BLA Clinical Review Memorandum

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Reviewer Name(s)	Paula Ehrlich Agger MD MPH Rebecca Reindel MD
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Supervisory Concurrence	Meghan Ferris MD MPH Andrea Hulse MD
Applicant	GlaxoSmithKline Biologicals
Established Name	Zoster vaccine recombinant, adjuvanted
(Proposed) Trade Name	SHINGRIX
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	Recombinant glycoprotein E subunit vaccine with $AS01_B$ adjuvant (QS21 and MPL with liposomes)
Dosage Form and Route of Administration	Lyophilized glycoprotein E antigen with liquid $AS01_B$ adjuvant in separate monodose vials, reconstituted prior to administration
Dosing Regimen	Two intramuscular administrations two to six months apart
Indication and Intended Population	Prevention of herpes zoster (shingles) in adults aged 50 years and older
Orphan Designated	No

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GLOSSARY

Ab	Antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ATP	According to protocol
BOI	Burden of illness
CAPA	Corrective and preventive actions
CBER	Center for Biologics Evaluation and Review
CDP	Clinical Development Plan
CI	Confidence interval
CRP	C reactive protein
CSR	Clinical study report
D	Day
DOPC	Dioleoylphosphatidylcholine
eCRF	Electronic case report form
EOP2	End of Phase 2
GCP	Good Clinical Practice
gE	Glycoprotein E
GMC	Geometric mean concentrations
GSK	GlaxoSmithKline
HCT	Hematopoietic stem cell transplantation
HIV	Human immunodeficiency virus
HLGT	Higher level group term
HLT	Higher level term
HZ	Herpes zoster
HZAC	Herpes Zoster Ascertainment Committee
IC	Immunocompromised
ICS	Intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
iPSP	Initial Pediatric Study Plan
IS	Injection site
JEO	Japanese ethnic origin
LB	Lower bound
M	Month
MAE	Medically attended event
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
MPL	Monophosphoryl lipid A
mTVC	Modified Total Vaccinated Cohort
PBMC	Peripheral blood mononuclear cells
PeRC	Pediatric equity in Review Committee
PHN	Post-herpetic neuralgia
PI	Package insert
pIMD	Potential immune-mediated inflammatory disease
PCR	Polymerase chain reaction
PT	Preferred term

QIV	Quadrivalent influenza vaccine
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SMQ	Standardized MedDRA query
SOC	System organ class
TVC	Total Vaccinated CohortUS United States
VE	Vaccine efficacy
VL	Viral load
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VZV	Varicella zoster virus
YOA	Years of age
ZBPI	Zoster Brief Pain Inventory

1. Executive Summary

Introduction: The Applicant, GlaxoSmithKline (GSK), has submitted BLA 125614 to support licensure of HZ/su, a recombinant glycoprotein E (gE) subunit vaccine with $AS01_B$, a proprietary adjuvant containing QS-21 and MPL with liposomes, for the prevention of herpes zoster (HZ) in adults ≥ 50 years of age (YOA). HZ is a condition caused by reactivation of the latent varicella zoster virus (VZV) following primary VZV infection, usually as varicella (chickenpox), in childhood. HZ occurs due to a decline in cell-mediated immunity associated with advancing age or immunocompromise, and generally presents as a unilateral, vesicular rash in a single dermatome accompanied by pain, which may be severe and persistent. Approximately one million cases of HZ occur annually in the United States (US) and it is estimated that one in three people experience HZ in their lifetime. HZ incidence, HZ-associated complications, and the severity of HZ increase with advancing age. The condition may cause substantial morbidity including pain, interference with activities of daily living (ADL) and reduction in quality of life (QoL), especially in older affected individuals. In support of licensure of their vaccine for the prevention of HZ in adults 50 years of age and older, the Applicant submitted the results of two randomized, placebo-controlled, observer-blind clinical endpoint studies, Zoster-006, and Zoster-022, which enrolled subjects ≥ 50 YOA and ≥ 70 YOA, respectively. The Applicant's rationale for conducting Zoster-022 was to enrich the overall database for subjects 70 years and older, anticipating that they would provide the most robust estimated VE against post-herpetic neuralgia (PHN), the most common complication of HZ. Conducting this study separately from Zoster-006 mitigated against the risk of negatively biasing VE against HZ if VE decreased, as originally assumed, with increasing age. Additionally, conducting a separate clinical endpoint study in subjects ≥ 70 YOA would enable a more robust evaluation of VE against HZ as well as providing more information about the safety of the product in the ≥ 70 YOA group.

The Applicant also submitted data from studies evaluating alternative dose scheduling of the vaccine (Zoster-026); concomitant administration of the vaccine with quadrivalent influenza vaccine [(QIV), Zoster-004)]; interim data to support lot consistency (Zoster-007); studies to support the antigen and adjuvant dose selection and need for a two-dose series (Explo-CRD-004, Zoster-003 and extension studies, Zoster-023, Zoster-010); as well as studies evaluating subcutaneous (SC) vaccine administration (Zoster-032), and vaccination of subjects with physician-diagnosed prior HZ (Zoster-033). Additionally, the application included the clinical

study reports (CSRs) of two studies (Zoster-001 and Zoster-015) conducted under IND 13879 which evaluated HZ/su in select immunocompromised populations.

Phase 3 clinical endpoint design and analysis - Zoster-006 and Zoster-022 were conducted in parallel, with subjects ≥ 70 YOA randomized to Zoster-006 or Zoster-022 prior to randomization to treatment group. The studies were performed at the same sites in eighteen countries (including the US) with a randomization ratio of 1:1 (HZ/su:saline placebo). The primary objective of each study was to evaluate HZ/su VE in the prevention of HZ as compared to placebo as measured by the reduction in HZ risk. Secondary objectives in both studies included evaluation of HZ/su VE in the prevention of overall PHN (evaluated in all subjects, not only in subjects with confirmed HZ), and HZ/su safety and reactogenicity. The immune responses and persistence of these responses to HZ/su vaccination were exploratory objectives. 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 as well as a minimum follow-up period to ensure adequate safety and efficacy data collection.

Both studies enrolled age-eligible subjects without a prior history of HZ, HZ or varicella vaccination and who had no confirmed or suspected immunodeficiency or immunocompromising conditions due to disease or therapy. Subjects received two doses of HZ/su or placebo, administered IM at Months 0 (M0) and 2 (Visits 1 and 2). There were four additional scheduled visits and monthly contacts after M3 between study visits to collect safety information and to document the occurrence of, or follow-up for, HZ. All subjects had blood sampling for immunogenicity assessment at M0 (pre-vaccination) and M3, and a randomized subset of subjects had sampling at subsequent visits to assess persistence of immune response to vaccination. Clinically suspected HZ cases were documented by rash history, digital photography, and sampling of available rash lesions for polymerase chain reaction (PCR) assay to test for VZV. Additional visits were scheduled for clinically suspected HZ cases at which time information relevant to the HZ episode was recorded, such as concomitant medications, medical attention, or HZ-related complications. Subjects with clinically suspected HZ were also provided with diary cards to document HZ-associated pain and effect on physical functioning and QoL. Visits or contacts ceased once the subject reported a 28-day/4-week pain-free interval. 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 PCR testing of lesion samples. The primary HZ efficacy endpoint was analyzed on the modified Total Vaccinated Cohort (mTVC), which consisted of subjects who received two doses and did not report a confirmed case of HZ prior to one month after Dose 2.

Safety monitoring for Zoster-006 and Zoster-022 included recording of 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 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, potential immune-mediated inflammatory diseases (pIMDs) and SAEs that were fatal or deemed vaccine-related 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 of study product, by product received.

Zoster-006 results - At the Final HZ efficacy analysis, there were 6 cases of confirmed HZ recorded in the mTVC of the HZ/su 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 HZ/su group and 9.1 per 1,000 PY in the Placebo group. Of the 216 total confirmed HZ cases, 89.4% were determined by PCR and 10.6% were determined by the HZAC. The primary endpoint of Zoster-006 was met as the lower bound (LB) of the two-sided 95% confidence interval (CI) of HZ/su HZ VE was above 25% [VE: 97.16% (95% CI: 93.72%, 98.97%)]. The study was powered to demonstrate HZ VE for the age strata 50 – 59 and 60 – 69 YOA; the endpoint was met as HZ VE was above 10% at 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. Considering all subjects (independent of the occurrence of HZ) there were 18 cases of overall PHN reported in the Placebo group and none reported in the HZ/su group at the End of Study (EOS) analysis for an overall PHN VE of 100.00% (95% CI: 77.11%, 100.00%).

The TVC (HZ/su group N = 7695, Placebo group N = 7,710) was the primary population for the evaluation of safety. Of subjects in the TVC, 57.9% (HZ/su group N = 4,457, Placebo group N = 4,464) were included in 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 with all subjects ≥ 70 YOA included)] 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 HZ/su 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 HZ/su 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 HZ/su group, respectively; Grade 3 redness and swelling were not reported by subjects in the Placebo group. The most commonly reported solicited general symptoms of any grade, overall by subject were myalgia, fatigue and headache reported by 46.3%, 45.9% and 39.2% of subjects in the HZ/su 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 HZ/su 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 21.5% (0.3%) of subjects in the HZ/su 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 HZ/su administration was 3 days and 1 – 2 days, respectively. The proportions of subjects in the HZ/su 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. Overall, 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, except for a small difference for the proportions of subjects reporting events in the supraordinate and subordinate Standardized MedDRA queries (sub-SMQ) of Cardiac arrhythmias and Supraventricular tachyarrhythmias (HZ/su > Placebo), mainly driven by imbalances in the proportions of subjects reporting the PTs of atrial fibrillation/flutter and to a lesser extent, arrhythmia. These imbalances were not noted in Zoster-022.

Zoster-022 results: At the end of study (EOS) analysis, there were 23 cases of confirmed HZ recorded in the mTVC of the HZ/su 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 HZ/su group and 9.2 per 1,000 PY in the Placebo group. Of the 246 total confirmed HZ cases, 92.3% were

determined by PCR and 7.7% were determined by the HZAC. The primary endpoint of Zoster-022 was met, as the LB of the two-sided 95% CI of HZ/su HZ VE was above 10% [VE: 89.79% (95% CI: 84.29%, 93.66%)]. Considering all subjects (independent of the occurrence of HZ) there were 28 cases of PHN reported in the Placebo group and 4 reported in the HZ/su 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% (HZ/su 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 HZ/su administration: overall by subject, any grade (Grade 3) was reported by 68.7% (4.4%) of subjects in the HZ/su 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 HZ/su 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 HZ/su administration overall by subject were fatigue and myalgia reported by 32.9% (3.2%) and 31.2% (2.4%) of subjects in the HZ/su 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 HZ/su and 2.6% (0.4%) of subjects in the Placebo groups. The approximate median durations of solicited local and solicited general symptoms reported after HZ/su administration were 2 – 3 days and 1 – 2 days, respectively.

There were no clinically significant differences between treatment groups for the proportions of subjects in the TVC who died or reported pIMDs or SAEs during select time points post-vaccination or for the nature of the events reported.

Integrated safety results - In the main pooling of safety (HZ/su TVC N = 14645, Placebo TVC N = 14660) no differences were observed between treatment groups in the proportions of subjects reported as having fatal events, SAEs or pIMDs during select time periods post-vaccination; nor were clinically significant differences noted for the nature of events reported. Although the Applicant did not consider any SAEs, pIMDs or deaths related to study product, Investigators ascribed causal association with vaccination to 15 subjects with SAEs (including serious pIMDs) in each treatment group and ascribed causal association to non-serious pIMDs reported by eleven and nine subjects in the HZ/su and Placebo groups respectively. CBER assessed that two subjects in the HZ/su group had SAEs (one subject each with lymphadenitis and reactogenicity symptoms including pyrexia > 39˚ C) that were vaccine-related due to biologic plausibility, temporal association with vaccination and no plausible alternative etiology. Although relationship with HZ/su could not be ruled out for the other SAEs or pIMDs, it also could not be ascribed to HZ/su vaccination by CBER due to one or more factors such as information suggesting an association with the vaccine procedure rather than vaccine, information suggesting other potential alternative etiologies, a lack of temporal association, lack of clustering of similar events temporally associated with vaccination, lack of biologic plausibility, and/or no difference between the HZ/su and Placebo groups for the occurrence of the event. Additionally, although causal association with HZ/su cannot be ascribed for the following events, imbalances were noted between treatment groups (HZ/su > Placebo) for the following events included in a proposed post-marketing safety study: gout and gouty arthritis, and arthralgia reported during the 30-day post-vaccination period, as well as optic ischemic neuropathy (3 subjects reporting the event within 50 days of vaccination in the HZ/su group and 0 in the Placebo group).

An additional 848 subjects from other studies were included in a broader pooled safety analysis; no safety signals were noted after review of the data from these subjects.

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%) and was concordant with the results of HZ VE in subjects ≥ 70 YOA from Zoster-022. No conclusions can be drawn from the analysis of PHN VE on subjects ≥ 50 YOA in the mTVC with confirmed HZ [PHN VE: 0.29% (95% CI: -161.53%, 65.57%)].

Results from select additional studies - The primary immunogenicity endpoints were met in studies evaluating the non-inferiority of the humoral immune response to HZ/su when administered on a M0/M6 as compared to a M0/M2 schedule (Zoster-026), the non-inferiority of the humoral immune responses to HZ/su and quadrivalent influenza vaccine (QIV) given concomitantly compared to sequentially (Zoster-004), and the lot-to-lot consistency of HZ/su (Zoster-007). A study comparing the safety and immunogenicity of HZ/su administered subcutaneously (SC) as compared to IM was terminated after safety halting rules were triggered due to higher local reactogenicity in the SC administration group as compared to the IM administration group (Zoster-032). Following administration of HZ/su to subjects with prior HZ (Zoster-033) in a one arm, uncontrolled non-IND study, the primary immunogenicity endpoint of the acceptability of the vaccine response rate (VRR) one month after Dose 2 was met, but 6 of the 96 vaccinated subjects reported 9 episodes of unconfirmed HZ. The Applicant proposed a more robust evaluation of HZ/su in this population.

Consultations – The Pediatric Equity in Review Committee (PeRC) agreed with the Applicant's plan for a full waiver of studies of HZ/su in all pediatric age groups as it is impossible or highly impracticable to conduct clinical endpoint studies in the US pediatric population because the estimated annual number of cases is low and widely dispersed. On September 13, 2017, the Vaccines and Related Biological Products Committee (VRBPAC) voted unanimously that the data presented supported the safety and efficacy of HZ/su in individuals ≥ 50 YOA.

Conclusions – Demonstrated HZ VE in Zoster-006 (subjects ≥ 50 YOA) and Zoster-022 (subjects ≥ 70 YOA) was 97.16% (95% CI: 93.72%, 98.97%) and 89.79% (95% CI: 84.29%, 93.66%), respectively. HZ VE appears comparable in all age strata evaluated and durable up to four years post-vaccination. While the point estimates of "overall" PHN VE, calculated on all subjects in the mTVCs of Zoster-006 and Zoster-022, were 100.00% and 85.49%, respectively, no conclusions could be drawn about PHN VE evaluated on subjects ≥ 50 YOA with confirmed HZ across both studies. CBER considers the benefit of HZ/su in preventing PHN to be attributable to VE against HZ. The majority of subjects in the HZ/su group experienced local and/or general reactogenicity of short duration, severe reactogenicity was common, and reactogenicity decreased with increasing age. Overall, SAEs, deaths, and pIMDs were reported in similar proportions of subjects in HZ/su and Placebo groups during select time periods evaluated. Planned pharmacovigilance activities include enhanced and active surveillance (in a targeted safety study) for fourteen conditions identified because of their frequency in the pivotal studies, their prevalence in the target population, or because they were events of interest, while routine post-marketing pharmacovigilance activities will surveil for rare events and events that may not have been observed given the sample size evaluated.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Because the proportions of subjects in some racial groups were too low to analyze separately, for the purposes of analyzing efficacy and safety by race, the Applicant grouped them into four broader groupings which included the following subjects in parentheses: African (African heritage/African-American), Asian (Central/South Asian heritage, East Asian heritage, Japanese heritage or Southeast Asian heritage), White (Caucasian/European heritage or of Arabic/North African heritage), and Other (American Indian, Alaskan native, Native Hawaiian, Pacific Islander or Other). The pre-specified ethnic groups were American Hispanic/Latino or Not American Hispanic/Latino.

HZ VE by gender
VE was comparable between genders. In Zoster-006 overall HZ VE (95% CI) was 97% (93%, 99%) for females and 95% (88%, 99%) for males. In Zoster-022, overall HZ VE (95% CI) was 88% (80%, 94%) for females and 91% (83%, 96%) for males.

HZ VE by race
HZ VE was comparable for three of the four racial groups analyzed in Zoster-006 and Zoster-022, with the point estimates of VE ranging from 87% to 99% for these three groups and with the lowest LB of VE of ranging from 37% (in the "Other" group, Zoster-022) to 95% (White group, Zoster-006). HZ VE could not be demonstrated in either study for the group of African heritage due to low numbers of these subjects reporting HZ in each treatment group.

HZ VE by ethnicity
HZ VE was comparable between the two pre-specified ethnic groups in Zoster-006 and Zoster-022 with point estimates of VE ranging from 85% to 98% and the lowest LB of VE of ranging from 49% (American Hispanic or Latino in Zoster-022) to 94% (Not American Hispanic/Latino, Zoster-006).

Safety analyses by gender, race and ethnicity (TVC of main pooling)
The study was not powered to evaluate differences in VE or safety for these demographic groupings, so the clinical significance of any differences noted between groupings in these analyses is unknown. However, there was only minor variability, if any, for the proportions of subjects who reported the various safety events by gender, race and ethnicity.

Deaths -- The proportion of males in the HZ/su group who died during the 365-day post last vaccination period (1.2%) and whole vaccination period (6.1%) was higher than the proportions of females who died during those periods (0.5% and 3.0% respectively). This was comparable between treatment groups. In the HZ/su treatment group, no clinically significant differences were noted between racial or ethnic groups for the proportions of subjects who died up to 365 days post last vaccination and during the whole post-vaccination period.

SAEs and pIMDs – In the HZ/su treatment group, no clinically significant differences were noted between gender, racial or ethnic groups for the proportions of subjects who reported SAEs or pIMDs up to 365 days post last vaccination.

Unsolicited AEs reported during the 30-day post-vaccination period – In the HZ/su group, the proportions of subjects reporting unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period by race ranged from 35.2% (African race) to 56.9% (Asian race) and the proportions of females reporting events was higher than males (53.9% vs. 45.8%, respectively).

No differences were noted for the proportions of subjects who received HZ/su and reported unsolicited AEs by ethnic group.

Solicited AEs during the 7-day post-vaccination period - In the HZ/su group, no clinically significant differences were noted between gender, racial or ethnic groups for the proportions of subjects who reported at least one solicited symptom overall by subject during the 7-day post vaccination period. There were ranges in the proportions of subjects reporting types of solicited symptoms between racial and ethnic groups. For local and general symptoms, the proportions of subjects reporting in the African group was lowest (72.2% reported local and 61.1% reported general symptoms) while the proportions reporting in the Asian group were highest (84.6% reported local and 71.8% reported general symptoms). The proportions of subjects reporting solicited local and general symptoms was approximately 5% lower in the American Hispanic or Latino group as compared to the Not American Hispanic or Latino group, and the proportions of females reporting solicited local and general symptoms was approximately 9% and 11% higher, respectively, than males.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Introduction

HZ, which typically manifests as a painful unilateral rash in a dermatomal distribution, is caused by the reactivation of the neurotropic varicella zoster virus (VZV) from latency. Following primary infection of VZV as varicella (chickenpox), the virus establishes latency in the dorsal root, cranial nerve or autonomic ganglia along the entire neuroaxis (Yawn, 2013). Immunity against HZ is boosted by subclinical reactivation (endogenous boosting) or exposure to circulating VZV (exogenous boosting). Reactivation of the virus in the form of HZ occurs when VZV-specific cellular immunity declines or is diminished due to age-related immunosenescence, immunodeficiency or immunosuppression. Pain, which can be severe, may be experienced by patients with HZ during all three phases of the condition: the prodromal phase, acute or eruptive phase and post-herpetic phase. In the immunocompetent population, the incidence and severity of HZ, as well as the incidence of HZ-related complications, increases with increasing age.

HZ clinical course

The clinical course of HZ varies; it is generally mild in children and young adults, and more severe in immunocompromised individuals and older adults.

Prior to rash onset, patients may experience prodromal symptoms, a sign of the active reactivation in sensory ganglia (Arvin 2005), lasting a few days although prodromes of more than a week have been described (Zerngast, 2013). Pain and abnormal skin sensations are the most common prodromal symptoms, and headache, photophobia and malaise have also been reported (Gnann, 2002). The burden of HZ prodromal pain is not insignificant – in one study of 251 subjects ≥ 50 YOA, 74% of subjects reported prodromal pain with a mean pain duration of 4.7 days and a severity of 6/10 on the Zoster Brief Pain Inventory (ZBPI), a validated scale used to measure HZ-related pain (Benbernou, 2011). The occurrence of pain prior to appearance of the HZ rash may pose a diagnostic dilemma; HZ-related prodromal pain has been misdiagnosed as angina, lumbar radiculopathy, biliary or renal colic, and other conditions [(Ozdemir, 2000), (Nair, 2012), (Sallami, 2015), (Hassan, 1996)].

The typical HZ rash begins as clustered maculopapular lesions surrounded by erythema, appearing unilaterally in a distribution usually corresponding to a single dermatome. The lesions are often accompanied by neuropathic pain and hyperesthesia in the affected dermatome. The eruption of new lesions generally occurs within a week, followed by crusting and complete healing within two to four weeks. The thoracic dermatomes, particularly T5 through T12, are involved in about 50% of cases, with the cranial nerves, most commonly the fifth (trigeminal) nerve, involved in 14% - 20% of cases and lumbosacral nerves, particularly L1 and L2, involved in approximately 16% of cases (Fields, 2007). Although less common, VZV reactivation as pain without a rash, known as zoster sine herpete, may occur (Blumenthal, 2011). Recurrent herpes zoster in immunocompetent subjects has been described. [(Yawn, 2011), (Tseng, 2012) and (Kawai, 2014)].

HZ Epidemiology

Incidence

From the literature, the overall incidence of HZ ranges from 1.5 – 5 per 1000 person-years, but since mild cases may not be medically attended, the incidence may be underestimated [(Yawn, 2013), (Kawai, 2014)]. The incidence of HZ rises with increasing age, with lifetime risk estimated to be approximately 30% (Yawn, 2013). It is estimated that there are between 600,000 and one million new cases of HZ in the U.S. per year (Johnson, 2015). Several studies indicate a trend for increasing incidence over time, irrespective of varicella vaccination programs. Estimates of HZ incidence vary due to the differences in methodology used to capture data (Cook, 2015), data sources, population evaluated, case definition and ascertainment and adjustment for co-variates but, incidence rates in the countries and regions evaluated appear to increase with age within a general range (Cook, 2015).

Risk factors

A key risk factor for HZ is age; incidence is generally low in children and younger adults, and begins to rise sharply between the ages of 40 and 50, increasing progressively with advancing age. Calculated incidence rates differ from study to study due to variability in study populations, data sources and methodology. In a recent retrospective, observational cohort study using administrative claims data from two US nation-wide research databases incorporating information from a broad range of sources during the year 2011, the following HZ age-specific incidence rates were estimated in immunocompetent individuals: 0.86/1000 person-years for individuals < 19 YOA, 2.7/1000 person-years for individuals 20 – 29 YOA, 3.6/1000 person-years for individuals 30 – 39 YOA, 4.5/1000 person-years for individuals 40 – 49 YOA, 6.7/1000 person-years for individuals 50 – 59 YOA, 9.3/1000 person-years for individuals 60 – 69 YOA, 12.0/1000 person-years for individuals 70 – 79 YOA and 12.8/1000 person-years for individuals ≥ 80 YOA (Johnson, B.). In a retrospective cohort study from 01-JAN-2007 to 31-DEC-2009 evaluating the efficacy of the licensed live attenuated HZ vaccine using the Kaiser Permanente Southern California database, the estimated incidence rates of HZ among unvaccinated older individuals were higher: 9.7 – 12.7/1000 person-years for individuals 60 through 69 YOA, 14.6 – 15.2/1000 person-years for individuals 70 through 79 YOA and 17.3/1000 person-years for individuals ≥ 80 YOA (Tseng, 2011). Finally, a systematic review of HZ incidence from 63 studies conducted in countries from North America, Europe, Asia, South America and the Middle East estimated the incidence of HZ at about 6 – 8/1000 person years at 60 and 8-12/1000 person-years at age 80 (Kawai, 2014).

Another key risk factor for HZ is immunosuppression. Immunocompromised (IC) individuals are at higher risk for HZ and recurrent HZ, and at higher risk of experiencing severe HZ and HZ-related complications such as disseminated HZ.

The incidence of HZ, when controlled for age, is higher in females than in males [(Opstelten, 2006), (Yawn, 2007)]. In one retrospective evaluation, which included a self-reported history of shingles in community dwelling subjects > 64 YOA, after controlling for age, cancer and demographic factors, subjects of African heritage had a significantly lower risk of experiencing HZ than Caucasian subjects (Schmader, 1995).

HZ Complications

Post-herpetic neuralgia

The most common complication of HZ is PHN, a syndrome of neuropathic pain that can persist at the site of the rash for months or possibly years following an episode of HZ. PHN is caused by changes in somatosensory processing within the affected nerves, nerve root and ganglion damaged by VZV reactivation (Hadley 2016). The pain of PHN may be severe and intractable, resulting in reduced function and psychosocial well-being (Schmader, 1999). Risk factors for PHN include advanced age, prodromal pain, HZ rash severity, acute (eruptive) HZ pain severity and ophthalmic involvement [(Dworkin, 1998), (Nagasako, 2002), (Whitley, 1999), (Forbes, 2016)]. Estimates of PHN risk, which can range from 5% to more than 30%, vary due to differences in study design, age of subjects, and PHN definition (Kawai, 2014). The incidence of PHN amongst subjects ≥ 60 YOA with confirmed HZ in the placebo group in a randomized clinical trial was 1.38/1000 person-years (Oxman, 2005). In a report from the literature, more than 30% of subjects reporting PHN experienced pain for more than one year (Kawai, 2014)

Herpes Zoster Ophthalmicus (HZO)

HZO, caused by VZV reactivation in the ophthalmic branch of the fifth (trigeminal) cranial nerve, occurs in up to 10 – 20% of HZ cases, and was reported in 10.5% of the HZ cases in the Placebo group of the Shingles Prevention Study (SPS), a randomized, placebo-controlled clinical endpoint study which supported the licensure of Zostavax, a live attenuated VZV vaccine, for prevention of HZ [(Liesegang, 2008), Zostavax package insert (PI), 2017]. Acute and long-term complications of HZO are due to direct viral toxicity and the inflammatory response within the eye (Catron, 2008). Acute complications of HZO include conjunctivitis, keratitis, uveitis and ocular cranial nerve palsies, and permanent sequelae include recurrent ocular inflammation and loss of vision (Tran, 2016).

Other complications

VZV has been associated with vasculopathies including cerebral vasculopathy associated with TIA, stroke, hemiparesis or altered mental status. Other reported complications include myelitis, encephalitis, peripheral and cranial nerve palsies, and ocular disease such as acute retinal necrosis. Disseminated HZ and visceral HZ, such as pneumonia, hepatitis, and pancreatitis have been reported. Ramsay-Hunt syndrome, or VZV reactivation in the geniculate ganglion of the sensory branch of the facial nerve, may result in sensorineural hearing loss, tinnitus and vestibular symptoms such as vertigo and nystagmus [(Gondivkar, 2010), (Nagel, 2013)]). Other unusual and rare presentations of VZV reactivation have been described, including HZ-associated intestinal pseudo-obstruction [(Masood, 2015), (Zhou, 2012)], burning mouth syndrome (Nagel MA, 2016), and dental complications such as osteonecrosis of the maxilla (Gupta, 2015).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Zostavax was licensed for the prevention of HZ by the FDA in May 2006; see Section 2.3 for details.

The goal of therapy for the acute phase of HZ is to minimize or eliminate pain and promote healing. Antiviral therapy with nucleoside analogs, such as acyclovir, famciclovir and valacyclovir, have been shown to reduce the duration of lesion formation and the time to rash healing, decrease the severity and duration of acute pain and possibly prevent the occurrence of PHN if taken within 48 - 72 hours of rash onset. Analgesics, including opioid analgesics may be prescribed to mitigate acute HZ-related pain and PHN. A combination of agents may be required to mitigate the side effects of the medications used to control HZ-related pain, which may have a narrow therapeutic to toxicity ratio, especially in the elderly (Hadley, 2016).

2.3 Safety and Efficacy of Pharmacologically Related Products

Zostavax, a live, attenuated VZV vaccine administered SC as a single dose, was licensed in the US for use in subjects ≥ 60 YOA in May 2006 and for use in subjects 50 – 59 YOA in March 2011.

While generally safe, the attenuated vaccine virus in Zostavax is capable of replication and can cause clinical disease; therefore, the vaccine is contraindicated in immunocompromised subjects (Zostavax PI, 2017).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The antigen has not been marketed or studied outside of the HZ/su development program.

According to the Applicant, over 15,000 subjects have been vaccinated with at least one dose of an AS01-containing vaccine outside of the HZ/su 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, *Hemophilus influenzae* and tuberculosis. While the Applicant reports that the overall safety profile of AS01-containing vaccines is aligned with the safety results of the HZ/su program, the following events were observed in the infant malaria program in which the antigen RTS,S 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, meningitis is considered a safety signal in infants which the Applicant plans to follow closely in future clinical trials.
- Increased incidence of 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.

Reviewer's comment - 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 not known.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following list includes references to selected submissions to CBER (pre-IND and IND), important protocol amendments, discussions between CBER and the Applicant that reflected either the Applicant's or CBER's current thinking about the clinical development plan (CDP), as well as regulatory activities that were milestones.

28 APR 2008 A pre-IND meeting was held to discuss the Applicant's plan to initiate US development of HZ/su with a Phase 3 clinical trial. CBER noted that the submitted Phase 1 and 2 data did not support initiation of a Phase 3 trial and asked the Applicant to conduct a trial to demonstrate the added benefit of the $AS01_B$ adjuvant. CBER also recommended that studies in immunocompromised adults be performed under a different IND, that saline (rather than adjuvant) be used as the control in the Phase 2 study and that the burden of illness (BOI) endpoint in clinical trials be evaluated as an exploratory, rather than a primary or secondary, endpoint.

24 OCT 2008 **Amendment 0** to IND 13857 contained a protocol for Zoster-010, a Phase 2 adjuvant dose-finding study evaluating the safety and immune responses to HZ/su (gE/$AS01_B$), gE/$AS01_E$ ($AS01_E$ is half the dose of $AS01_B$), and gE (without adjuvant) as compared to saline placebo in subjects ≥ 50 YOA.

29 JUN 2009 A **Type C meeting** was held to discuss the proposed statistical methodology to support the HZ/su CDP as proposed in the meeting materials submitted to IND 13857 under **Amendment 7**. CBER agreed with the sponsor's CDP and rationale for conducting two pivotal clinical endpoint studies as well as pooling results from both studies to support age-specific efficacy against HZ in subjects ≥ 70 YOA. However, CBER did not agree that pooled results could support overall efficacy against PHN in subjects ≥ 50 YOA, and expressed concerns about assessing PHN as a primary endpoint independent of HZ. CBER agreed with the proposed oversight by an Independent Data Monitoring Committee (IDMC) and that non-US and US data could be pooled for the assessment of HZ VE.

19 FEB 2010 A **Type B EOP 2 meeting** was held to discuss the proposed CDP and draft Phase 3 protocols submitted in Amendment 13 on 08-JAN-2010. In the amendment, the sponsor provided a rationale for conducting two parallel studies, which was that if a single study was conducted, the assessment of VE against PHN would require a large number of older (≥ 70 YOA) subjects to be enrolled, which might negatively bias the VE against HZ, since they assumed HZ VE would diminish with age. Based on the preliminary results of Zoster-010, CBER agreed with the selection of $AS01_B$ as the adjuvant dose for Phase 3 development. CBER agreed with the age stratification of the proposed safety subset in Zoster-006 (3:3:3:1 for age groups 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA instead of the study age stratification of 8:5:3:1) following the Applicant's explanation that the ratio selected may best reflect the age distribution of subjects receiving the vaccine post-licensure. CBER noted that decreasing reactogenicity with advancing age would require that reactogenicity be described by age group. CBER asked the Applicant to collect unsolicited events from Day 0 to Day 29 following each vaccination from all subjects, instead of a subset of subjects as proposed. CBER agreed with the proposed HZ VE endpoints for each clinical study, but disagreed with the proposed

pooled analysis of VE against PHN in subjects ≥ 50 YOA across studies, noting that the majority of PHN cases would likely occur in subjects ≥ 70 YOA, creating bias in the estimate of overall PHN VE across the age ranges. CBER also stated that an indication for prevention of PHN would require demonstration of prevention of clinically meaningful PHN in subjects who developed HZ.

21 DEC 2010 **Amendment 31** contained **Protocol Amendment 1** for Zoster-006 and Zoster-022. Among other changes, the protocols were amended at CBER's request to specify that subjects who experience an SAE after first vaccination judged as vaccine-related by the investigator would not receive a second vaccination. Additionally, case determination by HZAC was clarified such that a determination of a "case of HZ" was to be based on a unanimous decision by the committee.

02 APR 2012 **Amendment 62** contained **Protocol Amendment 2** for Zoster-006 and Zoster-022. This amendment clarified follow-up procedures and timelines for suspected and confirmed HZ cases. Narcolepsy was added to the listed of pIMDs.

21-FEB-2013 **Amendment 93** contained a protocol for Zoster-033, a Phase 3, non-IND, non-randomized, open-label study to be conducted in the Russian Federation and Canada, to assess the immunogenicity and safety of HZ/su when administered IM to subjects ≥ 50 YOA with a prior history of HZ. In a communication with the Applicant dated 28-MAR-2013, CBER noted that blinded, randomized studies with contemporary comparator groups were preferred to single arm, open label studies.

27-NOV-2013 **Amendment 120** contained a notification that holding rules related to local reactogenicity were met following SC administration of the vaccine in Part 1 of study Zoster-032, and that on 23-SEP-2013 the GSK US regional governing committee decided that only an IM indication was to be pursued in the US.

24-JAN-2014 **Amendment 128** contained a **draft for Protocol Amendment 4** for Zoster-006 and Zoster-022. The Applicant noted, without having any analysis performed that would have resulted in unblinding, that the conditions required for triggering the HZ efficacy analysis in Zoster-006 would occur more than six months prior to the conditions for the HZ efficacy analysis being reached in Zoster-022 and that accrual of PHN endpoints was slower than expected. The Applicant therefore proposed changes in the timing of final HZ and EOS analyses, the dissociation of analyses between the two studies, and changes in the status of and requirements for the analysis of the overall PHN endpoint. See information about the final version of Protocol Amendment 4 in Amendment 157 below. The Applicant also notified CBER of a change in the cut-off of the gE-specific ELISA assay from (b) (4) 97mIU/mL.

