Vaccines and Related Biological Products Advisory Committee Meeting

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FDA Briefing Document

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

Applicant:

GlaxoSmithKline Biologicals

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1.0 General Information

1.1 Product: Zoster Vaccine Recombinant, Adjuvanted (SHINGRIX) is a suspension for intramuscular injection consisting of a lyophilized recombinant varicella zoster virus (VZV) glycoprotein E (gE) antigen that is reconstituted at the time of use with $AS01_B$ adjuvant suspension. The antigen is a purified truncated form of the VZV gE expressed in Chinese Hamster Ovary cells. The $AS01_B$ adjuvant suspension is composed of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and a saponin molecule (QS-21) purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation consisting of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution.

1.2 Proposed Indication: (GSK proposal) - *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.*

1.3 Dosage and Administration: SHINGRIX is supplied as a vial of lyophilized recombinant VZV gE antigen, which is reconstituted at the time of use with the accompanying vial of $AS01_B$ adjuvant suspension. After reconstitution, each 0.5-mL dose of SHINGRIX is formulated to contain 50 µg of the recombinant VZV gE, 50 µg of MPL, and 50 µg of QS-21. The vaccine is administered intramuscularly (IM) in two doses at Month 0 (M0) and M2.

2.0 Executive Summary

The applicant, GlaxoSmithKline (GSK), submitted a Biologics License Application (BLA) on 21-OCT-2016 to support licensure of SHINGRIX for the prevention of herpes zoster (HZ). The BLA included the results of two randomized, placebo-controlled, observer-blind clinical endpoint studies Zoster-006 (ZOE-50) which enrolled subjects ≥ 50 years of age (YOA), and Zoster-022 (ZOE-70) which enrolled subjects ≥ 70 YOA. The applicant submitted results of additional studies, including a study of the safety and immunogenicity of SHINGRIX when administered concomitantly with quadrivalent influenza vaccine (Zoster-004), a study of the safety and immunogenicity of SHINGRIX when administered on a M0/M6 or M0/M12 schedule as compared to a M0/M2 schedule (Zoster-026), an uncontrolled study of the safety and immunogenicity of SHINGRIX when administered to subjects with prior HZ (Zoster-033), a study comparing the safety and immunogenicity of SHINGRIX when administered IM as compared to subcutaneously (Zoster-032), and interim safety and active phase (M0 – M3) immunogenicity data from a lot-to-lot consistency study (Zoster-007).

Zoster-006 and Zoster-022 had similar study designs and were conducted in parallel. Subjects ≥ 70 YOA were randomized to Zoster-006 or Zoster-022 prior to randomization to treatment group. These pivotal clinical endpoint trials were performed at the same study sites in eighteen countries (including the US) with a treatment group randomization ratio of 1:1 (SHINGRIX:saline placebo). Subjects in Zoster-006 were stratified 8:5:3:1 by age as follows: 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA. Subjects in Zoster-022 were stratified 3:1 by age as follows; 70 – 79 and ≥ 80 YOA.

The primary objectives of Zoster-006 and Zoster-022 were to evaluate SHINGRIX vaccine efficacy (VE) in the prevention of HZ compared to placebo as measured by the reduction in HZ risk; the primary endpoints for both studies were confirmed HZ cases. The co-primary objectives for the pooled analysis for both studies were to consolidate HZ VE in subjects ≥ 70 YOA across both studies, and to evaluate SHINGRIX VE in the prevention of "overall" post-herpetic neuralgia [overall reduction in post-herpetic neuralgia (PHN) risk independent of the occurrence of HZ] compared to placebo in subjects ≥ 70 YOA across both studies. Evaluation of the safety and reactogenicity of SHINGRIX were secondary objectives of Zoster-006 and Zoster-022, and humoral immune responses and persistence of these responses to SHINGRIX vaccination were exploratory objectives in these studies. The conditions for the analyses of Zoster-006 and Zoster-022 were in part event-driven, based on the number of confirmed HZ and PHN cases in the modified Total Vaccinated Cohort (mTVC) which excluded subjects who did not receive two doses or who developed HZ prior to one month after Dose 2, as well as a minimum follow-up period to ensure adequate safety and efficacy data collection.

Both studies enrolled age-eligible subjects without a history of HZ, HZ or varicella vaccination or confirmed or suspected immunodeficiency or immunocompromised status due to disease or therapy. Subjects received two doses of SHINGRIX or placebo IM at M0 and M2 (Visits 1 and 2). There were four additional scheduled visits and monthly contacts to collect safety information and to document the occurrence of HZ. Additional visits were scheduled should a case of clinically suspected HZ occur. Cases of HZ were confirmed in a hierarchical manner; while all cases were adjudicated by an expert Herpes Zoster Adjudication Committee (HZAC), the HZAC ruling served as final case confirmation only if a case could not be confirmed or excluded by polymerase chain reaction (PCR) testing of lesion samples.

Safety monitoring for Zoster-006 and Zoster-022 included solicited local [injection site (IS) pain, swelling and redness] and general (fever, headache, myalgia, GI symptoms, shivering and fatigue) signs and symptoms recorded on a diary card by a randomized subset of subjects for seven days (Days 0 – 6) following each vaccination; unsolicited adverse events (AEs) recorded on a diary card by all subjects for 30 days following each vaccination; serious adverse events (SAEs) collected on all subjects from M0 – M14; and deaths, related SAEs and potential immune-mediated inflammatory diseases (pIMDs) collected for the duration of the studies. Safety results were analyzed on the Total Vaccinated Cohort (TVC), which consisted of subjects receiving at least one dose in accordance with the product actually received.

Zoster-006 results: At the Final HZ efficacy analysis, there were 6 cases of confirmed HZ recorded in the mTVC of the SHINGRIX group (N= 7,344) and 210 cases of confirmed HZ recorded in the mTVC of the Placebo group (N = 7,415) for a HZ incidence rate of 0.3 per 1,000 person-years (PY) in the SHINGRIX group and 9.1 per 1,000 PY in the Placebo group. The breakdown of HZ case confirmation was 89.6% by PCR and 10.6% by HZAC adjudication. The primary endpoint of Zoster-006 was met as the lower bound (LB) of the two-sided 95% confidence interval (CI) of SHINGRIX HZ VE was above 25% [VE: 97.16% (95% CI: 93.72%, 98.97%)]. A secondary objective of Zoster-006 was to evaluate HZ VE by age strata; the study

was powered to demonstrate HZ VE for the age strata 50 – 59 and 60 – 69 YOA and the objective met if the LB of the 95% CI for the point estimate of HZ VE for these strata were > 10%. The objective was met as HZ VE was 96.57% (95% CI: 89.62%, 99.31%) for subjects 50 – 59 YOA and 97.36% (95% CI: 90.14%, 99.69%) for subjects 60 – 69 YOA. There were 18 cases of PHN reported in the Placebo group and none reported in the SHINGRIX group at the Final HZ efficacy analysis for an overall PHN VE of 100.00% (95% CI: 77.11%, 100.00%).

The TVC (SHINGRIX group N = 7695, Placebo group N = 7,710) was the primary population for the evaluation of safety. Of subjects in the TVC, 57.9% (SHINGRIX group N = 4,457, Placebo group N = 4,464) were randomized to the 7-day diary card subset [stratified in an approximately 3:3:4 ratio by age (50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA, respectively)] and recorded solicited symptoms on a diary card on Days 0 – 6 following each vaccination. IS pain was the most commonly reported solicited local symptom after SHINGRIX administration; overall by subject any grade (Grade 3/severe) IS pain was reported by 79.1% (6.7%) and 11.2% (0.4%) of subjects in the SHINGRIX and Placebo groups, respectively. Overall by subject, any grade (Grade 3) IS redness and swelling were reported by 38.0% (2.8%) and 26.3% (1.0%) of subjects in the SHINGRIX group, respectively; Grade 3 redness and swelling were not reported by subjects in the Placebo group. The most commonly reported solicited general symptoms (any grade) overall by subject were myalgia, fatigue and headache reported by 46.3%, 45.9% and 39.2% of subjects in the SHINGRIX group and 12.1%, 16.6% and 16.0% of subjects in the Placebo group, respectively. The most commonly reported Grade 3 solicited general symptoms in the SHINGRIX group overall by subject were fatigue (5.5%), myalgia (5.4%) and shivering (4.4%); these events were reported by 1.1%, 0.7% and 0.3% of subjects in the Placebo group, respectively. Overall by subject, any grade (Grade 3) temperature was reported by 23.5% (0.3%) of subjects in the SHINGRIX group and 3.0% (0.1%) of subjects in the Placebo group. The approximate median duration of solicited local and solicited general symptoms reported after SHINGRIX administration was 3 days and 1 – 2 days, respectively. The proportions of subjects in the SHINGRIX group reporting solicited symptoms generally decreased with increasing age.

There were no clinically significant differences between treatment groups in the proportions of subjects in the TVC who died or reported pIMDs during select time points post-vaccination and during the whole post-vaccination period, and no differences noted with respect to the nature of the pIMDs or fatal SAEs. There were no clinically significant differences between treatment groups in the proportions of subjects in the TVC who reported SAEs from M0 – M14, or at other select time periods, or with respect to the nature of the SAEs reported. No deaths were judged related to vaccination by the applicant or the investigators. No SAEs or pIMDs were judged related to vaccination by the applicant. SAEs judged related to vaccination by the investigator were reported by three subjects [reporting the specific preferred terms (PTs) of idiopathic thrombocytopenic purpura (also a pIMD), nervous system disorder and musculoskeletal chest pain] in the SHINGRIX group and seven subjects in the Placebo group. The SAEs reported in the SHINGRIX group judged related to vaccination by the investigator were reviewed by CBER; while causal association could not be fully ruled out, it also could not be ascribed because there

were alternative etiologies, indeterminate time lines, lack of concerning temporal association, and/or lack of clustering of similar events temporally associated with vaccination. Eight subjects in the SHINGRIX and 12 in the Placebo group reported pIMDs judged as related to vaccination by the investigator. The related pIMDs reported in the SHINGRIX group were reviewed by CBER; while causal association could not be fully ruled out, it also could not be ascribed because there were alternative etiologies, indeterminate time lines, lack of concerning temporal association, and/or lack of clustering of similar events temporally associated with vaccination.

Zoster-022 results: At the end of study (EOS) analysis, there were 23 cases of confirmed HZ recorded in the mTVC of the SHINGRIX group (N = 6,541) and 223 recorded in the mTVC of the Placebo group (N = 6,622) for an HZ incidence rate of 0.9 per 1,000 PY in the SHINGRIX group and 9.2 per 1,000 PY in the Placebo group. The breakdown of HZ case confirmation was 92.3% by PCR and 7.7% by HZAC adjudication. The primary endpoint of Zoster-022 was met, as the LB of the two-sided 95% CI of SHINGRIX HZ VE was above 10% [VE: 89.79% (95% CI: 84.29%, 93.66%)]. In the mTVC, there were 28 cases of PHN reported in the Placebo group and 4 reported in the SHINGRIX group for an overall PHN VE of 85.49% (95% CI: 58.52%, 96.30%).

The TVC (N = 6,950 in both treatment groups) was the primary population for the evaluation of safety. Of subjects in the TVC, 7.4% (SHINGRIX group N = 512, Placebo group N = 513) were randomized to the 7-day diary card subset and recorded solicited symptoms on a diary card on Days 0 – 6 following each vaccination. Pain was the most commonly reported solicited local symptom after SHINGRIX administration; overall by subject any grade (Grade 3) was reported by 68.7% (4.4%) of subjects in the SHINGRIX group and 8.5% (0.5%) of subjects in the Placebo group. Overall by subject, any grade (Grade 3) IS redness and swelling were reported by 39.2% (4.0%) and 22.6% (1.6%) of subjects in the SHINGRIX group, respectively. Any grade and Grade 3 redness and swelling were reported by ≤ 1.0% of subjects in the Placebo group. The most commonly reported solicited general symptoms of any grade (Grade 3) reported after SHINGRIX administration overall by subject were fatigue and myalgia reported by 32.9% (3.2%) and 31.2% (2.4%) of subjects in the SHINGRIX group and 15.2% (0.8%) and 8.1% (0.4%) of subjects in the Placebo group. Overall by subject, any grade (Grade 3) temperature was reported by 12.3% (0.0%) of subjects in the SHINGRIX and 2.6% (0.4%) of subjects in the Placebo groups. The approximate median durations of solicited local and solicited general symptoms reported after SHINGRIX administration were 2.0 – 3.0 days and 1.0 – 2.0 days, respectively.

There were no clinically significant differences between treatment groups for the proportions of subjects in the TVC who died or reported pIMDs during select time points post-vaccination and during the whole post-vaccination period, and no clinically significant differences with respect to the nature of the pIMDs or SAEs with fatal outcome. There were no clinically significant differences between treatment groups for the proportions of subjects in the TVC who reported SAEs from M0 – M14, or at other select time periods, or for the nature of the SAEs reported. One death in the SHINGRIX group was reported as vaccine-related by the investigator but not

the applicant. The subject was a 90 YO male with 10 year history of stable immune thrombocytopenia who received diagnoses of acute myeloid leukemia 75 days after Dose 1, neutropenic sepsis 97 days after Dose 1, and died (b) (6) days after Dose 1. CBER assessed this event as likely unrelated to vaccination as no clustering of similar events temporally associated with vaccination was noted in the SHINGRIX group nor were there differences between treatment groups in the proportions of subjects reporting similar events tabulated at time periods relative to vaccination. No SAEs were judged vaccine-related by the applicant; SAEs judged related to vaccination by the investigator were reported by 12 subjects in the SHINGRIX and 8 subjects in the Placebo group. Two subjects had SAEs that were judged likely related to SHINGRIX vaccination by CBER after review: one subject reported lymphadenitis occurring in temporal association with both vaccinations which led to a surgical intervention (lymph node resection) and another reported fever up to 40° C, and moderate (Grade 2) chills, IS pain, and IS erythema one day after Dose 1. The other SAEs reported in the SHINGRIX group judged related to vaccination by the investigator were reviewed by CBER; while causal association could not be fully ruled out for all events, it could not be ascribed because of alternative etiologies, lack of concerning temporal association, and/or lack of clustering of similar events temporally associated with vaccination. No pIMDs were judged vaccine-related by the applicant; eight subjects in the SHINGRIX and six subjects in the Placebo group reported pIMDs judged related to vaccination by the investigator. The related pIMDs reported in the SHINGRIX group were reviewed by CBER; while causal association could not be fully ruled out for all events, it could also not be ascribed because of alternative etiologies, lack of temporal association, and/or lack of clustering of similar events temporally associated with vaccination. The AE of optic ischemic neuropathy was reported in temporal association (within 48 days) post-vaccination in three study subjects in the SHINGRIX group, and was not reported by any subjects in the Placebo group. These events were judged as unrelated to vaccination by the investigator or applicant. The applicant is working with FDA to addresses safety concerns in their Pharmacovigilance Plan (PVP), including an evaluation of ocular AEs.

Integrated summary of efficacy results, pooled data from Zoster-006 and Zoster-022 – The PHN VE co-primary endpoint for subjects ≥ 70 YOA in the mTVC from the pooled analysis of Zoster-006 and Zoster-022 was met as the LB of the 95% CI for PHN VE was ≥ 0%; [PHN VE: 88.78% (95% CI: 68.70%, 97.10%)]. The re-estimation of HZ VE on the subjects ≥ 70 YOA in the mTVC from the pooled analysis of Zoster-006 and Zoster-022 was 91.30% (95% CI: 86.88%, 94.46%). The applicant could not conclude on the unpowered secondary objective for the pooled analysis evaluating PHN VE on subjects ≥ 50 YOA in the mTVC with confirmed HZ [PHN VE: 0.29% (95% CI: -161.53%, 65.57%)]. Based on the available data, CBER considers that the primary effect of SHINGRIX on the prevention of PHN is due to the vaccine effect on the prevention of HZ.

Additional studies - The primary immunogenicity endpoints were met in studies evaluating the non-inferiority of SHINGRIX when administered on a M0/M6 as compared to a M0/M2 schedule (Zoster-026), the non-inferiority of SHINGRIX and quadrivalent influenza vaccine (QIV) when co-administered compared to when the vaccines were administered sequentially (Zoster-004),

and the lot-to-lot consistency of SHINGRIX (Zoster-007). The non-inferiority of the immune response to SHINGRIX when administered on a M0/M12 schedule as compared to a M0/M2 schedule was not met (Zoster-026), and a study comparing the safety and immunogenicity of SHINGRIX administered subcutaneously (SC) as compared to IM was terminated after safety halting rules were triggered due to local reactogenicity in the SC group (Zoster-032). Following administration of SHINGRIX to subjects with prior HZ, the primary immunogenicity endpoint of the acceptability of the vaccine response rate (VRR) one month after Dose 2 was met, but six of the 96 vaccinated subjects reported nine episodes of unconfirmed HZ during the uncontrolled, one-arm study (Zoster-033).

