

# Vaccines and Related Biological Products Advisory Committee Meeting

## Herpes Zoster Vaccine Recombinant, Adjuvanted (SHINGRIX) Review of Efficacy and Safety

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## Presentation Outline

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- Background, including an introduction to the product and proposed indication and usage
- Overview of select clinical studies submitted to the BLA
- Efficacy and safety data from the clinical endpoint studies
- Select safety and efficacy data from the pooled analysis of pivotal studies
- Summary of efficacy and safety

## SHINGRIX

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50 µg recombinant VZV glycoprotein E antigen, lyophilized and presented in a single dose vial

50 µg AS01B adjuvant – QS-21, MPL with liposomes, in a liquid presentation of 0.5mL in a single dose vial

Mixed prior to administration and administered as a single 0.5 mL dose at Months 0 and 2

## Proposed Indication and Usage

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*SHINGRIX is a non-live, recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, SHINGRIX reduces the overall incidence of postherpetic neuralgia.*

## Two clinical endpoint studies

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Zoster-006 – A Phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess the prophylactic efficacy, safety and immunogenicity of SHINGRIX when administered intramuscularly (IM) on a M0/M2 schedule in adults  $\geq 50$  years of age (YOA)

Zoster-022 - A Phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess the prophylactic efficacy, safety and immunogenicity of SHINGRIX when administered intramuscularly (IM) on a M0/M2 schedule in adults  $\geq 70$  years of age (YOA)

## Additional studies

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### **Zoster-004**

- Evaluated the safety and non-inferiority of the humoral immune responses to SHINGRIX and quadrivalent influenza vaccine (QIV) when the vaccines were administered concomitantly as compared to non-concomitant administration
- Humoral immune responses to both vaccines after concomitant administration were non-inferior to when vaccines administered consecutively

### **Zoster-026**

- Evaluated the safety and immunogenicity of SHINGRIX when administered on a M0/M6 or M0/M12 schedule as compared to a M0/M2 schedule
- Humoral immune response of M0/M6 schedule non-inferior to M0/M2 schedule

## Additional Studies

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### **Zoster-032**

- Evaluated the safety and immunogenicity of SHINGRIX when administered subcutaneously (SC) as compared to IM
- Grade 3 solicited local symptoms (redness, swelling) in SC group higher than in IM group

### **Zoster-033**

- Evaluated the safety and immunogenicity of SHINGRIX when administered to 96 subjects with prior physician diagnosed HZ
- One arm, uncontrolled non-IND study,  $\approx$  14 months per subject
- 6 subjects reported 9 unconfirmed cases of HZ in  $\approx$  14 months
- Applicant has proposed a more robust evaluation of SHINGRIX in this population

## **Zoster-006 and Zoster-022**

### **Primary Objective, Endpoint and Analysis**

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- Primary objective – to evaluate SHINGRIX vaccine efficacy (VE) in the prevention of herpes zoster (HZ) as compared to placebo as measured by the reduction in HZ risk
- Primary endpoint – confirmed HZ cases during the study
- Analysis of the HZ VE primary endpoint evaluated the reduction in HZ risk stratified by age and region, considering the total number of HZ cases observed and time at risk



## Zoster-006 and Zoster-022 Select Common Secondary Objectives

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- VE in the prevention of overall post-herpetic neuralgia (PHN) in subjects  $\geq 70$  YOA (Zoster-022) or  $\geq 50$  YOA and within the following age groups: 50 – 59 YOA, 60 – 69 YOA and  $\geq 70$  YOA (Zoster-006)
- In subjects with confirmed HZ:
  - VE in reducing the duration of ‘severe’ worst HZ pain compared to placebo
  - VE in the reduction of HZ-related complications, hospitalization and mortality compared to placebo
  - VE in the reduction in use of pain medications compared to placebo
- SHINGRIX safety and reactogenicity

## Zoster-006 and Zoster-022 Common Study Design Elements

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- Conducted in parallel at same sites in 18 countries
- Enrolled age-eligible subjects
  - without a history of herpes zoster (HZ),
  - without prior varicella-zoster virus (VZV) or HZ vaccination
  - without immunodeficiency or immunosuppression
- Subjects randomized 1:1 receive SHINGRIX or Placebo at M0 and M2, subjects  $\geq 70$  years of age (YOA) randomized to Zoster-006 or Zoster-022 prior to randomization to treatment group

## Zoster-006 and Zoster-022 Common Study Design Elements

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- Subjects randomized 1:1 to Shingrix or placebo
- Six study visits at M0 (vaccination visit), M2 (vaccination visit), M3, M14, M26, M38 and a study conclusion contact
- Scheduled monthly contacts after M3
- Blood samples collected on all subjects at M0 and M3, and on a randomized subset at subsequent visits. Only results from the subset were provided in the application.

## Zoster-006 and Zoster-022 Common Study Design Elements

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- Solicited symptoms were recorded on a diary card by a subset of subjects Day 0-6 after each vaccination; local symptoms were injection site pain, redness and swelling, and general symptoms were fatigue, myalgia, shivering, headache, fever and GI symptoms
  - Intensity grading was as follows:
    - Non-ordinal events: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe (prevented normal activity)
    - Ordinal events: Fever (oral, axillary or tympanic)  $\geq 37.5^{\circ}$  C, Grade 3 fever  $> 39^{\circ}$  C, Grade 3 redness and swelling  $> 100$  mm diameter
- Unsolicited AEs recorded by all subjects on a diary card Day 0-29 after each vaccination
- Medically attended events (MAEs) recorded by all subjects from M0 – M8
- Serious AEs (SAEs) were recorded by all subjects from M0 – M14
- Potential immune-mediated inflammatory diseases (pIMDs), deaths and vaccine-related SAEs were recorded by all subjects throughout the study

## Zoster-006 and Zoster-022

### Common HZ-related Study Design Elements

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- Subjects with clinically suspected HZ had additional scheduled visits and assessments, including lesion sampling for VZV testing by polymerase chain reaction (PCR) assay and photographic documentation of rash, documentation of HZ-related pain on a diary card until a 4-week pain free interval achieved, and recording of HZ-related complications [including post-herpetic neuralgia (PHN)] and HZ-related activities (e.g., physician visits, concomitant medications)
- Clinically suspected HZ cases were confirmed by PCR assay assessment of lesion samples; if a case was unable to be confirmed or excluded by PCR, confirmation was by a Herpes Zoster Adjudication Committee (HZAC), comprised of five physicians with HZ expertise, which adjudicated each clinically suspected case

## **HZ and HZ-related case definitions**

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HZ definition - a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus, and other sensations) and no alternative diagnosis.