11-APR-2014 A Type C meeting was held to discuss the HZ/su CDP, how the results of clinical studies would be referenced in forthcoming licensing applications and to provide updates on the clinical development timelines. In response to the Applicant's question in the meeting materials (submitted in **Amendment 140**) about inclusion of interim safety and immunogenicity data from a subset of subjects age ≥ 50 YOA with various immunocompromising conditions enrolled in several studies conducted in the immunocompromised population, CBER disagreed with inclusion of these data, noting that interim data are generally not suitable for labeling as well as voicing a concern that inclusion of immunogenicity data from these studies may have the potential for implied effectiveness when there is no established immune correlate predictive of

	protection against HZ in healthy individuals and it is unknown whether an immune correlate established in healthy individuals would be predictive of protection in subjects with various immunocompromising conditions.
30-MAY-2014	**Amendment 157** (**Protocol Amendment 4** for Zoster-006 and 022) contained protocol revisions to the clinical endpoint studies including: dissociating the analyses of the studies in terms of timing, conducting a two-step analysis of Zoster-006 and revisions to the primary endpoints of Zoster-022 and the pooled analysis.
23-MAR-2015	In **Amendment 186**, the Applicant requested early termination of Zoster-006 and Zoster-022. Final analysis of HZ VE in Zoster-006 (performed by external statisticians to maintain study blinding at the individual subject level) in December 2014 showed high HZ VE for subjects in all age groups, and at the time of the amendment, criteria for minimum follow-up had been exceeded for both studies.
21-MAY-2015	Type C meeting held to discuss clinical assay methods and validation supporting use of the assays in the clinical development plan (CDP), with meeting materials submitted in **Amendment 190** on 20-APR-2015. The Applicant noted that the anti-gE ELISA was selected as the primary clinical assay for measurement of HZ/su-induced humoral responses for the CDP and would be used to compare immune responses between groups within and across studies, and would also be used to evaluate an immune correlate of protection (CoP) in efficacy studies.
05-DEC-2015	The Applicant reported to CBER an (b) (4) in the gE antigen identified in the manufacturing of the commercial consistency lots and the results of the root cause investigation along with their proposed corrective and preventive actions (CAPA).
24-MAY-2016	A Type B pre-BLA meeting was held to discuss the proposed clinical package to be submitted to support licensure of HZ/su as well as the indication and vaccine efficacy data proposed for the PI. Pre-BLA meeting documents were submitted in **Amendments 245 and 247** (revised) on 13-APR-2016 and 05-MAY-2016 respectively. Topics of discussion included the Applicant's proposed indication, studies selected for inclusion in the BLA and the format of their submission, a discussion of pooled studies eligible for safety analyses and the Applicant's global strategy for ex-US filings.
14-APR-2016	The Applicant provided the CAPA results regarding the (b) (4) of the gE antigen and a proposal of additional remediation including establishment of a new acceptance criterion for (b) (4) , which was acceptable to CBER.
07-JUL-2016	A Type B pre-BLA meeting was held to discuss CMC issues. Meeting materials were submitted in **Amendment 260** on 03-JUN-2016.
28-JUN-2016	The agreed initial pediatric study plan (iPSP) was presented to the PeRC. The PeRC agreed with the plan for a full waiver of studies in all pediatric populations due to the impracticability or impossibility of conducting clinical endpoint studies in the US because the incidence of HZ in the pediatric population is low and cases are widely dispersed.
21-OCT-2016	BLA submission received through FDA gateway.
13-SEP-2017	The VRBPAC voted unanimously that the clinical data presented by FDA and the Applicant supported licensure of HZ/su.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

- Although the submission was adequately organized, CBER identified the following issues during review: The Integrated Summary of Safety (ISS), which should contain an in-depth analysis of all clinical safety data, lacked text and consisted only of tables.
- Efficacy analyses by race and ethnicity and safety analyses by race, ethnicity and gender were not provided in the original application and were requested by CBER.
- Comparative analyses of SAEs provided by the Applicant in the SCS and in the Zoster-006 and Zoster-022 CSRs analyzed the proportions of subjects reporting SAEs during the entire study period (of approximately 4 years) instead of the pre-specified M0 – M14 (for Zoster-006 and Zoster-022) or 365-day post last vaccination (for the SCS) time period. As investigators were not required to collect all SAEs for the duration of the clinical endpoint studies (only fatal SAEs and SAEs judged related were collected for the duration of the study), these comparative analyses were likely not robust. The Applicant was asked to provide comparative analyses of the proportions of subjects reporting SAEs which occurred during time periods that were pre-specified for SAE reporting.
- The Applicant graded SAEs, which have a regulatory definition and do not require grading. In their tabulations of the number and proportions of subjects in each treatment group reporting Grade 3 unsolicited adverse events during the 30-day post-vaccination period, CBER analysis indicated that the Applicant included “Grade 3” SAEs but not “Grade 1” or “Grade 2” SAEs in the tabulations. Tabulations of the proportions of subjects with ≥ Grade 3 AEs (i.e., Grade 3 AEs and SAEs) or Grade 3 non-serious AEs would have been a more appropriate way to present these data from a clinical perspective. CBER requested that the Applicant provide tabulations of subjects reporting Grade 3 non-serious AEs during the 30-day post-vaccination period.
- The Applicant noted in text that the SCS Table 59 titled “Percentage of subjects reporting the occurrence of serious adverse events with fatal outcome classified by MedDRA Primary System Organ Class (SOC) and PT from the first administered dose up to 30 days post last vaccination period” represented the number and proportions of subjects who died in each treatment group during the period from first dose up to 30 days post last vaccination. However, this was not the case; the table included the number and proportions of subjects in each treatment group who reported the *onset* of a SAE during that time period that was fatal at some point; the date of death may have occurred during the specified time period or later, sometimes years later. Similarly titled tables in the SCS and Zoster-006 and Zoster-022 CSRs also included subjects who had an SAE that was fatal but not necessarily during the time period specified in the table title, rather than the numbers and proportions of subjects who died in each treatment group at time periods relative to vaccination. As the tabulations of subjects in each vaccination group who died at time periods relative to vaccination is a key safety analysis, CBER requested that these tabulations be submitted to the BLA.
- Many key and supportive demographic tables, including tables of subjects vaccinated, completed and withdrawn with reasons for withdrawal in each treatment group, were provided without proportions in the original application and were requested by CBER.

- Descriptive tabulations of the proportions of subjects in each vaccination group with pre-existing medical conditions and the nature of the conditions were not provided in the original application and were requested by CBER.

Reviewer's comment – Errors and omissions in the application necessitated a number of requests for information and teleconferences with the Applicant. The Applicant complied with all requests to submit additional information and analyses, and correct deficiencies. Please see Section 5.2 for a list of amendments reviewed with dates of submission, which included the information submitted in response to CBER's requests.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant provided an in-depth accounting of protocol deviations which led or did not lead to elimination from analyses in the Zoster-006 and Zoster-022 CSRs. They identified serious deviations from Good Clinical Practice (GCP) for two sites (one each for Zoster-006 and Zoster-022) in Mexico under the auspices of a single clinical investigator. The Applicant could not endorse the data from these sites, which resulted in the exclusion of the data from 671 subjects in Zoster-006 and 865 subjects in Zoster-022 from all statistical analyses. These subjects were analyzed for safety separately. The applicant reports all other studies were conducted according to GCP.

3.3 Financial Disclosures

The Applicant made reasonable efforts to obtain financial disclosure from all investigators and sub-investigators who participated in the studies submitted to the BLA.

Under "Significant Payments of Other Sorts from the Sponsor of the Covered Study [21 CFR 54.4(a)(3)(ii), 54.2(f)]", the Applicant listed one Principal Investigator and one sub-investigator for two studies whose sites contributed < 2.00% of the total recruitment for each study. The Applicant listed no investigators as having proprietary interest in the tested product. Under "Significant Equity Interest in the Sponsor of the Covered Study Product [21 CFR 54.4(a)(3)(iv), 54.2(b)]", the Applicant listed one Principal Investigator and one sub-investigator, each of whom recruited < 2.00% of subjects enrolled in the two pivotal efficacy studies, and approximately 5% (5.31%) of subjects recruited for Zoster-004, the study of concomitant administration with QIV.

Reviewer's comment – The financial disclosure forms from investigators and sub-investigators were reviewed by CBER, and there was no indication that any missing information or disclosed financial arrangements would impact the overall integrity of the data submitted.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

HZ/su composition
The vaccine is composed of 50 µg of gE antigen presented as a lyophilized pellet and 0.5 mL/dose of the liquid proprietary adjuvant system, $AS01_B$, presented as a liquid, both in monodose vials. To reconstitute the vaccine, the liquid $AS01_B$ adjuvant system is combined with the lyophilized antigen prior to administration.

The gE antigen is produced by recombinant deoxyribonucleic acid technology in Chinese Hamster Ovary cells. The $AS01_B$ adjuvant system consists of the following: 50 µg each of the

immune enhancers *Quillaja saponaria* Molina fraction 21 (QS-21) and 3-*0*-desacyl-4'-monophosphoryl lipid A (MPL) combined with liposomes. QS-21 is a natural saponin molecule (triterpene glycoside) purified from the (b) (4) of the *Quillaja saponaria* tree. MPL consists of a (b) (4) form of a lipopolysaccharide from the *Salmonella minnesota* bacterium. The liposomes are comprised of dioleoylphosphatidylcholine (DOPC) and cholesterol. The composition of the reconstituted vaccine is in the table below.

Table 1 – Composition of Reconstituted Vaccine

Ingredient‡	Quantity per 0.5 mL dose	Function
gE	50 µg	Antigen
Sucrose	20 mg	Stabilizer (b) (4)
Polysorbate 80	0.08 mg	(b) (4)
MPL	*50 µg*	(b) (4)
QS-21	*50 µg*	(b) (4)
DOPC	*1 mg*	*Liposomes membrane constituent*
Cholesterol	*0.25 mg*	*Liposomes membrane constituent* (b) (4)
NaCl	*4.385 mg*	*Tonicity agent*
$NaH_2PO_4.2H_2O$	0.160 mg	Buffering agent
K_2HPO_4	0.116 mg	Buffering agent
Na_2HPO_4	*0.15 mg*	*Buffering agent*
KH_2PO_4	*0.54 mg*	*Buffering agent*
Water for injection	(b) (4)	*Solvent*

Source: Adapted from BLA 125614/0 Summary of Clinical Safety Table 1, p. 20
‡ Active ingredient is gE, others are excipients. Excipients in the $AS01_B$ monodose vial are in italics.

The placebo was a (b) (4) provided in monodose vials (0.5 mL/dose) containing (b) (4) of (b) (4) per dose.

CMC issue identified during review cycle
A major Chemistry, Manufacturing and Controls (CMC) issue identified by CBER reviewers was a manufacturing deviation of an (b) (4) in the gE antigen in the (b) (4) The Applicant's investigation of the root cause and CAPA were found to be acceptable by CBER.

Reviewer's comment – The lots with the (b) (4) *were not used in the clinical studies. Please refer to the CBER CMC reviews for additional information.*

4.2 Assay Validation

Evaluation of HZ/su for licensure was based on the results of analyses of clinical endpoints; however, CBER assay reviewers confirmed that the immunologic assays used in the development program were adequately validated for their intended use.

Reviewer's comment – Please refer to the CBER CMC reviews.

4.3 Nonclinical Pharmacology/Toxicology

The candidate vaccine, HZ/su, 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 genotoxicology studies, 5 reproductive toxicology studies and 3 local tolerance studies.

In the repeat dose toxicity studies with HZ/su, 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 HZ/su vaccine with levels up to 9 times (male animals) and 5 times (female animals) higher compared to control animals. According to the toxicology reviewer, 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.

Reviewer's comment – According to the toxicology reviewer, the increase in popliteal lymph node weight, spleen weight, and thymus weight is most likely related to the immune response to the vaccine. With regard to the bilirubin levels, no histopathological adverse effects on the liver were noted. Changes in CRP levels are not unexpected as part of an acute-phase response to vaccination.

HZ/su 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 HZ/su 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 HZ/su 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.

Reviewer's comment – See the toxicology review for details.

4.4 Clinical Pharmacology

Pharmacodynamic data, comprised of immune response to the vaccine, can be found in the review of the clinical studies.

4.4.1 Mechanism of Action

$AS01_B$ 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 co-localization of 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.

4.5 Statistical

The statistical reviewer verified that the primary study endpoints of Zoster-006, Zoster-022 and the pooled analysis were supported by the submitted data. Please refer to the CBER statistical reviewer's memo for details.

4.6 Pharmacovigilance

The sponsor proposes addressing the potential risks of pIMD and ocular complications post-vaccination by supplementing routine pharmacovigilance with enhanced surveillance and active surveillance. Enhanced surveillance will occur for 12 pIMDs: polymyalgia rheumatica, rheumatoid arthritis, psoriasis, autoimmune thyroiditis, multiple sclerosis, Guillain-Barré syndrome, idiopathic thrombocytopenia, optic neuritis, inflammatory bowel diseases, Still's disease adult onset, leukocytoclastic vasculitis, gout, and 2 ocular complications: optic ischemic neuropathy, and temporal arteritis. The sponsor identified these conditions for enhanced surveillance based on their frequency in the two pivotal studies, the prevalence of the pIMD in the vaccine target population, or as events of medical interest.

Enhanced surveillance consists of generating background rates for the conditions of interest, conducting observed to expected analyses using passive surveillance data from routine pharmacovigilance, and utilizing follow-up questionnaires to gather data systematically for reported cases.

Active surveillance will occur through a Targeted Safety Study, which will be a postmarketing commitment (PMC). This study will monitor for the 14 conditions identified for enhanced surveillance, and medically-attended or serious AE utilizing a medical database. Specifics of the study protocol are being developed and the study will utilize an appropriate comparator for signal generation and detection. The sponsor anticipates gathering data from 60-70,000 HZ/su vaccinees, and a 60-70,000 patient comparator cohort.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Joint review responsibilities
Dr. Paula Agger reviewed Zoster-006, Zoster-022, the pooled analyses of these studies and the broader pooled analysis, as well as Zoster-010, Zoster-026 and Zoster-032. Dr. Rebecca Reindel reviewed the following studies: Explo-CRD-004 and extension studies, Zoster-003 and extension studies, Zoster-004, Zoster-007, Zoster-023, Zoster-033, and the CSRs for Zoster-001 and Zoster-015.

Approach to clinical review of pivotal studies and pooled data

Efficacy - As delineated in the protocols, pre-specified pooled analyses of efficacy data across Zoster-006 and Zoster-022 were planned by the Applicant if the primary objectives of the individual studies were demonstrated. CBER clinical review of Zoster-006 and Zoster-022 efficacy data was performed prior to review of the efficacy results of the pooled analyses.

Safety - There were two main safety poolings in the submission. The main pooling analysis included data from subjects in Zoster-006 and Zoster-022, and compared safety endpoints between the HZ/su and Placebo treatment groups. CBER considered it appropriate, after review of the safety data from each individual study, to review and analyze some pooled safety endpoints across studies (e.g., unsolicited AEs, SAEs, pIMDs and deaths) to assess any safety signals across studies. As reactogenicity decreased with increasing age, CBER's approach to reactogenicity data was to assess the data overall by study and within Zoster-006, by the pre-specified age strata.

The broader pooling analysis included an additional 848 subjects from other select studies. The data from the broader pooling was only used to analyze SAEs, pIMDs and deaths. These data were not provided, nor assessed, using a comparator group.

The coding dictionary for the clinical endpoint studies was MedDRA Version 18.0. CBER utilized safety review tools to evaluate safety data by MedDRA hierarchies (using the data analysis software tool (b) (4)) and MedDRA hierarchies and SMQs (utilizing a safety analytic software tool developed by FDA).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Presented below are the amendments, modules and content that were assigned to and reviewed by the clinical reviewers. Cover letters for each amendment were also reviewed.

- **125614/0** (received 21-OCT-2016) – Sections 1.3 (Administrative information including Debarment Certification and Financial Disclosure), 1.6 (Meetings), 1.9 (Pediatric Administrative Information), 1.4 (Labeling), 1.16 (Risk Management Plan), 2.2 (Introduction), 2.5 Clinical Overview, 2.7 (Clinical Summary), 5.2 (Tabular Listing of all Clinical Studies), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), 5.3.5.2 (Study Reports of Uncontrolled Clinical Studies), 5.3.5.3 (Reports of Analyses of Data from More than One Study)
- **125614/1** (received 04-NOV-2016) – Section 1.12.4 (Proprietary Name Review)
- **125614/2** (received 04-NOV-2016) – Section 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, Case Report Forms)
- **125614/3** (received 23-NOV-2016) – Section 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication, List of Investigators and Sites)
- **125614/4** (received 05-DEC-2016) – Section 1.11.4 (Multiple Module Information Amendment, Response to IR to clarify ISS structure, SAEs, Dataset Locations)
- **125614/7** (received 20-JAN-2017) – Section 1.11.4 (Multiple Module Information Amendment, Request for Additional Information of 06-JAN-2017)
- **125614/8** (received 27-JAN-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER Questions 4, 5, and 10 of 06-JAN-2017) and Section 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), Section 5.3.5.3 (Reports of Analyses of Data from More than One Study)
- **125614/9** (received 22-FEB-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER Request for Information of 10-FEB-2017 Word Version)

- **125614/10** (received 21-FEB-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER Request for Information of 10-FEB-2017)
- **125614/11** (received 02-MAR-2017) – Section 1.11.3 (Clinical Information Amendment, Responses to CBER Request for Information of 21-FEB-2017)
- **125614/13** (received 08-MAR-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER 23-FEB-2017 Information Request)
- **125614/16** (received 14-APR-2017) - Section 1.11.3 (Clinical Information Amendment, Responses to CBER IR 17-MAR-2017)
- **125614/18** (received 02-MAY-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER IR, Correction to Question 9 of 17-MAR-2017)
- **125614/20** (received 16-MAY-2017) – Section 1.11.3 (Clinical Information Amendment, Responses to CBER IR of 06-APR-2017)
- **125614/21** (received 05-JUN-2017) – Section 1.11.3 (Clinical Information Amendment, Responses to IR from the FDA of 08-MAY-2017)
- **125614/22** (received 12-JUN-2017) – Section 1.11.3 [Clinical Information Amendment, Response to CBER request for additional analyses, Submission Package 1, SAEs with Fatal Outcome (by time period for occurrence of death)]
- **125614/25** (received 21-JUN-2017) - Section 1.11.3 (Clinical Information Amendment, Response to CBER request for additional analyses, Submission Package 2, SAEs and pIMDs)
- **125614/26** (received 29-JUN-2017) – Section 1.11.3 (Clinical Information Amendment, Response to CBER request for additional analyses, Submission Package 3, Non-serious AEs Grade 3, AEs with Medically Attended Visit, Summary Tables Unsolicited AEs)
- **125614/29** (received 12-JUL-2017) - Section 1.11.3 (Clinical Information Amendment, Response to CBER request for additional analyses, Submission Package 4, Analyses by race, ethnicity and gender, Tables with missing percentages, Additional tables requested)
- **125614/31** (received 27-JUL-2017) - Section 1.11.3 (Clinical Information Amendment, Responses to CBER IRs of 30-JUN-2017, 03-JUL-2017, 20-JUL-2017)
- **125614/34** (received 09-AUG-2017) - Section 1.11.3 (Clinical Information Amendment, Responses to CBER RFI of 02-AUG-2017)
- **125614/36** (received 11-AUG-2017) – Section 1.6.2 (Meeting Background Materials, VRBPAC Briefing Document)
- **125614/40** (received 07-SEP-2017) – Section 1.11.3 (Clinical Information Amendment, Responses to IR Received 29-AUG-2017) and 1.16 (Risk Management Plan)
- **125614/46** (received 25-SEP-2017) – Section 1.6.3 (Correspondence Regarding Meetings, Late Cycle Meeting Summary) and Section 1.12.4 (Request for Comments and Advice, GSK proposal to CBER for update of Clinical modules)

5.3 Table of Studies/Clinical Trials

Table 2 – 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

Study ID	**Zoster-006**	**Zoster-022**	**Zoster-004**	**Zoster-007**	**Zoster-026**
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 HZ/su and QIV	Demonstrate lot consistency	Compare post-vaccination humoral immune responses following HZ/su administration on 3 different schedules
Control	Saline placebo	Saline placebo	See vaccination schedule below	None	None
Groups	2 groups, randomized 1:1 to receive HZ/su or placebo IM	2 groups, randomized 1:1 to receive HZ/su or placebo IM	2 groups, randomized 1:1 to receive QIV and HZ/su IM in control or co-administration groups	3 groups, randomized 1:1:1 - all groups receive HZ/su IM	3 groups, randomized 1:1:1 – all groups receive HZ/su IM
Vaccination Schedule	M0, M2	M0, M2	Co-Ad: QIV and HZ/su at M0, HZ/su at M2; Control: QIV M0, HZ/su 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
Location in review	Section 6	Section 6	Section 9	Section 9	Section 9

‡ Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Mexico, Republic of 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, of whom 15,411 received at least one dose and were included in TVC analysis
** Zoster -022 total enrollment was 14,816 subjects, of whom 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 analysis
€ For the mTVC at the Zoster-022 analysis

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 HZ/su 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 HZ/su 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 HZ/su (10 young adults), HZ/su with Varilrix (10 young adults), Varilrix (45 older adults), HZ/su (45 older adults) and HZ/su 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 HZ/su, 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; HZ/su, gE/AS01$_E$, gE/saline and saline placebo	1 group (stratified by age) who received 2 injections of HZ/su IM
Vaccination 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)
Location in review	Section 9	Section 9	Section 9	Section 9

‡ EXPLO-CRD-004 extension studies to evaluate persistence of immune response to HZ/su; 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 HZ/su; 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)]
* EXPLO-CRD-004 did not meet criteria requiring registration on ClinicalTrials.gov

Table 4- Additional Studies - Alternative Administration Schedule 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 HZ/su)	43 subjects ≥ 50 YOA total (28 were ≥ 50 YOA and received ≥ 1 dose of HZ/su)
Population	Japanese ethnic origin	Prior HZ	Autologous HCT	HIV
Purpose	Assess S&I[§] of HZ/su when administered SC as compared to IM in population above	Assess S&I of HZ/su when administered to population above	Assess S&I of HZ/su when administered to population above	Assess S&I of HZ/su when administered to population above
Control	HZ/su IM arm	None – one arm	Saline placebo	Saline placebo
Groups	Two groups randomized 1:1 to receive 2 doses of HZ/su SC or IM	One group received 2 doses HZ/su	Four groups randomized 1:1:1:1; 3 doses of HZ/su, gE/AS01$_E$, saline placebo or saline placebo followed by 2 doses of HZ/su	Two groups randomized 3:2 to receive 3 doses of HZ/su or placebo
Vaccination 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)
Location in review	Section 9	Section 9	Section 9	Section 9

[¥] Subjects ≥ 18 YOA were enrolled in Zoster-001 and Zoster-015.
§ S & I = safety and immunogenicity

5.4 Consultations

The Applicant requested a full waiver of studies in all pediatric age groups. The statutory rationale for the full waiver [see Section 505B(a)(4)(A)(i) of the Food, Drug and Cosmetic Act] was that it was impossible or highly impracticable to conduct clinical endpoint studies to evaluate the use of HZ/su in the United States pediatric population because the estimated annual number of cases is low and widely dispersed across the United States. The PeRC agreed with the Applicant's plan for no pediatric assessment of HZ/su in the United States.

Reviewer's comment – Vaccination against varicella is part of the routine pediatric vaccination schedule in the US. The incidence of HZ in children is low, and HZ incidence in vaccinated children is lower than in unvaccinated children (Weinmann, 2013).

5.4.1 Advisory Committee Meeting

The Applicant and CBER presented their reviews of the clinical data to the VRBPAC on September 13, 2017. The committee voted unanimously that efficacy and safety data supported licensure of HZ/su for the prevention of HZ in subjects ≥ 50 YOA.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Zoster-006 was a Phase 3, randomized, observer-blind, placebo-controlled, multicenter, clinical endpoint efficacy trial designed to assess the prophylactic efficacy, safety and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine (HZ/su) when administered intramuscularly on a 0, 2-month schedule to HZ-naive adults aged 50 years and older. Zoster-006 was conducted in parallel with and at the same sites as with Zoster-022. The study initiation date was 02-AUG-2010 and completion date was 27-JUL-2015. The data lock point for the Final HZ efficacy analysis was 01-JUL-2014 (which evaluated the primary efficacy endpoint), and the data lock point for the EOS analysis (which evaluated most secondary efficacy endpoints and all safety endpoints) was 12-OCT-2015.

6.1.1 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 VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period 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, with confirmed HZ
- To evaluate VE in the reduction of HZ-related mortality and hospitalizations 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 VE in the reduction in incidence of HZ-associated complications 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 with confirmed HZ
- To evaluate VE in the reduction in use of pain medications 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 with confirmed HZ
- To evaluate vaccine safety and reactogenicity

Reviewer's comment – CBER agreed with the Applicant early in the CDP that prevention of HZ as measured by the reduction in HZ risk was clinically relevant and an appropriate primary objective for the pivotal studies.

Select exploratory objectives:

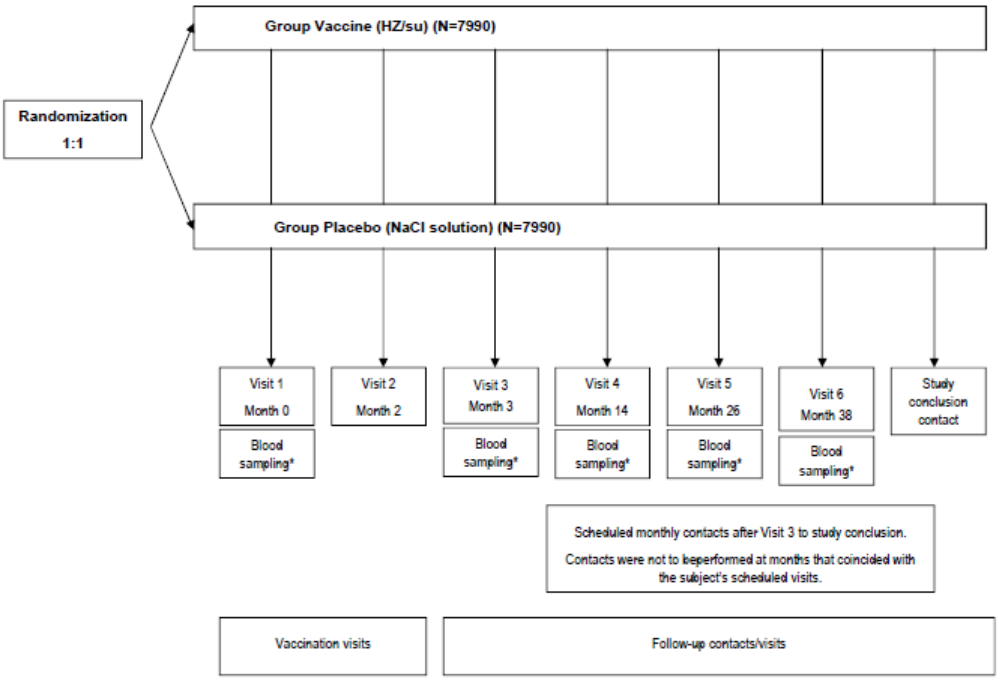
- To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA and by age strata

6.1.2 Design Overview

General study design

A pictorial representation of the study design is below.

Figure 1 – General study design



Source: From 125614/0 Zoster-006 CSR, p. 142

* 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 scheduled visits during the study at M0 and M2 (vaccination Visits 1 and 2) and Months 3, 14, 26 and 38 (Visits 3, 4, 5 and 6) and an end-of study contact for each subject. Subjects were educated about the signs and symptoms of HZ at Visit 1/M0, and instructed to contact the site if any signs or symptoms occurred. After Visit 3/M3, monthly contacts (at months other than those with scheduled visits) and the study conclusion contact were utilized to collect information about safety, the occurrence or follow-up of HZ or other protocol-defined events of interest. All subjects had blood sampling at Visit 1/M0 and Visit 3/M3. Additional blood samples were drawn from subsets of subjects to assess persistence of humoral immune response and cell mediated immune response at Visits 4, 5, and 6. The total length of follow-up post-vaccination differed by subject, due to staggered enrollment and the triggers for study analysis being, in part, event-driven (please see Section 6.1.9 for the triggers for study analyses). However, each subject was to be followed for a minimum of 30 months after Dose 2 for safety and to record the occurrence of HZ.

Subjects with clinically suspected HZ had additional assessments. The methods, procedures, tools and timing related to these efficacy assessments as well as the pre-specified safety assessments are detailed in Section 6.1.7.

Reviewer's comment – The length of study follow-up was adequate for the evaluation of safety and ensured that the point estimate for HZ VE would not be overestimated, as the peak of immune response to most vaccinations is thought to occur in the months immediately following vaccination, with waning of response over time.

Recruitment

Subjects were recruited during appointments with investigators and sub-investigators at their clinical practice, and some were referred to the investigators by their practitioners. Newspaper and/or radio advertising and recruitment letters to targeted age groups were utilized in some countries as per allowable local practice. There were no specific attempts to recruit subjects from nursing homes or physical rehabilitation facilities.

Randomization

Subjects were randomized 1:1 (vaccine:placebo) using a central randomization system on the internet. All subjects 50 – 69 YOA were randomized to receive vaccine or placebo in Zoster-006. Subjects ≥ 70 were randomized first to Zoster-006 or Zoster-022, then randomized to vaccine or placebo. Randomization of subjects ≥ 70 YOA to Zoster-006 or Zoster-022 at enrollment was done to facilitate the pooled evaluation of subjects in that age group. Subjects were stratified by region and by age cohort within each region and minimization techniques used for allocations by country within each region and by site within each country.

Reviewer's comment – The stratification ratio was selected by the Applicant to achieve a similar number of HZ cases in the main age strata (50 – 59, 60 – 69 and ≥ 70). The stratification ratio also roughly corresponds to the US population ratios. As the Applicant expected VE to be lower in the older age groups, enrollment of smaller numbers of the elderly in Zoster-006 may have biased the point estimate of VE in favor of HZ/su, if VE decreased with increasing age. However, as analysis of VE by age group was a secondary endpoint and HZ VE in subjects ≥ 70 YOA was the primary objective in Zoster-022 the stratification ratio was found to be acceptable.

Subjects 50 – 69 YOA were randomly allocated to be a part of the 7-day diary card subset, while all subjects ≥ 70 YOA were included in that subset. The diary card subset was randomized in the approximate ratio of 3:3:3:1 according to the following age groups: 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA. The provisional number of subjects expected by age group was 1410 subjects in each treatment group for the age strata 50 – 59 years, 60 – 69 years, and 70 – 79 years, and 470 subjects in each treatment group for the age stratum ≥ 80 YOA for a total of 4700 subjects in each treatment group in the subset.

Reviewer's comment – Collection of solicited AEs in approximately 60% of study subjects was considered adequate for the evaluation of reactogenicity.

The Applicant postulated that the age stratification of the diary card subset was representative of the likely vaccine uptake among the various age groups. Although CBER noted that the smaller proportion of younger subjects in the 7-day diary card subset as compared to the proportion overall in the study had the potential to bias overall reactogenicity tabulations for the HZ/su vaccine in the Zoster-006 analysis, CBER agreed that the proportions were acceptable, as reactogenicity tabulations would also be presented by age group.

Subjects (planned N = 2538) were also randomized to an Immunogenicity subset for the evaluation of humoral response to vaccination. CMI response to vaccination was analyzed in a subset of these subjects (planned N = 468) from the Czech Republic, US and Japan, at designated sites that had access to a peripheral blood mononuclear cells (PBMC) processing facility.

While an equal number of subjects from each vaccination group were enrolled in the immunogenicity subset to maintain the blind, only a fraction of placebo samples were run as this was deemed sufficient to assess immunogenicity levels in the placebo group.

Blinding
As the reconstituted HZ/su differed in appearance from the saline placebo, the study was conducted in an observer-blind manner, such that evaluation of any study safety, immunogenicity, or efficacy endpoint was performed by study staff who were blinded to treatment assignment. Preparation of study products were performed by medical personnel who did not participate in any clinical assessments, and the laboratory in charge of testing clinical samples were blinded as to treatment assignment, with codes used to link the subject and study to the sample devoid of links to treatment assignment.

Data collection
Data was collected via remote data entry on an electronic case report form (eCRF).

6.1.3 Population
Subjects were eligible for the study if they: were a male or female at least 50 years of age at the time of first vaccination, were capable of providing written informed consent, and could (in the investigator's opinion) comply with study requirements. Females of child-bearing potential could enroll in the study if they had practiced contraception for 30 days prior to vaccination, had a negative pregnancy test on the day of vaccination, and agreed to continue adequate contraception (as defined in the protocol) until two months after completion of the vaccination series.

Any of the following were exclusionary conditions for enrollment:

- Use of any investigational product other than study vaccine within 30 days preceding the first dose of study vaccine or planned use during the study period
- Concurrently participating in another clinical study, at any time during the study period, in which the subject was exposed to an investigational or non-investigational product
- Confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy
- History of HZ
- Previous vaccination against varicella or HZ
- History of allergic disease or reactions likely to be exacerbated by any component of vaccine or materials related to study participation
- Significant underlying illness that, in the opinion of the investigator, would have been expected to prevent completion of the study
- Receipt of immunoglobulins/and or blood products within 90 days preceding the first dose of study vaccine or administration of such products during study period
- Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit

vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, with or without adjuvant) could be administered up to 8 days prior to each dose and/or at least 14 days after any dose of study vaccine

- Any other condition that, in the opinion of the investigator might interfere with the evaluations required by the study (e.g., severe hearing loss, chronic pain syndrome, psoriasis, cognitive impairment)
- Acute disease and/or fever at the time of enrollment. Fever was defined as ≥ 37.5˚C/99.5˚F on oral, axillary or tympanic setting or ≥ 38.0˚C/100.4˚F on rectal setting. Subjects with a minor illness without fever could be enrolled at the discretion of the investigator
- Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune –modifying drugs within 6 months prior to the first vaccine dose. For corticosteroids, this meant prednisone < 20 mg/day or equivalent was allowed. Inhaled or topical steroids were allowed
- Pregnant or lactating female, or female planning to become pregnant or discontinue contraceptive precautions (if of child-bearing potential)

Reviewer's comment – As is typical in preventive vaccine clinical trials, a healthier subset of the older population was enrolled in the pivotal studies.

6.1.4 Study Treatments or Agents Mandated by the Protocol
See Section 4.1 for a description of the study products administered. Lot numbers of the VZV gE were as follows: DVZVA004A, DVZVAS004B, DVZV004C, DVZVA006A, DVZVA006B, DVZVA006C. Lot numbers for the $AS01_B$ component were as follows: DA01A023A, DA01A027A, DA01A029A, DA01A031A, DA01A031B, DA01A032A.

The lot number for the placebo was AD02B267B.

6.1.5 Directions for Use
The HZ/su vaccine and placebo were administered IM to the deltoid region of the non-dominant arm. Following product administration, subjects were observed for at least 30 minutes with appropriate medical treatment available in the case of an anaphylactic reaction.

6.1.6 Sites and Centers
There were 268 PIs involved in the study, with 215 centers in 18 countries in 4 regions. The majority of subjects (51.2%) were from Europe.