Conclusions – Demonstrated HZ VE in Zoster-006 and Zoster-022 was 97.16% (95% CI: 93.72%, 98.97%) and 89.79% (95% CI: 84.29%, 93.66%), respectively. While the point estimates of "overall" PHN VE in Zoster-006 and Zoster-022 were 100.00% and 85.49%, respectively, SHINGRIX PHN VE evaluated on subjects ≥ 50 YOA with confirmed HZ across both studies was not demonstrated in an unpowered analysis. The majority of subjects in the SHINGRIX group experienced local and/or general reactogenicity of short duration. Severe reactogenicity was common especially in the younger age strata. Overall, SAEs, deaths, and pIMDs were reported in similar proportions of subjects in Shingrix and Placebo groups during select time periods. Continued pharmacovigilance is needed to further evaluate the relationship to vaccination with regard to adverse events for which there were observed imbalances in the SHINGRIX as compared to the Placebo group, uncommon adverse events observed in temporal association with SHINGRIX vaccination, and other events that may not have been observed given the sample size evaluated.

3.0 Introduction and Background

3.1 Epidemiology: The overall incidence of HZ ranges from 1.5 – 5 per 1,000 PY, but since mild cases may not be medically attended, the incidence may be underestimated [Yawn, 2013]. The incidence of HZ rises with advancing age, with lifetime risk estimated to be approximately 30% [Kawai, 2014]. In the Shingles Prevention Study (SPS), a randomized, placebo-controlled study in which 38,546 subjects ≥ 60 YOA were randomized to receive ZOSTAVAX (a live, attenuated VZV vaccine) or placebo, the incidence rate of HZ in the Placebo group was 10.8 per 1000 PY for subjects 60 – 69 YOA, 11.4 per 1000 PY for subjects 70 – 79 YOA and 12.2 per 1000 PY for subjects ≥ 80 YOA [ZOSTAVAX Package Insert, 2017]. It is estimated that between 600,000 and 1 million cases occur in the US each year [Johnson, 2015]. Along with age, immunocompromised status or immunodeficiency are additional key risk factors for HZ. The most commonly reported complication of HZ is PHN, which was reported with an incidence of 1.38 per 1,000 PY in the SPS. The incidence of PHN increases with advancing age.

3.2 Currently Available Interventions: ZOSTAVAX, a live, attenuated VZV vaccine, was licensed by the FDA in May 2006 for the prevention of HZ in subjects ≥ 60 YOA. The license was extended to include subjects 50 – 59 YOA in March 2011.

Therapeutic treatment of HZ includes acyclovir, famciclovir and valacyclovir, started within 48 - 72 hours after rash onset. Effects of antiviral medication include shortening the time to lesion scabbing, healing and cessation of pain and reduction in the duration of viral shedding and new lesion formation. A variety of other therapeutic agents, including opioid analgesics, are used to manage the pain associated with HZ and PHN.

3.3 Mechanism of Action of $AS01_B$ Adjuvant: $AS01_B$ adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: MPL, which signals through Toll-like Receptor 4, and QS-21, which acts through as yet unknown receptor(s). It is believed that QS-21 signaling involves activity of the NLRP3 inflammasome complex. These two agonists activate antigen presenting cells loaded with antigen in the draining lymph node that enables recruitment of naive $CD4^+$ T cells. Studies performed by the applicant indicate that both MPL and QS-21 are required to induce the maximal frequencies of gE-specific cytokine-producing $CD4^+$ T cells and the highest titers of gE-specific antibodies.

3.4 Data from Non-clinical Toxicology Studies of SHINGRIX: The candidate vaccine, SHINGRIX, has been evaluated in two repeat dose toxicity studies in rabbits, one reproductive-developmental toxicity study in rats, one male fertility study in rats, two local tolerance studies in rabbits and one safety pharmacology study in rats. Additionally, the $AS01_B$ adjuvant or some of its components (MPL, QS21) were evaluated in 3 safety pharmacology studies, 10 general toxicology studies, 10 genotoxciology studies, 5 reproductive toxicology studies and 3 local tolerance studies.

In the repeat dose toxicity studies with SHINGRIX, the vaccine was well tolerated, but induced systemic as well as local reactogenicity. A transient but statistically significant increase in C-Reactive Protein (CRP) levels was observed in rabbits receiving the SHINGRIX vaccine with levels up to 9 times (male animals) and 5 times (female animals) higher compared to control animals. These changes in CRP levels reflect an activation of the acute-phase response and indicate increasing levels of systemic inflammation, which potentially may be correlated with clinical adverse events like malaise, fatigue, and nausea. Further, increases in bilirubin (up to 2 times compared to control), popliteal lymph node weight (up to 50%), spleen weight (up to 17%), and thymus weight (up to 24%) were reported. Locally, mixed inflammatory cell infiltrate in the muscle and an enhanced activated appearance in the draining popliteal lymph nodes were observed.

The SHINGRIX vaccine was evaluated in a male fertility study in rats, as well as in a reproductive developmental toxicity study in female rats. Treatment of male CD rats with SHINGRIX at 20% of the full human dose did not affect male mating performance, fertility or early embryonic development. Treatment of female CD rats with the candidate vaccine at 40% of the full human dose per occasion, was well tolerated, did not lead to maternal toxicity and did not adversely affect embryo-fetal or pre- and post-natal survival, growth or development of the offspring. A reproductive toxicology study evaluating QS21 adjuvant (formulated in DOPC and cholesterol) in rabbits at doses up to 200 µg/dose (4 times the human dose) resulted in maternal

toxicity as well as reduced fetal weight and malformations in the fetus at the highest dose while formulations containing 100 µg/dose or 20 µg/dose of QS21 did not induce any adverse effects on maternal condition or embryo-fetal and post-natal development. Neither SHINGRIX nor $AS01_B$ adjuvant was administered in this study.

Genotoxicity studies evaluating $AS01_B$ adjuvant, MPL, and DQ/QS21 did not reveal genotoxicity in the submitted *in vitro* or *in vivo* studies. Safety pharmacology studies evaluating the candidate vaccine formulation, $AS01_B$ adjuvant and MPL did not report clinically relevant adverse findings.

3.5 Relevant Prior Human Experience: According to the applicant, over 15,000 subjects have been vaccinated with at least one dose of an AS01-containing vaccine outside of the SHINGRIX development program. This includes more than 12,000 infants and toddlers participating in trials with GSK Biologicals' malaria vaccine and other vaccine candidates in development for adult and elderly populations for hepatitis B, HIV, cytomegalovirus, *Streptococcus*, cancer immunotherapeutics, *Haemophilus influenzae,* and tuberculosis. While the applicant reports that the overall safety profile of AS01-containing vaccines is aligned with the safety results of the SHINGRIX program, the following events were observed in the infant malaria program in which the RTS,S antigen combined with the adjuvant $AS01_E$ (half-dose $AS01_B$) has been administered:

- A higher incidence of meningitis cases of various etiologies were observed in one trial compared to control within 20 months after Dose 2. While the meningitis cases were not temporally related to vaccination, the applicant plans to closely monitor the occurrence of meningitis in future clinical trials.
- Increased incidence in severe malaria has been observed beginning around two years after the RTS,S/$AS01_E$ primary vaccination course in children 5 - 17 months of age at first dose. The applicant notes that the numbers are low and the increased incidence may be due to chance, but there is biologic plausibility for the minor increase related to timing of acquisition of natural immunity.

The relationship of the RTS,S vaccine or any of the components of the vaccine to the higher incidence of meningitis and severe malaria reported post-vaccination is unknown.

3.6 Dose Selection of $AS01_B$ Adjuvant: The applicant conducted a phase 2, randomized, placebo-controlled IND clinical study comparing the safety and immunogenicity of the following formulations administered IM in a 4:4:2:1 ratio on a M0/M2 schedule: SHINGRIX, 50 µg of the gE antigen with $AS01_E$, 50 µg of the gE antigen without adjuvant (gE/saline), and saline placebo. The study enrolled 410 generally healthy subjects ≥ 50 YOA without a history of HZ or VZV or HZ vaccination or any confirmed or suspected immunodeficient or immunosuppressed condition stratified 4:4:3:1 by age (50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA). Results of the study indicated that gE-specific humoral and cell-mediated immune responses were higher for all age strata in the SHINGRIX group as compared to the gE/$AS01_E$ group, and the safety and tolerability of SHINGRIX were acceptable.

4.0 Overview of Clinical Studies

Clinical studies (IND and non-IND) submitted to the BLA are presented in the tables below.

Table 1 – Phase 3 Studies Pertinent to Indication, Administration and Lot Consistency

Study ID	Zoster-006	Zoster-022	Zoster-004	Zoster-007	Zoster-026
Study number	110390	113077	117036	117177	116697
NCT ID	01165177	01165229	01954251	02075515	01751165
Phase	3	3	3	3	3
IND study	Yes	Yes	Yes	Yes	Yes
Countries	18‡	18‡	US, Canada, Germany	US, Canada, Belgium	US, Estonia
Initiation date	02AUG2010	02AUG2010	03OCT2013	13AUG2014	12MAR2013
Completion date	27JUL2015	24JUL2015	20MAR2015	29APR2015§	08APR2015
Enrollment	16,160*	14,816**	828	651	354
Age	≥ 50 YOA	≥ 70 YOA	≥ 50 YOA	≥ 50 YOA	≥ 50 YOA
Purpose	Evaluate VE for prevention of HZ (pivotal clinical endpoint study)	Evaluate VE for prevention of HZ (pivotal clinical endpoint study)	Compare post-vaccination humoral immune responses after concomitant and non-concomitant administration of SHINGRIX and QIV	Demonstrate lot consistency	Compare post-vaccination humoral immune responses following SHINGRIX administration on 3 different schedules
Control	Saline placebo	Saline placebo	See vaccination schedule below	None	None
Groups	2 groups, randomized 1:1 to receive SHINGRIX or placebo IM	2 groups, randomized 1:1 to receive SHINGRIX or placebo IM	2 groups, randomized 1:1 to receive QIV and SHINGRIX IM in control or co-administration groups	3 groups, randomized 1:1:1 - all groups receive SHINGRIX IM	3 groups, randomized 1:1 – all groups receive SHINGRIX IM
Schedule	M0, M2	M0, M2	Co-Ad: QIV and SHINGRIX at M0, SHINGRIX at M2; Control: QIV M0, SHINGRIX M2 and M4	M0, M2	M0/M2, M0/M6 or M0/M12
Total follow-up	Median 4.1 years¥	Median 3.9 years€	12 months after last dose	12 months after last dose	12 months after last dose

‡ Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Mexico, South Korea, Spain, Sweden, Taiwan, United Kingdom, US

§ Completion date for the active phase (up to Month 3)

* Zoster-006 total enrollment was 16,160 subjects, 15,411 received at least one dose and were included in TVC analysis

** Zoster-022 total enrollment was 14,816 subjects, 13,900 received at least one dose and were included in TVC analysis

¥ For the mTVC at the Zoster-006 EOS HZ and PHN analysis, median of 3.1 years at the HZ Final efficacy analysis

€ For the mTVC at the Zoster-022 analysis

Table 2 – Additional Studies - Alternative Administration Site and Specific Populations

Study ID	Zoster-032	Zoster-033	Zoster-001	Zoster-015
Study number	116760	116796	110258	112673
NCT ID	01777321	01827839	00920218	01165203
Phase	3	3	1/2a	1/2a
IND study	Yes	No	Yes	Yes
Countries	Japan	Canada, Estonia	US	US, UK, Germany
Initiation date	17JUN2013	10JUN2013	14JUL2009	30SEP2010
Completion date	11NOV2014	25NOV2014	21MAR2012	14MAY2013
Enrollment	60	96	120[¥]	123[¥]
Age	≥ 50 YOA	≥ 50 YOA	96 subjects ≥ 50 YOA total (45 were ≥ 50 YOA and received ≥ 1 dose of SHINGRIX	43 subjects ≥ 50 YOA total (28 were ≥ 50 YOA and received ≥ 1 dose of SHINGRIX)
Population	Japanese ethnic origin	Prior HZ	Autologous HCT	HIV
Purpose	Assess S&I of SHINGRIX when administered SC as compared to IM in population above	Assess S&I of SHINGRIX when administered to population above	Assess S&I of SHINGRIX when administered to population above	Assess S&I of SHINGRIX when administered to population above
Control	SHINGRIX IM arm	None – one arm	Saline placebo	Saline placebo
Groups	Two groups randomized 1:1 to receive 2 doses of SHINGRIX SC or IM	One group received 2 doses SHINGRIX	Four groups randomized 1:1:1:1; 3 doses of SHINGRIX , gE/AS01$_E$, saline placebo or saline placebo followed by 2 doses of SHINGRIX	Two groups randomized 3:2 to receive 3 doses of SHINGRIX or placebo
Schedule	M0, M2	M0, M2	M0, M1, M3	M0, M2, M6
Total follow-up	12 months after last vaccination (M14)	12 months after last vaccination (M14)	12 months after last vaccination (M15)	12 months after last vaccination (M18)

[¥] Subjects ≥ 18 YOA were enrolled in Zoster-001 and Zoster-015.

Table 3 – Phase 1 and 2 Supportive Studies

Study ID	Explo-CRD-004‡	Zoster-003§	Zoster-010	Zoster-023
Study number	101501	108494	112077	113819
NCTID	*	00434577	00802464	01086449
Phase	1/2	2	2	1
IND study	No	No	Yes	No
Countries	Belgium	Sweden, Czech Republic, The Netherlands, Germany	US, Czech Republic, Spain	Australia
Initiation date	14DEC2004	14FEB2007	12JAN2009	04MAR2010
Completion date	03FEB2006	04OCT2007	02JUL2010€	25NOV2010€
Enrollment	155 (20 young adults, 135 older adults)	715	410	20 (10 young adults, 10 older adults)
Age	18 – 30 YOA and 50 – 70 YOA	≥ 60 YOA	≥ 50 YOA	18 – 30 YOA and 50 – 69 YOA
Purpose	Assessment of safety and comparison of CMI responses post-vaccination after administration of SHINGRIX with and without Varilrix	Compare gE-specific CMI response in subjects ≥ 70 YOA one month after Dose 2	Compare gE-and VZV-specific humoral and CMI responses between the gE groups one month after Dose 2	Assessment of safety of SHINGRIX in healthy Japanese ethnic adults
Control	See groups	See groups	Saline placebo	None
Groups	5 groups randomized 2:2:9:9:9 to receive 2 IM injections of SHINGRIX (10 young adults), HZ/ with Varilrix (10 young adults), Varilrix (45 older adults), SHINGRIX (45 older adults) and SHINGRIX with Varilrix (45 older adults)	5 groups randomized 1:3:3:3:3 to receive IM either 2 injections of 100 µg gE/saline, 2 injections of 25 µg gE/AS01$_B$, 2 injections of SHINGRIX , 2 injections of100 µg gE/AS01$_B$ or saline as a 1st dose followed by 100 µg gE/AS01$_B$ as a second dose	4 groups randomized 4:4:2:1 to receive 2 IM injections; SHINGRIX , gE/AS01$_E$, gE/saline and saline placebo	1 group (stratified by age) who received 2 injections of SHINGRIX IM
Schedule	M0, M2	M0, M2	M0, M2	M0, M2
Total follow-up	10 months after last vaccination (M12), and up to M42 in extension studies	1 month after last vaccination (M3), and up to M72 in extension studies	12 months after last vaccination (M14)	6 months after last vaccination (M8)

‡ EXPLO-CRD-004 extension studies to evaluate persistence of immune response to SHINGRIX ; Zoster-018 EXT EXPLO CRD-004 M30 (109671) and Zoster-019 EXT EXPLO CRD-004 M42 (109674) initiated 25JUN2007 and completed 23JUN2008§ Zoster-003 extension studies to evaluate persistence of immune response to SHINGRIX ; Zoster-011 EXT 003 Y1 [108516, (07FEB2008 to 10JUL2008)], Zoster-012 EXT 003 Y2 [108518, (26JAN2009 to 13JUL2009)], Zoster-013 EXT 003 Y3 [108520, (03FEB2010 to 14JUL2010)] and Zoster-024 [114825, (28FEB2011 to 20JUN2013)]