PHN definition – the presence of HZ-associated severe ‘worst’ pain persisting or appearing more than 90 days after the onset of the HZ rash.

Severe ‘worst’ pain definition - HZ-associated pain rated as 3 or greater out of 10 on a scale included in a validated, HZ-specific pain assessment questionnaire.

## Zoster-006 and Zoster-022 Study Analysis Populations

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- Total Vaccinated Cohort (TVC) – subjects who received at least one dose by product actually administered (primary analysis population for safety)
- modified Total Vaccinated Cohort (mTVC) – subjects who received two doses and did not have an episode of HZ prior to one month after Dose 2 (primary analysis population for efficacy)

## Zoster-006 Design and Analysis Specifics

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- Subjects  $\geq 50$  YOA stratified 8:5:3:1 to the following age strata: 50 – 59 YOA, 60 – 69 YOA, 70 – 79 YOA and 80+ YOA
- Approximately 58% of population, including all subjects  $\geq 70$  YOA, included in the 7-day diary card subset for reactogenicity assessment
- Success criterion for the primary endpoint met if the lower bound (LB) of the 2-sided 95% CI for HZ VE in subjects  $\geq 50$  YOA was above 25%
- Two sequential analyses
  - Final HZ Efficacy analysis – analysis of primary efficacy endpoint, analysis was event driven, with a minimum follow-up period
  - End of study analyses – conducted at same time as end of study analysis of Zoster-022, evaluation of all safety endpoints and select secondary efficacy endpoints



## Zoster-006: Subject demographics (TVC-EOS)

Characteristic	Parameter/Category	SHINGRIX N = 7695	Placebo N = 7710
Age at Dose 1 (years)	Mean	62.4	62.3
	Median	60.0	60.0
Gender (%)	Female	61.2	61.1
	Male	38.8	38.9
Ethnicity (%)	American Hispanic or Latino	11.0	11.2
	Not American Hispanic or Latino	89.0	88.8
Geographic Ancestry (%)	African/African-American	1.8	1.7
	Asian	19.1	19.1
	White – Caucasian/European	71.3	71.3
	Other*	7.8	8.0
Baseline health status (%)	At least one pre-existing medical condition	88.3	88.6

\*Other includes American Indian, Alaskan Native, Native Hawaiian or other Pacific Islander, Whites of Arabic/North African heritage and “Other”

## Zoster-006: Subjects by region (TVC – EOS)

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	SHINGRIX N = 7695 n (%)	Placebo N = 7710 n (%)
Australasia	1642 (21.3%)	1642 (21.3%)
Europe	3941 (51.2%)	3948 (51.2%)
Latin America	770 (10.0%)	777 (10.1%)
North America	1342 (17.4%)	1343 (17.4%)

N = number of subjects

n = number of subjects in a given category

% =  $n / \text{Number of subjects with available results} \times 100$

## Zoster-006: Subject disposition

Numbers and proportions of subjects available for safety analyses in the TVC (EOS analysis)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
<b>Total Enrolled Cohort</b>	8068	100%	8078	100%
<b>Total Excluded</b>	373	4.6%	368	4.6%
<b>Total Vaccinated Cohort</b>	7695	95.4%	7710	95.4%

## Zoster-006: Subject disposition

Numbers and proportions of subjects in the TVC excluded from the mTVC with reason for exclusion (Final HZ efficacy analysis)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
<b>Total Vaccinated Cohort</b>	7698	100%	7713	100%
<b>Did not receive two doses</b>	337	4.4%	277	3.6%
<b>Other reasons</b>	17	0.3%	21	0.3%
<b>Modified Total Vaccinated Cohort</b>	7344	95.4%	7415	96.1%

## Zoster-006: Reasons for withdrawal from vaccination (TVC-EOS)

Categories	SHINGRIX % N = 338	Placebo % N = 276
INVESTIGATOR Protocol violation or outside of time window	7.1%	7.2%
INVESTIGATOR Suspected HZ episode	0.9%	5.1%
INVESTIGATOR non-serious unsolicited AE	3.8%	2.2%
SUBJECT Other	10.4%	8.7%
SUBJECT non-serious solicited AE(s)	3.8%	1.4%
SUBJECT non-serious unsolicited AE	5.6%	2.2%
<b>Visit not done</b>	<b>61.5%</b>	<b>67.4%</b>

## Zoster-006: Subjects completed and withdrawn

Number and proportions of subjects vaccinated, completed and withdrawn  
(TVC - EOS analysis)

	SHINGRIX N = 7695 n (%)	Placebo N = 7710 n (%)	Total N =15405 n (%)
Subjects completed	6773 (88.0%)	6808 (88.3%)	13581 (88.2%)
Subjects withdrawn	922 (12.0%)	902 (11.7%)	1824 (11.8%)

## Zoster-006: Reasons for study withdrawal (TVC – EOS)

	SHINGRI X N= 7695		Placebo N= 7710	
Reasons for withdrawal from study	n	%	n	%
<b>Serious Adverse Event</b>	<b>227</b>	<b>2.9</b>	<b>235</b>	<b>3.0</b>
Non-Serious Adverse Event	30	0.4	18	0.2
Protocol violation	19	0.2	21	0.3
<b>Consent withdrawal (not due to an adverse event)</b>	<b>368</b>	<b>4.8</b>	<b>354</b>	<b>4.6</b>
Migrated/moved from study area	48	0.6	43	0.6
Lost to follow-up (subjects with incomplete vaccination course)	31	0.4	24	0.3
<b>Lost to follow-up (subjects with complete vaccination course)</b>	<b>152</b>	<b>2.0</b>	<b>170</b>	<b>2.2</b>
Suspected HZ Episode	0	0.0	2	0.0
Sponsor study termination	0	0.0	0	0.0
Other	47	0.6	35	0.5