Table 5 Number of Subjects with Centers by Country and Region (Zoster-006 TVC, EOS analysis)

Country	Region	Centers	Subjects (%) HZ/su Total = 7695	Subjects (%) Placebo Total = 7710
Australia	Australasia	79213, 79214, 79215, 79894,87473, 87474, 87476	210 (2.7%)	208 (2.7%)
Hong Kong	Australasia	78389, 78392	236 (3.1%)	234 (3.0%)
Japan	Australasia	78722, 78723, 79459, 79546,79552, 79824, 79848, 80029, 80030, 80380	288 (3.7%)	289 (3.7%)
Korea	Australasia	73174, 73175, 73176, 73177,73178, 73179, 73181, 89065	268 (3.5%)	271 (3.5%)
Taiwan	Australasia	76843, 76850,76852, 78724	640 (8.3%)	640 (8.3%
	Australasia		1642 (21.3%)	1642 (21.3%)

Country	Region	Centers	Subjects (%) HZ/su Total = 7695	Subjects (%) Placebo Total = 7710
Czech Republic	Europe	79857, 79861, 79862	451 (5.9%)	454 (5.9%)
Germany	Europe	77901, 77902, 77904, 77909, 7911, 77912, 77913, 77914, 77916, 7917, 77918, 77921, 77922, 77924, 7925, 77926, 77927, 77928, 77929, 7931, 77932, 77934, 77935, 77936, 7937, 77938, 77939, 77940, 77970, 7971, 77972, 77973, 77974, 77977, 7980, 78225, 78230, 78242, 81226	394 (5.1%)	394 (5.1%)
Estonia	Europe	78566, 78567	555 (7.2%)	555 (7.2%)
Spain	Europe	78501, 78502, 78503, 78524,79375, 79378, 79380, 79381, 79383,89003, 89009, 89010	530 (6.9%)	526 (6.8%)
Finland	Europe	80503, 80505, 80506, 80507,80508, 80509, 80511, 80512, 81636,89084, 89086	711 (9.2%)	709 (9.2%)
France	Europe	79478, 79479, 79480, 79481,79482, 79483, 79484, 79585, 79489,79490, 79491, 79492, 79494, 79496,80265, 90266	311 (4.0%)	312 (4.0%)
Italy	Europe	78405, 78420, 78421, 78422,78423, 78425, 78427, 78527, 78530,78608, 78610, 79906	178 (2.3%)	180 (2.3%)
Sweden	Europe	77030, 77032, 77033, 77035,77036, 77037, 77038, 77039, 77040,77041, 77042, 88778	505 (6.6%)	507 (6.6%)
United Kingdom	Europe	77753, 77756, 77758, 77759,77760, 89543, 89545, 89558, 89559	306 (4.0%)	311 (4.0%)
	Europe		3941 (51.2%)	3948 (51.2%)
Brazil	Latin America	80910, 80912, 80925, 80927,84079, 88031, 88052	315 (4.1%)	309 (4.1%)
Mexico	Latin America	74897, 75780, 75783	455 (5.9%)	458 (5.9%)
	Latin America		770 (10.0%)	777 (10.1%)
Canada	North America	78783, 78784, 78785, 78785,78787, 78788, 78789, 78790, 78791,78833, 78834, 78835, 78891, 78893, 78901	315 (4.1%)	314 (4.1%)
United States	North America	80093, 80098, 80099, 80100,80101, 80102, 80103, 80104, 80105,80106, 80107, 80109, 80111, 80112,80113, 80114, 80115, 80116, 80117,80118, 80119, 80121, 80122, 80123,80124, 80125, 80126, 80157, 80158,80168, 80291, 87926, 87928, 87929,87931, 87932, 88426, 88439, 88451,88719, 88721, 88815, 90723	1027 (13.3%)	1029 (13.3%)
	North America		1342 (17.4%)	1343 (17.4%)
Total			7695	7710

Source: Adapted from BLA 125614/0 Zoster-006 CSR Table 6.54, p. 2431 - 2435 and Table 6.55, p. 2436

Of the centers enrolling subjects included in the TVC analysis at EOS, the majority enrolled < 1.0% of the TVC; only one site (78566 in Estonia) enrolled more than 5% of the study population (5.5%).

Reviewer's comment - The proposed proportion of US and North American subjects planned for enrollment in Zoster-006 (and Zoster-022) was discussed early in development with the Applicant, as was the validity of pooling VE results across countries and regions. CBER agreed with the Applicant that the following supported pooling of VE across regions: uniformly high seroprevalence of VZV in the regions and thus potentially similar risk for HZ, genetic stability of the gE protein with conserved T-cell epitopes, and generally similar age-specific incidence rates of HZ. While countries with and without universal mass vaccination (UMV) for varicella were included in the Zoster-006 and Zoster-022 studies, the role of exogenous boosting via exposure to circulating VZV in the reduction of individual and population-based risk of HZ has not been fully elucidated.

While CBER agreed that pooling of data from across regions would be appropriate for the analysis of HZ VE, and while acknowledging that the study was not powered to demonstrate HZ VE by country or region, CBER stated that we expected the trends for US subjects, and trends within regions and countries to support the overall estimate of HZ VE.

6.1.7 Surveillance/Monitoring

Study oversight
An Independent Data Monitoring Committee, consisting of an independent statistician and clinical experts not participating in the study, was appointed to ensure the safety of enrolled subjects and to make recommendations to the sponsors regarding the continuation, modification or termination of the trial. Unblinded evaluation of safety was performed by the IDMC every three months from commencement of both studies in August 2010 until August 2014, after which reviews were conducted every six months.

Safety assessment – solicited AEs
A diary card was utilized to collect solicited symptoms from a subset of subjects on Day 0 through Day 6 following each vaccination. The following local symptoms were solicited; IS pain, IS swelling and IS redness. The following general adverse symptoms were solicited: headache, fatigue, GI symptoms (nausea, vomiting, diarrhea and/or abdominal pain), myalgia, shivering and fever. Temperature was taken daily, preferably by the oral route. If taken more than once a day, the highest daily recording was recorded in the eCRF.

The maximum intensity of IS redness and swelling was scored by the Applicant using the following grading scale: Grade 0: < 20 mm diameter, Grade 1: ≥ 20 mm to ≤ 50 mm diameter, Grade 2: > 50 to ≤ 100 mm diameter, and Grade 3: > 100 mm diameter.

Temperature was graded by the Applicant as follows: Grade 0: < 37.5 ˚C, Grade 1: 37.5˚C to 38.0˚C, Grade 2: 38.1˚C to 39.0˚C, and Grade 3: > 39 ˚C.

For the local symptom of pain and the general solicited symptoms of headache, fatigue, GI symptoms, myalgia and shivering the following scale was used: 0 = normal, 1 = mild/event easily tolerated, 2 = moderate/event interfered with normal activity, 3 = severe/event prevented normal activity.

Reviewer's comment – The grading scale for intensity was based on FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

Safety assessment – unsolicited AEs

Unsolicited AEs were collected from Days 0 – 29 after each vaccination from all subjects using a diary card, which was collected at M2/Visit 2 and M3/Visit 3. There was space on the 30-day diary card for recording any AE that started or any medical condition that worsened after study vaccination, along with the maximum intensity, start and end dates, a check box for receipt of medical attention and space for recording any concomitant vaccinations and medications as indicated in the comment above. The scale for recording the intensity of any unsolicited AEs including SAEs was similar to that of the scales for IS pain and general solicited symptoms enumerated above. In addition to diary card collection of AEs, the subject was asked a non-leading question such as "have you felt any different in any way since receiving the vaccine or since the previous visit" at study contacts.

The investigator assessed the maximum intensity of each AE (including SAEs) based on clinical judgment (except for local injection site AEs, which were considered causally related to vaccination), as well as the relationship of the AE to the investigational product considering factors such as alternative plausible causes, natural history of underlying diseases, concomitant therapy, and temporal relationship between the event and administration of study product. The investigator also assessed the outcome of all AEs (including SAEs) as recovered/resolved, recovering/resolving, not recovered/not resolving, recovered/resolved with sequelae and fatal (SAEs only).

Safety assessment - medically attended events (MAEs)

The subject was asked if he/she had a medically attended visit for any reason other than a visit for routine health care from first vaccination until Month 8 and the information was reported on the eCRF.

Safety assessment - intercurrent medical conditions and concurrent medication and vaccination

Intercurrent medical conditions were collected and recorded throughout the study period. At each study visit and contact the subject was asked about any medications taken or vaccinations received. The following information was recorded on the eCRF: all concomitant medications received for treatment of an SAE from D0 – M14, concomitant medications received for SAEs related to study participation or any fatal SAE from D0 to study conclusion contact, concomitant medications administered for treatment of HZ, HZ-related complications, or pIMDs from D0 until study conclusion contact, vaccines not foreseen in the study protocol from D0 until M3, oral or parenteral antiviral agents that are active against VZV administered for > 14 consecutive days for an indication other than to treat suspected or confirmed HZ or an HZ-related complication from D0 until study conclusion contact, investigational medication or investigational vaccine, vaccine against HZ other than the study vaccine and immunoglobulins and/or any blood products from D0 until study conclusion contact, immunosuppressants or other immune-modifying drugs administered during the study period for > 15 consecutive days (for corticosteroids, this meant prednisone ≥ 20 mg/day or equivalent), all concomitant medications except vitamins or dietary supplements administered any time during Days 0 – 29.

Safety assessment - laboratory
Safety laboratory assessments were not collected in the trial, but clinically significant laboratory abnormalities were followed up until they had returned to normal or a satisfactory explanation had been provided.

Safety assessment - SAEs
The time period for routine SAE reporting was from first vaccination until M14, except for SAEs related to study participation, SAEs judged related to investigational vaccine by the investigator, SAEs related to a GSK medication or vaccine or fatal SAEs which were reported until study end.

Safety assessment - AEs of special interest (AESIs) or pIMDs
Due to the concern regarding the potentiation of immune-mediated AEs in non-alum adjuvanted vaccines, reporting of the occurrence or exacerbation of pIMDs (including autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology) was from first dose of study product to the study conclusion contact. The Applicant provided a list of these AESIs in the protocol, but the investigator was charged with using their judgment as to whether an AE or SAE was also a pIMD.

Reviewer's comment – Any list or categorization of conditions may not be all-inclusive. The Applicant's approach to allow the investigator or the Applicant to assign a potential immune-mediated etiology to an event not on the supplied list was acceptable to CBER. The list is provided in the Appendix.

Assessment of immunogenicity
Blood samples for the proposed CoP analysis and analysis of the immune response to vaccination were collected as per the table below.

Table 6 – Biological Samples Collected for Immunogenicity Assessments

Sample type	Quantity (mLs)	Time point	Group or subset
Blood (humoral immunogenicity)	10	Visit 1, 3	All subjects
Blood (humoral immunogenicity)	10	Visits 4, 5, and 6	Immunogenicity subset
Blood (cell-mediated immunogenicity)	20	Visits 1, 2, 3, 4, 5, 6	Cell-mediated immunogenicity component of the immunogenicity subset

Source: Adapted from BLA 125614/0, Zoster-006 Protocol Amendment 4 Final, Table 6, p. 76

The following assays for immunogenicity testing were utilized for anti-gE antibody (Ab) assessment:

Table 7 – Humoral Immunogenicity Testing

System	Component	Method	Cut off	Unit	Laboratory
Serum	gE Ab IgG	ELISA	97	mIU/mL	GSK Biologicals

Source: Adapted from BLA 125614/0 Zoster-006 CSR Table 12, p. 180
gE – glycoprotein E
Ab - antibody
ELISA – Enzyme-linked immunosorbent assay

Table 8 – Cell-Mediated Immunogenicity (CMI) Testing

System	Component	Challenge	Method	Unit	Laboratory
PBMCs	CD4 cell response to culture medium/antigens as measured by secretion of activation markers related to immunogenicity	gE	ICS	Events	(b) (4)
PBMCs	CD4 cell response to culture medium/antigens as measured by secretion of activation markers related to immunogenicity	VZV	ICS	Events	(b) (4)

Source: Adapted from BLA125614/0 Zoster-006 CSR Table 13, p. 181
PBMCs – peripheral blood mononuclear cells
ICS – intracellular cytokine staining
gE – glycoprotein E
VZV – varicella zoster virus
(b) (4)

A CoP analysis was not submitted for CBER review.

Reviewer's comment – According to the CMC reviewers, the anti-gE assay was validated for use for its intended purpose as the primary immunologic read-out for the development program. However, it is noted that adequate VZV-specific CMI is thought to be necessary for protection against HZ and no immune CoP or threshold of protection has been identified that corresponds to protection against HZ.

Assessment of efficacy - definitions

The following are definitions for HZ-related variables as per protocol:

- Suspected case of HZ - a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Suspected HZ was clinically diagnosed by the investigator, and if the investigator determined that the case was not suspected HZ, no further evaluations were performed.
- Acute pain – defined as pain measured during the 4-week period following the onset of confirmed HZ
- PHN – defined as presence of HZ-associated severe "worst" pain persisting or appearing more than 90 days after rash onset.
- Severe "worst" pain – defined as HZ-associated pain rated as 3 or greater on the "worst pain" question of the ZBPI questionnaire

Definitions were also provided for the HZ onset and end dates, as well as "cessation of pain".

For all HZ cases, the Applicant recorded HZ complications. The protocol provided pre-specified definitions for the following HZ complications: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke. The definitions are included in the presentation of any such complications.

Reviewer's comment – The definitions in the protocol were reviewed and found to be acceptable for their intended purpose.

Assessment of efficacy – HZ-specific questionnaires and scripts

HZ-specific diary card - An HZ-specific diary card was distributed to every subject at Visit 1 to document the presence of a rash, the presence of associated pain, the dates of onset of the rash and/or pain and medications taken during the suspected HZ episode (with reason/indication, route, dose and frequency, and start and end dates).

The ZBPI questionnaire was completed by the subject daily from Day HZ-0 until Day HZ-28, then weekly until a 4-week pain free interval was identified or until the cut-off date of the EOS analysis. For subjects with ongoing HZ-associated pain at the cut-off date for EOS analysis, questionnaire data were collected until a 4-week pain-free period was documented or until at least Day HZ-90 to document potential PHN episodes. The ZBPI question #3 "please rate your pain by circling the one number that best defines your pain at its worst in the last 24 hours" generated information on HZ-associated pain. The assessment also included evaluations of HZ pain and discomfort-related interference with seven functional status and ADL items such as general activity, mood, walking ability, work, relationship with others, sleep and enjoyment of life.

Assessment of efficacy – procedures for evaluation of suspected HZ

After Visit 1, subjects were educated about the signs and symptoms of HZ, told to contact the study site if they suspected they had HZ (within 48 hours, if possible) and given an HZ-specific diary card to complete and bring to the study site. The following procedures were performed for clinically diagnosed suspected HZ cases:

- Visit HZ-1/Day HZ-0:
  - Investigator examined the subject, and if HZ was suspected, verified and transcribed the subject's HZ-specific diary card, documented the rash by digital photography and collected three replicate samples for PCR assay.
  - Subject completed a ZBPI questionnaire to rate HZ-associated pain in the prior 24 hours, and an additional ZBPI if more than 24 hours had elapsed between HZ onset and Visit HZ-1 to document pain in that period
  - Subject was provided with a supply of ZBPI questionnaires to collect information on the severity and duration of HZ-associated pain
- Additional HZ visits and contacts were scheduled for Day HZ-7 (Visit HZ-2), Day HZ-14 (Contact HZ-3), Day HZ-21 (Contact HZ-4), Day HZ-28 (Visit HZ-5), Day HZ-56 (Contact HZ-6) and Day HZ-91 (Visit HZ-7). At these visits and contacts, the investigator recorded information about the suspected HZ case (location/nature of lesions, end date of rash, HZ-related complications if any, concomitant medications associated with HZ or HZ complications, intercurrent medical conditions and any medical attention for HZ or HZ complications). Follow-up of HZ-associated pain persisting beyond Visit HZ-7 or other complications occurred at monthly contacts between the subjects and the investigator/staff delegate.
- All cases clinically diagnosed as suspected HZ were followed for a minimum of 28 days.

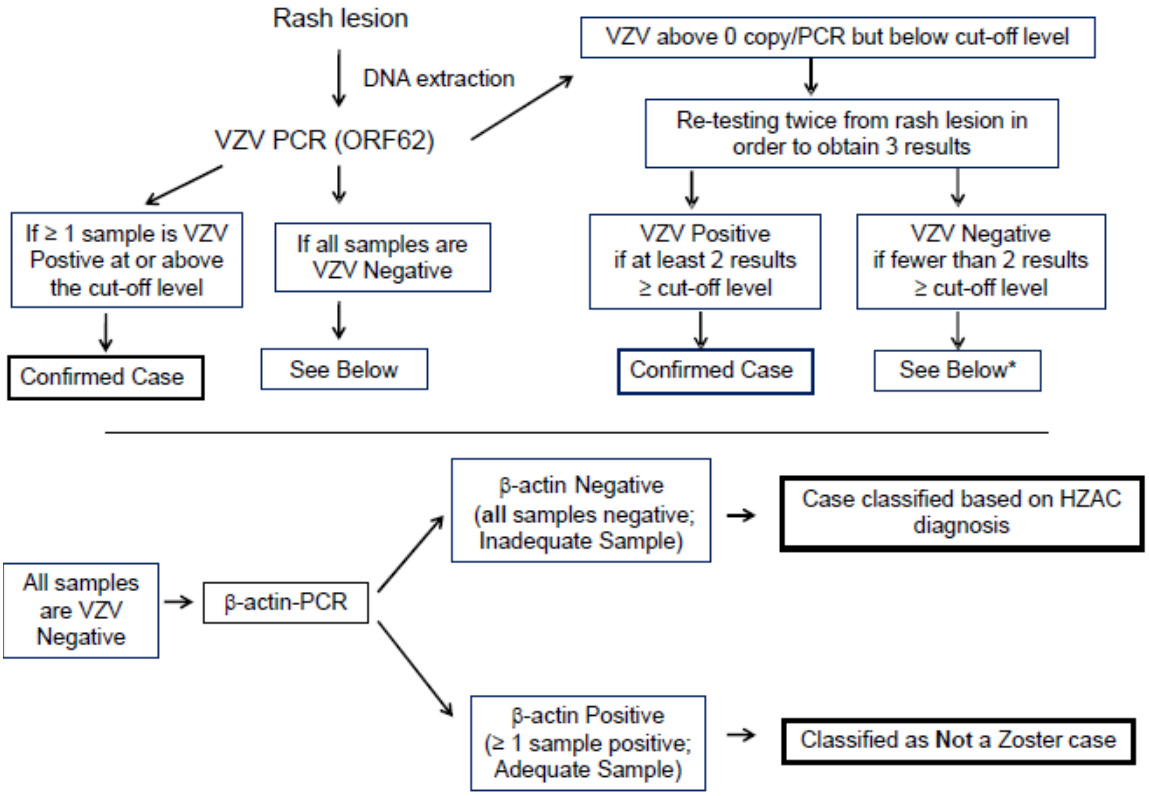
Assessment of efficacy – Confirmation of clinically diagnosed suspected HZ

Clinically diagnosed suspected cases of HZ were confirmed by either PCR, or by the Herpes Zoster Adjudication Committee (HZAC) if cases could not be confirmed or excluded by PCR

[e.g., when samples are inadequate (when VZV and β-actin PCR results were negative) or no lesion samples were available].

HZ cases were confirmed by a PCR-based algorithm presented below which assessed the presence of VZV DNA in samples (3 samples collected on the same day/subject) and sample adequacy (presence of β-actin DNA). Standardized and validated molecular assays were used.

Figure 2 – Algorithm for HZ case definition by PCR



The HZAC, which adjudicated each clinically suspected case, consisted of five physicians with HZ expertise who were not investigators in the study and who were blinded to treatment assignment and PCR results. Classification of a clinically suspected case of HZ as "HZ" or "not HZ" required that the committee members agreed unanimously. A "Not able to decide" decision occurred if the original and any subsequent images and data would not allow a clear clinical decision for the "HZ" or a "not HZ" determination by all members, and then the board would unanimously agree that they were not able to decide. For the purposes of analysis, a not able to decide classification was considered as not a case of HZ.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint - The primary endpoint of Zoster-006 was confirmed HZ cases during the study in the modified total vaccinated cohort (mTVC).

Reviewer's comment – CBER agreed with the sponsor that confirmed HZ cases, when determined by a reproducible, sensitive and specific method such as PCR, was an appropriate

endpoint for demonstration of VE. Please see Section 6.1.9 for definitions of and comments regarding the populations selected for analyses.

Select secondary endpoints:

- Occurrence of "overall" PHN calculated using the mTVC
- Duration of severe "worst" HZ-associated pain measured by the ZBPI in subjects with confirmed HZ
- Incidence of HZ-related mortality and hospitalizations
- Incidence of HZ complications in subjects with confirmed HZ
- Duration of pain mediation administered for HZ in subjects with confirmed HZ
- Occurrence of solicited local and general symptoms within 7 days (Days 0 – 6) in a subset of subjects, occurrence of unsolicited AEs during the 30 days (Days 0 – 29) after each vaccination in all subjects, occurrence of medically attended visits from M0 to M8 in all subjects, all SAEs from M0 – M14 in all subjects, SAEs related to study participation, GSK medication/vaccination and fatal SAEs during the entire study period in all subjects, occurrence/exacerbation of pIMDs during the entire study period in all subjects

Reviewer's comment – Duration of pain medication administered for HZ in subjects with confirmed HZ was an endpoint of the study, while VE in the use of pain medications was the corresponding objective. The statistical reviewer noted that the analysis program for the endpoint of duration of use of pain medication was not included in the statistical analysis plan (SAP) and thus the endpoint was not evaluated.

Select exploratory endpoints

- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38 – frequencies of CD4 T cells with antigen-specific IFN-γ and/or IL-2 and/or TNF-α and/or CD40L secretion/expression to gE and VZV as determined by ICS in a subset of subjects at Months 0, 3, 14, 26 and 38
- 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

Success criteria – The study was powered to demonstrate clinically meaningful overall HZ VE in subjects ≥ 50 YOA if the LB of the 95% CI for VE > 25%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Age groups selected for evaluation
The study randomization was stratified by region and by age cohort within regions. The age stratification was in an 8:5:3:1 ratio to achieve comparable numbers of HZ cases in the three main age strata: 50 – 59, 60 – 69 and ≥ 70 YOA.

Sample size
The sample size calculation for both studies was based on estimated incidence rates of HZ, PHN and HZ VE, as well as an expected dropout rate of 5% per year and 5% non-compliance to vaccination schedule. Sample sizes were selected to provide the required number of HZ cases within a follow-up time of approximately 3 years. It was estimated that approximately 196 confirmed HZ cases would provide approximately 97% power to demonstrate an overall VE of at

least 40% assuming a true HZ VE of 68%. In addition, the Zoster-006 sample size was sufficient to demonstrate a HZ VE of at least 10% in the 50 – 59 and 60 – 69 YOA strata with powers of 99% and 98%, respectively.

Reviewer's comment – The study success criterion for HZ VE demonstration of HZ VE in subjects ≥ 50 YOA above 25%, although the study was powered for a LB of 40%. Assumptions of VE were lower than demonstrated, and thus the study was well powered to evaluate the primary endpoint. The initial assumptions regarding HZ VE affected endpoints for Zoster-022 and the pooled analysis as well as the conditions and timing of study analyses which were amended in Protocol Amendment 4.

Significance level – The overall efficacy analyses were performed at the 5% 2-sided significance level.

Analysis populations – see Section 6.1.10.

Derived and transformed data
Safety data - For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced, so the analysis of solicited symptoms based on the TVC only included subjects/doses with documented safety data. For the analysis of unsolicited AEs, SAEs, and concomitant medication, all vaccinated subjects were considered and subjects who did not report an event were considered subjects without an event.

Efficacy data – For a given subject and a given efficacy measurement, missing or non-evaluable measurements were not imputed for the primary analysis. The HZ incidence rate was determined with reference to the first HZ episode in a subject, if a subject reported multiple HZ episodes. The HZ-free period for the mTVC was calculated from the HZ-case exclusion period for the mTVC to HZ onset, and calculated from first vaccination for the TVC. The number of Person-Years at risk over an interval of time was defined as the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject. The relative risk (RR) was defined as the ratio of the incidence rates of the HZ/su group over the placebo group, with VE defined as 1 – RR.

Immunogenicity data - For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced, therefore, analyses excluded subjects with missing or non-evaluable measurements. For the assessment of humoral immunogenicity, the following applied:

- Seronegative or seropositive subject - subject whose Ab concentration was below the cut-off value (seronegative subject), or a subject whose Ab concentration was ≥ the cut-off value (seropositive subject)
- Seropositivity rate - percentage of seropositive subjects
- Vaccine response for subjects seropositive or seronegative at baseline - a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination concentration (seropositive subjects) or a 4-fold increase at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity (seronegative subjects).

- The geometric mean concentration (GMC) calculations were performed by taking the anti-log of the mean log concentration transformations. For descriptive purposes only, Ab concentrations below the cut-off level were assigned an arbitrary value of half the cut-off for the purposes of GMC calculation. For inferential analyses, concentrations below the cut-off level were considered as missing.

Cell-mediated immune (CMI) response – The frequency of CD4 [2+] T cells producing at least 2 activation markers among IFN-γ, IL-2, TNF-α and/or CD40L upon *in vitro* stimulation with antigen was used to characterize CMI responses to vaccination. For responses to both gE and VZV, the cut-off of 320 positive events/10^6 CD4 T cells was used for vaccine response assessment, and the vaccine response rate (VRR) was defined as the percentage of subjects with at least a 2-fold increase as compared to the cut-off, for subjects with pre-vaccination T cell frequencies below the cut-off and at least a 2-fold increase as compared to pre-vaccination T cell frequencies for subjects with pre-vaccination frequencies above the cut-off.

Statistical analyses

The summary of inferential evaluations of the primary and secondary objectives for the study is below.

Table 9 – Summary of statistical inferential evaluations of the primary and secondary objectives for Zoster-006

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-

Source: Adapted from 125614/0 Zoster-022 CSR Table 19, p. 195
P: Primary objective, well powered
S: Secondary objective, appropriately powered
O: Study not well powered under protocol assumptions although could lead to significance
- : Per protocol, estimates not relevant or not considered for a statistical evaluation

All analyses were presented overall and by age strata, with the main age strata for reporting purposes being 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA with some analyses presented separately for 70 – 79 YOA and ≥ 80 YOA subjects. Demographic characteristics, cohort description and withdrawal status were summarized overall and by region.

Reduction in HZ risk - The primary analysis of efficacy on the mTVC was complemented by analyses based on the TVC and ATPc. Incidence rates and VE with 95% CI were tabulated for the primary efficacy endpoint. Overall VE considered the exact inference on the RR stratified for age and region conditionally to the total number of HZ cases observed and time at risk. Stratification included region alone when VE was analyzed by age strata. The follow up time for each subject started at the day after first vaccination or 30 days after the second vaccination if analyses were done on the TVC or mTVC, respectively. The follow up time for each subject was to end at one of the following times: at time of the event, at the date of last visit for subjects who completed the study and did not have an event, or at the latest visit for which data were

available for subjects who did not yet complete the study at the time of the final analysis and did not have an event. Sensitivity analyses were done by gender, region and time.

Reduction in "overall" PHN risk – The overall reduction in PHN risk was calculated similarly to the reduction in HZ risk.

Reviewer's comment – The VE analysis against "overall PHN" calculates the reduction in PHN risk in all subjects, including those subjects who never reported HZ.

Please see the statistical review for a discussion of the methods for analyses of other secondary and exploratory endpoints and further discussion of statistical methods.

Conditions for and sequence of analyses

The following were conditions for triggering the final HZ efficacy analysis of Zoster-006:

- At least 196 confirmed HZ cases across all age groups 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 were accrued
- ~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 and a total of at least 35 PHN cases in subjects ≥ 70 YOA from pooled data from Zoster-006 and Zoster-022 were accrued.

Reviewer's comment – The protocol was modified in Protocol Amendment 4 (protocol date 18-APR-2014), submitted to IND 13857/157 on 30-MAY-2014, in which the Applicant noted that the conditions for triggering the Zoster-006 final HZ analysis would occur approximately one year before the conditions being reached for Zoster-022. Therefore, the Applicant decided to dissociate the timing of the analyses of the two studies as allowed per protocol (13857/20 submitted 20-MAY-2010, protocol date 07-APR-2010), and analyze Zoster-006 in a step-wise manner. Further, endpoints related to overall PHN for Zoster-022 and the pooled analysis were changed and the target number of PHN cases needed to trigger pooled PHN analysis was reduced (from 88 to 35 cases) based on accrual rates, while maintaining statistical robustness.

Protocol Amendment 4 included information regarding the establishment of a Firewall Team consisting of a restricted group of individuals within GSK to allow planned analyses to be performed while maintaining the study blind (for the HZ/su team, Local Team, investigators and subjects) up to the EOS database freeze. A firewall charter was established. CBER reviewers concluded that as study blind would be maintained, and the conditions for safety follow-up maintained, the plan for a two-step analysis of Zoster-006 was acceptable.

At the final HZ Efficacy analysis (step 1) the final HZ VE analyses pertaining to the primary objective and the secondary efficacy objective by age were performed. At the EOS analysis (step 2), all objectives of Zoster-006 were analyzed, and objectives already analyzed at step 1

were re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise). Because each inferential objective in Zoster-006 was analyzed once during the two-step process, no adjustment in type 1 error was necessary.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All subjects enrolled belonged to the Total Enrolled Cohort. The Total Effective Cohort excluded subjects from the Total Enrolled Cohort who were enrolled at specific closed sites and other subjects excluded from all statistical analyses.

The primary populations for analyses were the following:

- Total Vaccinated Cohort (TVC) - included all vaccinated subjects (at least one dose) belonging to the Total Effective Cohort analyzed according to the vaccine actually administered. This was the primary population for the evaluation of safety.
- Total Vaccinated Cohort for the analysis of reactogenicity – included all TVC subjects belonging to the 7-day diary card subset
- Modified Total Vaccinated Cohort (mTVC) – excluded subjects in the TVC who were not administered the second vaccination, who developed a case of HZ prior to 30 days after the second vaccination or for whom one of the following criteria applied:
  - Site or route of study vaccine administration was wrong, unknown, or not according to protocol for reason (other than site or route) specified by the investigator and/or one of the administered doses was not compatible with the allocated treatment number
  - Wrong replacement or wrong study vaccine administered.

  The mTVC was the primary population for the analysis of efficacy.
- ATPcs for analysis of immunogenicity – The ATPc for the analysis of immunogenicity - humoral and the ATPc for the analysis of immunogenicity - CMI were the primary analysis cohorts for the analysis of immunogenicity. These cohorts included subjects who met all eligibility criteria, complied with procedures and intervals allowed for the analysis with no elimination criteria during the study and for whom data concerning immunogenicity endpoint measures were available. An Adapted ATPc for the analysis of immunogenicity was created to denote that at specific time points a corresponding ATP cohort for immunogenicity was utilized to include all evaluable subjects in the statistical analysis at a specific time point (i.e., include subjects who might qualify for the ATP cohort at a time point in the analysis of immunogenicity at that time point, even if they did not qualify for inclusion for the analysis at another time point).

According to protocol cohorts (ATPc) for efficacy and safety with additional elimination criteria were also established to support the evaluations of the efficacy and safety endpoints on the primary analysis populations.

Reviewer's comment – CBER agreed that the mTVC as defined was an appropriate population for the primary analysis of HZ VE.

6.1.10.1.1 Demographics

The summary of demographic characteristics of the TVC at the EOS is below.

Table 10 – Summary of demographic characteristics (TVC – EOS analysis)

Characteristics	Parameters or Categories	HZ/su N = 7695 Value or n	HZ/su N = 7695 %	Placebo N = 7710 Value or n	Placebo N = 7710 %
Age at vaccination dose 1	Mean	62.4	-	62.3	-
	SD	9.0	-	9.0	-
	Median	60.0	-	60.0	-
	Minimum	50	-	48	-
	Maximum	96	-	95	-
Gender	Female	4709	61.2	4711	61.1
	Male	2986	38.8	2999	38.9
Ethnicity	American Hispanic or Latino	847	11.0	864	11.2
	Not American Hispanic or Latino	6848	89.0	6846	88.8
Geographic Ancestry	African Heritage / African American	140	1.8	129	1.7
	American Indian or Alaskan Native	8	0.1	5	0.1
	Asian - Central/South Asian Heritage	5	0.1	5	0.1
	Asian - East Asian Heritage	1143	14.9	1137	14.7
	Asian - Japanese Heritage	311	4.0	309	4.0
	Asian - South East Asian Heritage	7	0.1	19	0.2
	Native Hawaiian or Other Pacific Islander	1	0.0	3	0.0
	White - Arabic / North African Heritage	43	0.6	41	0.5
	White - Caucasian / European Heritage	5488	71.3	5494	71.3
	Other	549	7.1	568	7.4

Source: Adapted from 125614/0 Zoster-006 CSR Table 29, p. 259
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Reviewer's comment – The median age and proportions of subjects by gender, race and ethnicity were comparable between treatment groups for the TVC at the EOS analysis. Most subjects were non-Hispanic or Latino (88.9%) and White of Caucasian/European heritage (71.3%), which is typical of clinical trial demographics conducted in developed countries. The very small proportions of subjects of African/African American heritage may limit generalizability of study results to that population.

There were no appreciable differences in the summary of demographics for the mTVC at the Final HZ analysis step (efficacy population) as compared to the TVC at the EOS analysis step (safety population). The demographics of the TVC diary card subset for the analysis of reactogenicity were also reviewed and were comparable to the TVC population demographics (EOS analysis) in terms of gender, ethnicity and geographic ancestry. The mean and median ages in the TVC diary card subset (65.9 and 66.0 respectively) were slightly older than the mean and median ages in the TVC (62.3 and 60.0 respectively). However, reactogenicity, which tended to diminish with age, will be described by age group.

The Applicant also provided demographic characteristics summaries by age and by region. In general, while there was some minor variability when comparing characteristics between age groups and regions (e.g., higher proportions of females as compared to males in the 50 – 59

and 60 – 69 YOA group as compared to the ≥ 70 YOA group and higher proportions of females in the analysis cohorts from Latin America as compared to other regions) and greater, but expected variability with regard to ethnicity and geographic ancestry between regions, the demographic characteristics by age and region were generally consistent between the TVC at the EOS analysis and the mTVC at the Final HZ Efficacy analysis as well as comparable between treatment groups.

In addition, CBER confirmed that the age ratio proposed in the protocol (8:5:3:1 for the 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA groups) was maintained for the mTVC at the Final HZ Efficacy analysis.

As can be seen below, most subjects (51.2%) in the TVC at the EOS analysis were from Europe and these proportions were consistent with the proportions of subjects by region in the mTVC at the Final HZ Efficacy analysis.

Table 11 – Number of subjects by region – (Zoster-006 TVC – EOS)

Region	**HZ/su N = 7695 n (%)**	**Placebo N = 7710 n (%)**	**Total N = 15405 n (%)**
Australasia	1642 (21.3%)	1642 (21.3%)	3284 (21.3%)
Europe	3941 (51.2%)	3948 (51.2%)	7889 (51.2%)
Latin America	770 (10.0%)	777 (10.1%)	1547 (10.0%)
North America	1342 (17.4%)	1343 (17.4%)	2685 (17.4%)

Source: 125614/0 Zoster-006 CSR Table 6.55, p. 2436
N= number of subjects
n = number of subjects in a given category
% = n/Number of subjects with available results x 100

The Applicant provided a summary of demographic characteristics for the TVC of the North American region. There were higher proportions of subjects of White or Caucasian/European ancestry (90.0% vs. 71.3%) and African/African-American ancestry (7.5% vs. 1.7%) and lower proportions of subjects with Asian ancestry (0.7% vs. 19.1%) and Hispanic/Latino ethnicity (3.6% vs. 11.1%) in the North American subset as compared to the overall TVC.

Reviewer's comment – The small differences in demographic composition of the North American subset as compared to the overall TVC did not appear to result in differences in HZ VE by region, see Section 6.1.11.3.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The Applicant provided tabulations of the numbers and percentages of subjects with pre-existing conditions with an incidence of ≥ 2% in one or more treatment groups by SOC and PT (TVC at the EOS analysis).

As expected in a population of subjects ≥ 50 years of age, large proportions of subjects in both vaccination groups (88.3% and 88.6% in the HZ/su and Placebo groups respectively) reported at least one pre-existing condition. The SOCs with the highest proportions of subjects reporting at least one prior condition were the Vascular disorders SOC (47.1% and 46.6% of subjects in the HZ/su and Placebo groups, respectively), the Metabolism and nutrition disorders SOC (40.2% and 40.1% of subjects in the HZ/su and Placebo groups, respectively, driven by the PTs of dyslipidemia, hyperlipidemia and hypercholesterolemia) and the Musculoskeletal and connective tissue disorders SOC (40.0% and 40.8% of subjects in the HZ/su and Placebo

groups, respectively). The most commonly reported conditions by PT were hypertension in the Vascular disorders SOC (41.9% and 41.0% of subjects in the HZ/su and Placebo groups, respectively) and osteoarthritis in the Musculoskeletal and connective tissue disorders SOC (19.5% and 20.3% of subjects in the HZ/su and Placebo groups, respectively).

Reviewer's comment – The proportions of subjects in the TVC reporting pre-existing conditions overall and by SOC and PT were comparable between treatment groups and typical of a study population of older subjects.

6.1.10.1.3 Subject Disposition

Subjects available for and excluded from analyses

The TVC at the EOS analysis (N = 15405 subjects total, 7695 and 7710 in the HZ/su and placebo groups respectively) was the primary population for the analysis of safety and the proportions of subjects available for the safety analysis at the EOS (cut-off date 21-APR-2015) compared to those enrolled is below. Of the subjects enrolled, 95.4% in each treatment group were included in the TVC.