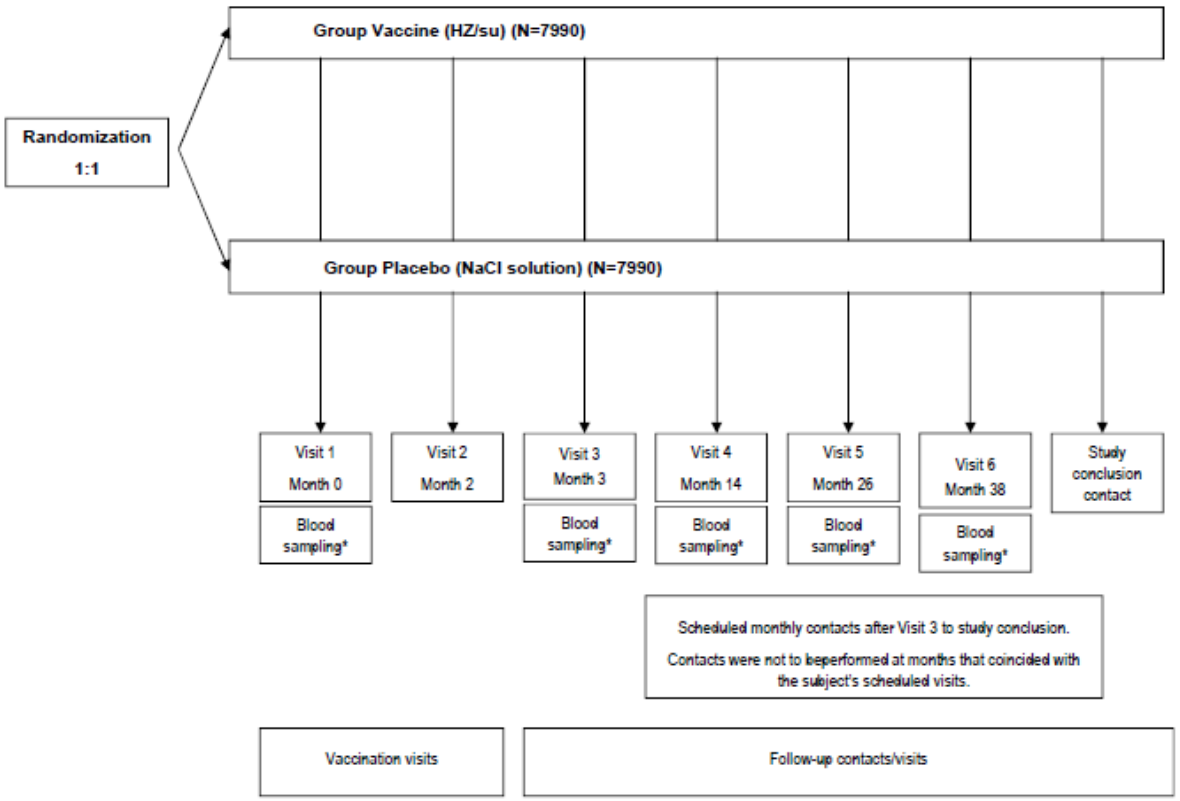
€ End of final phase

* EXPLO-CRD-004 did not meet criteria requiring registration on ClinicalTrials.gov

5.0 Pivotal Clinical Studies (Safety, Immunogenicity and Clinical Efficacy)

5.1 Study Zoster-006: Zoster-006 was a phase 3, randomized, observer-blind, placebo-controlled, multicenter, clinical endpoint efficacy study designed to assess the prophylactic efficacy, safety and immunogenicity of SHINGRIX when administered IM on a M0/M2 schedule to HZ-naive adults aged ≥ 50 YOA stratified 8:5:3:1 by age (50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA). Zoster-006 was conducted in parallel with and at the same sites as Zoster-022. The study initiation date was 02-AUG-2010 and completion date was 27-JUL-2015. The data lock point (DLP) for the Final HZ efficacy analysis (time point for primary efficacy analysis) was 01-JUL-2014, and the DLP for the EOS analysis (time point for safety analyses and most secondary efficacy analyses) was 12-OCT-2015.

5.1.1 Study Design: A pictorial representation of the study design is below.



Source: 125614/0 Zoster-006 CSR, p. 142
HZ/su = SHINGRIX
* Blood sampling was collected on all subjects pre-vaccination on M0 and at M3. Additional samples were collected on subjects in the Immunogenicity subset at Visit 4, 5, and 6.

There were six study visits and one study conclusion contact. Visits 1 and 2 (M0 and M2) were vaccination visits. At Visit 1 (pre-vaccination M0) and again at Visit 3 (M3), all subjects had blood sampling for immunogenicity assessment. After Visit 3, there were monthly contacts between scheduled visits to collect safety information, to assess for HZ or to follow-up ongoing

HZ cases. Additional visits (4, 5 and 6) were at M14, 26 and 38. Subjects randomized to the immunogenicity subset had additional blood sampling at Visits 4, 5 and 6 for assessment of persistence of immune response. There was a final contact at study conclusion.

For studies Zoster-006 and Zoster-022, a suspected case of HZ was defined as "a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis." PHN was defined by the presence of HZ-associated severe "worst" pain persisting or appearing more than 90 days after the onset of the HZ rash.

Subjects were educated about the signs and symptoms of HZ at enrollment. If a case of HZ was suspected, the subjects were to contact the study site (within 48 hours if possible) and complete a HZ-specific diary card at symptom onset to bring to the site. At the site, the investigator reviewed the information and performed a clinical examination (Day HZ-0). If HZ was not clinically suspected, no further action was necessary. If HZ was suspected, the rash was documented by digital photography, and three replicate lesion samples for PCR testing were collected. The subject was provided with diary cards to document HZ-associated pain and the effect of HZ on quality of life and physical functioning. Additional follow-up visits were scheduled for 7, 14, 21 28, 56 and 91 days after Day HZ-0 at which time information relevant to the HZ episode was recorded, such as concomitant medications, medical attention, or HZ-related complications. For pain persisting beyond the last scheduled visit, monthly contacts were arranged. Visits or contacts ceased once the subject reported a 28 day or 4 week pain-free interval.

All clinically suspected HZ cases were adjudicated by the HZAC, which consisted of five physicians with HZ expertise who were blinded to treatment assignment and PCR results and who were not participating as investigators in the study. Cases were ruled as "a case of HZ", "not a case of HZ", or if no consensus, "not able to decide" (for the purposes of analysis, "not able to decide" was counted as "not a case of HZ"). HZAC classification served as the final determination of a case only if the determination could not be confirmed or excluded by PCR.

5.1.2 Study Objectives

Primary objective - To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 50 YOA as measured by the reduction in HZ risk

Secondary objectives

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50 – 59 YOA, 60 – 69 YOA, and ≥ 70 YOA as measured by reduction in HZ risk
- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA
- To evaluate vaccine safety and reactogenicity
- Additional secondary objectives evaluated SHINGRIX VE compared to placebo with regard to reduction in the duration of severe 'worst' HZ-associated pain, reduction in HZ-

related complications (disseminated, neurologic, visceral or ophthalmic disease, stroke and HZ vasculitis), reduction in use of pain medications (all in subjects with confirmed HZ) and reduction in overall and HZ-related mortality and hospitalizations.

Select exploratory objectives

- To evaluate vaccine induced humoral immune responses and the persistence of response after two injections of study vaccine in subjects ≥ 50 YOA and by age strata

5.1.3 Study Population: Male or female subjects ≥ 50 YOA were eligible for the study if they were capable of giving informed consent, had no history of HZ or previous vaccination against HZ or VZV, or had no confirmed or suspected immunosuppressive or immunodeficient condition due to disease or therapy. If female, the subject had to be of non-childbearing potential or using adequate contraception.

5.1.4 Endpoints and Criteria for Study Success

Primary endpoint - Confirmed HZ cases during the study in the mTVC

Secondary endpoints

- Occurrence of overall PHN – incidence of PHN calculated using the mTVC
- Safety endpoints: solicited local and general symptoms recorded by a subset of subjects randomized to the 7-day diary card subset for 7 days (Days 0 – 6) after each vaccination, unsolicited AEs recorded on a diary card by all subjects during Days 0 – 29 after each vaccination, medically attended visits recorded by all subjects from M0 – M8, SAEs recorded by all subjects from M0 – 14 and SAEs judged vaccine related, SAEs related to a concurrent GSK medication/vaccination, fatal SAEs and pIMDs recorded by all subjects throughout the study
- Additional secondary endpoints - duration of severe 'worst' HZ-associated pain, incidence of HZ-related complications and duration of pain medication administered for HZ, all in subjects with confirmed HZ, as well as incidence of overall and HZ-related mortality and hospitalizations.

Select exploratory endpoints

- gE antigen-specific antibody (Ab) concentrations as determined by enzyme-linked immunosorbent assay (ELISA) in a subset of subjects at Months 0, 3, 14, 26 and 38

Criterion for study success - The primary objective was demonstrated if the LB of the two-sided 95% CI of VE was above 25%. The primary analysis was supported by sensitivity analyses by age strata; the applicant's criterion for clinically meaningful HZ VE for the age strata 50 – 59 and 60 – 69 YOA would be demonstrated if the LB of the 95% CI was above 10%. The study was not powered to demonstrate HZ VE for the ≥ 70 YOA stratum.

Triggers for study analyses

The Final HZ efficacy analysis for Zoster-006 was planned when the following conditions were reached:

- At least 196 confirmed HZ cases across all age strata in the mTVC for the overall HZ analysis.

- Approximately 60 HZ cases in both the 50 – 59 YOA and 60 – 69 YOA groups in the mTVC accrued.
- Approximately 75% of the initial sample size in each stratum completed at least 36 months of follow-up and the remaining subjects had completed at least 30 months of follow up after Dose 2.

Conditions for the EOS analysis of Zoster-006 occurred when all previous conditions were met for the Final HZ efficacy analysis in Zoster-022 (see Section 5.2.4) and a total of at least 35 PHN cases in subjects ≥ 70 YOA from pooled data from Zoster-006 and Zoster-022 were accrued. The conditions for the Final HZ efficacy analysis in Zoster-006 were reached prior to the conditions for this analysis in Zoster-022; thus, the Final HZ efficacy analysis was conducted prior to the EOS analysis in Zoster-006. A firewall was established by the applicant to allow planned analyses to be performed while maintaining the study blind.

5.1.5 Populations Analyzed

- TVC - The TVC was the primary population for the analysis of safety and included all vaccinated subjects with respect to the vaccine actually administered.
- mTVC - The mTVC, the primary population for the analysis of efficacy, excluded subjects in the TVC who did not receive two doses or who developed a confirmed case of HZ prior to one month after Dose 2.
- According to protocol and adapted according to protocol cohorts for evaluation of immunogenicity (ATPc and adapted ATPc) – The ATPc for analysis of immunogenicity included evaluable subjects (who met eligibility criteria, complied with procedures and intervals defined in the protocol, and who did not meet elimination criteria) for whom data at sampling time points were available.

5.1.6 Subject Disposition

Subjects vaccinated, completed and withdrawn - The number and proportions of subjects vaccinated, completed and withdrawn are presented below. Per protocol, a subject who completed the last contact was considered to have completed the study and a subject who did not complete the last contact was considered a withdrawal.

Table 4 – Number and proportions of subjects vaccinated, completed and withdrawn (Zoster-006 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%)

Source: Adapted from 125614/0 Zoster-006 CSR, Table 23, p. 246 and 125614/0.9 Response to CBER IR of 10-FEB-2017, Table 23 (revised), p. 24
N = number of subjects in the TVC, EOS analysis
n = number of subject in that category
% = n/N

The most commonly reported reasons for subject withdrawal from the study (> 1% of either treatment group) were consent withdrawal not due to an AE (4.7%), withdrawal due to an SAE (3.0%) and lost to follow-up with a complete vaccination course (2.1%). Non-serious AE was cited by 0.4% and 0.2% of subjects in the SHINGRIX and Placebo groups, respectively as a reason for withdrawal. The proportions of subjects who withdrew classified by reason for withdrawal were comparable between treatment groups. The proportions of subjects completing the study decreased with increasing age: 82.2% and 81.8% of subjects ≥ 70 YOA in the TVC of the SHINGRIX and Placebo groups, respectively, completed the study as compared to 89.9% and 90.9% of subjects 50 – 59 YOA in the TVC of the SHINGRIX and Placebo groups. The proportions of vaccinated subjects withdrawing consent not due to an AE and withdrawing due to an SAE were also higher in the older age strata, but similar between treatment groups.

Subjects available for analyses - The primary efficacy analysis occurred at the Final HZ efficacy analysis (DLP 01-JUL-2014) and safety analysis occurred at the EOS analysis (cut-off date 21-APR-2015). There were 14,759 subjects available for efficacy analysis; 7,344 from the SHINGRIX and 7,415 from the Placebo group. Overall, 95.4% and 96.1% of subjects from the TVCs of the SHINGRIX and Placebo groups, respectively, were included in the mTVC and evaluable for the primary analysis for HZ VE (secondary and tertiary efficacy VE analyses were performed on the mTVC at the EOS, and the same proportions of subjects in each treatment group were available for those analyses). The primary reason that subjects in the TVC were excluded from the mTVC was that the subject did not receive two doses (see Exposure section below).

Table 5 – Numbers and proportions of subjects in the TVC excluded from the mTVC with reason for exclusion (Zoster-006 – Final HZ efficacy analysis)

	SHINGRIX n	SHINGRIX %	Placebo n	Placebo %
Total Vaccinated Cohort	7698	100%	7713	100%
Study vaccine dose not administered according to protocol	4	0.1%	2	0.0%
Wrong replacement or study vaccine administered	9	0.1%	5	0.1%
Subjects who did not receive two doses	337	4.4%	277	3.6%
Subjects had an episode of HZ prior to 30 days after Dose 2	4	0.1%	14	0.2%
modified Total Vaccinated Cohort	7344	95.4%	7415	96.1%

Source: Adapted from 125614/0.9, Table 25 (revised), p. 9
% = percentage of subjects in the considered cohort relative to the Total Vaccinated Cohort

The proportions of subjects enrolled and available for the safety analyses (TVC) at the EOS (primary time point for safety analyses) are presented below. Of the subjects enrolled, 95.4% were evaluated for safety in the TVC. Of the subjects in the Total Enrolled Cohort excluded from all statistical analyses in Zoster-006, 671 were excluded from a single center in Mexico, due to serious deviations from Good Clinical Practice (GCP) including deficiencies in documentation of study procedures and inadequate investigator oversight. These subjects were analyzed for safety separately - see Section 6.0.

Table 6 – Numbers and proportions of subjects available for safety analyses in the TVC (Zoster-006 – EOS analysis)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
Total Enrolled Cohort	8068	100%	8078	100%
Subjects excluded from all statistical analyses	366	4.5%	365	4.5%
Total Effective Cohort	7702	95.5%	7713	95.5%
Study vaccine not administered but subject number allocated	7	< 0.1%	3	< 0.1%
Total Vaccinated Cohort	7695	95.4%	7710	95.4%

Source: Adapted from 125614/0.9 Table 6.24 (revised), p. 15

Exposure – Of subjects in the TVC at the EOS analysis, 4.4% in the SHINGRIX group and 3.6% in the Placebo group did not receive two doses. The most common reason for subjects not receiving two doses was "Visit not done" (61.5% and 67.4% of subjects who received one dose in the SHINGRIX and Placebo groups, respectively). The two other most common reasons for subjects not receiving both doses was subject decision of "Other" (10.4% and 8.7% of subjects who received one dose in the SHINGRIX and Placebo groups, respectively) and investigator decision of "Protocol violation or outside of time window" (7.1% and 7.2% of subjects who received one dose in the SHINGRIX and Placebo groups, respectively). Note that the category "Other" included subjects who did not specify as to whether the rationale for receiving one dose was or was not due to an AE. The proportions of subjects receiving one dose who reported non-serious solicited AEs (3.8% and 1.4% of the SHINGRIX and Placebo group, respectively) and non-serious unsolicited AEs (5.6% and 2.2% of the SHINGRIX and Placebo group, respectively) as the reason for not receiving two doses was low in both treatment groups but was numerically higher in the SHINGRIX as compared to the Placebo group.

5.1.7 Demographics and Baseline Characteristics

The majority of subjects (51.2%) in the TVC at the EOS analysis were from Europe; the remaining subjects were from Australasia (21.3%), North America (17.4%) and Latin America (10.0%). The proportions of subjects from each region in the mTVC at the Final HZ efficacy analysis were similar to those in the TVC at the EOS analysis.

Demographic characteristics were comparable between treatment groups. The mean and median age of subjects in the study was 62.3 and 60.0 years, respectively, with a maximum age of 96 years. The proportion of females to males was 61.1% to 38.9%. The majority of subjects were not American Hispanic or Latino (88.9%). The proportions of subjects by geographic ancestry (> 1.0% of study population) were as follows: White of Caucasian/European heritage (71.3%), Asian (19.1%), Other (7.3%), and African heritage/African American (1.7%). Compared to the demographics of the overall population, the North American cohort had higher proportions of subjects who were African-American (7.5%), and who were not American Hispanic or Latino (96.4%) and lower proportions of subjects of Asian heritage (0.6%).

The majority of subjects in both treatment groups (88.3% and 88.6% in the SHINGRIX and Placebo groups, respectively) reported at least one pre-existing condition. No clinically

significant differences were observed between treatment groups for the types of pre-existing conditions classified by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) or by specific PT.

5.1.8 Efficacy Results

The primary analysis method of VE considered the exact inference on the relative risk (RR) stratified by age and regions conditionally to the total number of HZ cases observed and time at risk.

There were 216 confirmed cases of HZ in the mTVC at the Final HZ efficacy analysis step, 6 in the SHINGRIX group and 210 in the Placebo group, after a median follow-up time of 3.1 years (range 0 to 3.7 years) and a mean follow-up time of 3.1 years (standard deviation 0.5 years). No subject reported more than one episode of HZ.