## Zoster-006: VE mTVC-Final HZ efficacy analysis

**Vaccine efficacy: First or only episode of HZ during the entire study period overall (adjusted by age and region)**

	SHINGRIX				Placebo				Vaccine efficacy		
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>OVERALL</b>	7344	6	23297.0	0.3	7415	210	23170.5	9.1	<b>97.16</b>	<b>93.72</b>	<b>98.97</b>

N – number of subjects in each group

n – number of subjects having at least once confirmed HZ case

T (year) – sum of follow up period (censored at the first occurrence of a confirmed HZ case) in years

n/T (per 1000) – incidence rate of subjects reporting at least one event

LL, UL – 95% lower and upper confidence limits

VE = vaccine efficacy by the Poisson method



## Zoster-006: Vaccine efficacy (mTVC-Final HZ efficacy analysis)

**VE: First or only episode of HZ during the entire study period by age strata  
(adjusted by region)**

Age strata	SHINGRIX				Placebo				Vaccine efficacy		
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>50-59 YOA</b>	3492	3	11161.3	0.3	3525	87	11134.7	7.8	<b>96.57</b>	<b>89.62</b>	<b>99.31</b>
<b>60-69 YOA</b>	2141	2	7007.9	0.3	2166	75	6852.7	10.8	<b>97.36</b>	<b>90.14</b>	<b>99.69</b>
<b>≥70 YOA</b>	1711	1	5127.9	0.2	1724	48	5083.0	9.4	<b>97.93</b>	<b>87.91</b>	<b>99.95</b>

N = number of subjects included in each group

n = number of subjects having at least one HZ confirmed case

T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

## Zoster-006: HZ case confirmation by method (mTVC – Final HZ Efficacy analysis)

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	<b>SHINGRIX n (%)</b>	<b>Placebo n (%)</b>	<b>Total n (%)</b>
PCR	4 (66.7%)	189 (90.0%)	193 (89.4%)
HZAC	2 (33.3%)	21 (10.0%)	23 (10.6%)
Total	6 (100.0%)	210 (100.0%)	216 (100.0%)

## Zoster-006: HZ VE analysis by time (mTVC - EOS)

	SHINGRIX				Placebo				Vaccine efficacy (VE)
Time	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	VE (95% CI)
Year 1*	7340	1	7279.8	0.1	7413	62	7312.1	8.5	98.38 (90.64, 99.96)
Year 2*	7190	4	7134.6	0.6	7192	68	7092.1	9.6	94.16 (84.36, 98.45)
Year 3*	7048	0	6972.6	0.0	6998	68	6891.0	9.9	100.00 (94.52, 100.00)
Year 4*	6859	4	7330.8	0.5	6741	56	7164.2	7.8	93.07 (81.26, 98.18)

N = number of subjects included in each group

n = number of subjects having at least one HZ confirmed case

T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

\*VE adjusted by age stratum and region

## Zoster-006 “overall” PHN VE (mTVC – EOS) analysis

First or only episode of PHN during the entire study period overall  
(adjusted by age and region)

	SHINGRIX N= 7340			Placebo N= 7413			Vaccine efficacy		
	n	T(year)	n/T (per 1000)	n	T(year)	n/T (per 1000)	%	LL	UL
Overall PHN	0	28734.6	0.0	18	28943.7	0.6	100.00	77.11	100.00

N = number of subjects included in each group

n = number of subjects having at least one PHN

T (year) = sum of follow-up period (censored at the first occurrence of PHN) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

## Zoster-006: Analyses of select secondary objectives (mTVC – EOS)

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- The following secondary objectives were pre-specified for analysis in the protocol and statistical analysis plan:
  - VE in reducing the duration of ‘severe’ worst HZ pain compared to placebo in subjects with confirmed HZ
  - VE in the reduction of HZ-related complications (other than PHN, hospitalization and mortality compared to placebo in subjects with confirmed HZ
  - VE in the reduction in use of pain medications compared to placebo in subjects with confirmed HZ
- The applicant was unable to conclude on these objectives.
- In subjects with confirmed HZ, there were no HZ complications in the SHINGRIX group (out of 9 subjects at EOS). In the Placebo group there were 6 subjects (out of 254 subjects at EOS) reporting complications: HZ vasculitis (1), disseminated disease (4), ophthalmic disease (1). No subjects reported more than one complication.

## ZOSTER-006: Overall per subject incidence of any solicited symptom (TVC diary card - EOS)

Study Group	Any solicited symptom % of subjects	Any Grade 3 solicited symptom % of subjects
SHINGRIX All ages	85.2	16.4
Placebo All ages	34.2	2.6
SHINGRIX 50-59 YOA	91.5	22.7
Placebo 50-59 YOA	41	3.5
SHINGRIX 60-69 YOA	87.6	16.6
Placebo 60-69 YOA	35.2	2.6
SHINGRIX ≥70 YOA	78.6	11.6
Placebo ≥70 YOA	28.4	1.9

## ZOSTER-006: Proportions of subjects reporting any and each solicited local symptom (TVC diary card – EOS)

	SHINGRIX group % of subjects	Placebo group % of subjects
Any solicited local symptom	81.5	11.9
Any Grade 3 solicited local symptom	9.5	0.4
Pain	79.1	11.2
Grade 3 Pain	6.7	0.4
Redness	38.0	1.3
Grade 3 Redness	2.8	0.0
Swelling	26.3	1.1
Grade 3 Swelling	1.0	0.0

- The median duration of solicited local symptoms in the SHINGRIX group was 3.0 days

## ZOSTER-006: Proportions of subjects reporting any and each solicited general symptom (TVC diary card – EOS)

- The overall per subject incidence of least one any grade (Grade 3) solicited general symptom in the SHINGRIX group and Placebo group with both doses considered was 66.1% (11.4%) and 29.5% (2.4%). The median duration of the solicited general symptoms in the SHINGRIX group was 1.0 to 2.0 days.
- The numbers and proportions of subjects in each vaccination group reporting any grade and Grade 3 of each solicited general symptoms (both doses considered) is below.