Table 12 – Subjects enrolled into the study as well as the number excluded from the TVC with reasons for exclusion (Zoster-006 – EOS)

	HZ/su N	HZ/su %	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 125614/9, Table 6.24 (revised), p. 15

* excludes 15 subjects characterized as "No assigned group"

Of the subjects in the Total Enrolled Cohort that were excluded from all statistical analyses, 671 were excluded from a single site in Mexico, due to serious deviations from GCP identified by the Applicant including deficiencies in documentation of study procedures and inadequate investigator oversight. Additionally, one study center closed in August 2014 for business reasons; as the investigator was not available to endorse the data, all 46 subjects from this site were excluded from analyses. Other reasons for subject exclusion from statistical analyses, identified for small numbers of subjects, included deviations in the informed consent process, loss of source documentation and data unable to be endorsed by the investigator.

Reviewer's comment – Safety data from the Mexican site excluded from analyses were reviewed. See Section 8.5.

Protocol deviations not leading to elimination from analyses (Section 5.11.2.1 of the CSR) were also reviewed. These deviations involved ICFs, ICF addenda, and Study Determination Agreements, late reporting of safety events, errors in biospecimen collection as well as various recording, reporting, documentation, and technical deviations.

Reviewer's comment - The Applicant's documentation of the events leading to subject exclusion from analyses and protocol deviations not leading to exclusion from analyses as well as corrective actions taken were reviewed and found to be acceptable.

The proportions of subjects in the TVC available for inclusion in the mTVC at the Final HZ Efficacy analysis (primary time period for the evaluation of efficacy) are below.

Table 13 -Subjects in the TVC excluded from the mTVC with reason for exclusion (Zoster-006 – Final HZ Efficacy analysis)

	HZ/su n	HZ/su %	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 having 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 125614/9, Table 25 (revised), p. 9
Note: Subjects may have had more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who had been assigned a lower elimination code number to the same corresponding cohort compared to the Total Vaccinated Cohort
% = percentage of subjects in the considered cohort relative to the Total Vaccinated Cohort
¥ = Numbers in TVC differ from Table 12 due to six subjects (three in each treatment group) further excluded at the later time analysis time point for whom data were not endorsed by the investigator or for whom the source documentation was lost.

At the Final HZ Efficacy analysis, 95.4% and 96.1% of subjects in the TVC of the HZ/su and Placebo groups, respectively, were included in the mTVC for the analysis of efficacy. Of the excluded subjects, the majority were excluded due to not receiving two doses: 4.4% and 3.6% in the Hz/su and Placebo groups, respectively, did not receive two doses. See the Exposure section below for details regarding why subjects did not receive two doses.

Reviewer's comment – The proportion of subjects in the TVC that were eligible for the mTVC for the analysis of efficacy at the Final HZ Efficacy analysis was comparable between treatment groups and similar to the proportion of subjects in the TVC that were eligible for the mTVC at the EOS analysis.

The Applicant provided tabulations and proportions of subjects included in the TVC but excluded from the mTVC by age (50 – 59, 60 – 69 and ≥ 70 YOA) and treatment group and region and treatment group. The proportions of subjects from the TVC participating in the mTVC ranged from 94.5% to 96.7% by age and treatment group. Within regions, the proportions of subjects from the TVC participating in the mTVC ranged from 92.1% to 97.0%, with the highest participation rate in Europe and the lowest in Latin America.

Reviewer's comment - The proportions of subjects in the TVC participating in the mTVC were generally consistent between age and treatment groups and region and treatment groups.

Exposure

As per the table below, 614 subjects in the TVC at the EOS analysis were administered only one dose; 338 subjects (338/7695 or 4.4%) in the HZ/su group and 276 subjects (276/7710 or 3.6%) in the placebo group.

Table 14 – Number and percentage of subjects who received study vaccine doses (Zoster-006 TVC – EOS)

Total doses received	HZ/su N = 7695 n (%)	Placebo N = 7710 n (%)	Total N = 15405 n (%)
1	338 (4.4%)	276 (3.6%)	614 (4.0%)
2	7357 (95.6%)	7434 (96.4%)	14791 (96.0%)
Any	7695 (100%)	7710 (100%)	15405 (100%)

Source: Adapted from 125614/0 Zoster-006 CSR Table 10.1, p. 3250
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified number of doses
Any = number and percentage of subjects receiving at least one dose

Treatment compliance by age strata was reviewed; 94.6% – 96.8% of subjects across the age strata received two doses with the proportions comparable between treatment groups.

Reviewer's comment – A high proportion of subjects in each treatment group received both doses.

Of note, although 338 and 276 subjects in the HZ/su and Placebo groups in the TVC at the EOS analysis did not receive two doses, the numbers for the respective treatment groups in the mTVC at the EOS analysis were slightly different (337 and 277 respectively) as it was confirmed at the EOS analysis step that one additional subject in the HZ/su group from the TVC did not receive dose 2, and the elimination code for only receiving one dose was removed for one subject in the placebo group that was eliminated from all statistical analyses at the EOS analysis step.

The reasons for subject withdrawal from vaccination are below, and the most common reason in both treatment groups was "visit not done". Of note, subjects were only categorized as a withdrawal from vaccination due to an AE if they specifically said that was the case, otherwise they were classified as "Subject – other".

Table 15 Tabulation of subjects who withdrawn from vaccination (did not receive Dose 2) with reason for withdrawal (Zoster-006 TVC – EOS)

Categories	HZ/su N = 338 n (%)	Placebo N = 276 n (%)	Total N = 614 n (%)
GSK decision	5 (1.5%)	5 (1.8%)	10 (1.6%)
INVESTIGATOR Other§	4 (1.2%)	3 (1.1%)	7 (1.1%)
INVESTIGATOR Protocol violation or outside of time window	24 (7.1%)	20 (7.2%)	44 (7.2%)
INVESTIGATOR SAE and/or pIMD	4 (1.2%)	4 (1.4%)	8 (1.3%)
INVESTIGATOR Suspected HZ episode	3 (0.9%)	14 (5.1%)	17 (2.8%)
INVESTIGATOR non-serious solicited AE(s)	4 (1.2%)	0 (0.0%)	4 (0.7%)
INVESTIGATOR non-serious solicited and unsolicited AE(s)	2 (0.6%)	0 (0.0%)	2 (0.3%)
INVESTIGATOR non-serious unsolicited AE	13 (3.8%)	6 (2.2%)	19 (3.1%)
SUBJECT Consent withdrawal, not due to an AE	2 (0.6%)	2 (0.7%)	4 (0.7%)
SUBJECT Other§	35 (10.4%)	24 (8.7%)	59 (9.6%)
SUBJECT SAE and/or pIMD	0 (0.0%)	2 (0.7%)	2 (0.3%)
SUBJECT non-serious AE	1 (0.3%)	0 (0.0%)	1 (0.2%)
SUBJECT non-serious solicited AE(s)	13 (3.8%)	4 (1.4%)	17 (2.8%)

Categories	HZ/su N = 338 n (%)	Placebo N = 276 n (%)	Total N = 614 n (%)
SUBJECT non-serious solicited and unsolicited AE(s)	1 (0.3%)	0 (0.0%)	1 (0.2%)
SUBJECT non-serious unsolicited AE	19 (5.6%)	6 (2.2%)	25 (4.1%)
Visit not done	208 (61.5%)	186 (67.4%)	394 (64.2%)

Adapted from 125614/9 Response to CBER IR of 10-FEB-2017, Table 7, p. 23 and response to Question 6
§ The term 'other' applies when it was not specified, whether or not the withdrawal from vaccination was or was not due to an AE

Reviewer's comment – A higher proportion of subjects in the HZ/su group self-selected withdrawal from vaccination as compared to the Placebo group. However, the numbers of subjects self-withdrawn from vaccination was low in both treatment groups.

Subjects vaccinated, completed and withdrawn

The numbers of subjects vaccinated, completed and withdrawn with reason for withdrawal at the EOS are below. Per protocol, a subject who returned for the concluding visit/was available for the concluding contact foreseen in the protocol was considered to have completed the study and for analysis purposes, a withdrawal from the study refers to a subject who did not return for the concluding visit or was not available for the concluding contact.

Table 16 - Number of subjects vaccinated, completed and withdrawn with reasons for withdrawal (Zoster-006 TVC - EOS)

	HZ/su 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%)
Reasons for withdrawal			
Withdrawal due to serious adverse event	227 (2.9%)	235 (3.0%)	462 (3.0%)
Withdrawal due to non-serious adverse event	30 (0.4%)	18 (0.2%)	48 (0.3%)
Withdrawal due to protocol violation	19 (0.2%)	21 (0.3%)	40 (0.3%)
Consent withdrawal not due to adverse event	368 (4.8%)	354 (4.6%)	722 (4.7%)
Migrated/moved from study area	48 (0.6%)	43 (0.6%)	91 (0.6%)
Lost to follow-up (incomplete vaccination course)	31 (0.4%)	24 (0.3%)	55 (0.4%)
Lost to follow-up (completed vaccination course)	152 (2.0%)	170 (2.2%)	322 (2.1%)
Suspected HZ episode	0 (0.0%)	2 (0.0%)	2 (0.0%)
Sponsor study termination	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	47 (0.6%)	35 (0.5%)	82 (0.5%)

Source: Adapted from 125614/0 Zoster-006 CSR, Table 23, p. 246 and 125614/9, Table 23 (revised), p. 24
N = number of subjects in the TVC, EOS analysis
n = number of subject in that category
% = denominator is N (number of subjects in the TVC – EOS of that treatment group

The most common reasons for withdrawal from the study for both treatment groups was consent withdrawal not due to an adverse event, withdrawal due to a serious adverse event and lost to follow-up after completion of the vaccination course.

Reviewer's comments - The proportions of subjects withdrawn overall were comparable between treatment groups. The numbers of subjects withdrawn by reasons for withdrawal were also generally comparable between treatment groups. Although the proportions were very

small, a higher proportion of subjects withdrew in the HZ/su group due to a non-serious AE than in the Placebo group.

Given the age groups enrolled and the length of the study follow-up period, completion rates of approximately 88% per group and overall is acceptable.

The Applicant provided a tabulation of the numbers of subjects withdrawn from the study by age strata and treatment group. The percentage of subjects who completed the study was lowest in the oldest age stratum, but the percentages of subjects who completed the study were comparable between treatment groups within the age strata.

Table 17 – Proportions of subjects completed and withdrawn by age and treatment group with reasons for withdrawal (Zoster-006 TVC – EOS)

	HZ/su 50 – 59 N = 3644	Placebo 50 – 59 N = 3642	HZ/su 60 – 69 N = 2243	Placebo 60 – 69 N = 2245	HZ/su ≥ 70 N = 1808	Placebo ≥ 70 N = 1823
Proportion of subjects completed	89.9%	90.9%	89.6%	89.4%	82.2%	81.8%
Proportion of subjects withdrawn	10.1%	9.1%	10.4%	10.6%	17.8%	18.2%
Reasons for withdrawal:						
Serious Adverse Event	1.4%	1.2%	2.6%	2.8%	6.5%	7.0%
Non-Serious Adverse Event	0.4%	0.2%	0.4%	0.2%	0.4%	0.4%
Protocol violation	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%
Consent withdrawal (not due to an adverse event)	3.7%	3.7%	4.7%	4.8%	7.1%	6.2%
Migrated/moved from study area	0.7%	0.5%	0.4%	0.5%	0.7%	0.8%
Lost to follow-up (incomplete vaccination course)	0.6%	0.4%	0.3%	0.3%	0.2%	0.2%
Lost to follow-up (complete vaccination course)	2.4%	2.6%	1.4%	1.5%	1.8%	2.2%
Suspected HZ Episode	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Sponsor study termination	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Others	0.7%	0.3%	0.4%	0.2%	0.8%	1.1%

Source: Adapted from 125614/0 Zoster-006 CR Table 6.37, p. 2323 and 125614/9 Table 6.37 (revised), p. 26

N = number of subjects vaccinated in that age and treatment group

% = Denominator is number of subjects vaccinated in that age and treatment group

Reviewer's comment – The percentage of withdrawals due to an SAE was highest in the oldest age stratum, an expected finding due to age-related infirmity and higher death rates. However, according to Table 23 the number of person-years of follow-up for HZ contributed by the ≥ 70 YOA group in the mTVC at the Final HZ Efficacy analysis was generally proportionate to that of the other age groups and adequate for the analysis of VE in that age group.

The number of subjects vaccinated, completed and withdrawn by region was provided.

Table 18 – Proportions of subjects completed and withdrawn with reason for withdrawal by region (Zoster-006 TVC - EOS)

	Australasia		Europe		Latin America		North America	
	HZ/su N = 1642	Placebo N = 1642	HZ/su N = 3941	Placebo N = 3948	HZ/su N = 770	Placebo N = 777	HZ/su N = 1342	Placebo N = 1343
Proportion completed	90.7%	89.8%	90.9%	90.1%	84.5%	88.4%	78.3%	78.5%
Proportion withdrawn	9.3%	10.2%	9.1%	9.0%	15.5%	11.6%	21.7%	21.5%
Reasons for withdrawal								
SAE	2.0%	2.8%	3.5%	3.0%	2.7%	3.7%	2.8%	3.2%
Non-serious AE	0.4%	0.3%	0.4%	0.2%	0.4%	0.0%	0.3%	0.4%
Protocol violation	0.0%	0.1%	0.4%	0.5%	0.0%	0.0%	0.2%	0.1%

	Australasia		Europe		Latin America		North America	
Consent withdrawal (not due to AE)	4.7%	3.5%	2.9%	2.9%	6.2%	4.8%	9.5%	10.7%
Moved from study area	0.4%	0.5%	0.3%	0.4%	1.7%	1.0%	1.2%	0.9%
Lost to follow up (incomplete vaccination course)	0.2%	0.1%	0.2%	0.2%	0.6%	0.3%	1.1%	0.9%
Lost to follow up (complete vaccination course)	1.2%	2.6%	1.1%	1.5%	1.7%	1.2%	5.6%	4.4%
Suspected HZ	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Sponsor study termination	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Other	0.4%	0.3%	0.3%	0.4%	2.1%	0.6%	1.0%	0.8%

Source: Adapted from 125614/9 Response to CBER IR of 10-FEB-2017, Table 6.57 (revised), p. 27
N = number of subjects vaccinated
% = number of subjects with that event/N

Reviewer's comment – According to the CBER statistical reviewer, although the proportions of subjects completing the study was lowest in the North American region, the sum of person-years (time at risk) was generally proportional to the number of subjects by region.

6.1.11 Efficacy Analyses

The final analysis of HZ VE was performed on the mTVC at the Final HZ analysis step. HZ VE was re-estimated on the mTVC at the EOS analysis time point. Efficacy analyses supportive to the primary analysis on the mTVC were also performed on the TVC and ATPc for efficacy.

The Applicant reported that three additional suspected HZ cases were reported to GSK after 21-APR-15 and were not included in the EOS analysis.

Investigator determination of suspected cases of HZ

Subjects who suspected they had HZ were instructed to complete a Suspected HZ rash diary card and to contact the PI for further assessments. In the suspected HZ screens of the eCRF, there was a leading question, "Has any suspected zoster episode been reported by the subject?" with yes or no responses available. If yes, the second leading question was, "Does the subject exhibit a clinical presentation of zoster?" with yes or no responses available. The Applicant provided the following information based on the investigator's responses to the questions in the table below.

Table 19 – Distribution of subjects with self-reported suspected HZ cases as judged by the investigator (Zoster-006 TVC)

	HZ/su N= 7695 n (%)	**Placebo N = 7710 n (%)**
Subjects presenting with presumptive case of HZ	227 (2.9%)	527 (6.8%)
Did the subject exhibit a clinical presentation of HZ per physician?		
• No	141 (1.8%)	152 (2.0%)
• Yes	86 (1.1%)	375 (4.9%)

Source: Adapted from 125614/21, Table 1, page 3
N = number of subjects in the TVC
n = number of subjects reporting a presumptive HZ case
% = proportion of subjects in the TVC reporting a presumptive HZ case

Reviewer's comment – The proportions of subjects presenting with a presumptive case of HZ that the investigators concluded were "not a clinically suspected case of HZ" was comparable between treatment groups – this addresses a concern that increased reactogenicity following HZ/su administration may have introduced bias in the determination of what was or was not a clinically suspected case of HZ.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of the study was confirmed HZ cases during the study in the mTVC. The final analysis of HZ VE occurred at the Final HZ Efficacy analysis step (step 1, data lock point 01-JUL-2014) and a descriptive analysis occurred at the EOS analyses (step 2, data lock point 12-OCT-2015).

There were 216 confirmed cases of HZ in the mTVC at the Final HZ Efficacy analysis step, 6 in the HZ/su 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.

Reviewer's comment – As VE is generally highest in the year following vaccination, adequate follow-up time reduces bias that might favor the vaccine.

Table 20 - Vaccine efficacy: First or only episode of HZ during the entire study period overall using Poisson method (Zoster-006 mTVC – Final HZ Efficacy analysis)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
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 HZ/su groups were 9.1 and 0.3 per 1000 person-years 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 lower bound of the 95% CI was above 25%.

Reviewer's comment – The incidence of HZ in the Placebo group is within the range expected given the age stratification of the study.

The method of HZ case confirmation by treatment group and overall is below.

Table 21 - Distribution of confirmed HZ episode determined by PCR or HZAC (Zoster-006 mTVC – Final HZ Efficacy analysis)

Confirmed HZ episode determined by:	HZ/su n	HZ/su %	Placebo n	Placebo %	Total n	Total %
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		210		216	

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

Of the 216 confirmed HZ cases in the mTVC at the Final HZ Efficacy analysis, 193 (89.4%) were confirmed by PCR and 23 (10.6%) were confirmed by HZAC. Of the confirmed HZ cases in the mTVC of HZ/su group, 4 (66.7%) were confirmed by PCR and 2 (33.3%) by the HZAC. Of the confirmed HZ cases in the mTVC of the Placebo group, 189 (90%) were confirmed by PCR and 21 (10.0%) by HZAC.

Reviewer's comment – The majority of HZ case confirmations were by PCR.

HZ incidence by treatment group and HZ VE on the mTVC at the EOS is in the table below. Compared to the mTVC at the Final HZ Efficacy analysis step, 47 additional confirmed HZ episodes were reported; 3 in the HZ/su group and 44 in the Placebo group. The mean follow-up time was 3.9 years (SD of 0.7 years) and the median follow-up time was 4.1 years with a minimum and maximum follow-up period of 0 and 4.5 years, respectively.

Table 22 – Vaccine efficacy: First or only episode of HZ during the entire study period overall using Poisson method (mTVC – EOS)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
OVERALL **	7340	9	28717.8	0.3	7413	254	28459.4	8.9	96.50	93.25	98.46

Source: Adapted from 125614/0 Zoster-006 CSR Table 7.1, p. 2556
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 strata and region

Reviewer's comment – HZ VE on the mTVC at the EOS analysis was consistent with that at the HZ Final Efficacy analysis.

There were three additional cases of HZ reported in the HZ/su group in subjects included in the TVC at the EOS but not the mTVC as follows:

- 67 YO male subject reported HZ confirmed by PCR 956 days after Dose 1. The subject had not received a second dose of HZ/su.
- 70 YO female reported HZ confirmed by PCR 51 days after Dose 1. The subject did not receive a second dose due to the episode of HZ.
- 75 YO female reported HZ confirmed by PCR 8 days after Dose 2.

HZ VE on the TVC at the EOS was 95.78% (95% CI: 95.52%, 97.85%) and HZ VE on the ATPc for efficacy at the EOS was 96.60% (95% CI: 93.18%, 98.55%).

Reviewer's comment - HZ/su VE against HZ on the TVC at the EOS analysis and the ATPc for efficacy at the EOS was concordant with that of the mTVC at the Final HZ Efficacy analysis.

6.1.11.2 Analyses of Secondary Endpoints

HZ VE by age strata

Evaluation of VE in the prevention of HZ compared to placebo in the age ranges 50 – 59, 60 – 69 and ≥ 70 YOA was a secondary objective and was analyzed at the Final HZ Efficacy analysis. The study was powered to demonstrate HZ VE in the 50 – 59 and 60 – 69 YOA strata if the LB of the 95% CI was > 10%. The study was not powered to demonstrate HZ VE in the ≥ 70 YOA age stratum. The follow-up time was generally consistent between age strata.

Table 23 - 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)

Age strata	**HZ/su N**	**HZ/su n**	**HZ/su T(year)**	HZ/su **n/T (per 1000)**	**Placebo N**	**Placebo n**	**Placebo T(year)**	Placebo **n/T (per 1000)**	**VE (%)**	VE LL **95% CI**	VE UL **95% CI**
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

Reviewer's comment – HZ VE appears consistent in the mTVC at the Final HZ analysis among the pre-specified age groups. Although the incidence of HZ has been shown to increase with increasing age, the incidence of HZ in placebo recipients 60 – 69 YOA was higher than that reported in Placebo recipients ≥ 70 YOA. However, the age-specific HZ incidence in the Placebo group is within the range reported in a meta-analysis of the global incidence of HZ and consistent with the results of Zoster-022 (Kawai, 2014).

Analyses of the following secondary endpoints are presented on the mTVC at the EOS analysis.

Incidence of overall PHN

No subjects in the HZ/su group reported PHN, and 18 subjects in the placebo group reported at least one PHN episode.

Table 24 – First or only episode of PHN during the entire study period overall using Poisson method (Zoster-006 mTVC – EOS)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
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 age strata and region

The Applicant performed descriptive analyses of VE against overall PHN by age strata on the mTVC at the EOS analysis - as there were no cases of PHN in the HZ/su group, overall PHN VE was 100% in all age strata. PHN incidence in the Placebo group overall was 0.6/1000 person-years and incidence by age was 0.6, 0.2 and 1.3 per 1000 person-years in the 50 – 59, 60 – 69 and ≥ 70 YOA strata, respectively and 0.7 per 1000 person-years for subjects ≥ 60 YOA.

Table 25 – First or only episode of PHN during the entire study period by age strata using Poisson Method (Zoster-006 mTVC – EOS)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
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
≥ 60YOA *	3849	0	14944.8	0.0	3890	10	15015.0	0.7	100.00	55.25	100.00

Source: Adapted from 125614/0 Zoster-006 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

Reviewer's comment – PHN VE could not be demonstrated in the 60 – 69 YOA stratum. The incidence of PHN reported by subjects 60 – 69 YOA in the Placebo group was low.

The incidence of PHN in subjects ≥ 60 YOA in the Placebo group of Zoster-006 (0.7/1000 person-years) is lower than the age-specific incidence in the Placebo group from the SPS (1.38/1000 person-years) which had a similar age stratification for subjects ≥ 60 YOA (Oxman,2005).

The method of calculation of the "overall PHN" VE endpoint is similar to the method for calculation of the HZ VE endpoint. As such, this method includes all subjects in the calculation of PHN VE, even those who did not report HZ (approximately 97% of subjects in the mTVC of the Placebo group in Zoster-006 did not experience HZ).

Reduction in duration of severe 'worst' HZ pain over the entire pain reporting period in subjects with confirmed HZ ≥ 50 YOA and in the age groups 50 – 59, 60 – 69 and ≥ 70 YOA -
Of the nine subjects with confirmed HZ at the EOS analysis, seven reported at least one day of severe 'worst' HZ associated pain with a median (minimum – maximum) duration of 11 days (3 – 78). Of the 254 subjects in the Placebo group with confirmed HZ, 221 reported at least one day with severe 'worst' HZ associated pain with a median (minimum – maximum) of 15 days (1 – 464). VE for the reduction in the duration of severe 'worst' pain was 26.9% (95% CI: - 59.6%, 66.5%). The Applicant was unable to conclude on this secondary objective overall or by age group.

Reduction in incidence of HZ-related mortality in subjects ≥ 50 YOA and in the age groups 50 – 59, 60 – 69 and ≥ 70 YOA - The Applicant was unable to conclude on the reduction in HZ-related mortality as no HZ-related mortality was reported.

Reduction in incidence of HZ-associated complications (other than PHN) in subjects with confirmed HZ ≥ 50 YOA and in the age groups 50 – 59, 60 – 69 and ≥ 70 YOA -
No HZ-related complications were reported for the nine subjects with confirmed HZ (EOS analysis) in the HZ/su group. Of the 254 subjects with confirmed HZ in the Placebo group, 6 reported an HZ-related complication and no subject reported more than 1 complication; one subject reported HZ vasculitis (defined as vasculitis or vasculopathy temporally associated with an HZ episode and judged causally associated with the episode by the investigator), one subject reported ophthalmic disease (defined as HZ affecting any eye structure) and four subjects reported disseminated disease (defined as ≥ 6 HZ lesions outside the primary dermatome). VE for the reduction of HZ-related complications was 100% (95% CI: - 1336.9%, 100.0%); the Applicant was unable to conclude on this secondary objective overall or by age group.

Reviewer's comment – According to Table 33 in the Zoster-006 CSR, there were 123 cases of HZ reported in subjects ≥ 60 YOA in the mTVC of the Placebo group, but only one case of ophthalmic HZ reported. From the Zostavax PI, the proportions of subjects who reported ophthalmic zoster among subjects ≥ 60 YOA in the Placebo group (which included subjects reporting HZ within 30 days post-vaccination) was 10.5%.

Reduction in incidence of HZ-related hospitalizations
The Applicant was unable to conclude on the reduction in incidence of HZ-related hospitalizations as no HZ-related hospitalizations were reported.

Reduction in use of pain medications administered for HZ in subjects with confirmed HZ ≥ 50 YOA and in the age groups 50 – 59, 60 – 69 and ≥ 70 YOA - Six of 9 subjects (66.7%) of subjects with confirmed HZ reported HZ-associated pain medication use. In the Placebo group, 190 of 254 subjects (74.8%) reported HZ-associated pain medication use. Overall VE in terms of reduction of HZ-associated pain medication use was 11.7% (95% CI: -19.4%, 53.6%). The Applicant was unable to conclude on this secondary objective.

Reviewer's comment – The statistical reviewer noted that the analysis plan for the endpoint of duration of use of pain medication for HZ in subjects with confirmed HZ was not described in the SAP and thus the analysis of this endpoint was not considered pre-specified and is not presented in this review.

According to the statistical reviewer, estimates of VE for the secondary endpoints analyzed on subjects with confirmed HZ could be biased and lack causal interpretation. Please refer to the statistical review regarding the secondary endpoints analyzed on the subjects with confirmed HZ.

6.1.11.3 Subpopulation Analyses

HZ VE by gender

A sensitivity analysis evaluating the first or only episode of HZ (mTVC at the EOS using Poisson method) by gender is presented below.

Table 26 – First or only episode of HZ during the entire study period by age strata and overall using Poisson method, by gender (Zoster-006 mTVC - EOS)

Gender	Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
Male	50-59YOA	1272	1	4981.5	0.2	1241	30	4789.7	6.3	96.80	80.72	99.92
	60-69YOA	829	2	3337.0	0.6	863	36	3356.2	10.7	94.41	78.30	99.35
	≥70YOA	759	1	2778.2	0.4	767	20	2740.6	7.3	95.07	69.16	99.88
	OVERALL *	2860	4	11096.8	0.4	2871	86	10886.6	7.9	95.42	87.83	98.78
Female	50-59YOA	2219	3	8798.5	0.3	2282	73	8924.3	8.2	95.83	87.33	99.16
	60-69YOA	1311	1	5280.3	0.2	1303	54	5142.3	10.5	98.20	89.52	99.96
	≥70YOA	950	1	3542.2	0.3	957	41	3506.2	11.7	97.59	85.77	99.94
	OVERALL *	4480	5	17621.0	0.3	4542	168	17572.8	9.6	97.04	92.95	99.05

Source : Adapted from 125614/0 Zoster-006 CSR Table 7.3, p. 2560
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 strata

Reviewer's comment - HZ incidence in the Placebo group was higher for females (9.6/1000 person-years) than males (7.9/1000 person-years). Female gender is considered a risk factor for HZ. HZ VE was comparable between genders.

HZ VE by region

A sensitivity analysis evaluating the age-adjusted first or only episode of HZ by region (mTVC at the EOS using Poisson method) in the table below revealed that while the incidence of HZ in the Placebo group varied across regions HZ VE was comparable.

Table 27 – Vaccine efficacy – First or only episode of HZ during the entire study period by region using Poisson method (Zoster-006 mTVC – EOS)

Region*	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE LL 95% CI	VE UL 95% CI
Australasia	1555	3	6318.3	0.5	1574	76	6183.5	12.3	96.14	88.27	99.22
Europe	3785	3	14986.9	0.2	3828	105	14878.7	7.1	97.16	91.48	99.42
Latin America	709	1	2560.2	0.4	724	27	2597.0	10.4	96.25	77.25	99.91
North America	1291	2	4852.4	0.4	1287	46	4800.3	9.6	95.74	83.71	99.50

Source : Adapted from 125614/0 Zoster-006 CSR Table 7.5, p. 2567

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 strata for the regions

Reviewer's comment – HZ VE was comparable across regions. Although HZ incidence in the Placebo group varied between regions, the incidence was consistent with variability seen in the literature.

HZ VE by race
Descriptive analysis of HZ VE for the four racial subgroups is below.

Table 28 – HZ VE by race overall using Poisson method (Zoster-006 - mTVC, Final HZ efficacy analysis)

Race	HZ/su n/N	HZ/su n/T per 1000	Placebo n/N	Placebo n/T per 1000	VE (95% CI)
African	0/126	0.0	3/123	8.4	100.00% (-138.37%, 100.00%)
Asian	3/1390	0.7	47/1405	10.3	93.69% (80.38%, 98.74%)
White	2/5321	0.1	144/5354	8.6	98.63% (94.98%, 99.84%)
Other	1/507	0.7	16/533	10.2	92.86% (53.66%, 99.83%)

Source: Adapted from 125614/21, Question 3, Table 2, p. 4
N = number of subjects in each group
n = number of subjects having at least one confirmed HZ episode
T = sum of follow-up period expressed in years
n/T per 1000 = incidence rate of subjects reporting at least one event
VE is adjusted by age strata and region

Reviewer's comment – The low numbers of subjects of African heritage overall, as well as the low numbers of subjects of African heritage who reported HZ from both treatment groups limits the ability to draw conclusions about HZ/su VE in that sub-group.

HZ VE by ethnicity
Descriptive analysis of HZ VE for the two pre-specified ethnic subgroups is below.

Table 29 – HZ VE by ethnicity overall using Poisson method (Zoster-006 - mTVC, Final HZ Efficacy Analysis)

Zoster-006	HZ/su n/N	HZ/su n/T per 1000	Placebo n/N	Placebo n/T per 1000	VE (95% CI)
American Hispanic or Latino	2/780	0.9	28/808	12.0	92.33% (69.55%, 99.12%)
Not American Hispanic or Latino	4/6564	0.2	182/6607	8.7	97.83% (94.35, 99.42%)

Source: Adapted from 125614/21, Question 3, Table 3, p. 5
Hispanic = American Hispanic or Latino
Not Hispanic = Not American Hispanic or Latino
n = number of subjects having at least one confirmed HZ episode
T = sum of follow-up period expressed in years
n/T per 1000 = incidence rate of subjects reporting at least one event
VE is adjusted by age strata and region

Reviewer's comment – HZ VE was comparable between the pre-specified ethnic groups.

6.1.11.5 Exploratory and Post Hoc Analyses

HZ VE by year

A descriptive analysis of HZ VE by year was performed on the mTVC at the EOS analysis.

Table 30 – First or only episode of HZ during the entire study period by time using Poisson method (Zoster-006 mTVC – EOS)

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

Source : 125614/0 Zoster-006 CSR Table 7.2, p. 2559
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 strata and region
Year 1 : From 30 days after second vaccination to 395 days after second vaccination
Year 2 : From >395 days after second vaccination to 760 days after second vaccination
Year 3 : From >760 days after second vaccination to 1125 days after second vaccination
Year 4 : From >1125 days after second vaccination until last contact date

Reviewer's comment – Descriptive analyses of HZ VE by year indicate that vaccine effect appears durable through four years post-vaccination.

Humoral immunogenicity

Anti-gE Ab concentrations as measured by the anti-gE ELISA at M0, M3, M14, M26 and M38 were exploratory objectives.

Reviewer's comment – Although anti-gE Ab concentrations were exploratory objectives, humoral immune responses were used to support regulatory decision making regarding HZ/su lot-to-lot consistency, dose scheduling and concomitant administration of HZ/su and quadrivalent influenza vaccine. Therefore, humoral immune response was reviewed and will be presented here. There is no humoral or cell-mediated immune correlate or surrogate of protection for HZ.

Anti-gE Ab concentrations are presented below (overall and by age and region) for the subjects included in the ATP cohort for immunogenicity – Humoral (or the Adapted ATP cohort for immunogenicity – Humoral as applicable). Of subjects in the TVC,15.6% were randomized into the TVC for immunogenicity - Humoral, and at M3, M14, M26 and M38, 13.9%, 13.4%, 13.1%, and 12.4% of the TVC were included in the adapted ATP cohorts for immunogenicity – Humoral.

At baseline pre-vaccination, 1059/1069 (99.1%) and 1057/1065 (99.2%) of subjects in the HZ/su and Placebo groups of the ATP cohort for immunogenicity were seropositive for anti-gE Ab by ELISA (seropositivity cut-off = 97 mIU/mL). At M3 and beyond, 100% of HZ/su recipients were

seropositive. Seropositivity rates for the Placebo group at Months 3, 14, 26 and 38 ranged from 98.9% - 99.6%.

Anti-gE Ab GMCs for the Placebo group at baseline pre-vaccination were 1311.9 mIU/mL (95% CI: 1234.8, 1393.9); and ranged from 1213.1 mIU/mL – 1336/3 mIU/mL at the pre-specified post-vaccination time points. The anti-gE Ab GMCs for the HZ/su group at the same post-vaccination time points are below.

Table 31 - Geometric Mean Concentrations of anti-gE Ab at Months 0, 3, 14, 26 and 38 (Zoster-006 HZ/su group Adapted ATP cohort for immunogenicity – Humoral)

Time Point	GMC value	GMC 95% CI (UL, LL)	GMC Minimum	GMC Maximum
PRE Month 0	1247.1	(1174.8, 1323.8)	< 97.0	233132.9
P2 Month 3	52376.6	(50264.1, 54577.9)	432.7	308834.6
P2 Month 14	17726.2	(16910.7, 18581.0)	512.3	160387.0
P2 Month 26	13933.3	(13290.4, 14607.2)	376.7	171049.4
P2 Month 38	11919.6	(11345.6, 12522.7)	302.6	121520.7

Source: Adapted from 125614/0 Zoster-006 CSR Table 36, p. 298
GMC – geometric mean Ab concentration in mIU/mL
UL, LL – upper and lower limit of the 95% CI
PRE - pre-vaccination
P2 - post-vaccination Dose 2

The mean geometric increase (MGI) of anti-gE concentrations at Months 3, 14, 26 and 38 over pre-vaccination in the HZ/su group was 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.

Reviewer's comment – MGIs were highest at one month after Dose 2, then trended lower subsequently, while there was little change in VE.

The proportions of subjects in the HZ/su Adapted ATP cohort for immunogenicity - Humoral that were vaccine responders using anti-gE Ab ELISA concentrations at M3, M14, M26 and M38 were 98.5%, 89.5%, 83.4% and 80.9% respectively (see Section 6.1.9 for the definition of vaccine response). In the Placebo group the VRR for anti-gE Ab concentrations was not higher than 3.8% at any time point.

Humoral immune responses were also evaluated by age and region.

By age - The seropositivity rate for HZ/su recipients (Adapted ATP cohort for immunogenicity – Humoral) in each age group (50 – 59, 60 – 69 and ≥ 70 YOA) was 100% at M3, M14, M26 and M38.

The MGI of anti-gE antibody concentrations over pre-vaccination at M3, M14, M26 and M38 was 48.4 (95% CI: 43.1, 54.5), 17.1 (95% CI: 15.2, 19.3), 13.6 (95% CI: 12.1 – 15.3), and 12.2 (95% CI: 10.8 – 13.7) for 50 – 59 YO HZ/su recipients, 42.9 (95% CI: 38.5 – 47.8), 14.8 (95% CI: 13.2 – 16.6), 11.5 (95% CI: 10.3 – 12.9), and 9.6 (95% CI: 8.5 – 10.7) for 60 – 69 YOA HZ/su recipients and 35.6 (95% CI: 31.6, 40.0), 11.9 (95% CI: 10.5, 13.3), 9.4 (95% CI: 8.4 – 10.5), and 7.8 (95% CI: 7.0 – 8.8), for HZ/su recipients ≥ 70 YOA.