Table 7 – Vaccine efficacy: First or only episode of HZ during the entire study period overall using Poisson method (Zoster-006 mTVC – Final HZ efficacy analysis)

									VE		
	SHINGRIX				Placebo					95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	N	T(year)	n/T (per 1000)	(%)	LL	UL
OVERALL **	7344	6	23297.0	0.3	7415	210	23170.5	9.1	97.16	93.72	98.97

Source: Adapted from 125614/0 Zoster-006 CSR Table 33, p. 268
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
** VE adjusted by age strata and region

The incidence of HZ in the Placebo and SHINGRIX groups was 9.1 and 0.3 per 1,000 PY, respectively for an overall VE against HZ in subjects ≥ 50 YOA of 97.16% (95% CI; 93.72%, 98.97%). The primary study objective regarding HZ VE in subjects ≥ 50 YOA was met, as the LB of the 95% CI was above 25%. HZ VE was re-analyzed on the mTVC at the EOS analysis when an additional 47 subjects reported a HZ episode (3 in the SHINGRIX group and 44 in the Placebo group); results were concordant with the analysis at the Final HZ efficacy analysis time point with HZ VE of 96.50% (95% CI: 93.25%, 98.46%).

Table 8 below presents the distribution of HZ cases in study Zoster-006 by method of HZ case confirmation by treatment group and overall, with 89.4% of cases overall confirmed by PCR and 10.6% determined by the HZAC.

Table 8 – Distribution of confirmed HZ episodes determined by PCR or HZAC (Zoster-006 mTVC – Final HZ efficacy analysis)

	SHINGRIX		Placebo		Total	
Confirmed HZ episode determined by:	n	%	n	%	n	(%)
PCR	4	66.7	189	90.0	193	89.4
HZAC	2	33.3	21	10.0	23	10.6
Total (either HZAC or PCR)	6	100	210	100	216	100

Source : 125614/0 Zoster-006 CSR Table 7.106, p. 2739
PCR = Polymerase Chain Reaction
n /%= number /percentage of confirmed HZ cases in a given category

Secondary objectives

To evaluate VE in the prevention of HZ compared to placebo in the following age strata; 50 – 59, 60 – 69, and ≥ 70 YOA, as measured by the reduction in HZ risk. This analysis was performed similarly to the analysis of the primary endpoint, but stratified only by region. Results were as follows:

Table 9 – Vaccine efficacy: First or only episode of HZ during the entire study period by age strata using Poisson method (Zoster-006 mTVC – Final HZ efficacy analysis)

									VE		
	SHINGRIX				Placebo					95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
50-59 YOA *	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.57	89.62	99.31
60-69 YOA *	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.36	90.14	99.69
≥ 70 YOA *	1711	1	5127.9	0.2	1724	48	5083.0	9.4	97.93	87.91	99.95

Source: Adapted from 125614/0 Zoster-006 CSR Table 33, p. 268
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)
* : VE adjusted by region

The secondary objective of HZ VE for the 50 – 59 and 60 – 69 YOA strata were met, as the LB of the 95% CI was > 10%. An analysis of HZ VE on subjects ≥ 60 YOA was conducted; for subjects in the mTVC at the Final HZ efficacy analysis, HZ VE was 97.58% with a 95% CI of (92.77%, 99.51%). HZ VE estimates for age strata 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA for the mTVC, TVC and the ATP cohort for efficacy at the EOS analysis time point were reviewed and found to be generally consistent with the results in Table 9 above.

To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA. The overall reduction in PHN risk was calculated similarly to the HZ risk using the exact inference on the RR stratified by age and regions conditionally to the total number of PHN cases observed and time at risk. No subject reported PHN in the SHINGRIX group and 18 subjects (8 each in the 50 – 59 and ≥ 70 YOA strata and 2 in the 60 – 69 YOA stratum) reported at least

one PHN episode in the Placebo group. Overall PHN VE results and PHN VE by age strata were as follows:

Table 10 – First or only episode of PHN during the entire study period by age strata and overall (Zoster-006 mTVC – EOS analysis)

	SHINGRIX				Placebo				VE		
										95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
50-59 YOA *	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.00	40.88	100.00
60-69 YOA *	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.00	-442.83	100.00
≥ 70YOA *	1709	0	6323.4	0.0	1724	8	6340.6	1.3	100.00	41.40	100.00
OVERALL **	7340	0	28734.6	0.0	7413	18	28943.7	0.6	100.00	77.11	100.00

Source: Adapted from 125614/0 Zoster-006 CSR Table 34, p. 272
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 region
** VE adjusted by age and region

The incidence rate for subjects reporting at least one episode of PHN in the Placebo group in Zoster-006 was 0.6 per 1,000 PY for subjects ≥ 50 YOA, 0.2 per 1,000 PY for subjects 60 – 69 YOA, and 1.3 per 1,000 PY for subjects ≥ 70 YOA. Although not a primary age stratum, PHN incidence for subjects ≥ 60 YOA in the Placebo group was 0.7 per 1,000 PY.

Reduction of duration of severe "worst" HZ-associated pain in subjects with confirmed HZ, reduction of confirmed HZ- associated hospitalizations, reduction in incidence of HZ-related mortality, reduction in duration of pain medication administered for HZ in subjects with confirmed HZ and reduction in use of pain medications administered for HZ in subjects with confirmed HZ: The applicant did not analyze reduction in overall mortality or overall hospitalizations, and was unable to conclude on the other objectives/endpoints. No HZ-related deaths or hospitalizations were reported.

Reduction in incidence of HZ-related complications (other than PHN) in subjects with confirmed HZ: At the EOS analysis, no HZ-related complications were reported for the nine subjects with confirmed HZ in the SHINGRIX group, 6 of 254 subjects (2.3%) in the Placebo group reported a total of 6 complications; HZ vasculitis (n=1), disseminated disease (n=4), ophthalmic disease (n=1).

Subpopulation analyses - Additional unpowered analyses were conducted to examine HZ VE by gender, by region, and over time. No clinically significant differences in VE were noted in the sub-population analyses by region, and VE was comparable between genders. The estimates of VE over time were as follows: Year 1 [98.38% (95% CI: 90.64%, 99.96%)], Year 2 [94.16% (95% CI: 84.36%, 98.45%)], Year 3 [100.00 (95% CI: 94.52%, 100.00%)], Year 4 [93.07% (95% CI: 81.26%, 98.18%)].

5.1.9 Immunogenicity Results

The primary immunogenicity read-out for the development program was anti-gE Ab concentrations as measured by ELISA. All subjects had blood drawn for immunogenicity assessment at M0 and M3 for a correlate analysis, but the M0 and M3 results were provided only on subjects in the immunogenicity subset and the correlate analysis was not included in the submission. A small proportion of randomly assigned subjects in the TVC (15.6% at baseline) were in the According to protocol cohort (ATPc) for immunogenicity - Humoral and adapted ATPc for immunogenicity – Humoral subset (primary population for analysis of humoral immune response) which included subjects who did not meet elimination criteria for the cohort at each sampling time point. Vaccine response was defined as ≥ a four-fold increase in anti-gE Ab concentration from baseline for subjects seropositive at baseline, and ≥ a four-fold increase in anti-gE Ab concentration from the cut-off for seropositivity (seropositivity cut-off = 97 mIU/mL) for subjects seronegative at baseline.

At baseline, 99.1% and 99.2% of SHINGRIX and Placebo recipients in the ATPc for immunogenicity - humoral were seropositive for anti-gE Ab. At M3 and beyond, 100% of SHINGRIX recipients in the adapted ATPc – humoral were seropositive.

The pre-vaccination anti-gE GMCs at baseline in the SHINGRIX group were 1247.1 mIU/mL (95% CI: 1174.8, 1323.8). One month post-vaccination Dose 2 at M3, the GMC value was 52376.6 mIU/mL, (95% CI: 50264.1, 54577.9). At M14, M26 and M38 the GMCs were 17726.2 mIU/mL (95% CI: 16910.7, 18581.0), 13933.3 mIU/mL (95% CI: 13290.4, 14607.2), and 11919.6 mIU/mL (95% CI: 11345.6, 12522.7).

The mean geometric increase (MGI) of anti-gE concentrations at Months 3, 14, 26 and 38 over pre-vaccination in the SHINGRIX group were 42.0 (95% CI: 39.3, 44.8), 14.4 (95% CI: 13.5, 15.5), 11.4 (95% CI: 10.6, 12.2), and 9.7 (95% CI: 9.1, 10.4). In the Placebo group, the MGI over pre-vaccination was not higher than 1.0 at any time point.

The proportions of subjects in the SHINGRIX Adapted ATP cohort for immunogenicity - Humoral that were vaccine responders at M3, M14, M26 and M38 were 98.5%, 89.5%, 83.4% and 80.9%, respectively. In the Placebo group the VRR for anti-gE Ab concentrations was not higher than 3.8% at any time point.

5.1.10 Safety Results

Solicited symptoms – Solicited symptoms were collected for 7 days (Days 0 – 6) on a randomized subset of subjects with a planned age stratification of 3:3:3:1 for the 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA age strata. Approximately 58% of the subjects in the TVC were randomized to this subset (SHINGRIX group N = 4,457, Placebo group N = 4,464). The proportion of subjects ≥ 80 was slightly smaller and the proportion of subjects 70 – 79 YOA was slightly greater than planned; however, the overall stratification plan for 40% of subjects being ≥ 70 YOA was maintained. As reactogenicity decreased with increasing age, the stratification ratio should inform conclusions about non-age stratified reactogenicity tabulations (e.g.,

proportions of subjects reporting at least one solicited event). Solicited general events (other than fever/pyrexia) and IS pain were graded as follows: mild = Grade 1, moderate = Grade 2 and severe = Grade 3, and Grade 3 events were described in terms as an event "which prevents normal, everyday activity." Fever (rectal, axillary or oral) was graded as follows: Grade 1 (37.5˚C to 38.0˚C), Grade 2 (38.1˚C to 39˚C) and Grade 3 (> 39˚C). IS swelling and erythema was graded as follows: Grade 1 (≥ 20 mm to ≤ 50 mm diameter), Grade 2 (> 50 mm to ≤ 100 mm diameter) and Grade 3 (> 100 mm diameter). Over 97% of subjects in both treatment groups complied with the return of general and local diary cards.

Overall by subject (both doses considered), 85.2% of SHINGRIX recipients and 34.2% of Placebo recipients reported at least one solicited symptom during the 7-day post-vaccination period; 66.1% of subjects in the SHINGRIX and 29.5% of subjects in the Placebo group reported at least one solicited general symptom and 81.5% of subjects in the SHINGRIX and 11.9% of subjects in the Placebo group reported at least one solicited local symptom. The proportions of subjects in the SHINGRIX group reporting any solicited symptom, any solicited local or any solicited general symptom were comparable after Dose 1 and Dose 2.

Overall by subject, the proportions of subjects in the SHINGRIX group reporting any solicited symptom, any solicited local symptom and any solicited general symptom by age strata decreased with increasing age is shown below in Table 11. Although not presented in the table, the proportions of subjects in the SHINGRIX group reporting any solicited symptom, any solicited local symptom and any solicited general symptom were generally comparable after each dose within each age stratum.

Table 11 – Incidence and nature of solicited symptoms reported during the 7-day post-vaccination period by age strata (Zoster-006 TVC diary card – EOS analysis)

	Any symptom	General symptoms	Local symptoms
50 – 59 YOA SHINGRIX	91.5%	76.7%	89.6%
50 – 59 YOA Placebo	41.0%	36.1%	14.9%
60 – 69 YOA SHINGRIX	87.6%	68.7%	84.6%
60 – 69 YOA Placebo	35.2%	30.1%	12.1%
≥ 70 YOA SHINGRIX	78.6%	56.4%	73.2%
≥ 70 YOA Placebo	28.4%	24.2%	9.6%

Source: Adapted from 125614/0 Zoster-006 CSR Table 10.99, p. 3922

Grade 3 solicited symptoms were reported by higher proportions of the younger SHINGRIX recipients as compared to the older recipients. Overall per subject, 22.7%, 16.6% and 11.6% of subjects 50 – 59, 60 – 69 and ≥ 70 YOA reported at least one Grade 3 solicited symptom. For subjects in the 50 – 59, 60 – 69 and ≥ 70 YOA age strata, at least one Grade 3 solicited general symptom was reported by 17.1%, 11.5% and 7.0%, and at least one Grade 3 solicited local symptom was reported by 13.4%, 9.2% and 6.8% of subjects in the SHINGRIX group. By dose, it appeared that Grade 3 solicited general, but not local, reactogenicity was slightly higher after Dose 2 than after Dose1 for each age stratum in the SHINGRIX group.

Pain was the most commonly reported solicited local symptom during the 7-day post-vaccination period; any grade (Grade 3) pain was reported by 79.1% (6.7%) of SHINGRIX recipients and 11.2% (0.4%) of Placebo recipients. Any grade (Grade 3) redness was reported by 38.0% (2.8%) of SHINGRIX recipients and 1.3% (0.0%) of Placebo recipients and any grade (Grade 3) swelling was reported by 26.3% (1.0%) of SHINGRIX and 1.1% (0.0%) of Placebo recipients. The proportions of subjects in the SHINGRIX group reporting each specific solicited local symptom (any grade or Grade 3) were comparable after Dose 1 and Dose 2, and any grade and Grade 3 solicited local symptoms were reported by higher proportions of the younger as compared to older SHINGRIX recipients. The median duration of pain, redness or swelling after SHINGRIX administration was 3.0 days after Doses 1 and 2.

The proportions of subjects in each treatment group reporting any grade and Grade 3 solicited general symptoms are shown below in Table 12. The most commonly reported solicited general events of any grade following SHINGRIX administration were myalgia, fatigue and headache. The most commonly reported Grade 3 solicited general events following SHINGRIX administration were fatigue, myalgia and shivering.

Table 12 – Incidence of solicited general symptoms reported during the 7-day (Days 0 – 6) post-vaccination period overall/subject (Zoster-006 TVC Diary card – EOS analysis)

	SHINGRIX N = 4372 n(%)	Placebo N = 4376 n(%)
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%)

Source: Adapted from 123614/0 Zoster-006 CSR Table 61, p. 343

The proportions of SHINGRIX recipients reporting any grade of each specific solicited general symptom was marginally increased between Dose 1 and Dose 2, except for shivering; any grade shivering was reported by 14.5% and 22.5% of SHINGRIX recipients after Dose 1 and Dose 2, and Grade 3 shivering was reported by 1.6% and 3.3% of SHINGRIX recipients after Dose 1 and Dose 2, respectively. All grade and Grade 3 solicited general reactogenicity reported by subjects in the SHINGRIX group decreased with increasing age. Overall by subject, Grade 3 solicited events reported by ≥ 5% of SHINGRIX subjects in a single age strata after any dose were fatigue (8.5%), headache (6.0%), myalgia (8.9%) and shivering (6.8%) in the 50 – 59

YOA group and fatigue (5.0%) and myalgia (5.3%) in the 60 – 69 YOA group. Overall per dose, the median duration of solicited general symptoms was between 1.0 – 2.0 days. The median duration of each specific solicited symptom following Dose 1 and Dose 2 were generally comparable.

Unsolicited AEs – Unsolicited AEs (serious and non-serious) were recorded by all subjects on a diary card for 30 days (Days 0 – 29) after each vaccination. The proportions of subjects reporting the occurrence of unsolicited AEs are presented below.

Overall (both doses considered), 45.9% and 31.5% of subjects in the TVC of the SHINGRIX group and Placebo group, respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period.

The most commonly reported unsolicited AEs reported within the 30-day post-vaccination period in the SHINGRIX group were reactogenicity events (IS pain, pyrexia, IS erythema, headache and IS swelling) primarily reported by subjects who were not included the 7-day diary card subset. A post-hoc tabulation performed by the applicant of the proportions of subjects in the 7-day diary card subset reporting unsolicited AEs during the 30-day post-vaccination period indicated that 29.6% and 27.7% of subjects in the 7-day diary card subset in the SHINGRIX and Placebo groups, respectively, reported at least one unsolicited AE during the 30-day post-vaccination period.

At least one Grade 3 non-serious unsolicited AE was reported by 7.5% and 3.3% of subjects in the SHINGRIX and Placebo groups, respectively, during the 30-day post-vaccination period. By SOC, the most reports were in the General disorders and administration site conditions SOC (3.7% and 0.3% of subjects in the SHINGRIX and Placebo groups, respectively); the most commonly reported Grade 3 non-serious unsolicited events in the SHINGRIX group were reactogenicity events (IS pain, pyrexia, headache and chills).

The proportions of subject in the SHINGRIX group reporting unsolicited AEs or Grade 3 non-serious unsolicited AEs during the 30-day post-vaccination period decreased with increasing age.

An additional CBER analysis indicated that a higher proportion of subjects in the SHINGRIX group (0.13%, N = 10) as compared to the Placebo group (0.03%, N = 2) reported unsolicited events in the MedDRA sub-SMQ of Supraventricular tachyarrhythmias during the 30-day post-vaccination period. This imbalance was not observed in Zoster-022. See Section 6.0.

