after 2-dose RZV, which persisted above pre-vaccination levels up to 9 years post-initial vaccination\(^5\)

Here we present persistence of humoral and cellular immunity up to 10 years and mathematical modeling to predict immune persistence up to 15 years post-initial vaccination in the same population

Study objectives and endpoints*

**Primary**
- Persistence of immune responses to RZV at Y9 and Y10
  - Anti-gE antibody concentrations measured by ELISA
  - Frequencies of gE-specific CD4+ T-cells expressing ≥2 activation markers (IFN-γ, IL-2, TNF-α, CD40L) measured by ICS

**Secondary**
- Persistence of immune responses to RZV by age strata at Y9 and Y10
- Safety between Y9 and Y10
  - Anti-gE antibody concentrations measured by ELISA
  - Frequencies of gE-specific CD4+ T-cells expressing ≥2 activation markers (IFN-γ, IL-2, TNF-α, CD40L) measured by ICS
  - Occurrence of serious adverse events related to study participation

**Exploratory**
- Mathematical modeling of persistence of immune responses up to Y15 post-initial vaccination
  - Functions fitting immunological data over three statistical models (Piece-wise, Power-law, Fraser)

---

IFN-γ, interferon-gamma; IL-2, interleukin 2; TNF-α, tumor necrosis factor-alpha; CD40L, CD40 ligand; ELISA, enzyme-linked immunosorbent assay; ICS, intracellular cytokine staining; Y, year. *selected study objectives are listed; **data not shown here; Note: Y9 and Y10 post-dose 1 from initial vaccination.
Study design: phase III B, open-label, extension trial in Europe*

Evaluation of immunological persistence

- Mathematical modeling – based on data collected from adults who received 2 doses of RZV in the parent study and were willing to participate in the follow-up studies

### Demographic characteristics

<table>
<thead>
<tr>
<th>According-to-protocol cohort for persistence</th>
<th>N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at primary vaccination</td>
<td>72.2 ± 4.3</td>
</tr>
<tr>
<td>mean ± SD (years)</td>
<td></td>
</tr>
<tr>
<td>Age at Y10 visit</td>
<td>82.6 ± 4.4</td>
</tr>
<tr>
<td>mean ± SD (years)</td>
<td></td>
</tr>
<tr>
<td>Sex, N (%) (male)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>White-Caucasian/European heritage, N (%)</td>
<td>68 (100)</td>
</tr>
</tbody>
</table>

N, number of adults; SD, standard deviation.
Immune responses persisted up to Y10 post-initial vaccination.

Cell-mediated immune responses remained 3.3-fold above pre-initial vaccination levels.

Humoral immune responses remained 5.9-fold above pre-initial vaccination levels.

According to protocol cohort for persistence. PRE, before vaccination in the initial study; GMC, geometric mean concentration; N, number of adults with available results; Q1, first quartile; Q3, third quartile; Min, minimum; Max, maximum.
Mathematical modeling

- 3 linear mixed models for repeated measurements were used to predict persistence of immune responses

- **Piece-wise linear model**: Based on assumption that the immune response declines linearly over time at a slope varying between non-overlapping time intervals (M3–M12, M12–M26, M26–onwards for anti-gE and M3–M12, M12–M49, M49–onwards for gE-specific CD4[2+] T-cells)

- **Power-law model**: Based on assumption that the immune response declines over time following a logarithmic function

- **Fraser model**: Modified Power-law model includes a constant in the logarithmic function
Cellular immune responses - predicted to remain above pre-vaccination levels for at least 15 years post-initial vaccination

Prediction modeling data up to Y15

According-to-protocol cohort for modeling.
Humoral immune responses - predicted to remain above pre-vaccination levels for at least 15 years post-initial vaccination

According-to-protocol cohort for modeling.
Y10 measured cellular and humoral responses are similar to predicted values

Predictions of the Y10 immune response based on Y6 data using the 3 models\textsuperscript{1,2}

Conclusions

• In adults vaccinated at ≥60 YOA, humoral and cellular immune responses induced by 2 RZV doses remain above pre-vaccination levels up to 10 years post-initial vaccination (end of observation period)

• Mathematical modeling predicts that the vaccine-induced immune response will be maintained for at least 15 years post-initial vaccination

• Similar results were obtained in 3 different mathematical models (Piece-wise, Power-law and Fraser) predicting immunological persistence
Thank you