	<b>SHINGRIX</b> <b>N = 4372</b> <b>n(%)</b>	<b>Placebo</b> <b>N = 4376</b> <b>n(%)</b>
Fatigue- any grade	2006 (45.9%)	728 (16.6%)
Fatigue – Grade 3	241 (5.5%)	46 (1.1%)
GI symptoms – any grade	787 (18.0%)	386 (8.8%)
GI symptoms – Grade 3	61 (1.4%)	25 (0.6%)
Headache – any grade	1714 (39.2%)	700 (16.0%)
Headache – Grade 3	157 (3.6%)	30 (0.7%)
Myalgia – any grade	2023 (46.3%)	529 (12.1%)
Myalgia – Grade 3	236 (5.4%)	31 (0.7%)
Shivering – any grade	1232 (28.2%)	259 (5.9%)
Shivering – Grade 3	192 (4.4%)	11 (0.3%)
Temperature – any grade	940 (23.5%)	132 (3.0%)
Temperature > 39° C	14 (0.3%)	6 (0.1%)



## Zoster-006: Proportions of subjects reporting SAEs during select time periods post-vaccination (TVC - EOS)

	SHINGRIX N = 7695 n (%)	Placebo N = 7710 n (%)
Subjects with at least 1 SAE reported (30-day post-vaccination period)	88 (1.1%)	97 (1.3%)
Subjects with at least 1 SAE reported (Month 0 – Month 3)	145 (1.9%)	137 (1.8%)
Subjects with at least 1 SAE reported (Month 0 – Month 14)	594 (7.7%)	590 (7.7%)

## Zoster-006: CBER Cardiac Arrhythmias SMQ Analysis

Event/ Time period	Narrow SMQ	SHINGRIX N = 7965 n (%)	Placebo N = 7710 n(%)
Unsolicited AEs (30 day post-vaccination)	Cardiac arrhythmias SMQ	14 (0.2%)	8 (0.1%)
	Supraventricular tachyarrhythmias sub-SMQ	10 (0.1%)	2 (0.0%)
Medically attended events Month 0 – Month 8	Cardiac arrhythmias SMQ	36 (0.5%)	24 (0.3%)
	Supraventricular tachyarrhythmias sub-SMQ	25 (0.3%)	14 (0.2%)
Serious AEs Month 0 – Month 14	Cardiac arrhythmias SMQ	32 (0.4%)	13 (0.2%)
	Supraventricular tachyarrhythmias sub-SMQ	22 (0.3%)	9 (0.1%)

## Zoster-006: Proportions of subjects reporting pIMDs during select time periods post-vaccination (TVC - EOS)

	SHINGRIX N=7695 n (%)	Placebo N=7710 n (%)
Subjects with at least one pIMD reported Month 0 to Month 3	13 (0.2%)	22 (0.3%)
Subjects with at least one pIMD reported Month 0 to Month 14	39 (0.5%)	59 (0.8%)
Subjects with at least one pIMD reported Whole post-vaccination follow-up period	87 (1.1%)	105 (1.4%)

## Zoster-006: Proportions of subjects who died during select time periods post-vaccination (TVC - EOS)

	<b>SHINGRIX N=7695 n (%)</b>	<b>Placebo N=7710 n (%)</b>
<b>Subjects who died 30-day post-vaccination period</b>	3 (0.0%)	3 (0.0%)
<b>Subjects who died Month 0 to Month 3</b>	7 (0.1%)	7 (0.1%)
<b>Subjects who died Month 0 to Month 14</b>	42 (0.5%)	52 (0.7%)
<b>Subjects who died Whole post-vaccination follow-up period</b>	208 (2.7%)	221 (2.9%)

## Zoster-022 Design and Analysis Specifics

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- Subjects  $\geq 70$  YOA eligible
- Stratified 3:1 into age strata: 70 – 79 YOA and  $\geq 80$  YOA
- Approximately 7% of population randomized into 7-day diary card subset
- Primary efficacy success criterion for HZ VE in subjects  $\geq 70$  YOA met if the lower bound (LB) of the 2-sided 95% CI was above 10%

## Zoster-022: Subject demographics (TVC-EOS)

Characteristic	Parameter/Category	SHINGRIX N = 6950	Placebo N = 6950
Age at Dose 1 (years)	Mean	75.6	75.6
	Median	74.0	74.0
Gender (%)	Female	54.5	55.2
	Male	45.5	44.8
Ethnicity (%)	American Hispanic or Latino	8.3	8.2
	Not American Hispanic or Latino	91.7	91.8
Geographic Ancestry (%)	African/African-American	1.1	1.0
	Asian	17.5	17.6
	White – Caucasian/European	76.4	76.3
	Other*	5.0	5.2
Baseline Health Status (%)	At least one pre-existing medical condition	94.9	95.4

\*Other includes American Indian, Alaskan Native, Native Hawaiian or other Pacific Islander, Whites of Arabic/North African heritage and “Other”

## Zoster-022: Subjects by region (TVC-EOS)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)
Australasia	1317 (18.9%)	1319 (19.0%)
Europe	3758 (54.1%)	3753 (54.0%)
Latin America	537 (7.7%)	538 (7.7%)
North America	1338 (19.3%)	1340 (19.3%)

## Zoster-022: Subject disposition

Numbers and proportions of subjects available for safety analyses in the TVC (EOS analysis)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
<b>Total Enrolled Cohort</b>	7408	100%	7406	100%
<b>Total Excluded</b>	458	6.2%	456	6.2%
<b>Total Vaccinated Cohort</b>	6950	93.8%	6950	93.8%