Medically attended events (MAEs) – From M0 – M8, 38.4% of subjects in the TVC of the SHINGRIX group and 39.8% of subjects in the TVC of the Placebo group reported an unsolicited AE with a medically attended visit. Higher proportions of subjects in the SHINGRIX group (2.7%) as compared to the Placebo group (1.9%) reported a MAE in the General disorders and administration site conditions SOC, driven primarily by medical attention sought for events that corresponded to those which were solicited on the 7-day diary card in the diary card subset. The most commonly reported MAEs from M0 – M8 for both groups was

nasopharyngitis and upper respiratory infection which were reported by comparable proportions of subjects in each treatment group. Comparative analysis indicated that from M0 – M8 a few MAEs by PT were reported more frequently by the SHINGRIX than the Placebo group (IS pain, IS erythema, IS swelling, pyrexia, respiratory tract infection, hyperlipidemia, macular degeneration, nerve compression, and skin ulcer) or more frequently by the Placebo than the SHINGRIX group (melanocytic nevus, cellulitis, bronchiectasis).

The proportions of subjects reporting a medically attended visit from M0 – M8 were comparable between treatment groups within each age stratum, and were comparable across the age strata.

SAEs – The proportions of subjects in each treatment group who reported SAEs during select time periods post-vaccination are below.

Table 13 – Global summary of SAEs (fatal and non-fatal) during selected time periods (Zoster-006 TVC – EOS analysis)

	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 (M0 – M3)	145 (1.9%)	137 (1.8%)
Subjects with at least 1 SAE reported (M0 – M14)	594 (7.7%)	590 (7.7%)

Source: Adapted from 125614/0.25, Table 170, p. 74

Comparative analysis indicated that there was no difference between treatment groups for the proportions of subjects reporting SAEs or for the proportions of subjects reporting SAEs by SOC or specific PT during the M0 – M14 time period. There were no imbalances noted between treatment groups for the proportions of subjects reporting SAEs during the other selected time periods overall or for events classified by PT or SOC during those periods, and no clustering temporally associated with vaccination was noted with regard to types of SAEs reported.

The proportions of subjects reporting SAEs during the select time periods increased with increasing age, but were comparable between treatment groups within each age stratum. The proportions of subjects reporting SAEs during select time periods were reviewed and were generally comparable between regions. See Section 6.0 for an accounting of the SAEs judged related to vaccination by the investigator.

Deaths - The table below presents proportions of subjects in the TVC of each treatment group who died during select time periods post-vaccination.

Table 14 – Subjects who died during select time periods (Zoster-006 TVC – EOS analysis)

	SHINGRIX N = 7695 n (%)	Placebo N = 7710 n (%)
Subjects with fatal SAE reported [30-day (Days 0 – 29) post-vaccination period]	3 (0.0%)	3 (0.0%)
Subjects with fatal SAE reported (Day 0/Month 0 – Month 3)	7 (0.1%)	7 (0.1%)
Subjects with fatal SAE reported (Day 0/Month 0 – Month 14)	42 (0.5%)	52 (0.7%)
Subjects with fatal SAE reported (whole post-vaccination period)	208 (2.7%)	221 (2.9%)

Source: Adapted from 125614/0.22 Annex 1 Table 13, p. 48
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

Comparative analysis indicated that there was no difference between treatment groups in the proportions of subjects reported as having fatal SAEs or for the proportions of subjects reported as having fatal SAEs by SOC or specific PT during M0 – M14. There were no imbalances noted between treatment groups for the proportions of subjects who died during the other selected time periods overall or for events classified by PT or SOC during this period, and no medically relevant clusters with regard to types of fatal events reported.

As expected, the proportions of subjects who died in each age stratum increased with advancing age, but within age stratum, the proportions were comparable between treatment groups as can be seen below.

Table 15 – Number and proportions of subjects with fatal SAEs (who died) during selected time periods by age strata (Zoster-006 TVC – EOS analysis)

	SHINGRIX 50 – 59 YOA N = 3644 n (%)	Placebo 50 – 59 YOA N = 3642 n (%)	SHINGRIX 60 – 69 YOA N = 2243 n (%)	Placebo 60 -69 YOA N = 2245 n (%)	SHINGRIX ≥ 70 YOA N = n (%)	Placebo ≥ 70 YOA N = n (%)
Subjects who died [30-day (Days 0 – 29) post-vaccination period]	0 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
Subjects who died (Day 0/Month 0 – Month 3)	2 (0.1%)	2 (0.1%)	2 (0.1%)	1 (0.0%)	3 (0.2%)	4 (0.2%)
Subjects who died (Day 0/Month 0 – Month 14)	12 (0.3%)	11 (0.3%)	9 (0.4%)	12 (0.5%)	21 (1.2%)	29 (1.6%)
Subjects who died (whole post-vaccination period)	44 (1.2%)	43 (1.2%)	51 (2.3%)	57 (2.5%)	113 (6.3%)	121 (6.6%)

Source: Adapted from 125614/0.22 Annex 1 Table 22, p. 72
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

AEs of special interest (pIMDs) – Reporting of pIMDs occurred throughout the whole post-vaccination period. The proportions of subjects reporting the occurrence of pIMDs during select time periods are below.

Table 16 – Subjects reporting the occurrence of pIMDs at selected time points (Zoster-006 TVC – EOS analysis)

	SHINGRIX N = 7695 n (%)	Placebo N = 7710 n (%)
Subjects with pIMDs M0 – M3	13 (0.2%)	22 (0.3%)
Subjects with pIMDs M0 – M14	39 (0.5%)	59 (0.8%)
Subjects with pIMD s whole post-vaccination period	87 (1.1%)	105 (1.4%)

Source: Adapted from 125614/0.25 Annex 3 Table 262, p. 32

Comparative analysis indicated that there was no difference between treatment groups in the proportions of subjects reporting pIMDs or subjects reporting pIMDs by SOC or PT during M0 – M14. Overall, no clinically significant imbalances were noted between treatment groups with regard to the nature and incidence of the most commonly reported pIMDs during any time period. See Section 6.0 for an accounting of the pIMDs judged related to vaccination by the investigator.

5.2 Study Zoster-022: Zoster-022 was a phase 3, randomized, observer-blind, placebo-controlled, multicenter, clinical endpoint efficacy trial designed to assess the prophylactic efficacy, safety and immunogenicity of SHINGRIX when administered IM on a M0/M2 schedule to HZ-naive adults aged 70 years and older stratified 3:1 by age (70 – 79 and ≥ 80 YOA). The study initiation date was 02-AUG-2010 and completion date was 24-JUL-2015. The DLP for the Final HZ efficacy analysis (time point for primary efficacy analysis) was 01-JUL-2014, and the DLP for the EOS database freeze was 12-OCT-2015.

5.2.1 Study Design: See Section 5.1.1.

5.2.2 Study Objectives

Primary objective - To evaluate VE in the prevention of HZ compared to placebo in adults ≥ 70 YOA, as measured by the reduction in HZ risk.

Secondary objectives

- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 70 YOA
- To evaluate vaccine safety and reactogenicity
- Additional secondary objectives evaluated SHINGRIX VE compared to placebo with regard to reduction in the duration of severe 'worst' HZ-associated pain, reduction in use of pain medication and reduction of HZ-associated complications compared to placebo in subjects with confirmed HZ as well as reduction in overall and HZ-related mortality and hospitalizations

Select exploratory objective

- To evaluate vaccine induced humoral immune responses and the persistence of response after two injections of study vaccine in subjects ≥ 70 YOA and by age strata

5.2.3 Study Population: Male or female subjects ≥ 70 YOA were eligible for the study if they were capable of giving informed consent, had no history of HZ or previous vaccination against HZ or VZV, or had a confirmed or suspected immunosuppressive or immunodeficient condition due to disease or therapy.

5.2.4 Endpoints and Criteria for Study Success

Primary endpoint - Confirmed HZ cases during the study in the modified Total Vaccinated Cohort (mTVC)

Secondary endpoints

- Occurrence of overall PHN – incidence of PHN calculated using the mTVC
- Safety endpoints – see secondary safety endpoint for Zoster-006
- Additional secondary endpoints: duration of severe 'worst' HZ-associated pain, incidence of HZ-complications and duration of pain medication administered for HZ, all in subjects with confirmed HZ, as well as incidence of overall and HZ-related mortality and hospitalizations.

Select exploratory endpoints

- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38 – anti-gE Ab concentration as determined by ELISA, in a subset of subjects at Months 0, 3, 14, 26 and 38

Criterion for study success - The primary objective was demonstrated if the LB of the two-sided 95% CI of HZ VE was above 10%.

Triggers for study analysis

The final HZ efficacy analysis for Zoster-022 was planned when the following conditions were reached:

- At least 278 confirmed HZ cases were accrued in the mTVC
- 75% of the initial sample size in each stratum had at least 36 months of follow-up and the remaining subjects had at least 30 months of follow-up

The EOS analysis was planned for when a total of at least 35 PHN cases in subjects ≥ 70 YOA were accrued when pooled across Zoster-006 and Zoster-022. The Final HZ efficacy analysis and the EOS analysis of Zoster-022 were conducted at the same time.

5.2.5 Populations Analyzed: See Section 5.1.5.

5.2.6 Subject Disposition

Subjects vaccinated, completed and withdrawn

The number and proportions of subjects vaccinated, completed and withdrawn are presented below. Per protocol, a subject who completed the last contact was considered to have completed the study and subjects who did not complete the last study were considered a withdrawal.

Table 17 – Numbers and proportions of subjects vaccinated, completed and withdrawn (Zoster-022 TVC)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)	Total N = 13900 n (%)
Subjects completed	5770 (83.0%)	5760 (82.9%)	11530 (83.0%)
Subjects withdrawn	1180 (17.0%)	1189 (17.1%)	2369 (17.0%)

Source: Adapted from 125614/0 Zoster-022 CSR, Table 20, p. 274 and 125614/0.29 Annex 8, Table 556, p. 101
N = number of subjects in the TVC, EOS analysis
n = number of subject in that category
% = n/N

The most commonly reported reasons for withdrawal from the study (> 1% of either treatment group) were serious adverse event (6.8%), consent withdrawal not due to an AE (5.6%), lost to follow-up with a complete vaccination course (1.7%) and 'other' (1.5%). Non-serious AE was cited by 0.7% and 0.2% of subjects in the SHINGRIX and Placebo groups, respectively, as a reason for withdrawal. The proportions of subjects withdrawn and the reasons for withdrawal were comparable between treatment groups.

Subjects available for analyses

The number and proportions of subjects available for safety analyses in the TVC of those enrolled are presented below.

Table 18 – Numbers and proportions of subjects available for safety analyses (Zoster-022 TVC)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
Total Enrolled Cohort	7408	100.0%	7406	100.0%
Subjects excluded from all statistical analyses	453	6.1%	450	6.1%
Total Effective Cohort	6955	93.9%	6956	93.9%
Study vaccine dose not administered but subject number allocated	5	<0.1%	6	<0.1%
Total Vaccinated Cohort	6950	93.8%	6950	93.8%

Source: Adapted from 125614/0 Zoster-022 CSR, Table 6.18, p. 3760

Of the subjects enrolled, 93.8% were evaluated for safety in the TVC overall and within each treatment group. Of the subjects excluded from all statistical analyses, 865 subjects (5.8% of the Total Enrolled cohort) were excluded from one site in Mexico due to deviations from GCP identified by the applicant. These subjects were analyzed for safety separately. See Section 6.0.

The number and proportions of subjects from the TVC who were eligible for efficacy analysis in the mTVC are presented below.

Table 19 – Numbers and proportions of subjects in the TVC excluded from the mTVC with reasons for exclusion (Zoster-022 TVC)

	SHINGRIX N	SHINGRIX %	Placebo N	Placebo %
Total Vaccinated Cohort	6950	100.0%	6950	100.0%
Study vaccine dose not administered per protocol	3	< 0.1%	4	<0.1%
Wrong replacement or study vaccine administered	12	0.2%	8	0.1%
Subjects who did not receive two doses	390	5.6%	305	4.4%
Subjects had an episode of HZ prior to 30 days after Dose 2	4	<0.1%	11	0.2%
mTVC	6541	94.3%	6622	95.2%

Source: Adapted from 125614/0 Zoster-022 CSR, Table 6.18, p. 3760

The primary reason subjects in the TVC were excluded in the mTVC for the primary analysis of efficacy was due to the subject not receiving two doses.

Exposure – Of subjects in the TVC at the EOS analysis, 5.6% in the SHINGRIX group and 4.4% in the Placebo group did not receive two doses. The most common reason for subjects not receiving two doses was "Visit not done" (65.6% and 62.3% of subjects who received one dose in the SHINGRIX and Placebo groups, respectively). Other common reasons for subjects receiving only one dose was investigator decision of "Protocol violation or outside of time window" (10.2% and 9.5% subjects who received one dose in the SHINGRIX and Placebo groups, respectively), subject decision of "Other" (7.1% and 6.9% subjects who received one dose in the SHINGRIX and Placebo groups, respectively) and subject decision of "Non-serious unsolicited AE" (8.7% and 5.6% of one-dose subjects in the SHINGRIX and Placebo groups, respectively).

5.2.7 Demographics and Baseline Characteristics

The majority of subjects (54.0%) in the TVC were from Europe; the remaining subjects were from North America (19.3%), Australasia (19.0%) and Latin America (7.7%).

Demographic characteristics were comparable between treatment groups. The mean and median age of subjects in the study was 75.6 and 74.0 years, respectively, with a maximum age of 96 years. The proportion of females to males was 54.9% to 45.1%. The majority of subjects were not American Hispanic or Latino (91.7%). The proportions of subjects by geographic ancestry (> 1.0% of study population) were as follows: White of Caucasian/European heritage (76.3%), Asian heritage (17.6%), Other (4.4%), and African heritage/African American (1.1%). Compared to the demographics of the overall population, the North American cohort had higher proportions of subjects who were African-American (3.5%), and were not American Hispanic or Latino (97.9%) and lower proportions of subjects of Asian heritage (0.7%).

The majority of subjects in both treatment groups (94.9% and 95.4% in the SHINGRIX and Placebo groups, respectively) reported at least one pre-existing condition. No clinically significant differences were observed between treatment groups for the types of pre-existing conditions classified by MedDRA SOC or by specific PT.

5.2.8 Efficacy Results

The primary analysis method for VE considered the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. Incidence rates and VE with 95% CIs were tabulated.

There were 246 confirmed cases of HZ in the mTVC at the EOS analysis step, 23 in the SHINGRIX group and 223 in the Placebo group after a median follow-up time of 3.9 years (range 0 to 4.5 years) and a mean follow-up time of 3.7 years (standard deviation 0.8 years). No subject reported more than one episode of HZ. Calculated VE overall and by age strata is presented below.

Table 20 – VE: First or only episode of HZ during the entire study period using Poisson method (Zoster-022 mTVC)

									VE		
	SHINGRIX				Placebo					95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
70 – 79 YOA	5114	17	19346.5	0.9	5189	169	19247.5	8.8	90.02	83.54	94.32
≥ 80 YOA	1427	6	5058.5	1.2	1433	54	4920.3	11.0	89.08	74.65	96.16
OVERALL **	6541	23	24405.1	0.9	6622	223	24167.8	9.2	89.79	84.29	93.66

Source: Adapted from 125614/0 Zoster-022 CSR Table 23, p. 283
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 age stratum and region

The incidence of HZ in the Placebo and SHINGRIX groups, respectively, were 9.2 and 0.9 per 1,000 PY for an overall VE against HZ in subjects ≥ 70 YOA of 89.79% (95% CI; 84.29%, 93.66%). The primary study objective regarding HZ VE in subjects ≥ 70 YOA was met as the LL of the 95% CI was above 10%.

The method of HZ case confirmation by treatment group and overall is below; 92.3% of cases overall were confirmed by PCR.

Table 21 – Distribution of confirmed HZ episode determined by PCR or HZAC (Zoster-022 mTVC)

	SHINGRIX		Placebo		Total	
Confirmed HZ episode determined by:	n	%	n	%	n	(%)
PCR	19	82.6%	208	93.3%	227	92.3%
HZAC	4	17.4%	15	6.7%	19	7.7%
Total (either HZAC or PCR)	23	100.0%	223	100.0%	246	100.0%

Source : 125614/0 Zoster-022 CSR Table 7.86, p. 4177
HZAC = Herpes Zoster Adjudication Committee
PCR = Polymerase Chain Reaction
n /%= number /percentage of confirmed HZ cases in a given category

Secondary objectives

The overall reduction in PHN risk was calculated similarly to the HZ risk using the exact inference on the RR stratified for age and region conditionally to the total number of PHN cases observed and time at risk.

Table 22 – Vaccine efficacy: First or only episode of PHN during the entire study period using Poisson method (ZOSTER-022 mTVC)

									VE		
	SHINGRIX				Placebo					95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
OVERALL **	6541	4	24436.9	0.2	6622	28	24601.4	1.1	85.49	58.52	96.30

Source: Adapted from 125614/0 Zoster-022 CSR Table 25, p. 288
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

Although it was not an objective, overall PHN VE was calculated by age strata (with adjustment by region) as seen below.