Reviewer's comment – The MGI for humoral immune responses in all age groups were highest at M3, decreasing but remaining relatively stable from Months 14 – 38. As expected, MGIs were highest in the youngest age group, declining with advancing age.

For subjects in the HZ/su group, the VRR for anti-gE Ab concentrations by age strata was 99.2%, 92.3%, 88.0%, and 87.3% for subjects 50 – 59 YOA, 98.9%, 90.7%, 83.7%, and 80.1% for subjects 60 – 69 YOA and 97.5%, 85.4%, 78.3%, and 75.2% for subjects ≥ 70 YOA for M3, M14, M26 and M38 respectively.

By region - Baseline seropositivity rates were comparable between regions, ranging from ranging from 98.6% to 100% across regions for both treatment groups. Post-vaccination at Months 3, 14, 26 and 38, the HZ/su group of every region had seropositivity rates of 100%.

GMCs of anti-gE antibody by ELISA were comparable between treatment groups at baseline, although numerically higher for North American subjects as seen below.

Table 32 – GMCs of anti-gE Ab at baseline pre-vaccination by region (Zoster-006 Adapted ATP cohort for immunogenicity – Humoral)

Group	GMC value	95% CI (UL, LL)
Australasia – HZ/su	1199.1 mIU/ML	(1082.6, 1328.2)
Australasia - Placebo	1349.5 mIU/ML	(1207.1, 1508.6)
Europe – HZ/su	1202.8 mIU/ML	(1104.6, 1309.6)
Europe - Placebo	1266.9 mIU/ML	(1164.5, 1378.2)
Latin America – HZ/su	1206.4 mIU/ML	(967.2, 1504.7)
Latin America - Placebo	1204.4 mIU/ML	(975.9, 1486.3)
North America – HZ/su	1632.9 mIU/ML	(1356.5, 1965.8)
North America - Placebo	1486.8 mIU/ML	(1234.3, 1791.0)

Source: Adapted from 125614 Zoster-006 CSR Table 9.9, p. 2975
GMC – geometric mean Ab concentration in mIU/mL
UL, LL – upper and lower limit of the 95% CI

For the HZ/su group at M3, the MGI of the anti-gE AB concentrations by ELISA over baseline ranged from 31.9 (North America) to 49.1 (Australasia). At M14, the MGI (M14/baseline) of the HZ/su group ranged from 11.9 (North America) to 18.2 (Australasia). At M28 the MGI (M26/baseline) ranged from 8.7 (North America) to 13.9 (Australasia). At M38 the MGI (M38/baseline) ranged from 7.7 (North America) to 12.1 (Australasia).

Reviewer's comment – There was some minor variability of the humoral immune response to vaccination between regions that appeared relatively consistent over time. However, responses appeared robust in all regions at the pre-specified time points for analysis.

Cell-mediated immunogenicity

The median fold increases of the frequency of gE specific CD4 T cells over pre-vaccination for the Adapted ATP cohort for immunogenicity – CMI in subjects ≥ 50 YOA who received HZ/su were 24.6, 9.8, 8.4 and 7.9 at Months 3, 14, 26 and 38 post-vaccination, while the median fold increase over pre-vaccination was not higher than 1.0 at any time point for the Placebo group. The VRR (refer to the definition of CMI vaccine response in Section 6.1.9). for the HZ/su recipients in the Adapted ATP cohort for immunogenicity-CMI at Months 3, 14, 26 and 38 were 93.3% (95% CI: 88.0%, 96.7%), 57.2% (95% CI: 49.0%, 65.2%), 57.6% (95% CI: 49.3%, 65.6%), and 52.6% (95% CI: 43.8%, 61.3%), while it was < 1.0% at all time points for subjects who received Placebo in that cohort.

Reviewer's comment – As cell-mediated vaccine response was an exploratory endpoint in Zoster-006 and was not used for regulatory decision-making in this application, a full review of CMI results will not be provided here. Other exploratory endpoints that will not be referenced in this review are acute HZ severity, interference of HZ with QoL, HZ BOI and anti-VZV antibody immune response.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please see Section 6.1.7 for an overview of the assessment of safety.

6.1.12.2 Overview of Adverse Events

At the EOS, the mean and median safety follow up time was 4.1 and 4.4 years respectively with a range of 0 to 5.0 years.

The primary population for the assessment of safety was the TVC which included 15405 subjects total, 7695 in the HZ/su group and 7710 in the Placebo group. A randomized subset of subjects in the TVC (TVC diary card subset) reported reactogenicity assessments. Descriptive safety analysis results are presented on the TVC at the EOS analysis.

SOLICITED AES

Solicited local and general event tabulations are presented for subjects ≥ 50 YOA who were included in the TVC diary card subset. Approximately 58% (8921/15405) of subjects in the TVC were enrolled in the subset. The following are the numbers of subjects by age and treatment group in the TVC diary card subset; subjects 50 – 59 YOA and 60 – 69 YOA were randomly allocated to this subset, while all subjects ≥ 70 YOA were included in this subset.

Table 33 - Number of subjects in the 7-day Diary card subset by age group and overall (Zoster-006 TVC diary card – EOS)

Age group	50-59 YOA		60-69 YOA		70-79 YOA		≥ 80 YOA		All	
Treatment group	HZ/su	Placebo	HZ/su	Placebo	HZ/su	Placebo	HZ/su	Placebo	HZ/su	Placebo
ZOSTER-006	1336	1331	1335	1331	1409	1421	377	381	4457	4464

Source: 125614/9 Table 10, p. 39

Reviewer's comment – Approximately 40% of the subjects in the 7-day diary card subset were ≥ 70 YOA, which should inform conclusions about the proportions of subjects reporting solicited symptoms that are not presented stratified by age.

Compliance with return of local symptom sheets and general symptom sheets for the TVC diary card subset for both treatment groups was above 97% (range 97.5% - 99%) following each dose and overall. Compliance with symptom sheet return by age strata was reviewed; compliance ranged from 97.2% to 99.3% for the pre-specified age strata (50 – 59, 60 – 69 and ≥ 70 YOA) for each dose and overall and was comparable between treatment groups.

Overall solicited AEs – any grade

Overall by subject, 85.2% and 34.2% of subjects in TVC diary card subsets of the HZ/su and Placebo groups, respectively, reported at least one solicited symptom during the 7-day post vaccination period. At least one general solicited symptom was reported by 66.1% and 29.5%

of subjects in the subset in the HZ/su and Placebo groups, respectively, and at least one local symptom was reported by 81.5% and 11.9% of subjects in the subset in the HZ/su and Placebo groups, respectively. The percentage of subjects in the HZ/su group of the TVC diary card subset reporting any symptom, any solicited general symptom, and any solicited local symptom after Dose 1 as compared to Dose 2 was 78.9% vs. 76.0%, 52.1% vs. 53.9%, and 74.6% vs. 70.2% respectively.

Reviewer's comment –The proportions of subjects reporting any grade of solicited symptoms and any grade local and general solicited symptoms in the HZ/su group overall was comparable following Dose 1 as compared to Dose 2.

The proportions of HZ/su recipients reporting any solicited symptom during the 7-day post vaccination period by age strata overall by subject was 91.5%, 87.6%, and 78.6% for the age strata 50 -59, 60 – 69 and ≥ 70 YOA, respectively. The percentage of HZ/su recipients reporting any local solicited symptoms during the 7-day post vaccination period was 89.6%, 84.6% and 73.2% for the age strata 50 -59, 60 – 69 and ≥ 70 YOA, respectively. The percentage of HZ/su recipients reporting any general solicited symptom during the 7-day post vaccination period was 76.7%, 68.7% and 56.4% for the age strata 50 -59, 60 – 69 and ≥ 70 YOA respectively.

The proportions of subjects in the HZ/su group reporting any symptom, any local symptom and any general symptom were generally comparable after each dose within each age group.

Reviewer's comment - The proportions of subjects reporting any, any local or any general symptom in the HZ/su group decreased with increasing age but was generally comparable after each dose within the age strata.

Overall solicited AEs – Grade 3

Overall by subject, 16.4% and 2.6% of subjects in the HZ/su and Placebo groups reported a Grade 3 solicited symptom. At least one Grade 3 solicited general symptom was reported by 11.4% and 2.4% of subjects in the HZ/su and Placebo groups, respectively, and at least one Grade 3 solicited local symptom was reported by 9.5% and 0.4% of subjects in the HZ/su and Placebo groups respectively. The proportions of subjects in the HZ/su group reporting any Grade 3 solicited general symptom was slightly higher after Dose 2 (8.1%) as compared to Dose 1 (5.4%).

Overall by subject by age, dose and treatment group, 22.7%, 16.6% and 11.6% of HZ/su recipients 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA reported at least one Grade 3 solicited symptom. At least one Grade 3 solicited general symptom was reported by 17.1%, 11.5% and 7.0% of HZ/su recipients 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA respectively, while at least one Grade 3 solicited local symptom was reported by 13.4%, 9.2% and 6.8% of HZ/su recipients 50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA, respectively.

Reviewer's comment – Overall by subject, Grade 3 reactogenicity was common in every age stratum following HZ/su administration. From Dose 1 to Dose 2, slightly higher proportions of subjects in each age stratum reported a Grade 3 symptom; this appeared to be due to a greater proportion of subjects in the HZ/su group reporting Grade 3 general symptoms after Dose 2 as compared to Dose 1 in each age stratum.

Overall solicited AEs – duration

For the mean and median duration of solicited local or general symptoms, see the sections on local and general symptoms below.

The Applicant performed a post hoc analysis of the proportions of subjects reporting solicited symptoms beginning during the 7-day post-vaccination period and lasting beyond that period. Overall per subject, 9.1%, 4.6% and 5.6% of HZ/su recipients in the TVC diary card subset reported at least one of any grade solicited symptom, solicited general symptom any solicited local symptom beginning in and lasting beyond the 7-day solicited reporting period. Overall per subject, 2.2%, 1.0% and 1.3% of HZ/su recipients in the TVC diary card subset reported at least one of any Grade 3 solicited symptom, Grade 3 solicited general and Grade 3 solicited local symptom respectively beginning in and lasting beyond this period.

Specific solicited local AEs

Overall by subject, at least one solicited local symptom was reported by 81.5% and 11.9% of subjects in the HZ/su group and Placebo group respectively and at least one Grade 3 solicited local symptom was reported by 9.5% and 0.4% of subjects in the HZ/su and Placebo groups respectively. The numbers and proportions of subjects in the TVC diary card subset reporting any grade and Grade 3 solicited local symptoms are below.

Table 34 – Incidence of solicited local symptoms reported during the 7-day post-vaccination period overall by subject (Zoster-006 TVC diary card - EOS)

Symptom/grade	HZ/su N = 4379 n	HZ/su N = 4379 %	Placebo N = 4375 n	Placebo N = 4375 %
Pain/any grade	3463	79.1%	490	11.2%
Pain Grade 3	293	6.7%	16	0.4%
Redness/any grade	1665	38.0%	59	1.3%
Redness >100 mm	121	2.8%	0	0.0%
Swelling/any grade	1153	26.3%	46	1.1%
Swelling >100 mm	43	1.0%	0	0.0%

Source: Adapted from 125614/0 Zoster-006 CSR, Table 60

For overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum

Overall by subject, pain (any grade) was the most commonly reported local symptom reported by subjects in both the HZ/su and Placebo groups (reported by 79.1% and 11.2% of subjects, respectively). Any grade of redness was reported by 38.0% and 1.3% of HZ/su and Placebo recipients, and any grade of swelling was reported by 26.3% and 1.1% of HZ/su and Placebo recipients, respectively. Although not presented here, the proportions of subjects in the HZ/su group reporting any grade and Grade 3 pain, redness or swelling was generally comparable between Dose 1 and Dose 2.

The proportions of subjects in the TVC diary card subset of each treatment group reporting specific local symptoms (any grade and Grade 3) overall by age strata with both doses considered are presented below.

Table 35 – Incidence of solicited local symptoms reported during the 7-day (Days 0 – 6) post-vaccination period overall by subject by age strata (Zoster-006 TVC diary card - EOS)

Symptom/Grade	HZ/su 50 – 59 YOA N = 1315 n (%)	Placebo 50 – 59 YOA N = 1312 n (%)	HZ/su 60 – 69 YOA N = 1311 n (%)	Placebo 60 – 69 YOA N = 1305 n (%)	HZ/su **≥70** YOA N = 1753 n (%)	Placebo **≥ 70** YOA N = 1758 n (%)
Pain/any grade	1162 (88.4%)	189 (14.4%)	1086 (82.8%)	145 (11.1%)	1215 (69.3%)	156 (8.9%)
Pain/Grade 3	135 (10.3%)	7 (0.5%)	90 (6.9%)	6 (0.5%)	68 (3.9%)	3 (0.2%)
Redness/any grade	509 (38.7%)	16 (1.2%)	503 (38.4%)	21 (1.6%)	653 (37.3%)	22 (1.3%)
Redness > 100 mm	37 (2.8%)	0 (0.0%)	34 (2.6%)	0.0 (0.0%)	50 (2.9%)	0 (0.0%)
Swelling/any grade	401 (30.5%)	10 (0.8%)	347 (26.5%)	13 (1.0%)	405 (23.1%)	23 (1.3%)
Swelling > 100 mm	14 (1.1%)	0 (0.0%)	7 (0.5%)	0 (0.0%)	22 (1.3%)	0 (0.0%)

Source: Adapted from 125614/16 Question 8a, Table 1, p. 2
N = number of subjects with at least one documented dose
n (%) = number/percentage of subjects reporting the symptom at least once when the intensity is maximum

Although not presented here, the proportions of subjects in the HZ/su group reporting any grade and Grade 3 of each specific solicited symptom after Dose 1 and Dose 2 within each age stratum by treatment group were similar.

Reviewer's comment - Pain (any grade and Grade 3) was the most commonly reported solicited local event reported by HZ/su recipients of all age groups, with the proportions of subjects reporting pain decreasing with increasing age. The proportions of subjects in the HZ/su reporting each solicited symptom of any grade and Grade 3 intensity were comparable after Doses 1 and 2.

Redness and swelling up to 380 mm and 200 mm respectively were reported after HZ/su administration.

Specific solicited local AEs – duration

Overall per dose, the mean (median) duration of pain, redness or swelling reported after HZ/su administration was 3.1 (3.0), 3.9 (3.0) and 3.4 (3.0) days, respectively. The mean and median duration of each specific event following Dose 1 and Dose 2 were generally comparable.

Reviewer's comment – In general, local AEs were of limited duration following HZ/su administration.

Specific general solicited AEs

Overall per subject at least one solicited general AE was reported by 66.1% and 29.5% of subjects in the HZ/su group and Placebo group, respectively, and at least one Grade 3 solicited general AE was reported by 11.4% and 2.4% of subjects in the HZ/su and Placebo groups, respectively. The number and percentage of subjects in the TVC diary card subset reporting any grade and Grade 3 specific solicited general symptom is below.

Table 36 - Incidence of solicited general symptoms reported during the 7-day (Days 0 – 6) post-vaccination period overall/subject (Zoster-006 TVC Diary card – EOS)

Symptom/ grade	HZ/su n N = 4372 n (%)	Placebo n N = 4376 n (%)
Fatigue- any grade	2006 (45.9%)	728 (16.6%)
Fatigue – Grade 3	241 (5.5%)	46 (1.1%)

Symptom/ grade	HZ/su n N = 4372 n (%)	Placebo n N = 4376 n (%)
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 125614/0 Zoster-006 CSR Table 61, p. 343
N - number of subjects with at least one documented dose
n/% - number/percentage reporting the symptom at least once
* Temperature as assessed via oral, axillary, rectal or tympanic route or setting

Reviewer's comment – The most commonly reported solicited general events of any grade following HZ/su administration were myalgia, fatigue and headache and the most commonly reported Grade 3 solicited general events after HZ/su administration were fatigue, myalgia and shivering.

The proportions of HZ/su recipients reporting any grade of specific solicited general events is below.

Table 37 - Proportions of subjects with any grade of specific general symptoms reported during the 7-day post-vaccination period following each dose (Zoster-006 TVC diary card – EOS)

Any Grade event	Fatigue	GI symptoms	Headache	Myalgia	Shivering	Temperature*
HZ/su Dose 1	32.1%	10.7%	25.6%	33.3%	14.5%	11.5%
HZ/su Dose 2	34.6%	11.8%	29.7%	35.1%	22.5%	15.3%
Placebo Dose 1	12.2%	6.0%	11.7%	8.6%	3.8%	1.5%
Placebo Dose 2	9.0%	4.3%	8.1%	6.5%	3.0%	1.7%

Source: Adapted from 125614/0 Zoster-006 CSR Table 61
% - proportion of subjects for each dose (n/N) derived from numerator n = number of subjects reporting the event at least once when the intensity is maximum and denominator N = number of subjects with at least one documented dose
* Temperature as assessed via oral, axillary, rectal or tympanic route or setting

Reviewer's comment – The proportions of subjects reporting any grade of each specific general symptom in the HZ/su group appeared comparable from Dose 1 to Dose 2 except for the event of shivering which was seen in higher proportions after Dose 2. From the table below, the proportion of subjects reporting Grade 3 shivering was also numerically higher after Dose 2 as compared to Dose 1.

Table 38 - Proportions of subjects with specific Grade 3 general symptoms reported during the 7-day post-vaccination period following each dose (Zoster-006 TVC diary card – EOS)

Grade 3 event	Fatigue	GI	Headache	Myalgia	Shivering	Temperature*
HZ/su Dose 1	2.5%	0.7%	1.5%	2.4%	1.6%	0.2%
HZ/su Dose 2	3.7%	0.8%	2.5%	3.8%	3.3%	0.2%

Grade 3 event	Fatigue	GI	Headache	Myalgia	Shivering	Temperature*
Placebo Dose 1	0.7%	0.3%	0.5%	0.5%	0.1%	0.0%
Placebo Dose 2	0.4%	0.3%	0.3%	0.3%	0.2%	0.1%

Source: Adapted from 125614/0 Zoster-006 CSR Table 61, p. 343
% - proportion of subjects for each dose (n/N) derived from numerator n = number of subjects reporting the event at least once when the intensity is maximum and denominator N = number of subjects with at least one documented dose
* Temperature as assessed via oral, axillary, rectal or tympanic route or setting

The proportions of subjects reporting each solicited general symptom (any grade and Grade 3) overall by subject by age and treatment group is presented below.

Table 39 – Incidence of solicited general symptoms reported during the 7-day (Days 0 – 6) post-vaccination period overall by subject and by age strata (Zoster-006 TVC diary card - EOS)

	HZ/su 50 – 59 YOA N = 1315 n (%)	Placebo 50 – 59 YOA N = 1312 n (%)	HZ/su 60 – 69 YOA N = 1311 n (%)	Placebo 60 – 69 YOA N = 1305 n (%)	HZ/su **≥70 YOA** N = 1753 n (%)	Placebo **≥ 70 YOA** N = 1758 n (%)
Fatigue- any grade	57.0	19.8	45.7	16.8	37.7	14.2
Fatigue –Grade 3	8.5	1.8	5.0	0.8	3.6	0.7
GI symptoms – any grade	24.3	10.7	16.7	8.7	14.2	7.5
GI symptoms – Grade 3	2.1	0.7	0.9	0.6	1.2	0.5
Headache – any grade	50.6	21.6	39.6	15.6	30.3	12.1
Headache – Grade 3	6.0	1.7	3.7	0.2	1.7	0.3
Myalgia – any grade	56.9	15.2	49.0	11.2	36.2	10.5
Myalgia – Grade 3	8.9	0.9	5.3	0.8	2.9	0.5
Shivering – any grade	35.8	7.4	30.3	5.7	20.8	5.0
Shivering – Grade 3	6.8	0.2	4.5	0.3	2.5	0.2
Temperature - any grade¥	27.8	3.0	23.9	3.4	14.9	2.7
Temperature ≥ 39˚ C	0.4	0.2	0.5	0.2	0.2	0.1

Source: Adapted from 125614/16 Question 8b, Table 2, p. 3
N = number of subjects with at least one documented dose
n (%) = number/percentage of subjects reporting the symptom at least once when the intensity is maximum
¥ = Temperature as assessed via oral axillary, rectal or tympanic route or setting

Reviewer's comment – All grade and Grade 3 general reactogenicity reported by subjects in the HZ/su group decreased with increasing age. Overall by subject, Grade 3 events reported by ≥ 5% of HZ/su 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.

The proportions of subjects in the HZ/su group reporting all grade and Grade 3 reactogenicity for each solicited general symptom following each dose was generally comparable between doses, being marginally higher after Dose 2, except for all grade (Grade 3) shivering which was reported by a higher proportion of subjects following Dose 2 in all age strata – the proportions were 20.3% (2.6%), 15.3% (1.6%), and 9.7% (0.8%) of subjects in the 50 – 59, 60 – 69 and ≥ 70 YOA strata after Dose 1 and 29.1% (5.3%), 23.9% (3.2%) and 16.5% (1.9%) of subjects in the 50 – 59, 60 – 69 and ≥ 70 YOA strata after Dose 2.

Specific general symptoms - duration
Overall per dose, the mean (median) duration of fatigue, GI symptoms, headache, myalgia, shivering and fever reported after HZ/su administration was 3.0 (2.0), 2.7 (2.0), 2.5 (2.0), 2.8 (2.0) 1.8 (1.0) and 1.7 (1.0) days, respectively. The mean and median duration of each specific event following Dose 1 and Dose 2 were generally comparable.

Reviewer's comment – Solicited general events reported by HZ/su recipients were mostly of limited duration following each dose and overall.

UNSOLICITED AES
Unsolicited AEs were recorded by all subjects on a diary card for 30 days (Days 0 – 29) after each vaccination.

Table 40 – Subjects reporting the occurrence of unsolicited AEs (Zoster-006 TVC – EOS analysis)

	HZ/su N=7695	Placebo N=7710
Subjects with at least one unsolicited AE (serious and non-serious) within the 30-day (Days 0-29) post-vaccination period	3534 (45.9%)	2426 (31.5%)

Source: Adapted from 125614/26 Annex 6, Table 459, p. 4N = number of subjects with at least one administered dose

Overall, 45.9% and 31.5% of subjects in the TVC of the HZ/su and Placebo groups, respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period. The most frequently reported unsolicited AEs in the HZ/su group were AEs that had been specified as solicited symptoms on the 7-day diary card such as injection site pain (18.1% of HZ/su and 1.3% of Placebo subjects, respectively), pyrexia (7.3% and 0.5% of HZ.su and Placebo subjects, respectively), injection site erythema (6.4% of HZ/su and 0.1% of Placebo subjects, respectively) of subjects), headache (6.4% of HZ and 3.3% of HZ/su and Placebo subjects, respectively) and injection site swelling (5.2% and 0.1% of HZ/su and Placebo subjects, respectively). The most frequently reported unsolicited AE in the Placebo group was nasopharyngitis (4.3%).

Imbalances in the General disorders and administration site conditions SOC (with 26.8% of HZ/su and 4.6% of Placebo group reporting) were due to differences in reporting of reactogenicity events. Imbalances in the proportions of subjects reporting events in the Musculoskeletal and connective tissue disorders SOC (9.4% of HZ/su subjects and 6.0% of Placebo subjects reporting) was driven in part by the difference in proportions of subjects reporting myalgia (3.3% and 0.6%% of subjects in the HZ/su group and Placebo group, respectively), and the difference in the Nervous system disorder SOC (8.6% of subjects in the HZ/su group reporting and 4.9% of Placebo subjects reporting) was driven in part by the difference in reports of headache (6.4% and 2.9% of subjects in the HZ/su group and Placebo group, respectively) and dizziness (1.2% and 0.5% of subjects in the HZ/su group and Placebo group, respectively).

Reviewer's comment – Although the numbers and proportions of subjects with these events were relatively small due to the short time period in which they were collected, imbalances between treatment groups were noted in these events: gout [11 subjects (0.1%) in the HZ/su group and 1 (0.0%) of subjects in the Placebo group], respiratory tract infection [27 subjects (0.4%) in the HZ/su group and 10 (0.1%) of subjects in the Placebo group], dyslipidemia [14 subjects (0.2%) in the HZ/su group and 4 (0.1%) of subjects in the Placebo group], and

arthralgia [138 subjects (1.8%) in the HZ/su group and 94 (1.2%) of subjects in the Placebo group]. See Section 8.5 for discussion of these events.

CBER analysis indicated that the proportion of subjects reporting unsolicited AEs by PT during the 30-day post-vaccination period in the narrow sub-SMQ (level 4) of supraventricular tachyarrhythmias was higher for the HZ/su group (10 subjects) than the Placebo group (2 subjects) during the 30-day post-vaccination period, mainly due to subjects reporting atrial fibrillation/flutter (9 in HZ/su and 2 in Placebo group). See Section 8.5.

The proportions of subjects reporting at least one unsolicited AE during the 30-day post-vaccination period decreased with increasing age, most notably in the HZ/su group: 56.0%, 44.0% and 28.0% of subjects 50 – 59, 60 – 69 and ≥ 70 YOA reported at least one unsolicited event during the 30-day post-vaccination period, while the corresponding proportions in the Placebo group were 34.6%, 31.0% and 25.9%.

Since the most commonly reported unsolicited AEs reported by subjects in the HZ/su group during the 30-day post vaccination period were due to local and general reactogenicity events, the Applicant provided an analysis of unsolicited AEs performed on the subjects in the TVC who were randomized to the 7-day diary card subset (TVC diary card). Overall, 29.6% and 27.7% of subjects in the 7-day diary card subset of the TVCs of the HZ/su and Placebo groups (TVC diary card) respectively reported an unsolicited AE during the 30-day post-vaccination period.

At least one Grade 3 non-serious unsolicited event was reported by 7.5% and 3.3% of subjects in the HZ/su and Placebo groups, respectively, during the 30-day post-vaccination period. The SOC with the highest proportion of HZ/su recipients reporting Grade 3 non-serious unsolicited events was the General disorders and administration site conditions SOC, with 3.7% of subjects reporting events compared to 0.3% of Placebo subjects reporting events. By PT, the most commonly reported Grade 3 non-serious unsolicited events were injection site pain (1.5% and <0.05% of HZ/su and Placebo recipients, respectively), pyrexia (1.2% and 0.1% of HZ/su and Placebo recipients, respectively), headache (0.7% and 0.2% of HZ/su and Placebo recipients, respectively) and chills (0.6% and 0.0% of HZ/su and Placebo recipients, respectively).

The proportions of subjects reporting at least one Grade 3 non-serious unsolicited AE during the 30-day post-vaccination period decreased with increasing age in the HZ/su group: 10.4%, 6.3% and 3.1% of subjects 50 – 59, 60 – 69 and ≥ 70 YOA in the HZ/su group reported at least one Grade 3 non-serious unsolicited event during the 30-day post-vaccination period, while the proportions in the Placebo group were 3.8%, 2.9% and 2.6%.

Reviewer's comment – Unsolicited AEs and Grade 3 non-serious unsolicited AEs were reported by higher proportions in the HZ/su as compared to the Placebo group during the 30-day post-vaccination period, primarily due to reporting of reactogenicity-type events.

MEDICALLY ATTENDED AES

The occurrence of medically attended visits, defined as a hospitalization, emergency room visit or a visit to or from medical personnel (physician) for any reason other than routine health care visits were collected and recorded on the eCRF from day of first vaccination to M8.

Table 41 – Number and proportions of subjects reporting at least one unsolicited AE with a medically attended visit (Zoster-006 TVC – EOS)

Time period for subjects reporting at least one unsolicited AE with a medically attended visit	HZ/su N = 7695 n (%)	Placebo N = 7710 n (%)
30 day (Days 0 – 29) post-vaccination period	1351 (17.6%)	1398 (18.1%)
Day 0/Month 0 – Month 8	2952 (38.4%)	3072 (39.8%)

Source: Adapted from 125614 Zoster-006 CSR Table 10.27, p.3323 and 125614/26 Annex 5 Table 416, p. 11

Overall 17.6% and 18.1% of subjects in the HZ/su and Placebo groups, respectively, reported the occurrence of an unsolicited AE with a medically attended visit during the 30-day post-vaccination period. The SOCs with the highest proportions of subjects reporting events were the Infections and infestations (with 7.2% and 7.3% of HZ/su and Placebo recipients reporting events, respectively) and the Musculoskeletal and connective tissue disorders (with 2.7% and 3.0% of HZ/su and Placebo recipients reporting events, respectively). The only specific preferred term reported by ≥ 1.0% of subjects in either treatment group was nasopharyngitis (reported by 1.4% and 1.6% of subjects in the HZ/su and Placebo groups, respectively).

From M0 – M8, 38.4% of subjects in the TVC of the HZ/su group and 39.8% of subjects in the TVC of the Placebo group reported the occurrence of an unsolicited AE with a medically attended visit in the HZ/su and Placebo groups, respectively. Comparative analysis of subjects reporting MAE during M0 – M8 indicated that higher proportions of subjects in the HZ/su as compared to the Placebo group reported medically attended events for PTs solicited on the 7-day diary card (IS pain, IS erythema, IS swelling and pyrexia, all reported by ≤ 0.5% of subjects in the HZ/su group) as well as the medically attended events of respiratory tract infection, hyperlipidemia, macular degeneration, nerve compression and skin ulcer and higher proportions of subjects in the Placebo group as compared to the HZ/su group reported melanocytic nevus, cellulitis and bronchiectasis. Comparative analysis indicated that by SOC, higher proportions of subjects in the HZ/SU (2.7%) as compared to the Placebo group (1.9%) reported a MAE in the General disorders and administration site conditions SOC from M0 – M8, which was driven primarily by medical attention sought for reactogenicity events including IS events and pyrexia. The most commonly reported MAEs during this period were nasopharyngitis and upper respiratory tract infection, and they were reported by comparable proportions of subjects in each treatment group.

Reviewer's comment - While more subjects in the HZ/su group compared to the Placebo group sought medical attention for specified events by PT listed on the 7-day diary card, the proportion of subjects seeking medical attention for these events was low.

The proportions of subjects reporting a medically attended visit from M0 – M8 were comparable between the age groups (50 – 59, 60 – 69 and ≥ 70 YOA) within and between treatment groups.

Reviewer's comment – Although reactogenicity was higher in the HZ/su as compared to the Placebo group, the proportions of subjects reporting at least one medically attended event overall from during the 30-day post vaccination period and from M0 – M8 were comparable between treatment groups. Although some specific PTs were reported more frequently in the HZ/su as compared to the Placebo group, the differences may be due to chance as no pattern of like events was discerned. Of note, while macular degeneration was reported by 8 subjects in the HZ/su and 1 subject in the Placebo group as MAEs during M0 – M8, it was reported by 4 and 7 subjects in the TVCs of the HZ/su and Placebo groups respectively in Zoster-022 as a MAE during M0 – M8.

According to CBER analysis, the proportion of subjects reporting MAEs by PTs contained in the narrow sub-SMQ of Supraventricular tachyarrhythmias within the 30-day post-vaccination period was higher for HZ/su recipients (10 subjects) as compared to Placebo recipients (2 subjects) which appears to be driven by the PTs of atrial fibrillation and flutter (reported by 9 and 2 subjects in the HZ/su and Placebo groups, respectively). See Section 8.5 for details.

6.1.12.3 Deaths

A summary of subjects in the TVC with fatal SAEs (who died) during select time periods by treatment group is below.

Table 42 - Subjects who died during select time periods (Zoster-006 TVC – EOS analysis)

	HZ/su 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 125614/22 Annex 1 Table 13, p. 48
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

During the 30-day post-vaccination period – Three subjects in each treatment group died within the 30-day post-vaccination period. The causes of death by PT were aneurysm perforation, skull fracture and asthma in the HZ/su group and myocardial infarction, cerebral infarction, and gastroenteritis with sepsis in the Placebo group.

During M0 – M3 – Seven subjects (0.1%) in each treatment group died during M0 – M3. Only one PT was reported as a cause of death more than once (cerebrovascular accident reported twice in the HZ/su group).

During M0 – M14 - During this period, 42 (0.5%) and 52 (0.7%) subjects died in the HZ/su and Placebo groups, respectively. By PT, the most frequently reported fatal events during the M0 – M14 period were pneumonia [reported by 6 (0.1%) and 2 (0.0%) of subjects in the HZ/SU and Placebo groups, respectively], acute myocardial infarction [reported by 2 (0.0%) and 6 (0.1%) of subjects in the HZ/SU and Placebo groups, respectively], and myocardial infarction [reported by 4 (0.1%) and 2 (0.0%) of subjects in the HZ/SU and Placebo groups, respectively]. The greatest proportions of subjects reported events in the Cardiac disorders, Neoplasms and Infections and infestations, SOCs, with the proportions of subjects reporting events in these SOCs generally comparable between treatment groups. Comparative analysis indicated that there was no difference between treatment groups in the proportions of subjects reporting fatal SAEs (who died) or subjects reporting fatal SAEs by SOC or PT during M0 – M14.

During the whole post vaccination period - During the whole post-vaccination period, 208 (2.7%) and 221 (2.9%) subjects died in the HZ/su and Placebo groups, respectively. By PT, the most commonly reported causes of death in the HZ/su and Placebo groups, respectively, were myocardial infarction (0.2% and 0.2%) and pneumonia (0.2% and 0.1%). The greatest proportions of subjects reported events in the Neoplasms and Cardiac disorders SOCs, with the

proportions of subjects reporting events in these and other SOCs generally comparable between treatment groups.

Reviewer's comment - There were no imbalances noted between treatment groups for the proportions of subjects who died during the selected time periods with events classified by PT or SOC, and no medically relevant clusters with regard to types of fatal events were noted.

Fatal SAEs by age group and region - The proportions of subjects who died in each age group increased with advancing age, but the proportions who died within each age group for the various time periods were comparable between treatment groups. Additionally, no clinically significant imbalances were noted between treatment groups for the proportions of subjects who died within the various time periods by region and the proportions of subjects who died during particular time periods for each region were consistent with the proportions of subjects in the TVC of each region overall.

Related fatal SAEs - No fatal SAEs were considered related to vaccination by the investigator or the Applicant.

Reviewer's comment – No clinically significant imbalances between the treatment groups for the proportions of subjects who died overall or in terms of incidence and nature of the causes of death by PT and SOC during different time periods were detected upon review. No clinically significant imbalances between the treatment groups were noted by CBER after analysis of the proportions of subjects reporting fatal SAEs in the available narrow SMQs during the whole post-vaccination period.

6.1.12.4 Serious Adverse Events

The Applicant included both fatal and non-fatal SAEs in their tabulations of SAEs.

SAEs reported during select time periods
A summary of SAEs occurring during select time points up to M14 is below.

Table 43 – Global summary of SAEs during the 30 day (Day 0 - 29) post-vaccination period and selected time points up to M14 (TVC – EOS analysis)

	HZ/su 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 125614/25, Table 170, p. 74
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

During the 30-day post-vaccination period, at least one SAE was reported by 88 (1.1%) and 97 (1.3%) of subjects in the HZ/su and Placebo groups, respectively. The most commonly reported events by PT were pneumonia [4 subjects (0.1%) in the HZ/su group, 2 subjects (0.0%) in Placebo group] and atrial fibrillation [5 subjects (0.1%) in the HZ/su group, 0 subjects (0.0%) in the Placebo group]. The SOCs with the greatest proportions of subjects reporting events were the Cardiac disorders and Neoplasms, Injury, poisoning and procedural complications SOCs with equal proportions of subjects in each treatment group reporting.

During M0 – M3, at least one SAE was reported by 145 (1.9%) and 137 (1.8%) of the HZ/su and Placebo group, respectively. The most commonly reported events by PT were atrial fibrillation [reported by 7 subjects (0.1%) in the HZ/su group, 0 subjects (0.0%) in Placebo group], pneumonia [reported by 6 subjects (0.1%) in the HZ/su group, 3 subjects (0.0%) in the Placebo group], and myocardial infarction [reported by 4 subjects (0.1%) in the HZ/su group and 5 subjects (0.1%) in the Placebo group]. The greatest proportions of subjects reported events in the Cardiac disorders, Neoplasms and Injury Poisoning and Procedural disorders SOCs, with the proportions of subjects reporting events in generally comparable between treatment groups.