## Zoster-022: Subject disposition

Numbers and proportions of subjects in the TVC excluded from the mTVC with reason for exclusion

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
<b>Total Vaccinated Cohort</b>	<b>6950</b>	<b>100%</b>	<b>6950</b>	<b>100%</b>
<b>Did not receive two doses</b>	390	5.6%	305	4.4%
<b>Other reasons</b>	19	0.3%	23	0.3%
<b>Modified Total Vaccinated Cohort</b>	<b>6541</b>	<b>94.3%</b>	<b>6622</b>	<b>95.2%</b>

% = percentage of subjects in the considered cohort relative to the Total Vaccinated Cohort

## Zoster-022: Reasons for withdrawal from vaccination (TVC – EOS)

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Categories	SHINGRIX N = 392	Placebo N = 305
GSK decision	2.3%	2.3%
INVESTIGATOR: Protocol violation or outside of time window	10.2%	9.5%
INVESTIGATOR: SAE or pIMD	1.5%	3.3%
INVESTIGATOR: Suspected HZ episode	0.8%	3.9%
INVESTIGATOR: Non-serious unsolicited AE	3.1%	3.0%
SUBJECT: Other	7.1%	6.9%
SUBJECT: Non-serious unsolicited AE	8.7%	5.6%
<b>Visit not done</b>	<b>65.6%</b>	<b>62.3%</b>

## Zoster-022: Subjects completed and withdrawn

Number and proportions of subjects vaccinated, completed and withdrawn (TVC - EOS)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)	Total N = 13900 n (%)
<b>Subjects completed</b>	5770 (83.0%)	5760 (82.9%)	11530 (82.9%)
<b>Subjects withdrawn</b>	1180 (17.0%)	1189 (17.1%)	2639 (17.0%)

## Zoster-022: Reasons for study withdrawal (TVC – EOS)

	SHINGRIX N= 6950		Placebo N= 6950	
Reasons for withdrawal from study	n	%	n	%
<b>Serious Adverse Event</b>	<b>456</b>	<b>6.6</b>	<b>487</b>	<b>7.0</b>
Non-Serious Adverse Event	47	0.7	15	0.2
Protocol violation	6	0.1	8	0.1
<b>Consent withdrawal (not due to an adverse event)</b>	<b>387</b>	<b>5.6</b>	<b>396</b>	<b>5.7</b>
Migrated/moved from study area	51	0.7	46	0.7
Lost to follow-up (subjects with incomplete vaccination course)	8	0.1	18	0.3
Lost to follow-up (subjects with complete vaccination course)	115	1.7	115	1.7
Suspected HZ Episode	2.0	0	2	0
Other	108	1.6	102	1.5

## Zoster-022: Vaccine Efficacy (mTVC-EOS)

**VE: First or only episode of HZ during the entire study period overall  
(adjusted by age and region)**

	SHINGRIX				Placebo				VE		
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>≥70 YOA</b>	6541	23	24405.1	0.9	6622	223	24167.8	9.2	<b>89.79</b>	<b>84.29</b>	<b>93.66</b>

N = number of subjects included in each group

n = number of subjects having at least one HZ confirmed case

T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

VE = Vaccine efficacy (Poisson method)

## Zoster-022: Vaccine efficacy by age strata (mTVC - EOS)

**VE: First or only episode of HZ during the entire study period by age strata  
(adjusted by region)**

	SHINGRIX				Placebo				Vaccine efficacy		
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>70-79 YOA</b>	5114	17	19346.5	0.9	5189	169	19247.5	8.8	<b>90.02</b>	<b>83.54</b>	<b>94.32</b>
<b>≥ 80 YOA</b>	1427	6	5058.5	1.2	1443	54	4920.3	11.0	<b>89.08</b>	<b>74.65</b>	<b>96.16</b>

N = number of subjects included in each group

n = number of subjects having at least one HZ confirmed case

T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

LL, UL = 95% Lower and Upper confidence limits

VE = Vaccine Efficacy (Poisson method)

## Zoster-022: HZ case confirmation by method (mTVC – EOS)

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	<b>SHINGRIX n (%)</b>	<b>Placebo n (%)</b>	<b>Total n (%)</b>
PCR	19 (82.6%)	208 (93.3%)	227 (92.3%)
HZAC	4 (17.4%)	15 (6.7%)	19 (7.7%)
Total	23 (100.0%)	223 (100.0%)	246 (100.0%)

## Zoster-022: HZ VE analysis by time (mTVC - EOS)

	SHINGRIX				Placebo				Vaccine efficacy (VE)
Time	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	VE (95% CI)
<b>Year 1*</b>	6541	2	6464.7	0.3	6622	68	6511.2	10.4	<b>97.04 (88.88, 99.65)</b>
<b>Year 2*</b>	6379	6	6281.0	1.0	6372	68	6240.4	10.9	<b>91.26 (79.97, 96.90)</b>
<b>Year 3*</b>	6137	9	6043.5	1.5	6076	48	5943.0	8.1	<b>81.55 (61.97, 92.04)</b>
<b>Year 4*</b>	5898	6	5615.9	1.1	5776	39	5473.2	7.1	<b>85.07 (64.47, 94.83)</b>

N = number of subjects included in each group

n = number of subjects having at least one HZ confirmed case

T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

\*VE adjusted by age stratum and region



# Zoster-022 “overall” PHN VE analysis (mTVC – EOS)

**First or only episode of PHN during the entire study period overall  
(adjusted by age and region)**

	SHINGRIX				Placebo				VE		
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>Overall</b>	6541	4	24436.9	0.2	6622	28	24601.4	1.1	<b>85.49</b>	<b>58.52</b>	<b>96.30</b>

N = number of subjects included in each group

n = number of subjects having at least one PHN

T (year) = sum of follow-up period (censored at the first occurrence of PHN) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