Table 23 – Vaccine efficacy: First or only episode of PHN during the entire study period by age stratum using Poisson method (ZOSTER-022 mTVC)

									VE		
	SHINGRIX				Placebo					95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
70-79YOA *	5114	2	19371.4	0.1	5189	22	19571.1	1.1	90.80	62.57	98.95
≥80YOA *	1427	2	5065.5	0.4	1433	6	5030.3	1.2	65.76	-91.58	96.62

Source: Adapted from 125614/0 Zoster-022 CSR Table 25, p. 288
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 region

Results of analyses of other secondary VE objectives were as follows:

- *Reduction in the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 with confirmed HZ* – the applicant was unable to conclude on this objective.
- *Reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 70* – VE with regard to reduction in overall mortality and overall hospitalizations was not performed. No HZ-related mortality was reported. There were five HZ-related hospitalizations reported in the Placebo group and none in the SHINGRIX group, but the applicant was unable to conclude on this objective.
- *Reduction in incidence of HZ-associated complications compared to placebo subjects ≥ 70 with confirmed HZ* – At least one HZ-related complication other than PHN in subjects

with confirmed HZ was reported by 4.3% (1/23) of subjects of the SHINGRIX group and 4.5% (10/223) of subjects in the Placebo group. Ophthalmic HZ was reported by 1 subject (1/23 or 4.3%) in the SHINGRIX group and 6 subjects (6/223 or 2.7%) in the Placebo group. Other complications reported by subjects with confirmed HZ in the Placebo group were 2 reports of disseminated disease and 3 reports of neurologic disease. The applicant was unable to conclude on this objective.

- *Reduction in use of pain medications compared to placebo in subjects ≥ 70 YOA with confirmed HZ* – Reduction in use of pain medication in subjects with confirmed HZ was a secondary objective while reduction in duration of pain medication in subjects with confirmed HZ was a secondary endpoint. The objective for VE in reduction in use of pain medication in subjects ≥ 70 YOA with confirmed HZ was met as 43.5% and 71.8% of subjects ≥ 70 YOA with confirmed HZ in the SHINGRIX and Placebo groups, respectively, reported HZ-associated pain medication use for a VE for reduction in use of pain medication of 39.6% (95% CI: 10.8%, 64.8%).
- *Reduction in duration of pain medication compared to placebo in subjects ≥ 70 YOA with confirmed HZ* – The endpoint for VE in reduction in duration of pain medication in subjects ≥ 70 YOA with confirmed HZ was met as the overall median (minimum, maximum) duration of pain medication administered for HZ was 30.0 (6.0 – 660) days for the SHINGRIX group and 38 (1.0 – 4529.0) days for the Placebo group. The mean duration (SD) for the SHINGRIX group and Placebo groups, respectively, were 109.5 (200.85) days and 199.3 (530.6) days. Overall VE in the reduction of duration of pain medication associated with HZ in subjects ≥ 70 YOA was 49.25% (95%CI: 2.92%, 73.47%).

Subpopulation analyses - Additional unpowered analyses were conducted to examine HZ VE by gender, by region, and over time. No clinically significant differences in VE were noted in the sub-population analyses by region, and VE was comparable between genders. The estimates of HZ VE over time were as follows: Year 1 [97.04% (95% CI: 88.88%, 99.65%)], Year 2 [91.26% (95% CI: 79.97%, 96.90%)], Year 3 [81.55 (95% CI: 61.97%, 92.04%)], Year 4 [85.07% (95% CI: 64.47%, 94.83%)].

5.2.9 Immunogenicity Results

Similarly to Zoster-006, all subjects had blood sampling for humoral immunogenicity assessment at M0 and M3 and a small proportion of randomly assigned subjects in the TVC (6.4% at baseline) were in the ATPc for immunogenicity - Humoral and adapted ATPc for immunogenicity – Humoral subset (primary population for analysis of humoral immune response) which included subjects who did not meet elimination criteria for the cohort at each sampling time point.

At baseline pre-vaccination, 99.5% of SHINGRIX and Placebo recipients in the ATPc for immunogenicity - Humoral were seropositive (seropositivity cut-off = 97 mIU/mL) for anti-gE Ab. At M3 and beyond, 100.0% of SHINGRIX recipients in the adapted ATPc for immunogenicity – humoral were seropositive.

The pre-vaccination anti-gE Ab GMCs at baseline in the SHINGRIX group were 1547.2 mIU/mL (95% CI: 1394.3, 1717.0). One month post-vaccination Dose 2 at M3, the GMC value was 51048.0 mIU/mL, (95% CI: 44796.2, 54521.1). At M14, M26 and M38 the GMCs were 16171.8 mIU/mL (95% CI: 14967.8, 17472.6), 13091.9 mIU/mL (95% CI: 12141.1, 14117.2), and 10452.2 mIU/mL (95% CI: 9654.4, 11315.9), respectively.

The MGI of anti-gE concentrations in the SHINGRIX group at Months 3, 14, 26 and 38 over pre-vaccination in the SHINGRIX group were 33.0 (95% CI: 29.4, 37.1), 10.6 (95% CI: 9.4, 12.0), 8.2 (95% CI: 7.3, 9.3), and 6.5 (95% CI: 5.7, 7.3), respectively. In the Placebo group, the MGI over pre-vaccination was not higher than 1.0 at any time point.

The proportions of subjects in the SHINGRIX adapted ATP cohort for immunogenicity - Humoral that were vaccine responders at M3, M14, M26 and M38 were 95.9%, 79.6%, 71.5% and 66.1%, respectively. In the Placebo group the VRR for anti-gE Ab concentrations was not higher than 3.7% at any time point.

5.2.10 Safety Results

Solicited AEs - Solicited AEs were collected for 7 days (Days 0 – 6) on a randomized subset of subjects with a planned age stratification of 1:1 for the 70 – 79 and ≥ 80 YOA age strata. Approximately 7.4% of the subjects in the TVC (SHINGRIX group N = 512, Placebo group N = 513) were randomized to this subset. Over 97% of subjects in both treatment groups complied with the return of general and local diary cards.

Overall by subject, 79.0% and 29.5% of subjects in the SHINGRIX and Placebo groups reported at least one solicited symptom during the 7-day post-vaccination period. By type of symptom, 53.0% of subjects in the SHINGRIX group and 25.1% of subjects in the Placebo group reported at least one solicited general symptom and 74.1% of subjects in the SHINGRIX group and 9.9% of subjects in the Placebo group reported at least one solicited local symptom. The proportions of subjects in the SHINGRIX group reporting any solicited symptom, any solicited local or any solicited general symptom were comparable after Dose 1 and Dose 2.

The proportions of subjects in the SHINGRIX as compared to the Placebo group reporting any Grade 3 solicited symptom, any Grade 3 solicited general symptom, any Grade 3 solicited local symptom were 11.9% vs. 2.0%, 6.0% vs. 2.0% and 8.5% vs. 0.2%, respectively. The proportions of subjects in the SHINGRIX group reporting any Grade 3 solicited symptom, Grade 3 solicited general symptom and Grade 3 solicited local symptom were comparable after Dose 1 as compared to Dose 2. The proportions of subjects ≥ 70 YOA in the 7-day diary card subsets of the SHINGRIX group who reported any grade and Grade 3 solicited events, solicited local events and solicited general events were comparable between Zoster-006 and Zoster-022.

Pain was the most commonly reported solicited local symptom; any grade (Grade 3) pain was reported by 68.7% (4.4%) of subjects in the SHINGRIX group and 8.5% (0.2%) of subjects in the Placebo group. Any grade (Grade 3) redness was reported by 39.2% (4.0%) of subjects in

the SHINGRIX group and 1.0% (0.0%) of subjects in the Placebo group. Any grade (Grade 3) swelling was reported by 22.6% (1.6%) of subjects in the SHINGRIX group and 0.4% (0.0%) of subjects in the Placebo group. The proportions of subjects in the SHINGRIX group reporting each specific solicited local symptom (any grade or Grade 3) were comparable after Dose 1 and Dose 2. The median duration of pain, redness or swelling after SHINGRIX administration was 2.0 to 3.0 days and was similar after Dose 1 as compared to Dose 2.

The proportions of subjects in the 7-day diary card subset in each treatment group reporting any grade and Grade 3 solicited general symptoms are below.

Table 24 – Incidence of solicited general symptoms reported during the 7-day (Day 0 – 6) post-vaccination period overall (Zoster-022 - TVC diary card)

	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%)

Source: Adapted from 125614/0 Zoster-022 CSR Table 36 p. 329
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
(*) = temperature defined on oral, axillary or rectal temperature

The proportions of SHINGRIX recipients reporting any grade of each specific solicited general symptom was marginally increased between Dose 1 and Dose 2, except for shivering; any grade shivering was reported by 7.6% and 12.0% of SHINGRIX recipients after Dose 1 and Dose 2 and Grade 3 shivering was reported by 0.2% and 1.0% of SHINGRIX recipients after Dose 1 and Dose 2, respectively. Overall per dose, the median duration of fatigue, GI symptoms, headache, myalgia, shivering and fever reported after SHINGRIX administration was 1.0 to 2.0 days. The median duration of each specific solicited event following Dose 1 and Dose 2 were generally comparable.

Unsolicited AEs – The proportions of subjects reporting the occurrence of unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period are presented below.

Overall, 55.5% and 32.6% of subjects in the TVCs of the SHINGRIX group and Placebo group, respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period.

The most commonly reported unsolicited AEs reported within the 30-day post-vaccination period in the SHINGRIX group were reactogenicity events (IS pain, IS erythema, pyrexia, headache and fatigue) primarily reported by subjects who were not included in the 7-day diary card subset. A post-hoc tabulation performed by the applicant of the proportions of subjects in the 7-day diary card subset reporting unsolicited AEs during the 30-day post-vaccination period indicated that 27.1% and 25.8% of subjects overall in the 7-day diary card subset in the SHINGRIX and Placebo groups, respectively, reported at least one unsolicited AE during the 30-day post-vaccination period. At least one Grade 3 non-serious unsolicited AE was reported by 5.9% and 2.8% of subjects in the SHINGRIX and Placebo groups, respectively. By SOC, the most reports were in the General disorders and administration site conditions SOC (3.2% and 0.4% of subjects in the SHINGRIX and Placebo groups, respectively). By PT, the most common Grade 3 non-serious unsolicited AEs was IS pain (1.4% and < 0.05% of SHINGRIX and Placebo groups, respectively).

MAEs – From M0 – M8, 41.5% and 41.9% of subjects in the TVCs of the SHINGRIX and Placebo groups, respectively, reported the occurrence of a MAE. Comparative analysis indicated that events by PT that were more commonly reported as MAEs by subjects in the SHINGRIX group were those that had been solicited on the 7-day diary card, such as IS pain, IS swelling, IS erythema and headache. By SOC, comparative analysis indicated that higher proportions of subjects in the SHINGRIX (3.4%) as compared to the Placebo group (2.7%) reported a MAE in the General disorders and administration site conditions SOC. The most commonly reported medically attended events from M0 – M8 for both groups were nasopharyngitis, urinary tract infection and bronchitis, which were reported by comparable proportions of subjects in each vaccination group. Comparative analysis indicated that from M0 – M8 a few MAEs by PT were reported more frequently by the SHINGRIX than the Placebo group (IS pain, IS erythema, IS swelling, asthenopia, headache, ear infection, and arthropod bite) or more frequently by the Placebo than the SHINGRIX group (gingivitis, peripheral swelling, cholelithiasis and rosacea). See Section 6.0 for MAEs of interest.

SAEs –The proportions of subjects in each treatment group who reported SAEs during select time periods post-vaccination are below.

Table 25 – Global summary of SAEs during selected time periods (Zoster-022 TVC)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)
Subjects with at least 1 SAE reported (30-day post-vaccination period)	157 (2.3%)	158 (2.3%)
Subjects with at least 1 SAE reported (M0 – M3)	248 (3.6%)	228 (3.3%)
Subjects with at least 1 SAE reported (M0 – M14)	891 (12.8%)	939 (13.5%)

Source: Adapted from 125614/0.25 Table 196, p. 258

Comparative analysis indicated that there was no difference between treatment groups for the proportions of subjects reporting SAEs during the M0 – M14 time period. There was no excess risk noted for the proportions of subjects in the SHINGRIX group reporting SAEs by SOC or by specific PT during M0 – M14, while the PT of aortic stenosis was reported more frequently in the Placebo group and more subjects in the Placebo group reported events in the Cardiac disorders SOC.

There were no imbalances noted between treatment groups for the proportions of subjects overall reporting SAEs during the other selected time periods or for proportions of subjects reporting events classified by specific PT or SOC, and no medically relevant clusters with regard to types of SAEs reported were noted. See Section 6.0 for an accounting of the SAEs judged related to vaccination by the investigator.

Deaths - The proportions of subjects in the TVC of each treatment group who died during select time periods post-vaccination are shown below.

Table 26 – Subjects with fatal SAEs (who died) during select time periods (Zoster-022 TVC)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)
Subjects with fatal SAE reported [30-day (Days 0 – 29) post-vaccination period]	3 (0.0%)	5 (0.1%)
Subjects with fatal SAE reported (Day 0/Month 0 – Month 3)	7 (0.1%)	11 (0.2%)
Subjects with fatal SAE reported (Day 0/Month 0 – Month 14)	71 (1.0%)	82 (1.2%)
Subjects with fatal SAE reported (whole post-vaccination period)	426 (6.1%)	461 (6.6%)

Source: 125614/0.22 Annex 1, Table 53, p. 134
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting symptom

Comparative analysis indicated that there was no difference between treatment groups for the proportions of subjects reporting fatal SAEs (who died) during M0 – M14 or for the proportions of subjects reporting fatal SAEs by SOC or specific PT during M0 – M14.
There were no clinically significant imbalances noted between treatment groups for the proportions of subjects who died during the selected time periods overall or for events classified

by PT or SOC, and no medically relevant clusters with regard to types of fatal events reported were noted. See Section 6.0 for a discussion regarding the death of a subject judged vaccine-related by the investigator.

AEs of special interest (pIMDs) – The proportions of subjects reporting the occurrence of pIMDs during select time periods are below.

Table 27 – Subjects reporting the occurrence of pIMDs during select time periods (Zoster-022 TVC)

	SHINGRIX N = 6950 n (%)	Placebo N = 6950 n (%)	Total N = 13900 n (%)
Subjects with ≥ 1 pIMD reported (M0 – M3)	19 (0.3%)	15 (0.2%)	34 (0.2%)
Subjects with ≥ 1 pIMD reported (M0 – M14)	52 (0.7%)	47 (0.7%)	99 (0.7%)
Subjects with ≥ 1 pIMD reported (whole post-vaccination period)	92 (1.3%)	97 (1.4%)	189 (1.4%)

Source: Adapted from 125614/0.25, Annex 3 Table 290, p. 74

Comparative analysis indicated that there was no difference between treatment groups for the overall proportions of subjects reporting pIMDs from M0 – M14 or the proportions of subjects reporting pIMDs by SOC or specific PT during M0 – M14. Overall, no clinically significant imbalances were noted between treatment groups with regard to the nature and incidence of the most commonly reported pIMDs during any time period. See Section 6.0 for an accounting of pIMDs judged related to vaccination by the investigator.

6.0 Integrated Summary of Safety: Key Points

The integrated summary of safety (ISS) evaluated two populations, subjects in the TVCs of Zoster-006 and Zoster-022, referred to as the TVC of the "main pooling" (N = 29,305 subjects, 14,645 in the SHINGRIX group and 14,660 in the Placebo group), and the "broader safety pooling" (N = 15,493) which consisted of 14,645 subjects who received SHINGRIX in the TVCs Zoster-006 and Zoster-022 and an additional 848 subjects who received at least one dose of SHINGRIX from other studies in the development program which qualified for inclusion in the broader pooling. The requirements for study inclusion in the broader pooling analysis were as follows: study participants had received the SHINGRIX formulation intended for licensure which was administered IM at M0 and M2, study was completed at time of the DLP used for the safety pooling (12-OCT-2015) with at least one year of safety follow-up post-vaccination. The following table contains the studies, number of subjects from each study, and number of US subjects included in the safety poolings.

Table 28 – Clinical studies with SHINGRIX included in the main and broader safety pooling analyses

Study	Age	Subjects in safety pooling analysis – SHINGRIX	Subjects in safety pooling analysis – Placebo	US subjects exposed to SHINGRIX	Main pooling	Broader pooling	Years of SAE follow-up post last vaccination
006	≥ 50	7695	7710	1027	yes	yes	4.4 years median/subject
022	≥ 70	6950	6950	939	yes	yes	4.2 years median/subject
003* 011* 012* 013* 024*	≥ 60	166	-	-	no	yes	1 month 10 months 22 months 34 months 70 months
004‡	≥ 50	406€	-	68	no	yes	12 months
010*	≥ 50	150	-	49	no	yes	12 months
032¥	≥ 50	30			no	yes	12 months
033θ	≥ 50	96		0	no	yes	12 months
Total		15493	14660	2083	14645 (SHINGRIX only)	15493 (SHINGRIX only)	

Source: Adapted from 125614, Summary of Clinical Safety, Table 2, p. 23
* = SHINGRIX group only
‡ = SHINGRIX staggered group/control
¥ = SHINGRIX IM group
€ = 415 subjects were part of TVC and received FLU-D-QIV at Dose 1 but only 406 received at least 1 dose of SHINGRIX at the subsequent doses – for NA although 133 subjects were part of the TVC and received FLU-D-QIV at Dose 1, only 129 of them received at least 1 dose of SHINGRIX at subsequent doses
θ = subjects had a prior history of HZ

The proportion of subjects who were not in Zoster-006 and Zoster-022 comprised only 5.5% of the subjects in the broader pooling analysis, and safety data on these subjects will be presented separately (i.e., not pooled with the subjects in the main pooling).