From M0 – M14, at least one SAE was reported by 594 (7.7%) subjects in the HZ/su group and 590 (7.7%) of subjects in the Placebo group. The most commonly reported SAEs during this period were pneumonia [reported by 31 (0.4%) and 20 (0.3%) subjects in the HZ/su and Placebo groups respectively] and myocardial infarction [reported by 16 (0.2%) subjects in each treatment group]. The greatest proportions of subjects reported events in the Infections and Infestations, Cardiac disorders and Neoplasms SOCs, with the proportions of subjects reporting events in generally comparable between treatment groups. Comparative analysis indicated that there was no difference between treatment groups in the proportions of subjects reporting SAEs or subjects reporting SAEs by SOC or PT during M0 – M14.

Reviewer's comment – CBER analysis detected a difference between treatment groups for the numbers of subjects reporting SAEs (HZ/su > Placebo) in the narrow sub-SMQ (level 4) of Supraventricular tachyarrhythmias during M0 – M3 (9 subjects vs. 1 subject) and during M0 – M14 (22 subjects vs. 9 subjects) and also for the number of subjects reporting SAEs in the narrow supraordinate SMQ of Cardiac arrhythmias (32 vs. 13) during M0 – 14. During the M0 – M3 time period, differences in the Supraventricular tachyarrhythmias SMQ appears due to the number of subjects reporting atrial fibrillation and flutter (8 vs. 1). For Cardiac arrhythmias during the M0 – M14 time period, the differences appear driven in part by the numbers of subjects reporting atrial fibrillation, flutter and tachycardia (21 vs. 9), and arrhythmia (5 vs. 0).

For the M0 – M3 period, there was also a difference in the numbers of subjects (HZ/su > Placebo) reporting events in the narrow sub-SMQ (level 2) of Central nervous system hemorrhage and cerebrovascular conditions (8 subjects vs 1 subject). After CBER review, alternative etiologies were noted for three of the subjects in the HZ/su group who reported an intracranial aneurysm (PID17246), bilateral chronic subdural hematomas (PID 8608), subdural and subarachnoid hemorrhage following a seizure in a subject with a seizure disorder (PID 3297). The other subjects reported a cerebral infarction (b) (6) days after Dose 2 (PID 11349), cerebrovascular accident (two subjects) (b) (6) and (b) (6) days after Dose 1 (PIDs 11278 and 492) and transient ischemic attacks (two subjects) 4 days and 32 days after Dose 1. No difference was noted between vaccination groups for the numbers or proportions of subjects reporting SAEs from M0 – M14 in this level 2 sub-SMQ [38 (0.49%) in HZ/su group and 33 (0.43%) in Placebo group.]

See Section 8.5 for a discussion of these events in the main pooling analysis.

Subjects reporting SAEs by age and region

The proportions of subjects in each age stratum reporting at least one SAE during select time periods post-vaccination is below.

Table 44 – Subjects reporting the occurrence of SAEs select time periods by age strata (TVC – Zoster-006 EOS analysis)

	HZ/su 50 – 59 N = 3644 n (%)	Placebo 50 – 59 N = 3642 n (%)	HZ/su 60 – 69 N = 2243 n (%)	Placebo 60 – 69 N = 2245 n (%)	HZ/su **≥ 70** N = 1808 n (%)	Placebo ≥ 70 N = 1823 n (%)
Subjects with at least one SAE reported during within the 30-day post-vaccination period	31 (0.9%)	29 (0.8%)	21 (0.9%)	32 (1.4%)	36 (2.0%)	36 (2.0%)
Subjects with at least one SAE reported during M0 – M3	52 (1.4%)	49 (1.3%)	39 (1.7%)	39 (1.7%)	54 (3.0%)	49 (2.7%)
Subjects with at least one SAE reported during M0 – M14	206 (5.7%)	192 (5.3%)	162 (7.2%)	166 (7.4%)	226 (12.5%)	232 (12.7%)

Source: Adapted from 125614/25 Table 175, p. 111
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

The proportions of subjects reporting at least one SAE during the select time periods above were generally comparable by region.

SAEs with causal relationship to vaccination
The investigators assessed 3 SAEs in 3 HZ/su recipients and 8 SAEs in 7 Placebo recipients to be causally related to vaccination. The Applicant did not consider any SAE causally related to vaccination.

Reviewer's comment – See Section 8.4.2 for an accounting of the SAEs judged vaccine-related by the investigator.

6.1.12.5 Adverse Events of Special Interest (AESIs)

New onset and exacerbations of serious and non-serious potential immune-mediated inflammatory diseases were to be collected and recorded for the entire post-vaccination period. The proportions of subjects reporting pIMDs at select time points by vaccination group is below.

Table 45 - Subjects reporting the occurrence of pIMDs at selected time points (Zoster-006 TVC – EOS analysis)

	HZ/su 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 125614/25 Annex 3 Table 262, p. 32
N = number of subjects with at least one administered dose
n (%) = number/percentage reporting the symptom

From M0 – M3, pIMDs were reported for 0.2% and 0.3% of subjects in the HZ/su and Placebo groups, respectively. The SOC with the highest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC with 3 and 9 subjects in the HZ/su and Placebo group reporting. The most commonly reported event was rheumatoid arthritis, reported by 5 subjects and 1 subject, respectively, in the HZ/su and Placebo groups.

From M0 – M14, pIMDs were reported by 0.5% and 0.8% of subjects in the HZ/su and Placebo groups, respectively. The SOC with the highest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC with 0.1 and 0.2% of subjects in the HZ/su and Placebo groups reporting. The most commonly reported pIMD by PT was rheumatoid arthritis with 3 (0.0%) and 11 (0.1%) subjects reporting in the HZ/su and Placebo groups, respectively. Comparative analysis indicated that there was no difference between vaccination groups in the proportions of subjects reporting pIMDs or subjects reporting pIMDs by SOC or PT during M0 – M14.

During the whole reporting period, pIMDs were reported by 1.1% and 1.4% of subjects in the HZ/su and Placebo groups, respectively. The SOC with the greatest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC. The PTs with the greatest number of subjects reporting at least one event was rheumatoid arthritis (reported by 0.1% subjects in the HZ/su group and 0.2% in the Placebo group) and psoriasis (reported by 0.1% of subjects in both vaccination groups).

Reviewer's comment – No imbalances were noted between vaccination groups for the proportions of subjects reporting the most common pIMD events by PT or by SOC during the specified time periods. See CBER analysis of pIMD reporting over time in Section 8.4.8.

6.1.13 Study Summary and Conclusions
Demonstrated HZ VE in subjects ≥ 50 YOA in Zoster-006 was 97.16% (95% CI: 93.72%, 98.97%), was comparable between the pre-specified age strata, and appeared durable to Year 4. "Overall" PHN VE, calculated on all subjects independent of the occurrence of HZ was 100% (95% CI: 77.11%, 100.00%). CBER considers the benefit of HZ/su in preventing PHN to be attributable to VE against HZ. Local and general reactogenicity and severe reactogenicity were commonly reported after HZ/su administration, but decreased with increasing age and were generally of limited duration. Overall, SAEs, pIMDs and deaths were reported in comparable proportions by subjects in both treatment groups, except for some cardiac arrhythmias which were reported slightly more frequently in the HZ/su as compared to the Placebo group.

6.2 Trial #2

Zoster-022 was a Phase 3, randomized, observer-blind, placebo-controlled, multicenter, clinical endpoint evaluation trial to assess the prophylactic efficacy, safety and immunogenicity of GSK Biologicals' gE/AS01$_B$ vaccine (HZ/su) when administered intramuscularly on a 0, 2-month schedule to HZ-naive adults aged 70 years and older. Zoster-022 was conducted in parallel with and at the same sites as with Zoster-006. The study initiation date was 02-AUG-2010 and completion date was 24-JUL-2015. The data lock point for the EOS analysis was 12-OCT-2015.

6.2.1 Objectives
Primary objective of Zoster-022: 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 of Zoster-022

- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 70 YOA
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA, with confirmed HZ

- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects in subjects ≥ 70 YOA
- To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 70 YOA with confirmed HZ
- To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 70 YOA with confirmed HZ
- To evaluate vaccine safety and reactogenicity

Select exploratory objectives of Zoster-022

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

Reviewer's comment - The primary objectives and endpoints of Zoster-006 and Zoster-022 were the same. The objectives of the pooled analysis of Zoster-006 and Zoster-022 are in Section 7.1.1.

6.2.2 Design Overview

See Section 6.1.2.

Recruitment – See Section 6.1.2.

Randomization
Subjects ≥ 70 YOA were randomized to Zoster-006 and Zoster-022 by a central randomization system on the internet prior to randomization in a 1:1 ratio to the HZ/su or Placebo arms. The stratification and minimization algorithms for region, country, site and age cohorts are discussed in the Randomization portion of Section 6.1.2.

The number of subjects planned for randomization into the Zoster-022 7-day diary card subset for the evaluation of reactogenicity can be seen in the table below.

Table 46 - Provisional number of subjects in the 7-day diary card subset in studies ZOSTER-022 and ZOSTER-006

Age cohort	50-59 YOA		60-69 YOA		70-79 YOA		≥ 80 YOA		All	
Treatment group	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
ZOSTER-022	-	-	-	-	252	252	252	252	504	504
ZOSTER-006	1410	1410	1410	1410	1410	1410	470	470	4700	4700
ZOSTER-022 and -006 combined	1410	1410	1410	1410	1662	1662	722	722	5204	5204

Source: 125614/0 Zoster-022 CSR Table 8, p. 101

Reviewer's comment – Although fewer subjects overall were enrolled in the 7-day diary card subset in Zoster-022, the numbers of subjects planned for inclusion in the subset in each age group overall were adequate for the evaluation of reactogenicity.

A total of 920 subjects were planned for randomization into the Immunogenicity subset. CMI response to vaccination was not evaluated in Zoster-022.

Blinding
See Section 6.1.2.

Data collection
Data was collected via remote data entry on an electronic case report form (eCRF).

6.2.3 Population
Subjects were eligible for the study if all of the following applied: they were a male or female at least 70 years of age at the time of first vaccination, were capable of providing written informed consent, and could (in the investigator's opinion) comply with study requirements.

Exclusion criteria were the same as in Zoster-006 except for those regarding pregnancy and lactation, which were not included in Zoster-022. See Section 6.1.3.

6.2.4 Study Treatments or Agents Mandated by the Protocol
See Section 4.1 for a description of the study products administered. Lot numbers for the VZV gE were as follows: DVZVA004A, DVZVA004B, DVZVA004C, DVZVA006A, DVZVA006B, DVZVA006C. Lot numbers for the $AS01_B$ component were as follows: DA01A023A, DA01A027A, DA01A029A, DA01A031A, DA01A031B, DA01A032A.

6.2.5 Directions for Use
See Section 6.1.5.

6.2.6 Sites and Centers
There were 267 PIs involved in the study, with 215 centers in 18 countries in 4 regions.

Table 47 –Number of Subjects with Centers by Country and Region (TVC, EOS analysis)

Country	Region	Centers	HZ/su Subjects (%) Total = 6950	Placebo Subjects (%) Total = 6950
Australia	Australasia	79217, 79219, 79220, 79895, 87477, 87478, 87480	153 (2.2%)	156 (2.2%)
Hong Kong	Australasia	78390, 78393	91 (1.3%)	89 (1.3%)
Japan	Australasia	78721, 78758, 79458, 79548, 79550, 79823, 79849, 80028, 80031, 80378	256 (3.7%)	255 (3.7%)
Korea	Australasia	73182,73184, 73185, 73187, 73188, 73191, 73192, 89066	263 (3.8%)	265 (3.8%)
Taiwan	Australasia	77159, 77160, 77162, 78725	554 (8.0%)	554 (8.0%)
	Australasia		1317 (18.9%)	1319 (19.0%)
Czech Republic	Europe	80012, 80013, 80014	162 (2.3%)	159 (2.3%)

Country	Region	Centers	HZ/su Subjects (%) Total = 6950	Placebo Subjects (%) Total = 6950
Germany	Europe	78015, 78017, 78024, 78029, 78103, 78105, 78107, 78108, 78113, 78115, 78116, 78117, 78118, 78122, 78124, 78126, 78128, 78130, 78131, 78132, 78133, 78134, 78136, 78139, 78144, 78145, 78146, 78147, 78148, 78149, 78150, 78151, 78152, 78153, 78155, 78235, 78238, 78243, 81227	599 (8.6%)	602 (8.7%)
Estonia	Europe	78564, 78565	507 (7.3%)	508 (7.3%)
Spain	Europe	78504, 78505, 78506, 78507, 78508, 78509, 78522, 78523, 79387, 89006, 89011, 890138	469 (6.7%)	465 (6.7%)
Finland	Europe	80513, 80514, 80515, 80516, 80518, 80519, 80520, 80521, 81638, 89085, 89087	853 (12.3%)	852 (12.3%)
France	Europe	79563, 79565, 79566, 79567, 79568, 79570, 79571, 79573, 79576, 79577, 79578, 79579, 79580, 79581, 80267, 90267,	287 (4.1%)	286 (4.1%)
Italy	Europe	78436, 78437, 78439, 78440, 78441, 78442, 78443, 78531, 78609, 79908	54 (0.8%)	55 (0.8%)
Sweden	Europe	77046, 77047, 77049, 77050, 77051, 77053, 77054, 77055, 77056, 77057, 77058, 88779	480 (6.9%)	481 (6.9%)
United Kingdom	Europe	77762, 77765, 77766, 77767, 77768, 89546, 89547, 89561, 89562	347 (5.0%)	345 (5.0%)
	Europe		3758 (54.1%)	3753 (54.0%)
Brazil	Latin America	80920, 80921, 80931, 80932, 84078, 88021, 88051	312 (4.5%)	311 (4.5%)
Mexico	Latin America	75257, 75840, 75842	225 (3.2%)	227 (3.3%)
	Latin America		537 (7.7%)	538 (7.7%)
Canada	North America	78792, 78793, 78794, 78795, 78796, 78797, 78798, 78799, 78800, 78836, 78837, 78838, 78894, 78895, 78900	399 (5.7%)	401 (5.8%)
United States	North America	80127,80128, 80129,80130, 80131, 80132,80133, 80134 80135, 80136, 80137, 80138, 80139, 80140, 80143, 80144, 80145, 80146, 80147, 80148, 80149, 80150, 80151, 80152, 80153, 80155, 80156, 80159, 80160, 80169, 80292, 87935, 87937, 87938, 87940, 87941, 88435, 88440, 88452, 88720, 88722, 88816, 90724	939 (13.5%)	939 (13.5%)
	North America		1338 (19.3%)	1340 (19.3%)

Country	Region	Centers	HZ/su Subjects (%) Total = 6950	Placebo Subjects (%) Total = 6950
Total			6950	6950

Source: Adapted from 125614/0 Zoster-022 CSR Tables 6.41 (p. 3891) and 6.42 (p. 3895)

The majority of subjects enrolled in the TVC were from Europe. See Section 6.1.6 regarding discussions between CBER and the Applicant about enrollment by region, including the proposed proportion of subjects enrolled in the US and North America.

Of the centers enrolling subjects included in the TVC analysis at EOS, the majority enrolled < 1.0% of the TVC. Only one center in Estonia (78564), which enrolled 6.7% of subjects, enrolled more than 5% of subjects in the TVC.

6.2.7 Surveillance/Monitoring
See Section 6.1.7.

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint – Confirmed HZ cases during the study in the mTVC.

Select secondary endpoints:

- PHN cases in the mTVC
- Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the ZBPI in subjects with confirmed HZ
- Incidence of HZ-related mortality during the study
- Incidence of HZ complications during the study in subjects with confirmed HZ
- Incidence of HZ-related hospitalizations
- Duration of pain medication administered for HZ during the study in subjects with confirmed HZ

The secondary safety endpoints of Zoster-022 were the same as the last five bullets in the secondary endpoints section of Zoster-006 (Section 6.1.8).

Select exploratory endpoints of Zoster-022

- 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

Success criteria – Zoster-022 was designed to demonstrate clinically meaningful overall HZ VE in subjects ≥ 70 YOA. The Applicant stated that clinically meaningful VE would be demonstrated in that age group if the LL of the 95% CI was above 10%.

6.2.9 Statistical Considerations & Statistical Analysis Plan
Most major statistical considerations for Zoster-022 are similar to that of Zoster-006 and were addressed in Section 6.1.9 of this review.

The following major elements of the Zoster-022 statistical plan differed from that of Zoster-006 or were statistical considerations for the pooled analysis follow.

Summary of statistical inferential evaluations of the primary and secondary endpoints of Zoster-022
Zoster-022 was powered to evaluate HZ VE in subjects ≥ 70 YOA. For a comparison of the statistical inferential evaluations of the primary and secondary objectives for Zoster-022 (as well as Zoster-006 and the pooled analyses, see Section 7.1.1.

Sample size considerations
The sample size of Zoster-022 was selected to provide the required number of HZ cases for triggering of analyses within approximately 3 years. The accumulation of a least 278 confirmed HZ cases would provide approximately 99% power to demonstrate HZ VE of at least 10%. The accumulation of at least 35 PHN cases in subjects ≥ 70 YOA across both studies would provide approximately 90% power to demonstrate PHN VE above 0%.

Reviewer's comment – See Section 6.1.9 for the assumptions of HZ and PHN incidence used for sample size calculations.

Age groups selected for evaluation
Subjects were stratified by age (70 – 79 and ≥ 80 YOA) in approximately a 3:1 ratio, with the strata combined for primary analysis. Zoster-022 was not powered prospectively to demonstrate HZ VE in these two strata separately.

Conditions for triggering analyses
According to the protocol, 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 when pooled with Zoster-006 PHN cases were accrued.

Reviewer's comment – The analysis of the HZ VE primary endpoint for Zoster-022 was conducted at the EOS. See Section 6.1.9 for a discussion about the sequence of analyses in Zoster-006 and the dissociation of the pivotal studies in terms of the timing of analyses.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

See Section 6.1.10.1 for the definitions of the analysis populations. As in Zoster-006, the TVC was the primary population for the analysis of safety and the mTVC was the primary population for the analysis of efficacy.

CMI was not analyzed in Zoster-022, so no analysis population for CMI was defined.

6.2.10.1.1 Demographics
The summary of demographic characteristics of the study population is below.

Table 48 – Summary of demographic characteristics (Zoster-022 TVC)

Characteristics	Parameters or Categories	HZ/su N = 6950 n	HZ/su N = 6950 %	Placebo N = 6950 n	Placebo N = 6950 %
Age (years) at vaccination dose: 1	Mean	75.6	-	75.6	-
	SD	4.7	-	4.7	-
	Median	74.0	-	74.0	-
	Minimum	69	-	62	-
	Maximum	96	-	95	-
Gender	Female	3789	54.5	3836	55.2
	Male	3161	45.5	3114	44.8
Ethnicity	American Hispanic or Latino	579	8.3	570	8.2
	Not American Hispanic or Latino	6371	91.7	6380	91.8
Geographic Ancestry	African Heritage / African American	79	1.1	67	1.0
	American Indian or Alaskan Native	1	0.0	8	0.1
	Asian - Central/South Asian Heritage	3	0.0	6	0.1
	Asian - East Asian Heritage	907	13.1	908	13.1
	Asian - Japanese Heritage	298	4.3	300	4.3
	Asian - South East Asian Heritage	8	0.1	4	0.1
	Native Hawaiian or Other Pacific Islander	3	0.0	3	0.0
	White - Arabic / North African Heritage	40	0.6	47	0.7
	White - Caucasian / European Heritage	5307	76.4	5301	76.3
	Other	304	4.4	306	4.4

Source : 125614/0 Zoster-022 CSR Table 21, p. 279
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Reviewer's comment – The median age and proportions of subjects in the TVC by gender, race and ethnicity were comparable between vaccination groups. Most subjects were non-Hispanic/Latino (91.7%) and White of Caucasian/European heritage (76.3%), which is not atypical of demographics of clinical trial conducted in developed countries. The small proportions of subjects of African or African-American heritage may limit generalizability of study results to that population.

There were no clinically significant differences in the overall demographics of subjects in the mTVC as compared to the TVC overall and between vaccination groups. The demographics of the 7-day diary card subset were also comparable to that of the TVC, except the mean and median ages were slightly higher (77.6 and 78.0 respectively).
The Applicant also provided demographic summaries by age and by region. In general, while there was some minor variability when comparing characteristics between age groups and regions (e.g., slightly higher proportions of females as compared to males in the ≥ 70 - 79 YOA group as compared to the ≥ 80 YOA group in the TVC and higher proportions of females as compared to males in the TVC from Latin America as compared to other regions) and greater, but expected variability with regard to ethnicity and geographic ancestry between regions, the demographic characteristics by age and region were comparable between the mTVC and TVC and between vaccination groups. This minor variability did not impact efficacy results.

CBER noted a slight deviation in the mTVC and TVC from the 3:1 ratio for the age strata (70 – 79 YOA and ≥ 80 YOA) delineated for enrollment in the protocol. While it was proposed that

25% of subjects in Zoster-022 would be ≥ 80 YOA, the proportion of subjects in this age group was 22.1% and 21.8% in the TVC and mTVC, respectively. This small deviation is unlikely to affect the overall conclusions regarding the safety and efficacy of the product in Zoster-022.

As can be seen below, most subjects (54.0%) were from Europe.

Table 49 – Number of subjects by region (Zoster-022 TVC)

Categories	HZ/su N = 6950 n	HZ/su N = 6950 %	Placebo N = 6950 n	Placebo N = 6950 %	Total N = 13900 n	Total N = 13900 %
Australasia	1317	18.9	1319	19.0	2636	19.0
Europe	3758	54.1	3753	54.0	7511	54.0
Latin America	537	7.7	538	7.7	1075	7.7
North America	1338	19.3	1340	19.3	2678	19.3

Source: 125614/0 Zoster-022 CSR Table 6.42, p. 3895
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

The Applicant provided a summary of demographic characteristics for the TVC of North American region. While generally similar, there were lower proportions of subjects of American Hispanic or Latino ethnicity (8.3% vs. 2.9%) and of Asian ancestry (0.7% vs. 17.6%) and higher proportions of subjects who were of White of European ancestry (93.6% vs. 76.3%) in the TVC of the North American region compared to the TVC overall.

Reviewer's comment – The small differences in demographic composition of the North American subset as compared to the overall TVC did not appear to result in differences in HZ VE by region. See Section 6.2.11.3.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In 125614/8, the Applicant provided, per CBER's request of 06-JAN-2017, comparative tabulations of the numbers and percentages of subjects in the TVC of each vaccination group with pre-existing conditions with an incidence of ≥ 2% in one or more vaccination groups by SOC and PT. Pre-existing conditions were to be recorded on the eCRF (Section 5.7.2.3 of the Zoster-022 Protocol Amendment 4 Final).

At least one pre-existing condition was reported by 94.9% and 95.4% of subjects in the TVCs of the HZ/su and Placebo groups, respectively. The SOCs with the highest percentages of subjects reporting at least one prior condition were the Vascular disorders SOC (reported by 64.7% and 64.6% of subjects in the HZ/su and Placebo groups, respectively), the Metabolism and nutrition disorders SOC (reported by 51.6% and 52.0% of subjects in the HZ/su and Placebo groups, respectively, driven by the PTs dyslipidemia, hyperlipidemia and hypercholesterolemia), and Musculoskeletal and connective tissue disorders SOC (reported by 51.4% and 51.7% of subjects in the HZ/su and Placebo groups, respectively). The most commonly reported conditions by PT were hypertension in the Vascular disorders SOC (reported by 59.7% and 59.5% of subjects in the HZ/su and Placebo groups, respectively) and osteoarthritis in the Musculoskeletal and connective tissue disorders SOC (reported by 31.5% and 30.2% of subjects in the HZ/su and Placebo groups, respectively).

Reviewer's comment – The proportions of subjects in the TVC reporting pre-existing conditions overall and by SOC and PT were comparable between vaccination groups and typical of a study population of older subjects.

6.2.10.1.3 Subject Disposition

Subjects available for and excluded from analyses

Of the 7408 and 7406 subjects enrolled in the HZ/su and Placebo groups, respectively of Zoster-022, 903 (6.1% of the Total Enrolled Cohort) were excluded from all statistical analyses and were not included in the Total Effective cohort. Overall, 93.8% of enrolled subjects in each treatment group were included in the TVC.

Table 50 – Number of subjects enrolled into the study and number excluded from the TVC for with reason for exclusion (Zoster-022)

	HZ/su N	HZ/su %	Placebo N	Placebo %
Total enrolled cohort	7408	100%	7406	100%
Subjects excluded from all stat analysis	453	6.1%	450	6.1%
Total effective cohort	6955	93.9%	6956	93.9%
Study vaccine dose not administrated 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 903 subjects excluded from all analyses, 865 subjects (5.8% of the Total Enrolled cohort) were excluded from Center 75256 due to deviations from GCP identified by the Applicant (see Section 6.1.10.1.3). Center 80993 was closed in August 2014 due to business reasons; as the PI was unable to endorse the data collected, 34 subjects from this site were excluded from all analyses. An additional 4 subjects were excluded from all statistical analyses; 2 for ICF deviations and 2 for whom source documents were lost.

Reviewer's comment – See Section 8.5 for the pooled analysis of safety (SAEs and pIMDs) from both pivotal studies for the subjects enrolled at Center 75256.

The numbers and proportions of subjects included in the TVC and mTVC by vaccination group are below.

Table 51 – Number of subjects included in the TVC and excluded from the mTVC with reason for exclusion (Zoster-022)

	HZ/su N	HZ/su %	Placebo N	Placebo %
Total Vaccinated Cohort	6950	93.8%	6950	93.8%
Study vaccine dose not administered according to 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 having an episode of HZ prior to 30 days after dose 2	4	< 0.1%	11	0.2%
modified Total Vaccinated Cohort	6541	94.1%	6622	95.3%

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

Of subjects in the TVC, 94.7% overall were included in the mTVC for efficacy analysis; for the HZ/su and Placebo groups, respectively, 94.1% (6541/6950) and 95.3% (6622/6950) of the TVC subjects were included in the mTVC. 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; 697 of 13900 subjects (5.0%) of subjects in the TVC did not receive a second dose. By

vaccination group, 390 (5.6%) subjects in the HZ/su group and 305 (4.4%) subjects in the Placebo group did not receive a second dose.

Reviewer's comment – The proportions of subjects in the TVC that were eligible for the mTVC for the analysis of efficacy is acceptable and is comparable between vaccination groups. The majority of subjects received the second dose.

See the next section (Subjects vaccinated, completed and withdrawn) for the tabulation of subjects withdrawn from vaccination (did not receive a second dose) by reason for withdrawal.

The Applicant provided tabulations of subjects included in the TVC but excluded from the mTVC by age (70 – 79 and ≥ 80 YOA) and vaccination group and by region and vaccination group. The proportions of subjects from the TVC participating in the mTVC ranged from 93.5% to 95.7% by age and vaccination group. Within regions, the proportions of subjects from the TVC participating in the mTVC ranged from 91.8% to 95.5%, with the highest participation rate in Europe and the lowest in Latin America.

Reviewer's comment – The proportions of subjects in the TVC participating in the mTVC were generally consistent between age and vaccination groups and region and vaccination groups.

Protocol deviations not leading to elimination from analyses were also reviewed. These deviations involved ICF and ICF addenda, late reporting of safety events, errors in biospecimen collection, as well as recording, reporting, documentation and technical deviations.
Reviewer's comment - The Applicant's documentation of the events leading to subject exclusion from analyses and protocol deviations not leading to exclusion from analyses as well as corrective actions taken were reviewed and found to be acceptable.

Exposure
From the table below, 5.0% (697/13900) of subjects in the TVC (5.6% in the HZ/su group and 4.4% in the Placebo group) did not receive a second dose of study product.

Table 52 – Number and percentage of subjects receiving doses (Zoster-022 TVC)

Total number of doses received	HZ/su N = 6950 n	HZ/su N = 6950 %	Placebo N = 6950 n	Placebo N = 6950 %
1	392	5.6%	305	4.4%
2	6558	94.4%	6645	95.6%
Any	6950	100%	6950	100%

Source: Adapted from 125614/0 Zoster-022 CSR Table 10.1, p. 4482
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Treatment compliance by age strata was reviewed; 93.3% – 96.1% of subjects across the age strata received two doses with the proportions comparable between treatment groups.

Reviewer's comment – A high proportion of subjects in each treatment group received both doses.

The reasons for subject withdrawal from vaccination by vaccination group are below.

Table 53 – Number and proportions of subjects withdrawn from vaccination with reasons for withdrawal (Zoster-022 TVC)

	HZ/su N = 392 n	HZ/su N = 392 %	Placebo N = 305 n	Placebo N = 305 %
GSK decision	9	2.3	7	2.3
INVESTIGATOR GSK decision	0	0.0	1	0.3
INVESTIGATOR OTHER	2	0.5	3	1.0
INVESTIGATOR Protocol violation or outside of time window	40	10.2	29	9.5
INVESTIGATOR SERIOUS ADVERSE EVENT AND/OR PIMD	6	1.5	10	3.3
INVESTIGATOR SUSPECTED HZ EPISODE	3	0.8	12	3.9
INVESTIGATOR non-serious unsolicited AE	12	3.1	9	3.0
SUBJECT Consent withdrawal, not due to an AE	0	0.0	2	0.7
SUBJECT OTHER	28	7.1	21	6.9
SUBJECT Protocol violation or outside of time window	0	0.0	1	0.3
SUBJECT SERIOUS ADVERSE EVENT AND/OR PIMD	1	0.3	2	0.7
SUBJECT SUSPECTED HZ EPISODE	0	0.0	1	0.3
SUBJECT non-serious unsolicited AE	34	8.7	17	5.6
VISIT NOT DONE	257	65.6	190	62.3

Source: Adapted from 125614/29 Annex 9, Table 612, p. 18
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

Reviewer's comment – The reasons for subject withdrawal were generally comparable between vaccination groups. Similarly to Zoster-006, visit not done was the primary reason for subjects not receiving a second dose.

Subjects vaccinated, completed and withdrawn

The number of subjects vaccinated, completed and withdrawn in the TVC with reason for withdrawal is below.

Table 54 – Number and proportions of subjects vaccinated, completed and withdrawn with reasons for withdrawal by treatment group (Zoster-022 TVC)

	HZ/su n	HZ/su %	Placebo n	Placebo %
Number of subjects vaccinated	6950	100	6950	100
Number of subjects completed	5770	83.0	5760	82.9
Number of subjects withdrawn	1180	17.0	1189	17.1
Number of subjects with unknown completion status	0	0.0	1	0.0
Reasons for withdrawal:				
Serious Adverse Event	456	6.6	487	7.0
Non-Serious Adverse Event	47	0.7	15	0.2
Protocol violation	6	0.1	8	0.1
Consent withdrawal (not due to an adverse event)	387	5.6	396	5.7
Migrated/moved from study area	51	0.7	46	0.7
Lost to follow-up (subjects with incomplete vaccination course)	8	0.1	18	0.3
Lost to follow-up (subjects with complete vaccination course)	115	1.7	115	1.7
Suspected HZ Episode	2	0.0	2	0.0
Sponsor study termination	0	0.0	0	0.0
Others	108	1.6	102	1.5

Source: Adapted from 125614/29 Annex 8, Table 562, p. 196
Vaccinated = number of subjects who were vaccinated in the study

Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
% = (n / Number of subjects vaccinated) x 100

The most common reasons for withdrawal from the study were for an SAE or consent withdrawal not due to an adverse event.

Reviewer's comment - The proportions of subjects withdrawn overall were comparable between treatment groups. Given the age groups enrolled and the length of follow-up pre-specified in the protocol, completion rates of approximately 83% per group and overall is acceptable.

The Applicant provided a tabulation of the numbers of subjects withdrawn from the study by age and vaccination group. The percentage of subjects completing the study was lowest in the older age group, but the percentages of subjects completed and withdrawn were comparable between vaccination groups.

Table 55 - Number of subjects vaccinated with number and percentage completed and withdrawn by age and vaccination group with reasons for withdrawal (Zoster-022 TVC)

	HZ/su 70 – 79 YOA	Placebo 70 – 79 YOA	HZ/su **≥ 80** YOA	Placebo **≥ 80** YOA
Number of subjects vaccinated	5414 (100.0%)	5420 (100.0%)	1536 (100.0%)	1530 (100.0%)
Number and % of subjects completed	4647 (85.8%)	4678 (86.3%)	1123 (73.1%)	1082 (70.7%)
Number and % of subjects withdrawn	767 (14.2%)	741 (13.7%)	413 (26.9%)	448 (29.3%)

Source: Adapted from 125614/29, Annex 8 Zoster-022 Table 562, p. 196
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Unknown = number of subjects who have not come for the last visit yet
% = (n / Number of subjects vaccinated) x 100

Higher proportions of subjects completed the study in the 70 – 79 as compared to the ≥ 80 YOA strata and this was comparable between treatment groups. This appeared due to higher proportions of subjects withdrawing due to serious adverse events in the older age stratum.

The numbers and percentages of subjects vaccinated and withdrawn by region were provided. The proportions were generally comparable between treatment groups and regions, ranging from 74.0% to 86.6% completing. The proportions completing the study were lowest in the North American region.

Reviewer's comment – According to the CBER statistical reviewer, although the proportions of subjects completing the study was lowest in the North American region, the sum of person-years (time at risk) was generally proportional to the number of subjects by region.

6.2.11 Efficacy Analyses

Analyses for the primary efficacy endpoints of Zoster-022 and the pooled analysis of both studies are presented below.

Investigator determination of suspected cases of HZ
The process for determination of a clinically suspected case of HZ is in Section 6.1.11. The investigator's determination of the proportions of presumptive HZ cases as compared to clinically suspected HZ cases as determined by the investigator is below.

Table 56 – Distribution of subjects with self-reported suspected cases of HZ as judged by the investigator (Zoster-022 TVC)

	HZ/su N= 6950 n (%)	Placebo N = 6950 n (%)
Subjects presenting with presumptive case of HZ	222 (3.2%)	478 (6.9%)
Did the subject exhibit a clinical presentation of HZ per physician?		
• No	140 (2.0%)	148 (2.1%)
• Yes	82 (1.2%)	330 (4.7%)

Source: Adapted from 125614/21, Table 2, p. 3
n = number of subjects reporting a presumptive case of HZ
% = proportion of subjects reporting/TVC

Reviewer's comment – The proportions of subjects presenting with a presumptive case of HZ that the investigators concluded were "not a clinically suspected case of HZ" was comparable between treatment groups – this addresses a concern that increased reactogenicity following HZ/su administration may have introduced bias in the determination of what was or was not a clinically suspected case of HZ.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of Zoster-022 was confirmed HZ cases during the study in the mTVC. The cut-off date for the final HZ efficacy analysis at the EOS was 21-APR-2015.
There were 246 confirmed HZ cases in the mTVC, 23 in the HZ/su group and 223 in the Placebo group, after a median follow-up time of 3.9 (range 0 – 4.5) years and a mean follow-up time of 3.7 years (standard deviation 0.8 years). No subject reported more than one case of HZ.

Reviewer's comment – As VE is generally highest in the year following vaccination, adequate follow-up time reduces bias that might favor the vaccine with regard to the point estimate of VE.

Table 57 – VE: First or only episode of HZ during the entire study period overall using Poisson method (Zoster-022 mTVC)

	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
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 HZ/su groups were 9.2 and 0.9 per 1000 person-years respectively for an overall VE against HZ in subjects ≥ 70 YOA of 89.79% (95% CI: 84.3% -

93.7%). The primary study objective regarding HZ VE in subjects ≥ 70 YOA was met as the lower bound of the 95% CI of the point estimate of VE was above 10%.

The method of HZ case confirmation overall and by vaccination group is below.

Table 58 – Distribution of confirmed HZ episodes determined by either PCR or HZAC (Zoster-022 mTVC)

Confirmed HZ episodes determined by:	HZ/su n	HZ/su %	Placebo n	Placebo %	Total n	Total (%)
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		223		246	

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

Of the 246 confirmed cases in the mTVC, 92.3% of the confirmed HZ cases were confirmed by PCR and 7.7% were confirmed by HZAC. Of the 23 confirmed cases in the mTVC of the HZ/su group, 82.6% were confirmed by PCR and 17.4% were confirmed by HZAC. In the 223 confirmed cases in the mTVC of the Placebo group, 93.3% were confirmed by PCR and 6.7% confirmed by HZAC.