LL, UL = 95% Lower and Upper confidence limits

VE = Vaccine Efficacy (Poisson method)

## Zoster-022: Analyses of select secondary objectives (mTVC – EOS)

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- The following secondary objectives were pre-specified for analysis in the protocol and statistical analysis plan:
  - VE in reducing the duration of ‘severe’ worst HZ pain compared to placebo in subjects with confirmed HZ – unable to conclude
  - VE in the reduction of HZ-related complications (other than PHN), hospitalizations and mortality compared to placebo in subjects with confirmed HZ – unable to conclude
  - VE in the reduction in use of pain medications compared to placebo in subjects with confirmed HZ – concluded with a VE: 39.60% (95% CI: 10.79%, 64.75%)
- In subjects with a confirmed HZ episode, 1 of 23 (4.3%) subjects in the SHINGRIX group and 10 of 223 (4.5%) of subjects in the Placebo group reported at least one HZ-related complication
  - In the SHINGRIX group one subject reported ophthalmic HZ
  - In the Placebo group the following complications were reported: disseminated disease (2), ophthalmic disease (6) and neurologic disease (3)

## ZOSTER-022: Overall per subject incidence of any solicited symptom (TVC diary card - EOS)

Study Group	Any solicited symptom % of subjects	Any Grade 3 solicited symptom % of subjects
SHINGRIX All ages	79.0	11.9
Placebo All ages	29.5	2.0
SHINGRIX 70-79 YOA	82.3	11.7
Placebo 70-79 YOA	27.8	0.7
SHINGRIX ≥80 YOA	74.8	12.2
Placebo ≥80 YOA	31.7	3.6

## ZOSTER-022: Proportions of subjects reporting any and each solicited local symptom by vaccination group (TVC diary card – EOS)

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	SHINGRIX group % of subjects	Placebo group % of subjects
Any solicited local symptom	74.1	9.9
Any Grade 3 solicited local symptom	8.5	0.2
Pain	68.7	8.5
Grade 3 Pain	4.4	0.2
Redness	39.2	1.0
Grade 3 Redness	4.0	0.0
Swelling	22.6	0.4
Grade 3 Swelling	1.6	0.0

- The median duration of solicited local symptoms in the SHINGRIX group was 2.0 to 3.0 days.

## ZOSTER-022: Proportions of subjects reporting any and each solicited general symptom by vaccination group (TVC diary card – EOS)

- The overall per subject incidence of least one any grade (Grade 3) solicited general symptom in the SHINGRIX group and Placebo group with both doses considered was 53.0% (6.0%) and 25.1% (2.0%). The median duration of the solicited general symptoms in the SHINGRIX group was 1.0 to 2.0 days.
- The numbers and proportions of subjects in each vaccination group reporting any grade and Grade 3 of each solicited general symptoms (both doses considered) is below.

	SHINGRIX N = 504 n (%)	Placebo N = 505 n (%)
Fatigue – any grade	166 (32.9%)	77 (15.2%)
Fatigue – Grade 3	16 (3.2%)	4 (0.8%)
Myalgia – any grade	157 (31.2%)	41 (8.1%)
Myalgia – Grade 3	12 (2.4%)	2 (0.4%)
Headache – any grade	124 (24.6%)	55 (10.9%)
Headache – Grade 3	5 (1.0%)	4 (0.8%)
Shivering – any grade	75 (14.9%)	22 (4.4%)
Shivering – Grade 3	6 (1.2%)	2 (0.4%)
Temperature – any grade	62 (12.3%)	13 (2.6%)
Temperature – Grade 3	0 (0.0%)	2 (0.4%)
Gastrointestinal symptoms – any grade	55 (10.9%)	40 (7.9%)
Gastrointestinal symptoms – Grade 3	5 (1.0%)	2 (0.4%)

## Zoster-022: Proportions of subjects reporting SAEs during select time periods post-vaccination (TVC - EOS)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)
Subjects with at least one serious adverse event reported in the 30-day post-vaccination period	157 (2.3%)	158 (2.3%)
Subjects with at least one serious adverse event reported Month 0 to Month 3	248 (3.6%)	228 (3.3%)
Subjects with at least one serious adverse event reported Month 0 to Month 14	891 (12.8%)	939 (13.5%)

## Zoster-022: Proportions of subjects reporting pIMDs during select time periods post-vaccination (TVC - EOS)

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	<b>SHINGRIX</b> <b>N=6950</b> <b>n (%)</b>	<b>Placebo</b> <b>N=6950</b> <b>n (%)</b>
<b>Subjects with at least one potential immune-mediated disease reported Month 0 to Month 3</b>	19 (0.3%)	15 (0.2%)
<b>Subjects with at least one potential immune-mediated disease reported Month 0 to Month 14</b>	52 (0.7%)	47 (0.7%)
<b>Subjects with at least one potential immune-mediated disease reported Whole post-vaccination follow-up period</b>	92 (1.3%)	97 (1.4%)

## Zoster-022: Proportions of subjects who died during select time periods post-vaccination (TVC - EOS)

	<b>SHINGRIX N=6950 n (%)</b>	<b>Placebo N=6950 n (%)</b>
<b>Subjects who died 30-day post-vaccination period</b>	3 (0.0%)	5 (0.1%)
<b>Subjects who died Month 0 to Month 3</b>	7 (0.1%)	11 (0.2%)
<b>Subjects who died Month 0 to Month 14</b>	71 (1.0%)	82 (1.2%)
<b>Subjects who died Whole post-vaccination follow-up period</b>	426 (6.1%)	461 (6.6%)



## Integrated Summary of Safety – Key Points

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- **Main pooling analysis**
  - TVCs of Zoster-006 and Zoster-022, SHINGRIX N = 14645, Placebo N = 14660
- **Broader pooling analysis**
  - N = 15493 subjects who received SHINGRIX, including 14645 subjects from the main pooling and 848 subjects who received at least one dose of SHINGRIX in other Phase 2 and 3 studies
  - Qualifications for study and subject inclusion in the broader pooling: SHINGRIX was administered IM at M0/M2 and study completed at the data lock point for safety analysis with at least one year of safety follow-up post-vaccination.
  - For the broader pooling analysis, only SAEs, pIMDs and deaths were analyzed, no safety signals were identified after review of the safety data from the 848 subjects included in the broader, but not the main, pooling.