Safety information from studies not included in the broader safety pooling was evaluated during the review of each study. The rationale for exclusion of these studies from the broader safety analysis and the number of subjects in each study who received at least one dose of SHINGRIX is as follows:

- Explo-CRD-004 and extension studies (45 subjects) - only had 10 months of safety follow-up and in extension studies (Zoster-018 and Zoster-019) only SAEs related to the study procedure and suspected cases of HZ were recorded
- Zoster-023 (20 subjects) – only had 6 months of follow-up after last vaccination
- Zoster-001 and Zoster-015 (59 subjects and 74 subjects, respectively) – included only immunocompromised adults
- Zoster-026 (354 subjects) - one year safety data was not available at the time of the DLP for the safety pooling

- Zoster-007 (651 subjects) – only safety data up to 1 month after last vaccination was available at the time of file preparation

Safety results for the co-administration group for Zoster-004 (413 subjects) and the SC administration group for Zoster-032 (30 subjects) and Zoster-007 were evaluated in the context of their respective reviews. See Section 8.0.

Deaths

Main pooling analysis - The proportions of subjects who died overall during select time periods relative to vaccination is below.

Table 29 – Main safety pooling analysis – number and percentage of subjects who died during select time periods (Main pooling TVC)

	SHINGRIX N = 14645 n (%)	Placebo N = 14660 n (%)
Subjects who died from first dose up to 30 days post last vaccination	6 (0.0%)	8 (0.1%)
Subjects who died from first dose up to 365 post last vaccination	113 (0.8%)	132 (0.9%)
Subjects who died during the whole post-vaccination period	634 (4.3%)	682 (4.7%)

Adapted from 125614/0.22 Table 91, p. 237
N = number of subjects with at least one administered dose
n (%) = number (percentage) reporting the symptom at least once

Comparative analysis indicated that there was no difference between treatment groups with regard to the overall proportions of subjects reporting fatal events from first dose to 365 days post last vaccination period and the proportions of subjects reporting fatal events during that period by SOC and by specific PT. There were no clinically significant imbalances with regard to the proportions of subjects reporting fatal events overall, or by SOC or specific PT for the selected time periods.

One death was judged vaccine-related by the investigator, but not the applicant. The subject, a 90 YO male with a past medical history of stable immune thrombocytopenia for approximately 10 years prior to vaccination, was noted to be pancytopenic 72 days after Dose 1, and diagnosed with acute myeloid leukemia (AML) on the basis of a bone marrow biopsy 75 days after Dose 1. He was treated with ondansetron in preparation for treatment for AML but developed neutropenic sepsis 97 days after Dose 1, which resulted in his death (b) (6) later. No clustering of similar events in the SHINGRIX group was noted temporally associated with vaccination and CBER analysis did not detect a difference between treatment groups for the proportions of subjects in the main pooling reporting events contained in the narrow Standardized MedDRA query (SMQ) of hematopoietic cytopenias and narrow sub-SMQ of hematopoietic leukopenias reported as MAEs from M0 – M3 and M0 – M8 or as SAEs during M0 – M14.

Broader pooling analysis – No subjects in the broader pooled analysis (ex-Zoster-006 and Zoster-022) died within the 30 day post last vaccination period. Six subjects died from first dose

to 365 days last vaccination and an additional three subjects died during the whole post-vaccination period. No safety signals were identified after review of the fatal SAEs.

SAEs

Main pooling analysis - The proportions of subjects reporting SAEs during select time periods relative to vaccination are below.

Table 30 – Main safety pooling analysis – number and percentage of subjects reporting SAEs during select time periods (Main pooling TVC)

	SHINGRIX N = 14645 n (%)	Placebo N = 14660 n (%)
Subjects reporting SAEs from first dose up to 30 days post last vaccination	342 (2.3%)	327 (2.2%)
Subjects reporting SAEs from first dose up to 365 post last vaccination	1482 (10.1%)	1525 (10.4%)

Adapted from 125614/0.25 Annex 2, Table 219, p. 420
N = number of subjects with at least one administered dose
n (%) = number (percentage) reporting the symptom at least once

Comparative analysis indicated that there was no difference between treatment groups with regard to the overall proportions of subjects reporting SAEs from first dose to 365 days post last vaccination period. There was no excess risk noted for the proportions of subjects in the SHINGRIX group reporting SAEs by SOC during the 365 day post last vaccination period. One specific PT, supraventricular tachycardia, was reported more frequently during this period by subjects in the SHINGRIX group (N = 6) than the Placebo group (N = 0) while aortic stenosis, retinal detachment and cardio-respiratory arrest were reported more frequently by Placebo subjects during this period. To evaluate the excess number of subjects reporting the PT of supraventricular tachycardia in the SHINGRIX group, CBER evaluated the proportions of subjects in the main pooling reporting MAEs by the PTs contained in the narrow SMQ of Cardiac arrhythmias and the narrow sub-SMQ of supraventricular tachyarrhythmias from M0 – M3 and from M0 – M8, as well as the proportions of subjects reporting events in these SMQs as SAEs reported within 30 days post-vaccination and reported from M0 – M14. Therefore, while there was a difference between the vaccination groups with regard to the proportions of subjects reporting SAEs by the specific PT of supraventricular tachycardia during the 365 day post-vaccination period, no differences were found between vaccination groups for the proportions of subjects reporting events included in the narrow sub-SMQ of supraventricular tachyarrhythmia which contains the PT of supraventricular tachycardia along with terms for other events that are pathophysiologically similar to or synonymous with supraventricular tachycardia.

The most frequently reported SAEs by PT (main pooling) from first dose up to 365 days post last vaccination were as follows: pneumonia, atrial fibrillation, myocardial infarction, coronary artery disease, cerebrovascular accident, and cardiac failure. There was no clinically significant difference between treatment groups for the proportions of subjects reporting these SAEs by PT during the 365 day post last vaccination period as per the applicant. For signal detection, CBER analyzed the proportions of subjects reporting these SAEs from M0 – M14 using available

narrow SMQs and sub-SMQs containing these PTs [Cardiac failure SMQ, Ischemic heart disease SMQ, Other ischemic heart disease sub-SMQ, Myocardial infarction sub-SMQ, Central nervous system (CNS) vascular disorders SMQ and Ischemic and hemorrhagic CNS vascular conditions sub-SMQs] or when SMQs were unavailable, by higher level MedDRA terms containing the reported events by PT (e.g., for pneumonia the higher level term "Lower respiratory tract and lung infections"). After CBER analysis, no difference was noted between treatment groups for the most commonly reported SAEs by available narrow SMQ or higher grouping during the M0 – M14 period.

During the whole post-vaccination period, 30 subjects, 15 in each treatment group, reported SAEs that were assessed as related to vaccination by the investigator. None of the SAEs were assessed by the applicant as related to vaccination. CBER assessed the following events as likely related to SHINGRIX administration given the information provided:

- Lymphadenitis – An 82 YO male with a non-contributory past medical history developed left axillary lymphadenopathy two days after administration of SHINGRIX Dose 1 to the left deltoid muscle on study Day 0 (D0). Pyrexia (beginning on D0 and lasting two days) and ecchymosis of the left axilla and the thoracic trunk (beginning on D2 and resolving on Study day 11) were also reported. As the lymphadenopathy diminished prior to the second vaccination, Dose 2 of SHINGRIX was administered to the left deltoid muscle on D55. After Dose 2 the left axillary lymph nodes remained enlarged for a month. A decision was made to remove the nodes to rule out a malignant process. The pathology report indicated benign non-specific lymphadenitis. The event was reported as resolved on D289.
- IS pain, IS erythema, chills, pyrexia – A 73 YO female with a non-contributory medical history reported fever up to 40˚ C (104˚ F), and moderate IS erythema, chills and IS pain one day after receipt of Dose 1 of SHINGRIX. According to the narrative, no treatment was necessary and the reported events lasted up to three days. The subject withdrew from the study and did not receive a second dose.

Other SAEs judged by the investigator as related to SHINGRIX administration were assessed by CBER as less likely due to SHINGRIX administration for one or more of the following reasons: a) potentially related to the vaccination procedure but not the vaccine, b) lack of temporal association, lack of biologic plausibility, or lack of clustering of similar events temporally associated with SHINGRIX vaccination (and as compared to receipt of Placebo), c) having potential alternative etiologies or d) unable to determine (e.g., rare event potentially due to chance, nature of event includes frequent exacerbations). The SAEs (some of which were serious pIMDs) were as follows: nervous system disorder, Guillain-Barre syndrome (GBS), bacterial arthritis, allergic granulomatous angiitis, pancreatitis, immune thrombocytopenic purpura (exacerbation), musculoskeletal chest pain, eczema (exacerbation), erysipelas, ulcerative colitis, HZ oticus, and acute MI. The SAEs in the Placebo group judged related to vaccination by the investigators were as follows: syncope (two subjects), hypotension, immune thrombocytopenic purpura, polymyalgia rheumatica, rheumatoid arthritis (two subjects), gastric

adenocarcinoma, cerebral infarction, cerebrovascular accident, GBS, IVth nerve paralysis, loss of consciousness, mononeuritis, glomerulonephritis, and neurosensory deafness.

Broader pooling analysis – No SAEs reported by subjects in the broader pooling (excluding subjects in Zoster-006 and Zoster-022) were judged by the investigator or applicant to be causally related to SHINGRIX.

pIMDs

Main pooling analysis – The proportions of subjects in the main pooling reporting the occurrence of pIMDs during select time periods are presented below.

Table 31 – Main safety pooling analysis – number and percentage of subjects reporting the occurrence of a pIMD by time window (Main pooling TVC)

	SHINGRIX 50 – 69 N = 5887 n (%)	SHINGRIX ≥ 70 N = 8758 n (%)	Placebo 50 – 69 N = 5887 n (%)	Placebo ≥ 70 N = 8773 n (%)	Overall SHINGRIX N = 14645 n (%)	Overall Placebo N = 14660 n (%)
pIMD - during whole post-vaccination period	69 (1.2%)	110 (1.3%)	84 (1.4%)	118 (1.3%)	179 (1.2%)	202 (1.4%)
pIMD from first dose up to 365 days post last vaccination	33 (0.6%)	57 (0.7%)	44 (0.7%)	61 (0.7%)	90 (0.6%)	105 (0.7%)
pIMD from first dose up to 30 days post last vaccination period	13 (0.2%)	17 (0.2%)	14 (0.2%)	16 (0.2%)	30 (0.2%)	30 (0.2%)

Source: Adapted from 125614/0.25. Annex 3, Table 321, p. 120

Comparative analysis indicated that there was no difference between treatment groups for the proportions of subjects reporting the occurrence of pIMDs during the first dose up to 365 day post last vaccination period or for the proportions of subjects reporting events by SOC or specific PT. No substantial differences were noted between treatment groups for subjects reporting pIMDs by specific PT or by SOC during the select periods.

During the whole post-vaccination period, 16 subjects in the SHINGRIX group and 18 subjects in the Placebo groups reported pIMDs judged vaccine-related by the investigator. None of the pIMDs were assessed by the applicant as related to vaccination.

Serious pIMDs were discussed in the SAE section above. The following non-serious pIMDs were judged related to SHINGRIX vaccination by the investigator: rheumatoid arthritis (two subjects), reactive arthritis, psoriasis (exacerbation, two subjects), myasthenic syndrome, thrombocytopenia, exfoliative dermatitis, polymyalgia rheumatica (PMR), alopecia areata and hypersensitivity vasculitis. Although it could not be ruled out, causality of these events could not be ascribed to SHINGRIX administration due to alternative etiologies, lack of temporal association, and/or lack of clustering of similar events associated with vaccination. The non-serious pIMDs judged related to vaccination in the Placebo group were PMR (two subjects),

Sjogren's syndrome (2 subjects), psoriasis, erythema nodosum, Behcet's syndrome, ulcerative colitis, inclusion body myositis and uveitis.

Broader pooling analysis - Five additional SHINGRIX recipients reported six pIMDs in the broader pooling analysis during the whole post-vaccination period. From first dose up to 365 days post last vaccination period, two subjects reported exacerbations of ulcerative colitis (5 days after Dose 2 and 27 days after Dose 1) and one subject reported vocal cord paralysis (268 days after Dose 2). None of the pIMDs were judged vaccine related by the investigator or applicant.

Unsolicited events during the 30 day post-vaccination period (main pooling)

The following events were reported with an incidence of > 1.0% in the SHINGRIX group during the 30-day post-vaccination period and were reported with a higher frequency in the SHINGRIX as compared to the Placebo group (main pooling): IS pruritus, malaise, pain, IS warmth, dizziness, upper respiratory tract infection, arthralgia and pain in extremity. Other events which occurred in less than 1% of SHINGRIX recipients but were reported with higher frequencies in that group include feeling hot, feeling cold, decreased appetite, flushing, asthenia, influenza like illness, lethargy, somnolence, insomnia, and hyperhidrosis. Additionally, although reported by less than 1% of subjects in the SHINGRIX group, there were imbalances between treatment groups in the number of subjects reporting gout during this time period; 27 and 8 subjects in the SHINGRIX and Placebo groups, respectively, reported gout or gouty arthritis.

Other events of interest

Inclusion of the events below do not imply causal association with SHINGRIX; some events were included due to imbalances noted in their occurrence between treatment groups and/or an incidence higher than expected, and others are of general interest when assessing vaccine safety. Unless otherwise indicated, these assessments were made on subjects in the TVC of the main pooling.

Optic ischemic neuropathy - Three events of optic ischemic neuropathy temporally associated with vaccination were reported in the SHINGRIX group. Optic ischemic neuropathy was not reported in the Placebo group. The events, none of which were judged related by the investigators, were as follows:

- A 72 YO female with a current medical history of hypertension and senile cataract reported the non-serious event of optic ischemic neuropathy 29 days after administration of the first dose of SHINGRIX. No medications or ophthalmologic assessment were reported by the site. The AE was assessed as not recovered/not resolved at the end of the study.
- An 85 YO female with a history of non-critical carotid disease bilaterally, coronary artery disease, and headache noted diplopia in her right eye 17 days after Dose 1 of SHINGRIX. Work-up included a computed tomography scan (negative) and referral to a neurologist. The subject subsequently noted visual loss in the left eye 47 days after vaccination, and was seen shortly thereafter by an ophthalmologist who reported

complete vision loss in the left eye with a diagnosis of arteritic anterior optic neuropathy. The subject was treated with steroids and had a temporal artery biopsy (which showed inflammation but no giant cells). This SAE was recorded as recovered/resolved with sequelae at study end.

- An 81 YO female subject with a history of cystoid macular degeneration of the right eye and prior bilateral cataract removal reported sudden loss of vision in her right eye 48 days after administration of the first dose of SHINGRIX. After the diagnosis of optic ischemic neuropathy was made, prednisone was prescribed pending the results of a temporal artery biopsy. The temporal artery biopsy was negative and the subject was titrated off steroids. The SAE was recorded as not recovered/not resolved at study end.

No clinically significant imbalances between treatment groups were noted with regard to other ocular inflammatory, ocular neurovascular or ocular vascular events temporally associated with vaccination.

Arteritic optic ischemic neuropathy is associated with vasculitis such as temporal arteritis and the more common, non-arteritic type is associated with small vessel circulatory insufficiency. Arteritic and non-arteritic optic ischemic neuropathy have been reported at rates of 0.4 to 1.3 and 2.3 to 10.2 per 100,000 PY, respectively [(Chen, 2016), (Johnson, 1994) and (Hattenhauer, 1997)].

Nine subjects reported temporal arteritis during the whole post-vaccination period, six in the SHINGRIX group and three in the Placebo group. Of these, three subjects, all in the SHINGRIX group, reported temporal arteritis during the 365 day post last vaccination period, at 14, 204 and 235 days after Dose 2. PMR is associated with temporal arteritis [Gonzales-Gay, 2005]; there were 17 and 12 subjects in the SHINGRIX and Placebo groups, respectively, who reported PMR as a pIMD during the 365 day post last vaccination period.

Amyotrophic lateral sclerosis (ALS) – There were three subjects in the SHINGRIX group reporting ALS in the 365 day post last vaccination period, at 80, 173 and 211 days post-Dose 2. In the Placebo group, ALS was mentioned in the narrative of one subject with the SAE of "death" during this period; the onset of ALS in this subject appears to be during the year post last vaccination. The incidence rate of ALS is approximately 2/100,000 PY [Chio, 2013].