Reviewer's comment – The majority of HZ case confirmations were by PCR.
The following seven subjects in the HZ/su group were not included in the mTVC for the calculation of efficacy, but were in the TVC and had confirmed HZ.

- 76 YO male reported HZ confirmed by PCR beginning 1084 days after Dose 1. The subject had not received Dose 2.
- 84 YO male reported HZ confirmed by PCR 37 days after Dose 1.
- 74 YO female reported HZ confirmed by PCR 1562 days after Dose 1. The subject did not receive Dose 2 due to local injection site pain after Dose1.
- 72 YO male reported HZ confirmed by PCR three days after Dose 1.
- 79 YO male diagnosed with diffuse large B-cell lymphoma 17 days after receipt of Dose 1 reported HZ confirmed by adjudication (no sample taken for PCR) 225 days after Dose 1. The subject had completed a course of chemotherapy the month before onset of HZ.
- 70 YO female reported HZ confirmed by PCR 1035 days after Dose 1 (subjects' back pain precluded a visit to the center for the second dose).
- 81 YO female reported HZ confirmed by PCR 241 days after Dose 1. The subject did not receive Dose 2 due to hospitalization for a cerebrovascular accident.

HZ/su VE on the TVC was 87.74% (95% CI: 82.04%, 91.91%) and on ATPc for efficacy was 90.33% (95% CI: 84.66%, 94.21%).

Reviewer's comment - HZ VE on the TVC and ATPc for efficacy was concordant with that of the mTVC.

6.2.11.2 Analyses of Secondary Endpoints

The mTVC was the primary analysis population for the evaluation of the secondary efficacy endpoints in Zoster-022.

PHN cases in the mTVC – From the table below, of the 32 subjects who reported PHN in the mTVC, 4 were in the HZ/su group and 28 were in the Placebo group, for a VE against overall PHN in subjects ≥ 70 YOA of 85.5% (95% CI: 58.5%, 96.3%).

Table 59 - Vaccine efficacy: First or only episode of PHN during the entire study period by age stratum and overall using Poisson method (ZOSTER-022 mTVC)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI 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
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 region
** : VE adjusted by age stratum and region

Reviewer's comment – VE against overall PHN was demonstrated for the 70 – 79 YOA group but not the ≥ 80 YOA group.

Reduction of duration of severe 'worst' HZ-associated pain in subjects with confirmed HZ – Eighteen subjects (15 in the 70 – 79 YOA stratum and 3 in the ≥ 80 YOA stratum) in the mTVC of the HZ/su group and 198 (150 in the 70 – 79 YOA stratum and 48 in the ≥ 80 YOA stratum) of 223 subjects in the mTVC of the Placebo group with confirmed HZ reported severe 'worst' HZ pain. The median (minimum, maximum) duration of severe 'worst' pain was 13.5 (1.0, 162.0) days in the HZ/su group and 19.0 (1.0 – 834.0) days in the Placebo group and the mean duration (SD) was 34.6 (45.54) days in the HZ/su group and 48.5 (101.40) in the Placebo group. Overall VE with regard to duration of severe 'worst' HZ-associated pain was 28.4% (95% CI: -17.69%, 56.44%) with a lower bound of the 95% CI below 0, thus the Applicant was unable to conclude on this objective.

Reduction in incidence of HZ-related mortality –No HZ-related mortality was reported by subjects with confirmed HZ in either group. The Applicant was unable to conclude on this objective.

Reduction in incidence of HZ complications (other than PHN) in subjects 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 HZ/su 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 HZ/su 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 (defined as cranial or peripheral nerve palsies, myelitis, stroke, meningoencephalitis, etc. temporally associated with HZ and judged causally related to HZ by the investigator). Overall VE against HZ complications was 0.97% (95% CI: -433.32%, 83.16%) with a lower bound of the 95% CI below 0, thus the Applicant was unable to conclude on this objective.

Reviewer's comment – The proportions of subjects reporting ophthalmic HZ in the Placebo group was lower in this study and in Zoster-006 as compared to the SPS (Zostavax PI, 2017).

Reductions in incidence of HZ-related hospitalizations – HZ-related hospitalizations were reported for 5 subjects (3 subjects 70 – 79 YOA and 2 subjects ≥ 80 YOA) in the Placebo group and none in the HZ/su group. Although the point estimate of VE with regard to reduction in HZ-related hospitalizations was 100% (Poisson method) the 95% CI was (-9.92, 100.0) and the Applicant was unable to conclude on this endpoint.

Reduction of use of pain medication in subjects with confirmed HZ –In subjects ≥ 70 YOA, 10 of 23 (43.5%) subjects in the HZ/su group and 160/223 (71.8%) of subjects in the Placebo group with confirmed HZ reported HZ-associated pain medication use for an overall VE for reduction in use of pain medication associated with HZ of 39.6% (95% CI: 10.8%, 64.8%).

Reviewer's comment – The Applicant stated that results of the analysis on the reduction in duration of HZ-associated pain medication in subjects ≥ 70 YOA was met as the LB of the 95% CI was > 0 [VE: 49.25% (95%CI: 2.92%, 73.47%)]. However, CBER's statistical reviewer noted that the analysis plan for the endpoint of duration of use of pain medication for HZ was not described in the SAP and thus the analysis presented in the clinical study report was not considered as pre-specified.

See the comment from the statistical reviewer about estimates of VE for secondary endpoints analyzed on subjects with confirmed HZ in Section 6.1.11.2.

6.2.11.3 Subpopulation Analyses

HZ VE by age group

Zoster-022 was not prospectively powered to evaluate VE in the two age strata separately. VE by age group is below.

Table 60 – First or only episode of HZ during the entire study period by age stratum using Poisson method (Zoster-022 mTVC)

Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
70-79YOA *	5114	17	19346.5	0.9	5189	169	19247.5	8.8	90.02	83.54	94.32
≥80YOA *	1427	6	5058.5	1.2	1433	54	4920.3	11.0	89.08	74.65	96.16

Source : Adapted from Zoster-022 CSR Table 23, p. 283
70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
N = number of subjects included in each group
n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000) = Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Poisson method)
* : VE adjusted by region
** : VE adjusted by age stratum and region

Reviewer's comment – HZ incidence in the Placebo group subjects 70 – 79 YOA is within, but on the lower end, of incidence reported in that age group in the literature ([Insinga, 2005), (Johnson, 2015), (Kawai, 2014), (Yawn, 2007)]. The overall incidence of HZ in the Placebo group was, as expected, higher in the older age stratum.

The point estimates of VE appear comparable in the two age strata.

HZ VE by gender

A sensitivity analysis on HZ VE by gender was performed.

Table 61 – First or only episode of HZ during the entire study period by age strata and overall using Poisson method, by gender (Zoster-022 mTVC)

Gender	Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
Male	70-79YOA	2317	6	8726.7	0.7	2296	74	8520.7	8.7	92.08	81.94	97.19
	≥80YOA	660	3	2322.5	1.3	690	29	2336.1	12.4	89.59	66.43	97.97
	OVERALL *	2977	9	11049.2	0.8	2986	103	10856.8	9.5	91.40	83.02	96.17
Female	70-79YOA	2797	11	10619.8	1.0	2893	95	10726.7	8.9	88.30	78.11	94.35
	≥80YOA	767	3	2736.0	1.1	743	25	2584.3	9.7	88.67	62.85	97.81
	OVERALL *	3564	14	13355.8	1.0	3636	120	13311.0	9.0	88.38	79.74	93.83

Source: Adapted from 125614/0 Zoster-022 CSR Table 7.1, p. 4022
70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
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 strata

Reviewer's comment – Estimates of HZ VE were consistent when evaluated overall by gender and by age group and gender.

HZ VE by region

HZ VE analysis by region is below. Point estimates of VE were comparable across regions, ranging from 83.0% (Latin America) to 95.6% (Australasia). HZ incidence in the Placebo group varied and was highest in Australasia and lowest in Europe.

Table 62 - Vaccine efficacy: First or only episode of HZ during the entire study period by region using Poisson method (ZOSTER-022 mTVC)

Region*	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
Australasia	1211	3	4588.6	0.7	1240	67	4559.6	14.7	95.55	86.42	99.10
Europe	3567	11	13526.5	0.8	3604	92	13439.0	6.8	88.15	77.80	94.29
Latin America	485	3	1664.0	1.8	493	18	1675.2	10.7	83.04	41.88	96.80
North America	1278	6	4625.9	1.3	1285	46	4494.1	10.2	87.33	70.26	95.58

Source: Adapted from 125614/0 Zoster-022 CSR Table 7.3, p. 4028
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 strata

Reviewer's comment – Lower incidence of HZ in Europe as compared to other regions has been reported [(Pinchinat, 2013), Paganino, 2015)].

HZ VE by race
Descriptive analysis of HZ VE for the four racial subgroups is below.

Table 63 – HZ VE by race overall using Poisson method (Zoster-022 mTVC)

Race	HZ/su n/N	HZ/su n/T per 1000	Placebo n/N	Placebo n/T per 1000	VE (95% CI)
African	0/74	0.0	1/61	4.8	100.00% (-4544.34%, 100.00%)
Asian	3/1114	0.7	67/1142	15.9	95.49% (86.23%, 99.09%)
White	19/5081	1.0	144/5134	7.7	86.98% (78.92%, 92.39%)
Other	1/272	1.1	11/285	11.2	90.78% (36.52%, 99.79%)

Source: Adapted from 125614/21, Question 3, Table 7, p. 11
N = number of subjects in each group
n = number of subjects having at least one confirmed HZ episode
T = sum of follow-up period expressed in years
n/T per 1000 = incidence rate of subjects reporting at least one event
VE is adjusted by age strata and region

Reviewer's comment – The low numbers of subjects of African heritage overall, as well as the low numbers of subjects of African heritage who reported HZ from both treatment groups limits the ability to draw conclusions about HZ/su VE in that sub-group.

HZ VE by ethnicity
Descriptive analysis of HZ VE for the two pre-specified ethnic groups is below.

Table 64 – HZ VE by ethnicity overall using Poisson method (Zoster-022 mTVC)

Zoster-022	HZ/su n/N	HZ/su n/T per 1000	Placebo n/N	Placebo n/T per 1000	VE (95% CI)
American Hispanic or Latino	3/526	1.7	20/525	11.2	84.77% (48.63%, 97.10%)
Not American Hispanic or Latino	20/6015	0.9	203/6097	9.1	90.26% (84.56%, 94.17%)

Source: Adapted from 125614/21, Question 3, Table 8, p. 12
Hispanic = American Hispanic or Latino
Not Hispanic = Not American Hispanic or Latino
n = number of subjects having at least one confirmed HZ episode
T = sum of follow-up period expressed in years
n/T per 1000 = incidence rate of subjects reporting at least one event
VE is adjusted by age strata and region

Reviewer's comment – HZ VE was comparable between the pre-specified ethnic groups.

6.2.11.5 Exploratory and Post Hoc Analyses

HZ VE by year
A descriptive analysis of the first or only episode of HZ VE by year on the mTVC was provided.

Table 65 – First or only episode of HZ during the entire study period by time using Poisson method (Zoster-022 mTVC)

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

Source : 125614/0 Zoster-022 CSR Table 24, p. 287
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
Year 1 : From 30 days after second vaccination to 395 days after second vaccination
Year 2 : From >395 days after second vaccination to 760 days after second vaccination
Year 3 : From >760 days after second vaccination to 1125 days after second vaccination
Year 4 : From >1125 days after second vaccination until last contact date

Reviewer's comment – Reviewer's comment – Descriptive analyses of HZ VE by year indicate that vaccine effect may be durable through four years post-vaccination.

Humoral immunogenicity

Vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 70 YOA and by age stratum was an exploratory endpoint. The ATPc for immunogenicity-Humoral (or adapted ATPc for immunogenicity-Humoral) was the primary population for immunogenicity analyses. Humoral immune responses were measured on a small proportion of subjects; 5.7% of subjects in the TVC were in the ATP cohort for immunogenicity – Humoral at M3.

At baseline pre-vaccination, 384/386 (99.5%) and 410/412 (99.5%) of subjects in ATP cohort for immunogenicity in the HZ/su and Placebo groups respectively were seropositive for anti-gE Ab by ELISA (seropositivity cut-off = 97 mIU/mL). At M3 and beyond, 100% of HZ/su recipients in the ATP (adapted) cohort for immunogenicity were seropositive. Seropositivity rates for the corresponding Placebo group at Months 3, 14, 26 and 38 ranged from 99.2% - 99.7%.

The Anti-gE Ab GMC for the Placebo group at baseline pre-vaccination was 1508.1 mIU/mL (95% CI: 1369.6, 1660.6); and ranged from 1250.4 mIU/mL – 1532.8 mIU/mL at the pre-specified post-vaccination time points. The anti-gE Ab GMCs for the HZ/su group at the same post-vaccination time points are below.

Table 66 - Geometric Mean Concentrations of anti-gE Ab at Months 0, 3, 14, 26 and 38 (Zoster-022 HZ/su group, Adapted ATP cohort for immunogenicity – Humoral)

	GMC value	GMC 95% CI (UL, LL)	GMC Minimum	GMC Maximum
PRE Month 0	1547.2	(1394.3, 1717.0)	< 97.0	49273.2
P2 Month 3	51048.0	(44796.2, 54521.1)	2119.1	279027.0
P2 Month 14	16171.8	(14967.8, 17472.6)	1125.0	85563.7
P2 Month 26	13091.9	(12141.1, 14117.2)	1088.1	55320.4
P2 Month 38	10452.2	(9654.4, 11315.9)	330.2	53938.5

Source: Adapted from 125614/0 Zoster-022 CSR Table 27, p. 311
GMC – geometric mean Ab concentration in mIU/mL
UL, LL – upper and lower limit of the 95% CI
PRE - pre-vaccination
P2 - post-vaccination Dose 2

Reviewer's comment – The anti-gE Ab GMCs rose substantially from M0 to M3, declining, but still remaining above baseline, at subsequent time points.

The mean geometric increases (MGI) of anti-gE concentrations at Months 3, 14, 26 and 38 over pre-vaccination in the HZ/su 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). In the Placebo group, the MGI over pre-vaccination was not higher than 1.0 at any time point.

Reviewer's comment – The GMCs post-vaccination at each time point for the HZ/su subjects in the ATP cohort for immunogenicity were lower for subjects in Zoster-022 as compared to Zoster-006.

The vaccine response rates in the HZ/su group as measured by anti-gE Ab ELISA concentrations at M3, M14, M26 and M38 were 95.9%, 79.6%, 71.5% and 66.1% respectively (see Section 6.1.9 for the definition of vaccine response). In the Placebo group the VRR for anti-gE Ab concentrations was not higher than 3.7% at any time point.

Reviewer's comment – The VRR of HZ/su recipients ≥ 70 YOA in Zoster-022 were lower than that of HZ/su recipients 50 – 59 and 60 – 69 YOA enrolled in Zoster-006.

Fold rise (MGIs), VRRs, and GMCs declined in the years post-vaccination, but efficacy remained relatively high.

Humoral immune responses were also analyzed by age and region.

By age – Baseline seropositivity rates for the 70 – 79 and ≥ 80 YOA stratum were ≥ 98.8% for subjects in both treatment groups. The seropositivity rates for all HZ/su recipients in both age groups (70 – 79, ≥ 80 YOA) were 100% at each post-vaccination time point.

The pre-vaccination anti-gE GMCs of Hz/su recipients and Placebo recipients across age and treatment groups were comparable, ranging from 1483.2 to 1585.3. The post-vaccination VRRs, anti-gE Ab GMCs and MGIs of HZ/su recipients were comparable between the 70 – 79 and ≥ 80 YOA groups at the pre-specified time points.

Reviewer's comment – Immune response to HZ/su as measured by anti-gE ELISA were robust in both age groups.

By region – Baseline seropositivity was similar among regions, ranging from 99.2% to 100%. Anti-gE Ab GMCs in HZ/su recipients were highest at M3, and comparable at that and the other pre-specified time points among the regions. VRR were also comparable, ranging from 91.9% to 100% at M3, and were also comparable between regions at the other time points. Mean fold increases over pre-vaccination in the HZ/su group at M3 ranged from 57.4 – 76.3, and were comparable between regions at that and the other time points.

Reviewer's comment – Immune responses following HZ/su vaccination were robust in all regions.

6.2.12 Safety Analyses

6.2.12.1 Methods

At the EOS, the mean and median safety follow up time was 4.0 and 4.2 years respectively with a range of 0 to 5.0 years.

The primary population for the assessment of safety was the TVC which included 13900 subjects total, and 6950 in each treatment group. A randomized subset of subjects in the TVC (TVC diary card subset) reported reactogenicity assessments. Descriptive safety analysis results are presented on the TVC at the EOS analysis.

6.2.12.2 Overview of Adverse Events

The mean and median safety follow up time in the TVC was 4.1 [standard deviation (SD) 0.9 years], and 4.4 years respectively with a minimum of 0 and maximum of 5 years.

Solicited local and solicited general events were recorded for subjects ≥ 70 YOA who were randomized into the diary card subset and are presented below for the TVC diary card subset. Other safety results presented below are from analysis of the TVC (HZ/su group N = 6950, Placebo group N = 6950).

SOLICITED AES
The following are the numbers of subjects by age and treatment group in the TVC diary card subset. According to the protocol, planned randomization was 1:1 for the 70 – 79 and ≥ 80 YOA age strata.

Table 67 – Number of subjects in the 7-day diary card subset by age group (Zoster-022 TVC diary card)

Age group	**70-79 YOA**	**70-79 YOA**	**≥ 80 YOA**	**≥ 80 YOA**	**All**	**All**
Treatment group	**HZ/su**	**Placebo**	**HZ/su**	**Placebo**	**HZ/su**	**Placebo**
ZOSTER-022	286	288	226	225	512	513

Source: Adapted from 125614/0 Zoster-022 CSR Table 6.36 and 6.17, p. 3759 and 3884

Reviewer's comment – Only 7.4% of subjects in the TVC were in the TVC diary card subset of Zoster-022. However, all eligible subjects ≥ 70 YOA (total 3588, with 1786 subjects from the

HZ/su group and 1802 subjects from the Placebo group) were in the TVC diary card subset of Zoster-006. There was an adequate number of subject ≥ 70 YOA for the assessment of reactogenicity for the ≥ 70 YOA stratum.

Compliance with return of local symptom sheets and general symptom sheets for the TVC diary card subset for both treatment groups was above 97% (range 97.9% - 99.2%) following each dose and overall. Compliance with symptom sheet return by age stratum was reviewed; compliance ranged from 97.5% to 100% for the pre-specified age strata (70 – 79 and ≥ 80 YOA) for each dose and overall and were comparable between treatment groups.

Overall solicited AEs – any grade

Overall by subject, 79.0% and 29.5% of subjects in the HZ/su and Placebo groups respectively, reported at least one solicited symptom during the 7-day post-vaccination period. At least one solicited general symptom was reported by 53.0% and 25.1% of subjects in the HZ/su and Placebo groups respectively and at least one solicited local symptom was reported by 74.1% and 9.9% of subjects in the HZ/su and Placebo groups respectively. The percentage of subjects in the HZ/su group reporting any solicited symptom, any solicited general symptom, and any solicited local symptom after Dose 1 as compared to Dose 2 was 71.9% vs. 66.7%, 39.1% vs. 39.8%, and 65.3% and 62.4% vs. respectively.

Reviewer's comment – The proportions of subjects reporting solicited symptoms (any, any grade general and any grade local) was higher in the HZ/su group as compared to the Placebo group. There were no clinically significant differences between the proportions of HZ/su recipients reporting all grade general or local symptoms of following Dose 1 as compared to Dose 2.

Overall solicited AEs – Grade 3

The proportions of subjects in the HZ/su 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 HZ/su group reporting any Grade 3 solicited symptom, any Grade 3 solicited general symptom, and any Grade 3 solicited local symptom after Dose 1 as compared to Dose 2 was 6.2% vs. 8.1%, 3.0% vs. 3.9%, and 4.2% and 5.7% vs. respectively.

Reviewer's comment – Reports of Grade 3 solicited AEs following HZ/su administration were not uncommon.

Overall solicited AEs - duration

For the duration of each specific solicited symptom, see the tabulations of specific solicited local and general symptoms below.

The Applicant performed a post hoc analysis of the proportions of subjects reporting solicited symptoms beginning during the 7-day post-vaccination period and lasting beyond that period. Overall per subject, 5.7%, 3.7% and 2.3% of HZ/su recipients in the TVC diary card subset reported at least one of any grade solicited symptom, solicited general symptom any solicited local symptom beginning in and lasting beyond the 7-day solicited reporting period. Overall per subject, 0.8%, 0.4% and 0.4% of HZ/su recipients in the TVC diary card subset reported at least one of any Grade 3 solicited symptom, Grade 3 solicited general and Grade 3 solicited local symptom respectively beginning in and lasting beyond this period.

Reviewer's comment – A small proportion of HZ/su subjects reported Grade 3 reactogenicity starting in but lasting beyond the 7-day post-vaccination period.

Specific solicited local AEs

Overall per subject, at least one solicited local symptom of any grade was reported for 74.1% and 9.9% of subjects in the HZ/su and Placebo groups, respectively, and at least one Grade 3 solicited local symptom was reported for 8.5% and 0.2% of HZ/su and Placebo recipients, respectively. The numbers and proportions of subjects in the TVC diary card subset reporting any and Grade 3 specific solicited local symptoms by treatment group are below.

Table 68 – Incidence of solicited local symptoms reported during the 7-day (Day 0 – 6) post-vaccination period overall by subject (Zoster-022 TVC diary card)

Symptom/Type	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Pain/any grade	505	347	68.7%	505	43	8.5%
Pain/ Grade 3	505	22	4.4%	505	1	0.2%
Redness/ any grade	505	198	39.2%	505	5	1.0%
Redness >100 mm	505	20	4.0%	505	0	0.0%
Swelling/any grade	505	114	22.6%	505	2	0.4%
Swelling >100 mm	505	8	1.6%	505	0	0.0%

Source: Adapted from 125614/0 Zoster-022 CSR Table 35, p. 326

Pain was the most commonly reported local symptom by subjects in both treatment groups.

The proportions of subjects in the HZ/su group reporting specific local symptoms after Dose 1 and Dose 2 were reviewed. After Dose 1 and Dose 2, 59.2% and 57.3% of HZ/su recipients, respectively, reported any grade pain and Grade 3 pain was reported by 2.4% of subjects after Dose 1 and after Dose 2. After Dose 1 and Dose 2, 28.5% and 27.8% of subjects reported any grade of redness, respectively, and Grade 3 (> 100 mm) of redness was reported 1.8% and 3.0% of subjects after Dose 2. After Dose 1 and Dose 2, any grade of swelling was reported by 16.9% and 13.8% of subjects respectively, and 0.4% and 1.4% of subjects reported Grade 3 swelling after Dose 1 and Dose 2, respectively.

Reviewer's comment – The proportions of subjects in the HZ/su group reporting specific local symptoms of any grade and Grade 3 were comparable between doses, and less than 5% reported any specific Grade 3 solicited local symptom.

Specific solicited local AEs – duration

Overall per dose, the mean (median) duration of pain, redness or swelling reported after HZ/su administration was 2.7 (2.0), 3.7 (3.0) and 3.3 (3.0) days, respectively. The mean and median duration of each specific event following Dose 1 and Dose 2 were generally comparable. The minimum/maximum duration of pain, redness and swelling reported after HZ/su administration overall/dose was 1.0/19.0, 1.0/39.0 and 1.0/12.0 days, respectively.

Reviewer's comment – In general, the mean and median duration of each specific solicited local symptom reported following HZ/su administration were relatively short.

Specific solicited general AEs

At least one solicited general symptom was reported by 53.0% and 25.1% of subjects in the HZ/su and Placebo groups, respectively, and at least one Grade 3 solicited general symptom was reported for 6.0% and 2.0% of HZ/su and Placebo recipients, respectively. The numbers

and proportions of subjects in the TVC diary card reporting any grade and Grade 3 specific solicited general symptoms by treatment group are below.

Table 69 – Incidence of solicited general symptoms reported during the 7-day (Day 0 – 6) post-vaccination period overall (Zoster-022 TVC diary card)

	HZ/su N	HZ/su n	HZ/su %	Placebo N	Placebo n	Placebo %
Fatigue – any grade	504	166	32.9%	505	77	15.2%
Fatigue – Grade 3	504	16	3.2%	505	4	0.8%
Gastrointestinal symptoms – any grade	504	55	10.9%	505	40	7.9%
Gastrointestinal symptoms – Grade 3	504	5	1.0%	505	2	0.4%
Headache – any grade	504	124	24.6%	505	55	10.9%
Headache – Grade 3	504	5	1.0%	505	4	0.8%
Myalgia – any grade	504	157	31.2%	505	41	8.1%
Myalgia – Grade 3	504	12	2.4%	505	2	0.4%
Shivering – any grade	504	75	14.9%	505	22	4.4%
Shivering – Grade 3	504	6	1.2%	505	2	0.4%
Temperature* – any grade	504	62	12.3%	505	13	2.6%
Temperature* – Grade 3	504	0	0.0%	505	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 as assessed via oral, axillary, rectal or tympanic route or setting

The proportions of subjects in the HZ/su group reporting each solicited general symptom of any grade (grade 3) event following each dose are as follows: fatigue Dose 1 – 20.8% (1.6%), fatigue Dose 2 – 24.8% (1.8%), GI symptoms Dose 1 – 5.0% (0.6%), GI symptoms Dose 2 – 7.5% (0.6%), headache Dose 1 – 14.4% (0.4%), headache Dose 2 – 15.4% (0.8%), myalgia Dose 1 – 21.2% (1.2%) , myalgia Dose 2 – 23.0% (1.4%), shivering Dose 1 – 7.6% (0.2%), shivering Dose 2 – 12.0% (1.0%), temperature Dose 1 – 7.8% (0.0%), temperature Dose 2 – 7.7% (0.0%).

Reviewer's comment - The most commonly reported solicited general symptoms following vaccination were fatigue and myalgia, and both were reported by higher proportions of subjects in the HZ/su group. Any grade temperature, shivering and myalgia were frequently reported by subjects in the HZ/su group. GI symptoms were reported by comparable proportions of subjects in each group. No specific Grade 3 general symptom was reported by more than 4% of subjects in the HZ/su group.

The proportions of subjects reporting any grade and Grade 3 of most of the specific solicited general symptoms were generally comparable between Dose 1 and Dose 2; the proportions of subjects reporting shivering of any grade and Grade 3 was numerically higher after Dose 2.

Specific solicited general AEs – duration

Overall per dose, the mean (median) duration of fatigue, GI symptoms, headache, myalgia, shivering and temperature reported after HZ/su administration was 2.9 (2.0), 2.9 (2.0), 2.3 (2.0), 2.7 (2.0), 1.8 (1.0) and 2.0 (2.0) days, respectively. The mean and median duration of each specific event following Dose 1 and Dose 2 were generally comparable. The minimum duration of each specific solicited general symptom reported after HZ/su administration overall/dose was 1 day and the maximum duration of fatigue, GI symptoms, headache, myalgia, shivering and temperature was 49.0, 15.0, 13.0, 14.0, 10.0 and 7.0, respectively.

Reviewer's comment – In general, the mean and median durations of each specific solicited general symptom reported following HZ/su administration were relatively short.

UNSOLICITED AES

Overall, 55.5% and 32.6% of subjects in the TVC of the HZ/su group (N = 6950) and Placebo group (N = 6950), respectively, reported at least one unsolicited (serious or non-serious) AE in the 30-day post-vaccination period.

In the HZ/su group, injection site pain (28.4% of HZ/su and 2.1% of Placebo group reporting), injection site erythema (12.4% of HZ/su group and 0.4 of Placebo group reporting), pyrexia (6.8% of HZ/su group and 0.6% of Placebo group reporting), headache (6.65 and 2.7% of HZ/su group and Placebo group reporting) and fatigue (4.4% of HZ/su group and 1.3% of Placebo group reporting) were the most frequently reported unsolicited AEs, while in the Placebo group, nasopharyngitis (3.0%), was the most frequently occurring unsolicited AE.

There were imbalances noted in the proportions of subjects reporting events in several SOCs due to the occurrence of reactogenicity events. Imbalances in the General disorders and administration site conditions SOC (39.9% vs. 6.7% of HZ/su and Placebo recipients reporting respectively) were driven by IS events as well as pyrexia, fatigue and chills. Imbalances in the Nervous system disorders SOC (9.5% vs. 5.3% of HZ.su and Placebo recipients reporting, respectively) were due mainly to reports of headache. Imbalances in the Musculoskeletal and connective tissue disorders SOC (9.4% and 6.3% of HZ/su and Placebo recipients reporting, respectively) were driven by arthralgia (reported by 1.6% and 1.1% of the HZ/su and Placebo groups, respectively, and myalgia (reported by 3.2% and 0.8% of the HZ/su and Placebo groups, respectively).

Gout and gouty arthritis were reported by 16 subjects and 7 subjects, dyslipidemia reported by 7 subjects and 2 subjects, respiratory tract infections by 15 and 11 subjects, and arthralgia by 114 and 77 subjects in the HZ/su and Placebo groups respectively during the 30-day post-vaccination period.

Reviewer's comment – CBER analysis of subjects in the Zoster-022 TVC reporting most specific AEs by PT during the 30-day post-vaccination periods did not reveal any clinically significant imbalances between treatment groups; while some imbalances were noted, they were most often were reported for events that were solicited from the 7-day diary card subset or other events by specific PT that might be related to general discomfort due to receipt of HZ/su, such as malaise and decreased appetite. See Section 8.5 for details.

Since the most commonly reported unsolicited AEs reported by subjects in the HZ/su group during the 30-day post vaccination period were local and general reactogenicity events, the Applicant provided an analysis of unsolicited AEs performed on the subjects in the TVC who were randomized to the 7-day diary card subset (TVC diary card). Overall, 26.0% and 26.1% of subjects in the HZ/su group and Placebo groups respectively reported an unsolicited AE within the 30-day post-vaccination period.

Reviewer's comment – No clinically significant imbalances were noted between treatment groups for specific unsolicited events by PT reported during the 30-day post-vaccination period by the TVC diary card subset.

At least one Grade 3 non-serious unsolicited event was reported by 5.9% and 2.8% of subjects in the HZ/su and Placebo groups respectively within the 30-day post-vaccination period. By PT,

the most commonly reported events were injection site pain [1.4% (100 subjects) and <0.05% (3 subjects) in the HZ/su and Placebo groups, respectively], headache [0.6% (45 subjects) and 0.1% (8 subjects) in the HZ/su and Placebo groups, respectively], pyrexia [0.6% (44 subjects) and 0.1% (5 subjects) in the HZ/su and Placebo group, respectively] and chills [0.6% (41 subjects) and 0% (2 subjects) in the HZ/su and Placebo groups, respectively]. Due to the reporting of these events, imbalances were noted in the SOCs of General disorders and administration site conditions (3.2% and 0.4% of HZ/su and Placebo recipients reporting), Nervous system disorders (1.1% and 0.3% of HZ/su and Placebo recipients reporting) and Musculoskeletal and connective tissue disorders (1.0% and 0.5% of HZ/su and Placebo recipients reporting) driven by IS events, headache and myalgia, respectively.

MEDICALLY ATTENDED AES

During the 30-day post-vaccination period, 20.1% (1400/6950) and 19.8% (1376/6950) of subjects in the HZ/su and Placebo groups, respectively, reported the occurrence of an unsolicited AE with a medically attended visit.

From M0 – M8, 41.5% and 41.9% of subjects in the TVCs of the HZ/SU and Placebo groups, respectively, reported the occurrence of a MAE. By PT, comparative analysis indicated that the proportions of subjects reporting the MAEs of IS pain, IS swelling, IS erythema and headache were higher in the HZ/su groups as compared to the Placebo group, but each of these MAEs were reported by ≤ 0.7% of subjects in the HZ/su group. Additionally, higher proportions of subjects in the HZ/su group (but ≤0.7%) as compared to the Placebo group reported the MAEs of asthenopia, ear infection, and arthropod bite. By SOC, comparative analysis indicated that higher proportions of subjects in the HZ/SU (3.4%) as compared to the Placebo group (2.7%) reported a MAE in the General disorders and administration site conditions SOC. The most common MAEs reported during this period by PT was nasopharyngitis, urinary tract infection and bronchitis, reported in comparable proportions between treatment groups.

Reviewer's comment – Generally, no clinically significant imbalances were observed between treatment groups with regard to the proportions of subjects reporting AEs by PT that were medically attended from M0 – M8. The proportions of subjects reporting medically attended events related to reactogenicity in the HZ/su group were low.

6.2.12.3 Deaths

A summary of subjects in the TVC with fatal SAEs (who died) during select time periods by treatment group is below.

Table 70- Subjects with fatal SAEs (who died) during select time periods (Zoster-022 TVC)

	HZ/su 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: 125614/22 Annex 1, Table 53, p. 134
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting symptom

During the 30-day post-vaccination period - Three and five subjects in the HZ/su and Placebo groups respectively died within the 30-day post-vaccination period. The fatal SAEs by PT in the HZ/su group were myocardial infarction, accident and cerebrovascular accident. The fatal SAEs by PT in the Placebo group were cardio-respiratory arrest, myocardial infarction, COPD and cerebrovascular accident (2).

During M0 – M3 - Seven subjects (0.1%) and eleven subjects (0.2%) had fatal SAEs in the HZ/su and Placebo groups respectively during M0 – M3. The only fatal SAE by PT reported by more than one subject in each treatment group was cerebrovascular accident, reported by 3 subjects in the HZ/su group and two subjects in the Placebo group.

During M0 – M14 - During this period, 71 (1.0%) and 82 (1.2%) subjects died in the HZ/su and Placebo groups, respectively. By PT, the most frequently reported fatal events during the M0 – M14 period were myocardial infarction [reported by 5 (0.1%) and 7 (0.1%) of subjects in the HZ/SU and Placebo groups, respectively], cardiac failure [reported by 3 (0.0%) and 9 (0.1%) of subjects in the HZ/SU and Placebo groups, respectively], and acute myocardial infarction [reported by 5 (0.1%) and 4 (0.0%) of subjects in the HZ/SU and Placebo groups, respectively]. The SOCs with highest proportions of subjects reporting events were the Cardiac disorders (0.4% and 0.5% of subjects in the HZ/su and Placebo groups reporting events, respectively), Infections and infestations (0.2% of subjects in both groups reporting events) and the Neoplasms SOCs (0.1% and 0.2% of subjects in the HZ/su and Placebo groups reporting events, respectively). Comparative analysis indicated that there was no difference between vaccination groups for the proportions of subjects reporting fatal SAEs (who died) or subjects reporting fatal SAEs by SOC or PT during M0 – M14.

During the whole post-vaccination period - During the whole post-vaccination period, 6.1% and 6.6% (461/6950) of subjects died in the HZ/su and Placebo groups, respectively. This proportion is comparable between treatment groups and consistent with the proportions of subjects ≥ 70 YOA who died during the whole post-vaccination time period in Zoster-006. By PT, the most commonly reported causes of death in the HZ/su and Placebo group respectively were cardiac failure (0.4% and 0.5%), myocardial infarction (0.3% and 0.4%), pneumonia (0.3% and 0.5%), cardiac arrest (0.3% and 0.2%), and death not otherwise specified (0.2% and 0.4%). The greatest proportions of subjects reported events in the Neoplasms, Cardiac disorders and Infections and infestations SOCs with the proportions of subjects reporting events in these SOCs comparable between vaccination groups.

Reviewer's comment - There were no 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 were noted.

Fatal SAEs by age group and region - The proportions of subjects who died during the time periods and during the whole post-vaccination period by age strata were similar between treatment groups, with the proportions increasing with advancing age. During M0 – M14, 0.7% of subjects 70 – 79 YOA died in both treatment groups; and 2.0% and 2.8% of subjects ≥ 80 YOA in the HZ/su and Placebo groups, respectively, died during that period. For the HZ/su and Placebo groups, respectively, 4.5% and 4.2% of subjects 70 - 79 YOA, and 11.8% and 15.3% of subjects ≥ 80 YOA died during the whole post-vaccination period. There were no clinically significant imbalances between treatment groups for the proportions of subjects who died during the time periods above by region.