## Main pooling: Proportions of subjects reporting SAEs during select time periods post-vaccination (TVC)

	SHINGRIX N = 14645 n (%)	Placebo N = 14660 n (%)
<b>Subjects with at least one serious adverse event reported from the first administered dose up to 30 days post last vaccination period</b>	342 (2.3%)	327 (2.2%)
<b>Subjects with at least one serious adverse event reported from the first administered dose up to 365 days post last vaccination period</b>	1482 (10.1%)	1525 (10.4%)

## Main pooling: Proportions of subjects reporting common SAEs by PT during 365 post last vaccination period (TVC)

MedDRA Preferred Term	SHINGRIX N = 14645 %	Placebo N = 14660 %
Pneumonia	83 (0.6%)	66 (0.5%)
Atrial fibrillation	55 (0.4%)	58 (0.4%)
Myocardial infarction	40 (0.3%)	42 (0.3%)
Coronary artery disease	37 (0.3%)	38 (0.3%)
Cerebrovascular accident	39 (0.3%)	27 (0.2%)
Cardiac failure	34 (0.2%)	43 (0.3%)

## Main pooling: CNS Vascular Disorders and Lower respiratory tract and lung infections reported as MAEs - D0 up to D244 (M0 – M8)

MedDRA Search Terms*	SHINGRIX N = 14645 n (%)	Placebo N = 14660 n (%)
CNS vascular disorders SMQ	92 (0.63%)	90 (0.61%)
CNS hemorrhages and cerebrovascular conditions	92 (0.63%)	90 (0.61%)
Ischemic CNS vascular conditions	80 (0.55%)	73 (0.50%)
Hemorrhagic CNS vascular conditions	37 (0.25%)	34 (0.23%)
Lower Respiratory Tract and Lung Infections (Higher Level Term)	429 (2.93%)	428 (2.92%)

\*SMQ analysis using MedDRA Version 18.0

## Main pooling: SAEs judged related by investigator

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- 15 subjects in each treatment group experienced SAEs determined related by investigator (no events judged related to vaccination by applicant)
- SAEs judged related by investigators in SHINGRIX group: **lymphadenitis, administration site erythema/administration site pain/ chills/pyrexia**, immune thrombocytopenic purpura, acute myocardial infarction, ulcerative colitis, acute pancreatitis, allergic granulomatous angiitis, arthritis bacterial, erysipelas, herpes zoster oticus, neutropenic sepsis/acute myeloid leukemia, musculoskeletal chest pain, Guillain-Barre syndrome, nervous system disorder, and eczema
- SAEs judged related by investigators in the Placebo group: syncope (2 subjects), hypotension, immune thrombocytopenic purpura, polymyalgia rheumatica, rheumatoid arthritis (2 subjects), gastric adenocarcinoma, cerebral infarction, cerebrovascular accident, Guillain-Barre syndrome, IVth nerve paralysis, loss of consciousness, mononeuritis, glomerulonephritis, and neurosensory deafness

## Main pooling: Proportions of subjects reporting pIMDs during select time periods post-vaccination (TVC)

	<b>SHINGRIX N = 14645</b>	<b>Placebo N = 14660</b>
<b>Subjects with <math>\geq 1</math> potential Immune Mediated Diseases reported from first vaccination up to 30 days post last vaccination</b>	30 (0.2%)	30 (0.2%)
<b>Subjects with <math>\geq 1</math> potential Immune Mediated Diseases reported from first vaccination up to 365 days post last vaccination</b>	90 (0.6%)	105 (0.7%)
<b>Subjects with <math>\geq 1</math> potential Immune Mediated Diseases reported during the whole post-vaccination follow-up period</b>	179 (1.2%)	202 (1.4%)

## **Main pooling: Non-serious pIMDs determined related by investigator**

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- Shingrix group: rheumatoid arthritis (2 subjects), reactive arthritis, psoriasis (exacerbation, 2 subjects), myasthenic syndrome, thrombocytopenia, exfoliative dermatitis, polymyalgia rheumatica, alopecia areata and hypersensitivity vasculitis
- Placebo group: polymyalgia rheumatica (2 subjects), Sjogren's syndrome (2 subjects), psoriasis, erythema nodosum, Behcet's syndrome, ulcerative colitis, inclusion body myositis and uveitis
- No pIMDS judged related to vaccination by applicant

## Main pooling: Proportions of subjects who died during select time periods post-vaccination (TVC)

	<b>SHINGRIX N=14645 n (%)</b>	<b>Placebo N=14660 n (%)</b>
<b>Subjects who died from first dose up to 30-days post last vaccination period</b>	6.0 (0.0%)	8 (0.1%)
<b>Subjects who died from first dose up to 365 days post last vaccination period</b>	113 (0.8%)	132 (0.9%)
<b>Subjects who died whole post-vaccination follow-up period</b>	634 (4.3%)	682 (4.7%)



## Main pooling: Unsolicited AEs during the 30-day post vaccination period

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**Adverse events reported by > 1.0% of subjects in the TVC of the SHINGRIX group, with a higher frequency in the SHINGRIX as compared to Placebo group**

Adverse Event	SHINGRIX group %	PLACEBO group %
IS pruritus	2.16	0.24
Malaise	1.73	0.29
Pain	1.39	0.23
IS warmth	1.02	0.03
Dizziness	1.24	0.77
Upper respiratory tract infection	1.58	1.24
Arthralgia	1.72	1.17
Pain in extremity	1.06	0.73
Nausea	1.35	0.47

The following adverse events (AEs) by specific PT (non-injection site and not listed on the 7 day diary card) were reported by < 1.0% but at least 30 subject total of the subjects in the SHINGRIX group, and had frequencies higher in SHINGRIX as compared to the Placebo group: influenza like illness, asthenia, feeling hot, feeling cold, upper respiratory tract infection, respiratory tract infection, decreased appetite, somnolence, lethargy, insomnia, hyperhidrosis and gout.