Osteonecrosis – Five subjects in the SHINGRIX group reported six AEs (five serious, one non-serious) of osteonecrosis in the 365 day post-vaccination period and no cases were reported in the Placebo group. Two subjects reported three exacerbations of osteonecrosis at 75 (non-serious event) and 178 days (both hips) after Dose 2. The other events were reported at 4 days after Dose 1 (with pain reported for a half year prior to presentation), 95 and 132 days after Dose 2. Narratives suggested that several of these subjects reported worsening prior to vaccination.

Convulsions – According to CBER analysis, eight subjects in the SHINGRIX group and one subject in the Placebo group reported events by PT during the 30-day post-vaccination period that are included in the narrow SMQ of convulsions. Available narratives were reviewed; of these subjects two had alternative etiologies for their event (intracranial aneurysm, acute subdural hematoma after a fall) and two had a prior history of convulsions. A higher proportion of subjects reporting events in the MedDRA higher level term (HLT) of Disturbances in consciousness (under the Higher level group term Neurological disorders NEC) during the 30-day post-vaccination period, which includes such PTs as lethargy (reported by 0.22% and 0.05% of subjects in the SHINGRIX and Placebo groups, respectively) and somnolence (reported by 0.25% vs. 0.08% of subjects in the SHINGRIX and Placebo group, respectively). As previously noted, dizziness was also reported by higher proportions of subjects in the SHINGRIX (1.24%) as compared to the Placebo group (0.77%).

Arthralgia – In the main pooling, arthralgia was reported by 252 (1.72%) and 171 (1.17%) subjects in the SHINGRIX and Placebo groups, respectively, during the 30-day post-vaccination period.

Supraventricular tachyarrhythmias – CBER detected an imbalance between vaccination groups (SHINGRIX N = 10, Placebo N = 2) for the proportions of subjects in the TVC of Zoster-006 reporting events in the MedDRA narrow sub-SMQ of supraventricular tachyarrhythmias as unsolicited AEs and MAEs during the 30-day post-vaccination period. For signal detection purposes, CBER analyzed the proportions of subjects in the main pooling reporting events in the narrow Cardiac arrhythmia SMQ, Tachyarrhythmias sub-SMQ and Supraventricular tachyarrhythmias sub-SMQ as unsolicited AEs during the 30-day post-vaccination period or MAEs during M0- M14, and did not detect a difference for events in these narrow SMQs during those time periods.

Anaphylaxis – One subject, a 54 YO female in Zoster-006, had an event coded with the PT of anaphylaxis rated of mild intensity. This subject reported the AEs of Grade 1 (mild) IS pain and erythema and Grade 3 pyrexia, fatigue, nausea, chills and disorientation on D0 after Dose 1. The events resolved by Day 3 without medical attention or treatment. The applicant assessed this event as not a case of anaphylaxis according to the Brighton case definition of anaphylaxis.

GBS and acute polyneuropathies – There were five cases of GBS recorded during the whole postvaccination period; two in the SHINGRIX group (181 and 716 days after Dose 2) and three in the Placebo group (39 days after Dose 1 and 1201 and 1292 days after Dose 2). One case of Miller-Fisher syndrome reported in the Placebo group 419 days after Dose 2. No imbalance was noted by CBER between treatment groups for the proportions of subjects reporting MAEs by specific PT under the higher level term of acute polyneuropathies from M0 – M8.

<u>Post-hoc safety analysis for subjects from closed site in Mexico</u>

The applicant provided an analysis of safety (SAEs, fatal SAEs and pIMDs) for 1,536 subjects in the total enrolled cohorts from two sites in Mexico (one in Zoster-006 and one in Zoster-022)

under the auspices of a single PI, which were closed due to significant violations of GCP. Overall, an equal number of subjects (768) were in each vaccination group. Similar proportions of subjects (4.1% and 4.8% in the SHINGRIX and Placebo group, respectively) from these centers reported an SAE during M0 – M14. No clinically significant differences between vaccination groups were noted with regard to reports of SAEs by SOC. No SAEs were considered related to vaccination by the investigator. During the whole post-vaccination period, 57 (7.4%) subjects in the SHINGRIX group and 49 (6.4%) subjects in the Placebo group died. The most commonly reported causes of death by PT during the whole post-vaccination period were similar to that seen in the main pooling; acute myocardial infarction, cardio-respiratory arrest, and pneumonia, and no clinically significant imbalances were noted between vaccination groups for these events by PT. Five subjects reported pIMDs, 2 (0.3%) in the SHINGRIX group and 3 (0.4%) in the Placebo group. Only one pIMD was reported within 6 months of vaccination; a serious pIMD of inflammatory bowel disease in a 78 YO (PID 21933 Zoster-022) in the SHINGRIX group with a history of irritable bowel syndrome at baseline occurring eight days after Dose 1. None of the pIMDs were considered related to vaccination by the investigator.

7.0 Integrated Summary of Efficacy: Key Points

There were pre-specified objectives and endpoints for the pooled analysis of Zoster-006 and Zoster-022.

Primary objectives and corresponding endpoints of the pooled analysis

- To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 70 YOA across both studies (this was a powered primary objective). Corresponding endpoint – incidence of PHN in the mTVC during the entire study period in subjects ≥ 70 YOA
- To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥ 70 YOA across both studies (this was a re-estimation of VE for an objective already demonstrated previously). Corresponding endpoint – occurrence of confirmed HZ during the entire study period in subjects ≥ 70 YOA.

Select secondary objective and corresponding endpoint of the pooled analysis

- To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA with confirmed HZ. Corresponding endpoint – occurrence of PHN during the entire study period in all subjects with confirmed HZ.

Success criteria for the primary objectives of the pooled analysis – The VE PHN objective was demonstrated if the LB of the 95% CI was > 0% and the HZ VE objective would be demonstrated if the LB of the 95% CI was > 10%.

PHN VE primary objective results - Of the 40 subjects reporting PHN in the pooled analysis of subjects ≥ 70 YOA, 4 were in the SHINGRIX group and 36 were in the Placebo group. The incidence of PHN in the SHINGRIX group was 0.1/1000 PY and the incidence in the Placebo group was 1.2/1000 PY for a PHN VE of 88.78% (95% CI: 68.70%, 97.10%) as seen below.

Table 32 – First or only episode of PHN during the entire study period overall using Poisson method (mTVC, subjects ≥ 70 YOA, pooled 006/022)

										VE		
		SHINGRIX				Placebo					95% CI	
Study	Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
Pooled	≥70YOA**	8250	4	30760.3	0.1	8346	36	30942.0	1.2	88.78	68.70	97.10

Source: Adapted from 125614/0 Zoster-022, Table 85
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

The co-primary objective regarding SHINGRIX VE against PHN for subjects ≥ 70 YOA in the pooled analysis was met as the LB of the 95% CI > 0.

HZ VE primary objective results - Of the 309 subjects ≥ 70 YOA with confirmed HZ episodes in the mTVC for the pooled analysis, 284 subjects were in the Placebo group and 25 were in the SHINGRIX group. The overall HZ VE in subjects ≥ 70 YOA was 91.30 (95% CI: 86.9%, 94.5%) and were comparable between age groups as seen below.

Table 33 – 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)

										VE		
		SHINGRIX				Placebo					95% CI	
Study	Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL
Pooled	70 – 79 YOA	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.27	86.04	94.85
Pooled	≥ 80 YOA	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.37	80.22	96.94
Pooled	≥70YOA**	8250	25	30725.5	0.8	8346	284	30414.7	9.3	91.30	86.88	94.46

Source: Adapted from 125614/0 Zoster-022 CSR Table 83, p. 486
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 age stratum and region

The primary objective of the pooled analysis of HZ VE for subjects ≥ 70 YOA in the pooled analysis was met as the LB of the 95% CI was > 10%. The HZ VE results are similar to the results of HZ VE in Zoster-022 and consistent with the results in subjects ≥ 70 YOA in Zoster-006.

PHN VE secondary objective results - In subjects with a confirmed HZ episode, PHN was reported in 4 of 32 subjects (12.5%) of subjects in the SHINGRIX group and 46 out of 477 (9.6%) of subjects in the Placebo group. The overall VE for reduction in PHN incidence in

subjects ≥ 50 with confirmed HZ was 0.29% (95% CI: -161.53%, 65.57%). The applicant was unable to conclude on this objective.

8.0 Additional Clinical Studies

Zoster-026 was a phase 3, randomized, open-label, multicenter clinical trial designed to assess the safety and immunogenicity of SHINGRIX when administered IM as two doses to 354 generally healthy adults ≥ 50 YOA randomized to receive SHINGRIX in a 1:1:1 ratio on one of three schedules; M0/M2 (original schedule), M0/M6 or M0/M12. Acceptability criteria were based on the VRR for anti-gE Ab by ELISA at one month post-Dose 2 being ≥ 60% for each schedule, and non-inferiority criteria were based on comparisons of the anti-gE GMCs [upper bound (UB) of the 97.5% CI for the anti-gE ELISA GMC ratio (M0/M2 over M0/M6 and M0/M2 over M0/M12) at one month post-Dose 2 is below 1.5]. The humoral immune response to SHINGRIX at one month post-Dose 2 when administered on a M0/M6 schedule was acceptable and non-inferior to that of the M0/M2 schedule. The non-inferiority of the M0/M12 schedule as compared to the M0/M2 schedule was not demonstrated. Safety was comparable between scheduling groups.

Zoster-004 was a phase 3, randomized, open-label, multicenter clinical trial designed to assess the safety and immunogenicity of SHINGRIX when co-administered with GSK Biologicals' quadrivalent influenza vaccine (QIV) versus non-concomitant administration of the two vaccines to 828 generally healthy adults ≥ 50 YOA randomized to receive the vaccines in a 1:1 ratio on one of two schedules; SHINGRIX and QIV at M0 and SHINGRIX at M2 (co-administration group) or QIV at M0 and SHINGRIX at M2 and M4 (control group). Acceptability criteria were based on the VRR for anti-gE Ab by ELISA at one month post-Dose 2 being ≥ 60% for the co-administration group, and non-inferiority criteria were based on comparisons of the anti-gE GMCs [upper bound (UB) of the 95% CI for the anti-gE ELISA GMC ratio (control group over co-administration group) at one month post-Dose 2 is below 1.5] and the hemagglutinin inhibition (HI) antibody geometric mean titers (GMTs) [upper bound (UB) of the 95% CI for the HI ELISA GMT ratio (control group over co-administration group) at one month post-Dose 2 is below 1.5] for each strain included in the QIV vaccine. The humoral immune response to SHINGRIX at one month post-Dose 2 when co-administered with QIV schedule was acceptable and non-inferior to that of the control schedule. The HI antibody humoral immune response after co-administration of the QIV dose with SHINGRIX was non-inferior to that of the control schedule. Safety was comparable between the co-administration and control groups.

Zoster-007 was a phase 3, randomized, double blind multicenter study to evaluate the consistency, immunogenicity, safety, and reactogenicity of three lots of SHINGRIX when administered intramuscularly on a M0/M2 schedule to adults ≥ 50 years of age. Three parallel groups were randomized to receive one of three lots of SHINGRIX (SHINGRIX Lot A, SHINGRIX Lot B, and SHINGRIX Lot C), each composed of unique randomized combinations of antigen and adjuvant lots. The clinical study interim report provided in the BLA presents immunogenicity results for the active phase, which was up to the 1 month post-dose 2 (M3) assessment. The safety data provided was collected for approximately 3.5 months after completion of the active phase. The primary confirmatory objective for the lot-to-lot consistency

in terms of anti-gE humoral immune response between the three manufacturing lots of the SHINGRIX at one month post-Dose 2 was met as all 95% CIs around the GMC ratios between all pairwise comparisons of lots were within the interval bound by 0.67 and 1.5. No safety signals were identified from the active phase data provided in the BLA.

Zoster-032 - Zoster-032 was a phase 3, randomized, open-label, single center clinical trial which assessed the safety and immunogenicity of SHINGRIX when administered SC as compared to IM in 60 adults ≥ 50 YOA of Japanese ethnic origin. The study, originally designed as multicenter with a planned enrollment of 500 subjects (60 subjects of JEO in Part 1 followed by 440 additional subjects in Part 2), had confirmatory co-primary immunogenicity and safety objectives comparing IM and SC administration of SHINGRIX. As a safety holding rule related to the proportions of subjects reporting Grade 3 local reactions in the SC group as compared to the IM group was met during Part 1 of the study, the applicant suspended Part 2 of the study. Safety results indicated that while Grade 3 solicited general symptoms were reported by similar proportions of subjects in each vaccination group, Grade 3 solicited local symptoms were reported by 56.7% of subjects in the SC group as compared to 6.7% of subjects in the IM group; Grade 3 redness and swelling (defined as > 100 mm in diameter) were reported by 56.7% and 33.3% of subjects in the SC group and 6.7% and 6.7% of subjects in the IM group, respectively. However, only one subject in the SC group reported Grade 3 limitation of arm movement (defined as preventing daily activity). Comparison of humoral immune responses between vaccination groups indicated that the VRRs were 100% for both groups and the geometric mean concentrations (GMCs) were comparable at M3 (one month post-Dose 2).

Zoster-033 – Zoster-033 was a phase 3 open-label, one-arm, non-IND study which evaluated the safety and immunogenicity of SHINGRIX when administered IM on a M0/M2 schedule to 96 subjects with a prior physician-documented history of HZ. The primary immunogenicity endpoint of the VRR at one month after Dose 2 being ≥ 60% was met. The occurrence of HZ was not an endpoint of the study; HZ was to be reported as an AE or SAE as applicable. Six subjects, two of whom had reported more than one prior episode of HZ, reported nine episodes of unconfirmed HZ during the study period of M0 – M14. Five of the subjects received anti-viral medication. Additionally, two subjects reported acute herpetic neuralgia in temporal association with vaccination without reporting HZ during the study; the applicant notes that clinical details which would inform a robust conclusion regarding these events are lacking. The applicant plans to discuss with CBER the design of an additional study (Zoster-062) in this population to collect "robust and rigorous data on the use" of SHINGRIX in subjects with previous HZ.

9.0 Pharmacovigilance Plan

GSK submitted a PVP to monitor safety concerns that could be associated with the administration of SHINGRIX. The applicant identified hypersensitivity reactions including anaphylaxis, and pIMDs as important potential risks, and recommends routine pharmacovigilance for both. For pIMDs, GSK also plans to closely monitor for these AEs in proposed clinical studies to gauge long-term efficacy.

The applicant has a pre-defined list of pIMDs that are likely due to autoimmune or immune mediated inflammatory processes that they include in study protocols. The applicant has submitted an extensive list of MedDRA PTs, including pathology such as arteritis, encephalitis, and Guillain-Barré syndrome, which it will use to identify cases of pIMDs as part of routine pharmacovigilance activities.

In addition, the applicant also states that long-term efficacy and the need for a booster dose, and long-term immunogenicity in adults 50 years of age and older, are safety concerns for which there is missing information. GSK proposes two long term follow-up studies of individuals administered SHINGRIX in the premarket clinical trials to assess these safety concerns. The study addressing the need for a booster dose will measure the persistence of immune responses, and administer one or two additional doses.

In addition to the safety concerns enumerated by GSK, FDA requested that the applicant update their PVP to address imbalances discovered in the pre-licensure clinical trial data. Specifically, FDA requested that the applicant address risks from inflammation after exposure to SHINGRIX, which could result in ocular pathology (e.g., optic ischemic neuropathy, temporal arteritis, polymyalgia rheumatica), and osseous pathology (e.g., arthralgia and gout).

The applicant submitted a proposal for revising the PVP, and is working with FDA to ensure this adequately addresses safety concerns. The sponsor will describe their proposed plans during the VRBPAC.

10.0 Summary and Focus of Questions to the Committee

In studies Zoster-006 and Zoster-022, two IM doses of SHINGRIX demonstrated HZ VE efficacy of 97.16% [95% CI: (93.72%, 98.97%)] and 89.79% [95% CI: (84.29%, 93.66%)], respectively. While the point estimate of VE against PHN was 100.00%, 85.49% and 88.78% in Zoster-006, Zoster-022 and the pooled analysis of subjects ≥ 70 YOA across both studies, CBER considers the value of the vaccine with regard to prevention of PHN to be due to its efficacy against HZ based on the results of PHN VE in subjects ≥ 50 YOA across both studies with confirmed HZ being 0.29% (95% CI: -161.53%, 65.57%).

The majority of subjects experienced local and/or general reactogenicity of short duration. Severe reactogenicity was common especially in the younger age strata. Overall, SAEs, deaths, and potentially immune mediated diseases were reported in similar proportions of subjects in Shingrix and Placebo groups included in the submitted safety database. Continued pharmacovigiliance is needed to further evaluate the relationship to vaccination with regard to adverse events for which there were observed imbalances, for uncommon adverse events reported temporally associated with SHINGRIX vaccination as well as other events that may not have been observed given the sample size evaluated.

The Committee will be asked whether the safety and efficacy data support licensure of SHINGRIX for the prevention of HZ in adults aged 50 years and older.

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