## **Main pooling: Select Events (Vaccine-associated events of interest)**

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- Anaphylaxis
  - One subject reporting in SHINGRIX group, judged not anaphylaxis by Brighton criteria
- Guillain Barre syndrome
  - Two subjects reported GBS during the year post-vaccination, one in the SHINGRIX group (181 days after Dose 2) and one in the Placebo group (39 days after Dose 2)

## Main pooling: Select Events

Event	Notes
Osteonecrosis*	5 subjects and 0 subjects reporting in SHINGRIX and Placebo groups in year post-vaccination
Gout and gouty arthritis*	27 and 8 subjects reporting in SHINGRIX and Placebo groups - 30 day post-vaccination period
Arthralgia*	1.72% and 1.17% reporting in SHINGRIX and Placebo groups – 30 day post-vaccination period

\* Events addressed in Pharmacovigilance Plan

## Main pooling: Select Events

Event	Notes
Optic ischemic neuropathy*	3 subjects SHINGRIX group, 0 subjects in Placebo group reporting within 50 days post-vaccination
Convulsions*	8 and 1 subjects in the SHINGRIX and Placebo groups - 30-day post vaccination period in narrow SMQ of Convulsions
Supraventricular tachyarrhythmias*	Imbalance noted in Cardiac arrhythmias and Supraventricular tachyarrhythmia SMQs in Zoster-006 but not in Zoster-022 or main pooling
Amyotrophic lateral sclerosis	3 subjects in SHINGRIX group and 1 in Placebo group reporting in year post-vaccination, incidence $\approx$ 2/100K person years

\* Events addressed in Pharmacovigilance Plan

## Integrated Summary of Efficacy - Objectives

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- Co-primary objectives for the pooled analysis of Zoster-006 and Zoster-022:
  - Consolidate VE estimation in the prevention of HZ in subjects  $\geq 70$  YOA across both studies
  - Evaluate VE in prevention of overall PHN in subjects  $\geq 70$  YOA across both studies: Success criterion for PHN VE was that the LB of the 95% CI  $> 0\%$
- Select secondary objective for the pooled analysis of Zoster-006 and Zoster-022:
  - Evaluate VE in the prevention of PHN in subjects  $\geq 50$  YOA with confirmed HZ across both studies

## Integrated Summary of Efficacy – Pooled HZ VE Results in Subjects ≥ 70 YOA

First or only episode of HZ during the entire study period by study and by age stratum and overall using Poisson method (mTVC, subjects ≥ 70 YOA, pooled 006/022)

	SHINGRIX				Placebo				VE		
Age Strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>70-79 YOA*</b>	6468	19	24410.9	0.8	6554	216	24262.8	8.9	<b>91.27</b>	<b>86.04</b>	<b>94.85</b>
<b>≥80 YOA*</b>	1782	6	6314.6	1.0	1792	68	6151.9	11.1	<b>91.37</b>	<b>80.22</b>	<b>96.94</b>
<b>≥ 70 YOA**</b>	8250	25	30725.5	0.8	8346	284	30414.7	9.3	<b>91.30</b>	<b>86.88</b>	<b>94.46</b>

N = number of subjects included in each group

n = number of subjects having at least one confirmed HZ episode

T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

LL, UL = 95% Lower and Upper confidence limits

VE (%) = Vaccine Efficacy (Poisson method)

\* = VE adjusted by region

\*\* = VE adjusted by age stratum and region

# Integrated Summary of Efficacy – Pooled PHN VE Results in Subjects ≥ 70 YOA

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**First or only episode of PHN during the entire study period overall using Poisson method  
(mTVC, subjects ≥ 70 YOA, pooled 006/022)**

	SHINGRIX				Placebo				VE		
Age Strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
<b>≥ 70 YOA**</b>	8250	4	30760.3	0.1	8346	36	30942.0	1.2	<b>88.78</b>	<b>68.70</b>	<b>97.10</b>

N = number of subjects included in each group

n = number of subjects having at least one PHN

T (year) = sum of follow-up period (censored at the first occurrence of PHN) expressed in years

n/T (per 1000)= Incidence rate of subjects reporting at least one event

LL, UL = 95% Lower and Upper confidence limits

VE = Vaccine Efficacy (Poisson method)

\*\* = VE adjusted by age stratum and region

# Integrated Summary of Efficacy – PHN VE in Subjects $\geq 50$ YOA with Confirmed HZ

Reduction in PHN incidence in subjects with a confirmed HZ episode overall (mTVC, subjects  $\geq 50$  YOA, pooled 006/022)

	SHINGRIX			Placebo			VE
	N	n	% (95% CI)	N	n	% (95% CI)	% (95% CI)
<b><math>\geq 50</math> YOA*</b>	32	4	12.50 (3.51, 28.99)	477	46	9.64 (7.15, 12.65)	<b>0.29 (-161.53, 65.57)</b>

N = number of subjects with confirmed HZ episode  
n = number of subjects reporting at least one event in each group  
LL, UL = 95% Lower and Upper confidence limits  
\* = VE adjusted by age strata



## SUMMARY - Efficacy

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- The clinical endpoint studies confirmed SHINGRIX HZ VE
- HZ VE appears durable up to Year 4
- The value of SHINGRIX with regard to prevention of PHN appears to be attributable to the prevention of HZ

## SUMMARY - Safety

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- Local and general reactogenicity and Grade 3 reactogenicity were commonly reported after SHINGRIX vaccination
- While common in all age groups, reactogenicity was higher in younger, as compared to older, subjects
- Overall, SAEs, deaths and pIMDs were reported in similar proportions of subjects during time periods post-vaccination
- Continued pharmacovigilance is planned to further inform the safety profile of SHINGRIX