Related fatal SAEs – One subject had a fatal SAE that was considered related to vaccination by the investigator, but not the Applicant. See Section 8.4.2.

Reviewer's comment – No clinically significant imbalances between the treatment groups for the proportions of subjects who died overall or in terms of incidence and nature of the causes of death by PT and SOC during different time periods were detected upon review. CBER analysis grouping by narrow SMQs (MedDRA version 18.0) did not reveal any imbalances between the treatment groups with regard to the proportions of subjects reporting fatal SAEs during the whole post-vaccination period.

6.2.12.4 Serious Adverse Events

The Applicant included fatal and non-fatal SAEs in their SAE tabulations.

SAEs reported during select time periods
A summary of the proportions of subjects with at least one SAE reported during selected time periods up to M14 is below.

Table 71 – Global summary of SAEs during selected time periods (Zoster-022 TVC)

	HZ/su 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 125614/25 Table 196, p. 258

During the 30-day post-vaccination period, at least one SAE was reported by 157 (2.3% %) and 158 (2.3%) subjects in the HZ/su and Placebo groups, respectively. The most commonly reported SAEs by PT were pneumonia [8 subjects (0.1%) in the HZ/su group, 4 subjects (0.1%) in Placebo group] and cerebrovascular accident [5 subjects (0.1%) in the HZ/su group, 7 subjects (0.1%) in the Placebo group]. No single event by PT was reported by > 0.1% of subjects in either treatment group. The greatest proportions of subjects reported events in the Cardiac disorders, Infections and infestations and Injury, Poisoning and Procedural disorders SOCs, with the proportions of subjects reporting events in these SOCs generally comparable between vaccination groups.

During M0 – M3, at least one SAE was reported by 248 (3.6%) and 228 (3.3%) of the HZ/su and Placebo group, respectively. The most commonly reported SAEs by PT were pneumonia [12 subjects (0.2%) in the HZ/su group, 11 subjects (0.2%) in Placebo group], atrial fibrillation [5 subjects (0.1%) in the HZ/su group, 14 subjects (0.2%) in the Placebo group], and cerebrovascular accident [9 subjects (0.1%) in the HZ/su group and 7 subjects (0.1%) in the Placebo group]. No single event by PT was reported by > 0.2% of subjects in either treatment group. The greatest proportions of subjects reported events in the Cardiac disorders, Infections and infestations and Injury, Poisoning and Procedural disorders SOCs, with the proportions of subjects reporting events in these SOCs generally comparable between vaccination groups.

During M0 – M14, at least one SAE was reported by 891 (12.8%) and 939 (13.5%) subjects in the HZ/su and Placebo groups, respectively. The most commonly reported SAEs by PT were

pneumonia (reported by 0.7% of subjects in both treatment groups) and atrial fibrillation (reported by 0.5% and 0.8%) of subjects in the HZ/su and Placebo groups, respectively). The greatest proportions of subjects reported events in the Cardiac and Infections and infestations SOCs, with the proportions of subjects reporting events in these SOCs generally comparable between vaccination groups. Comparative analysis of subjects indicated that there was no clinically significant difference between treatment groups for the proportions of subjects reporting SAEs during the M0 – M14 time period. However, the events in the SOC category of Cardiac disorders (reported by 2.6% and 3.2% of subjects in the HZ/su and Placebo group, respectively) was reported more frequently by the Placebo group and the specific PT of aortic stenosis (0 and 7 subjects in the HZ/su and Placebo group, respectively) was reported more frequently by the Placebo group.

Reviewer's comment – No clinically significant imbalances were noted between the treatment groups for the proportions of subjects reporting SAEs during the specified time periods by specific PT by SOC or by narrow MedDRA SMQs.

Subjects reporting SAEs by age and region
The proportions of subjects in each age stratum reporting at least one SAE during select time periods post-vaccination is below.

Table 72 – Subjects reporting the occurrence of SAEs select time periods by age strata (Zoster-022 TVC)

	HZ/su 70 – 79 N = 5414 n (%)	Placebo 70 – 79 N = 5420 n (%)	HZ/su **≥ 80** N = 1536 n (%)	Placebo **≥ 80** N = 1530 n (%)	HZ/su All N = 6950 n (%)	Placebo All N = 6950 n (%)
Subjects with at least one SAE reported during within the 30-day post-vaccination period	123 (2.3%)	109 (2.0%)	34 (2.2%)	49 (3.2%)	157 (2.3%)	158 (2.3%)
Subjects with at least one SAE reported during M0 – M3	190 (3.5%)	152 (2.8%)	58 (3.8%)	76 (5.0%)	248 (3.6%)	228 (3.3%)
Subjects with at least one SAE reported during M0 – M14	611 (11.3%)	653 (12.0%)	280 (18.2%)	286 (18.7%)	891 (12.8%)	939 (13.5%)

Source: Adapted from 125614/25 Table 201, p. 292

The proportions of subjects reporting at least one SAE during the select time periods above were generally consistent by region.

6.2.12.5 Adverse Events of Special Interest (AESIs)

The occurrence of pIMDs (serious and non-serious) was collected throughout the whole post-vaccination period. The number and proportions of subjects reporting the incidence of pIMDs in each treatment group during select time periods is below.

Table 73 – Subjects reporting the occurrence of pIMDs during select time periods (Zoster-022 TVC)

	HZ/su 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%)

	HZ/su N = 6950 n (%)	Placebo N = 6950 n (%)	Total N = 13900 n (%)
Subjects with ≥ 1 pIMD reported (whole post-vaccination period)	92 (1.3%)	97 (1.4%)	189 (1.4%)

Source: Adapted from 125614/25, Annex 3 Table 290, p. 74

From M0 – M3, pIMDs were reported for 0.3% and 0.2% of subjects in the HZ/su and Placebo groups, respectively. The SOC with the highest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC with 8 and 3 subjects in the HZ/su and Placebo group reporting. The most commonly reported event by PT was PMR, reported by 4 subjects in the HZ/su group and 2 subjects in the Placebo group.

From M0 – M14, pIMDs were reported by 0.7% of subjects in both treatment groups. The SOC with the highest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC with 0.3% of subjects in both vaccination groups reporting. The most commonly reported pIMD by PT was PMR with 13 (0.2%) and 9 (0.1%) subjects reporting in the HZ/su and Placebo groups, respectively. Comparative analysis indicated that there was no difference between treatment groups for the proportions of subjects pIMDs or subjects reporting pIMDs by SOC or PT during M0 – M14.

During the whole post-vaccination period, pIMDs were reported by 1.3% and 1.4% of the HZ/su and Placebo groups, respectively. The SOC with the highest proportions of subjects reporting events was the Musculoskeletal and connective tissue disorders SOC with 0.6% of subjects in both treatment groups reporting. PMR was the most commonly reported pIMD with 22 (0.3%) and 21 (0.3%) subjects in the HZ/su and Placebo groups reporting, respectively.

Reviewer's comment – No clinically significant imbalances were noted between treatment groups for the proportions of subjects reporting the most common pIMD events by PT or by SOC during the specified time periods. See CBER analysis of pIMD reporting over time in Section 8.4.8.

6.2.13 Study Summary and Conclusions

Demonstrated HZ VE in subjects ≥ 70 YOA in Zoster-022 was 89.79% (95% CI: 84.29%, 93.66%), was comparable between the pre-specified age strata, and appeared durable to Year 4. "Overall" PHN VE, calculated on all subjects independent of the occurrence of HZ was 85.49% (95% CI: 58.52%, 96.30%). CBER considers the benefit of HZ/su in preventing PHN to be attributable to VE against HZ. Local and general reactogenicity were commonly reported, but were generally of limited duration. Overall, SAEs, pIMDs and deaths were reported in comparable proportions by subjects in both treatment groups.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Objectives and endpoints were pre-specified for the pooled analysis across Zoster-006 and Zoster-022.

7.1.1 Methods of Integration

Primary objectives of the pooled analysis of Zoster-006 and Zoster-022

- To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 70 YOA across both Phase 3 studies
- To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥ 70 YOA across both Phase 3 studies

Secondary objectives of the pooled analysis of Zoster-006 and Zoster-022

- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA
- To evaluate VE in the prevention of PHN compared to placebo in subjects ≥ 50 YOA with confirmed HZ
- To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 70 YOA with confirmed HZ

Primary endpoints of the pooled analysis of Zoster-006 and Zoster-022

- Occurrence of overall PHN - incidence of PHN calculated using the mTVC during the entire study period in subjects ≥ 70 YOA
- Occurrence of confirmed HZ during the entire study period in subjects ≥ 70 YOA

Secondary endpoints of the pooled analysis of Zoster-006 and Zoster-022

- Occurrence of overall PHN - incidence of PHN calculated using the mTVC during the entire study period in subjects ≥ 50 YOA
- Duration of severe 'worst' HZ/associated pain following the onset of an HZ rash over the entire pain reporting period as measured by the ZBPI in subjects ≥ 70 YOA with confirmed HZ
- Occurrence of PHN during the entire study period in all subjects (≥ 50 YOA) with confirmed HZ

The secondary safety endpoints of the pooled analysis of Zoster-006 and Zoster-022 were the same as the last five bullets in the secondary endpoints section of Zoster-006 (Section 6.1.8), but were evaluated on all subjects ≥ 70 YOA.

Reviewer's comment – The evaluation of safety and humoral immunogenicity in subjects ≥ 70 YOA across both studies were secondary and exploratory endpoints. However, the results of these analyses will not be presented, as CBER considers that these endpoints were adequately characterized by the results from Zoster-022.

See the comment from the statistical reviewer about estimates of VE for the secondary endpoints analyzed on subjects with confirmed HZ in Section 6.1.11.2.

Success criterion for the pooled analysis – The pooled analysis of Zoster-006 and Zoster-022 was powered to demonstrate statistically significant PHN VE in subjects ≥ 70 YOA. PHN VE in subjects ≥ 70 YOA across the studies would be demonstrated if the LB of the 95% CI was above 0%.

The power of the pooled analysis for the evaluation of the main objectives of the pooled analysis as compared to the endpoints of the individual pivotal studies is below.

Table 74 – Summary of statistical inferential evaluations of primary and secondary objectives for studies Zoster-006, Zoster-022 and the pooled analysis

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
ZOSTER-022	HZ VE	-	-	P	-
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
Pooled analysis	HZ VE	-	-	R	-
	PHN VE	-	-	P	S
	PHN VE in HZ subjects	-	-	-	S*

Source: 125614/0 Zoster-022 CSR Table 17, p. 226
P: Primary objective, well powered
R: Re-estimation of VE for an objective already demonstrated previously in ZOSTER-006 or ZOSTER-022.
S: Secondary objective, appropriately powered
S*: Secondary objective, low power
O: Study not well powered under protocol assumptions although could lead to significance
- : Per protocol, estimates not relevant or not considered for a statistical evaluation

Of the 17531 subjects ≥ 70 YOA in the TVC of the pooled analysis, 8758 were in the HZ/su group [with 1808/8758 (20.6%)] from Zoster-006 and 6950/8758 (79.4%) from Zoster-022] and 8773 were in the Placebo group [with 1823/8773 (20.8%) from Zoster-006 and 6950/8773 (69.2%) from Zoster-022)]. The mTVC of the pooled analysis consisted of 16596 subjects, 8250 from the HZ/su group and 8346 from the Placebo group. See Section 7.1.3 below for an accounting of subjects included in the TVC but excluded from the mTVC.

7.1.2 Demographics and Baseline Characteristics
The demographic characteristics of the pooled population of subjects ≥ 70 YOA in the mTVC for the evaluation of PHN VE and the re-estimation of HZ VE is below.

Table 75 – Summary of demographic characteristics by age group (mTVC, subjects ≥ 70 YOA, pooled Zoster-006/022)

Characteristics	Parameters or Categories	HZ/su 70-79YOA N = 6468 n (%)	Placebo 70-79YOA N = 6554 n (%)	HZ/su **≥80YOA** N = 1782 n (%)	Placebo **≥80YOA** N = 1792 n (%)	HZ/su **≥70 YOA** N = 8250 n (%)	Placebo **≥70YOA** N = 8346 n (%)
Age (years) at vaccination dose: 1	Mean	73.5	73.5	82.7	82.7	75.5	75.5
	SD	2.7	2.7	2.7	2.7	4.7	4.7
	Median	73.0	73.0	82.0	82.0	74.0	74.0
	Minimum	70	62	80	80	70	62
	Maximum	79	79	96	95	96	95
Gender	Female	3544 (54.8)	3653 (55.7)	970 (54.4)	940 (52.5)	4514 (54.7)	4593 (55.0)
	Male	2924 (45.2)	2901 (44.3)	812 (45.6)	852 (47.5)	3736 (45.3)	3753 (45.0)
Ethnicity	American Hispanic or Latino	524 (8.1)	528 (8.1)	124 (7.0)	127 (7.1)	648 (7.9)	655 (7.8)
	Not American Hispanic or Latino	5944 (91.9)	6026 (91.9)	1658 (93.0)	1665 (92.9)	7602 (92.1)	7691 (92.2)

Characteristics	Parameters or Categories	HZ/su 70-79YOA N = 6468 n (%)	Placebo 70-79YOA N = 6554 n (%)	HZ/su **≥80YOA** N = 1782 n (%)	Placebo **≥80YOA** N = 1792 n (%)	HZ/su **≥70 YOA** N = 8250 n (%)	Placebo **≥70YOA** N = 8346 n (%)
Geographic Ancestry	African Heritage / African American	70 (1.1)	67 (1.0)	15 (0.8)	14 (0.8)	85 (1.0)	81 (1.0)
	American Indian or Alaskan Native	3 (0.0)	9 (0.1)	0 (0.0)	0 (0.0)	3 (0.0)	9 (0.1)
	Asian - Central/South Asian Heritage	3 (0.0)	5 (0.1)	1 (0.1)	1 (0.1)	4 (0.0)	6 (0.1)
	Asian - East Asian Heritage	808 (12.5)	819 (12.5)	241 (13.5)	243 (13.6)	1049 (12.7)	1062 (12.7)
	Asian - Japanese Heritage	271 (4.2)	270 (4.1)	77 (4.3)	89 (5.0)	348 (4.2)	359 (4.3)
	Asian - South East Asian Heritage	7 (0.1)	6 (0.1)	2 (0.1)	1 (0.1)	9 (0.1)	7 (0.1)
	Native Hawaiian or Other Pacific Islander	3 (0.0)	3 (0.0)	0 (0.0)	1 (0.1)	3 (0.0)	4 (0.0)
	White - Arabic / North African Heritage	38 (0.6)	39 (0.6)	11 (0.6)	15 (0.8)	49 (0.6)	54 (0.6)
	White - Caucasian / European Heritage	4995 (77.2)	5055 (77.1)	1379 (77.4)	1366 (76.2)	6374 (77.3)	6421 (76.9)
	Other	270 (4.2)	281 (4.3)	56 (3.1)	62 (3.5)	326 (4.0)	343 (4.1)

Source: Adapted from 125614/0 Zoster-022 CSR Table 12.20, p. 7752
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Reviewer's comment – Demographic characteristics were balanced between the treatment groups for subjects ≥ 70 YOA the mTVC of the pooled analysis.

7.1.3 Subject Disposition

The proportions of subjects in the TVC included in the mTVC for analyses of the co-primary endpoints of the pooled analysis are below.

Table 76 – Number and proportions of subjects in the TVC and the mTVC with reason for exclusion (subjects ≥ 70 YOA – pooled 006/022)

	HZ/su N	HZ/su %	Placebo N	Placebo %
Total Vaccinated Cohort	8758	100%	8773	100%
Study vaccine dose not administered as per protocol	4	0.0%	5	0.1%
Wrong replacement or study vaccine administered	13	0.1%	9	0.1%
Subjects who did not receive two doses	487	5.6%	400	4.6%
Subjects who had HZ prior to 30 days after Dose 2	4	0.0%	13	0.1%
Modified Total Vaccinated Cohort	8250	94.2%	8436	95.1%

Source: Adapted from 125614/29, Annex 8, Table 584, p. 317
% = n / Number of subjects from Total Vaccinated Cohort x 100

7.1.4 Analysis of Primary Endpoint(s)

Methods for evaluation of the HZ and PHN endpoints were discussed in Section 6.1.7. The methods were the same for the pooled analysis of subjects ≥ 70 YOA. The primary population for the pooled analyses of these endpoints was the mTVC (defined in Section 6.1.10.1).

<u>VE in the prevention of HZ in subjects ≥ 70 (pooled analysis of 006/022)</u>

The HZ VE pooled analysis was performed on cases with the data lock point of 12-OCT-2015. The median follow up period was 4.0 years (range: 0 – 4.5 years) and the mean follow-up period was 3.8 years (standard deviation 0.7 years).

Of the 309 subjects with confirmed HZ episodes in the mTVC for the pooled analysis, 284 subjects were in the Placebo group and 25 were in the HZ/su group. The overall HZ VE was 91.30 (95% CI: 86.9%, 94.5%), and was similar for both age strata, as seen below.

Table 77 – 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)

Study	Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
Pooled zoster 006-022	70-79YOA*	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.27	86.04	94.85
Pooled zoster 006-022	≥80YOA*	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.37	80.22	96.94
Pooled zoster 006-022	≥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 82, 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 region
**VE adjusted by age stratum and region

The re-estimation of HZ VE on the pooled analysis of subjects ≥ 70 YOA across both studies was concordant with HZ VE results on subjects ≥ 70 YOA in Zoster-022.

<u>VE in the prevention of PHN in subjects ≥ 70 (pooled analysis of 006/022)</u>
Of the 40 subjects reporting PHN in the pooled analysis of subjects ≥ 70 YOA, 4 were in the HZ/su group and 36 were in the Placebo group. The incidence of PHN in the HZ/su group was 0.1/1000 person-years and the incidence in the Placebo group was 1.2/1000 person-years for a PHN VE of 88.78% (95% CI: 68.70%, 97.10%) as seen below.

Table 78 - First or only episode of PHN during the entire study period by age stratum and overall using Poisson method (mTVC, subjects ≥ 70 YOA, pooled 006/022)

Study	Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
Pooled Zoster 006-022	70-79YOA*	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.04	72.47	99.19
Pooled Zoster 006-022	≥80YOA*	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.16	-51.51	97.08
Pooled Zoster 006-022	≥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 region
**VE adjusted by age stratum and region

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

7.1.5 Analysis of Secondary Endpoints

There were three secondary efficacy endpoints for the pooled analysis.

Incidence of PHN calculated using the mTVC during the entire study period in subjects ≥ 50 YOA – There were 50 subjects ≥ 50 YOA with at least one PHN episode in the mTVC for the pooled analysis, 4 subjects in the HZ/su group and 46 in the Placebo group. The incidence of PHN for HZ/su recipients and Placebo recipients for this age group was 0.1/1000 PY and 0.9/1000 PY respectively for an overall PHN VE of 91.22% (95% CI: 75.95%, 97.70%), as seen below.

Table 79 - First or only episode of PHN during the entire study period in subjects ≥ 50 YOA using Poisson method (mTVC, subjects ≥ 50 YOA, pooled 006/022)

Study	Age strata	HZ/su N	HZ/su n	HZ/su T(year)	HZ/su n/T (per 1000)	Placebo N	Placebo n	Placebo T(year)	Placebo n/T (per 1000)	VE (%)	VE 95% CI LL	VE 95% CI UL
Pooled	≥50YOA**	13881	4	53171.5	0.1	14035	46	53545.0	0.9	91.22	75.95	97.70

Source: Adapted from 125614/0 Zoster-022 CSR Table 86, p. 493
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

Of the four cases of PHN in the HZ/su group, all occurred in the Zoster-022 study, two each in the 70 – 79 and ≥ 80 YOA strata.

Reviewer's comment – Overall PHN VE on subjects ≥ 50 YOA from the pooled analysis was a secondary endpoint that was "appropriately powered" (see Section 6.2.8). This analysis does not account for the co-variate of age on the incidence of PHN and considers all subjects in the mTVC, regardless of whether they reported HZ. CBER considers that the main effect of HZ/su on PHN is due to the reduction in incidence of HZ.

Occurrence of PHN in subjects ≥ 50 YOA with confirmed HZ over the entire study period – In subjects with a confirmed HZ episode, PHN was reported in 4 of 32 subjects (12.5% of subjects) in the HZ/su group and in 46 out of 477 subjects (9.6% of subjects) in the Placebo group. 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.

Reviewer's comment – No conclusions can be drawn regarding PHN VE on subjects ≥ 50 YOA with confirmed HZ across both studies.

Reduction in duration of severe 'worst' HZ/associated pain over the entire pain reporting period as measured by the ZBPI in subjects ≥ 70 YOA with confirmed HZ – In subjects with confirmed HZ, the mean duration (SD) of severe 'worst' HZ-associated pain over the entire pain reporting period was 32.1 days (43.80) in 20 subjects in the HZ/su group and 47.5 days (95.98) in 254 subjects in the Placebo group. The median duration of pain in the HZ/su and Placebo groups was 11.5 and 19.0 days respectively. The overall VE in terms of reduction of duration of severe 'worst' HZ-associated pain in subjects ≥ 70 YOA was 30.48% (95% CI: -10.52%, 56.27%), thus the Applicant was unable to conclude on this objective.

Reviewer's comment - See the statistical reviewer's comment about VE analyses conducted on subjects with confirmed HZ in Section 6.1.11.2.

7.1.11 Efficacy Conclusions
The re-estimation of HZ VE on subjects ≥ 70 YOA pooled across Zoster-006 and Zoster-022 was concordant with that of Zoster-022 and overall PHN VE on all subjects ≥ 70 YOA (regardless of the occurrence of HZ) pooled across Zoster-006 and Zoster-022 was demonstrated. CBER considers the benefit of HZ/su in preventing PHN to be attributable to VE against HZ.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Summary of Clinical Safety (SCS) and Integrated Summary of Safety (ISS) included results from a main pooled analysis of the two efficacy trials and a broader pooled analysis from additional clinical studies delineated in Section 8.2.1 below. Safety information from studies not included in the broader analysis were included in the individual study reports or synopses. The reviews of these studies can be found in Section 9.

The analysis of solicited symptoms will not be presented as the analyses performed in Zoster-006 and Zoster-022 adequately characterized the reactogenicity associated with HZ/su vaccination. Pooled analyses of unsolicited AEs and unsolicited AEs with a medically attended

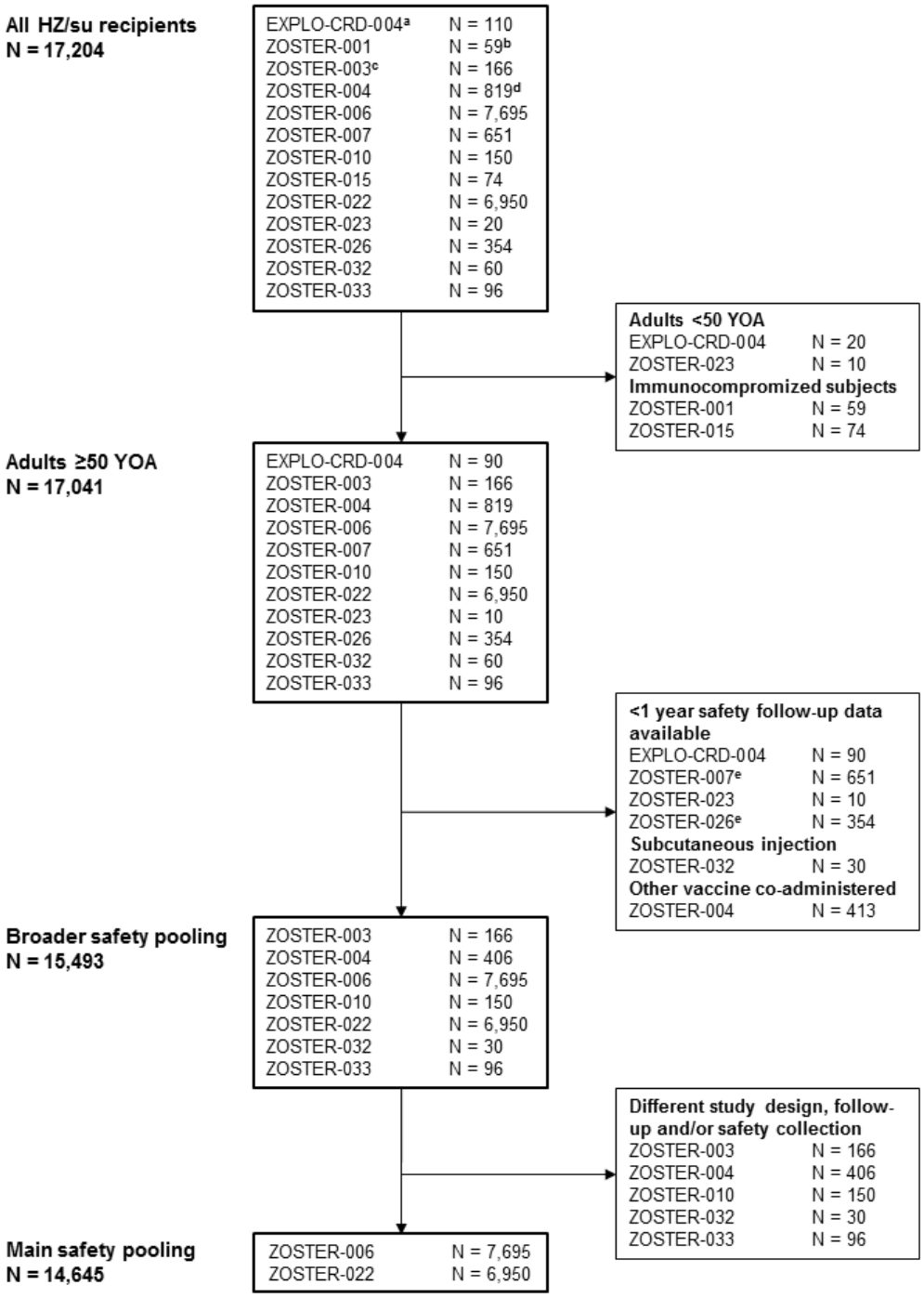
visit will be presented only on subjects in the TVC of the main pooling analysis. Analyses of SAEs, pIMDs and deaths will be presented for the subjects in the TVCs of the main and broader poolings, which included all subjects with at least one vaccine administration documented. Safety assessment methods for Zoster-006 and Zoster-022 (main pooling) were presented in Section 6.1.7; differences in reporting of safety data in the broad as compared to the main pooling are delineated in Section 8.3.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

A diagram of subjects with HZ/su exposure in studies included in the application is below. As can be seen from the diagram, the broader safety pooling includes 848 subjects who received HZ/su from studies other than Zoster-006 and Zoster-022. Of the subjects in the broader safety pooling analysis, 94.5% of those ≥ 50 YOA and 96.5% of those ≥ 70 YOA were enrolled in the Zoster-006 and Zoster-022 (main safety pooling).

Figure 3 – Subjects with HZ/su exposure



Source: 125614/0, SCS Figure1, p. 59

[a] ZOSTER-018 and -019 are extension studies of EXPLO-CRD-004 without HZ/su administration.

[b] Although 31 subjects in group gE/AS01$_B$2 were part of the TVC and received Placebo at Dose 1, only 29 of them received at least 1 dose of HZ/su at the subsequent doses.

[c] ZOSTER-011, -012, -013 and -024 are extension studies of ZOSTER-003 without HZ/su administration.

[d] Although 415 subjects were part of the TVC and received FLU-D-QIV at Dose 1, only 406 of them received at least 1 dose of HZ/su at the subsequent doses.

[e] 1-year safety follow-up data post last vaccination were not available at the time of the DLP used for the safety pooling.

The requirements for including a study in the broader pooling analysis was as follows: study completed at time of the data lock point used for the safety pooling (12-OCT-2015) with at least 1 year of safety follow-up post-vaccination and planned HZ/su formulation administration IM at M0 and M2.

Table 80 - Clinical studies with HZ/su included in the main and broader safety pooling analysis

Study	Age	Subjects in safety pooling analysis – HZ/su	Subjects in safety pooling analysis – Placebo	N.A.§ subjects exposed to HZ/su	US subjects exposed to HZ/su	Main pooling	Broader pooling	Years of SAE follow-up post last vaccination
006	≥ 50	7695	7710	1342	1027	x	x	4.4 years median/subject
022	≥ 70	6950	6950	1338	939	x	x	4.2 years median/subject
003* 011* 012* 013* 024*	≥ 60	166	-	-	-		x	1 month 10 months 22 months 34 months 70 months
004‡	≥ 50	406€	-	129€	68		x	12 months
010*	≥ 50	150	-	49	49	-	x	12 months
032¥	≥ 50	30					x	12 months
033θ	≥ 50	96		48	0		x	12 months
Total		15493	14660	2906	2083	14645 (HZ/su only)	15493 HZ/su Only)	

Source: Adapted from 125614, Summary of Clinical Safety, Table 2, p. 23
§ - NA – North America
* - HZ/su group only
‡ - HZ/su staggered group/control
¥ - HZ/su 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 HZ/su 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 HZ/su at subsequent doses
θ – subjects had a prior history of HZ

Some studies were submitted to the BLA but excluded from the broader pooling analysis. The rationale for their exclusion and the number of subjects in each study who received at least one dose of HZ/su in these excluded studies 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) – are part of CDP of HZ/su in IC adults and review of the datasets from these studies were not a part of this BLA review
- 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 the Applicant prepared the file.

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 and safety data from the subjects in the bulleted studies above are described separately in their respective reviews.

Reviewer's comment – As the majority of the subjects in the broader pooling were included in the main safety pooling, tabular demographic information will be presented on the main pooled analysis.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Demographics

The demographic composition of the main safety pooling analysis is provided in tabular format below.

Table 81 – Summary of demographic characteristics of the Main safety pooling (TVC)

Characteristics	Parameters or Categories	HZ/su N = 14645 Value or n	HZ/su N = 14645 %	Placebo N = 14660 Value or n	Placebo N = 14660 %
Age (years) at vaccination dose: 1	Mean	68.6	-	68.6	-
	SD	9.8	-	9.9	-
	Median	71.0	-	71.0	-
	Minimum	50	-	48	-
	Maximum	96	-	95	-
Gender	Female	8498	58.0	8547	58.3
	Male	6147	42.0	6113	41.7
Ethnicity	American Hispanic or Latino	1426	9.7	1434	9.8
	Not American Hispanic or Latino	13219	90.3	13226	90.2
Geographic Ancestry	African Heritage / African American	219	1.5	196	1.3
	American Indian or Alaskan Native	9	0.1	13	0.1
	Asian - Central/South Asian Heritage	8	0.1	11	0.1
	Asian - East Asian Heritage	2050	14.0	2045	13.9
	Asian - Japanese Heritage	609	4.2	609	4.2
	Asian - South East Asian Heritage	15	0.1	23	0.2
	Native Hawaiian or Other Pacific Islander	4	0.0	6	0.0
	White - Arabic / North African Heritage	83	0.6	88	0.6
	White - Caucasian / European Heritage	10795	73.7	10795	73.6
	Other	853	5.8	874	6.0

Source: Adapted from 125614/0 SCS Table 12, p. 65
N = total number of subjects
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = Standard Deviation
Note: this analysis is conducted on the pooled data from studies ZOSTER-006 and -022

Demographic characteristics of the TVC of the HZ/su group in the broader safety pooling were similar to that presented in the table above. The demographic profile for North American subjects was also reviewed. Compared to the main and broader pooling populations, median age and gender characteristics were similar, but with regard to ethnicity and geographic ancestry, a larger proportion of subjects were not American Hispanic or Latino (97.2%), a larger proportion were of White [Caucasian/European heritage (91.8%)] or African-American heritage (5.5%), while a smaller proportion were of East Asian heritage (0.2%).

Exposure

In the TVC of the main safety pooling, 95.0% of subjects randomized to receive HZ/su received two doses and 5.0% received one dose compared to 96% and 4.0% of subjects in the Placebo group who received two doses and one dose respectively.

Table 82 – Summary of exposure (TVC- main pooling)

Total number of doses received	**HZ/su N = 14645 n (%)**	**Placebo N = 14660 n (%)**
1	730 (5.0%)	581 (4.0%)
2	13915 (95.0%)	14079 (96.0%)
Any	14645 (100.0%)	14660 (100.0%)

Source: Adapted from 125614/0 Table 4 ISS, p. 45
n (%) = number (percentage) of subjects in each defined group

In the broader safety pooling (HZ/su recipients N = 15493) the proportion of subjects receiving two doses was comparable (95.1%) and was similar between age groups; 96.1% of subjects 50 – 69 YOA and 94.5% of subjects ≥ 70 YOA received two doses.

Reviewer's comment – The majority of subjects received a second dose in the clinical efficacy studies (main pooling) and additional studies (broader pooling).

8.2.3 Categorization of Adverse Events

Version 18.0 of the MedDRA coding dictionary Version 18.0 was used for all studies except Zoster-026, for which Version 18.1 was used.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Pooling of Zoster-006 and Zoster-022 safety data in the main pooling is supported by the similar study design, eligibility criteria (except for age), safety assessment methods, follow-up and duration of safety follow-up, conduction of the trials at the same sites, and randomization of subjects ≥ 70 YOA to Zoster-006 or Zoster-022 prior to randomization to a vaccination arm.

There were some differences in safety endpoints between studies in the main and broader pooling:

- SAEs were collected during the whole post-vaccination period in most studies, including fatal SAEs and SAEs with causal relationship to vaccination. In Zoster-006 and Zoster-022 (main pooling) all SAEs were recorded up to one year post last vaccination, while fatal SAEs and SAEs related to study participation and concurrent GSK medication/vaccination were collected during the whole post-vaccination period.
- The occurrence of SAEs during the 30-day post-vaccination period was analyzed separately in Zoster-006, Zoster-007, Zoster-022, Zoster-026, Zoster-032 and Zoster-033
- The occurrence of pIMDs during the 30-day post-vaccination period was analyzed separately in Zoster-006, Zoster-007, Zoster022, Zoster-026, Zoster-032 and Zoster-003. pIMDs were not recorded in Zoster-003.

- The occurrence of pIMDs during the whole post-vaccination follow-up period was recorded for studies with a safety follow-up extending beyond 1 year post last vaccination (Zoster-006, Zoster-022 and Zoster-024).

8.4 Safety Results

The main pooling analysis included 29,305 subjects from the TVCs of Zoster-006 and Zoster-022. Of these 29,305 subjects, 15,405 were in the TVC of Zoster-006 and 13,900 were in the TVC of Zoster-022; and 14,645 received HZ/su and 14,660 received Placebo. The number and proportion of subjects in the TVC of the main pooling who died during select time periods is below.

8.4.1 Deaths

Main pooling analysis – overall tabulation of fatal SAEs/deaths

The number and proportion of subjects in the TVC of the main pooling who died during select time periods is below.

Fatal SAEs were reported for 1,316 subjects in the TVC of the main pooling. Of these subjects, 634/14545 (4.3%) subjects in the HZ/su group and 682/14660 (4.7%) subjects in the Placebo group died during the whole post-vaccination period.

Table 83 - Main safety pooling analysis – number and percentage of subjects who died during select time periods (TVC – main pooling)

	HZ/su 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 125614/22 Table 91, p. 237
N = number of subjects with at least one administered dose
n (%) = number (percentage) reporting the symptom at least once

Reviewer's comment – The proportion of subjects who died in the TVC of the main pooling during the entire reporting period and at additional time windows were comparable between treatment groups overall and by age strata.

From first administered dose up to 30 days post last vaccination period, 6 subjects in the HZ/su and 8 subjects in the Placebo group died. The causes of death were typical of that expected of an elderly population, and only two specific PTs were reported more than once as a symptom (myocardial infarction reported by two subjects in the Placebo group and cerebrovascular accident, reported by two subjects in the Placebo group and one in the HZ/su group).

Reviewer's comment – There were few events of death reported from first dose up to 30 days post last vaccination. No imbalances were noted between treatment groups with regard to SAEs with fatal outcomes by PT and SOC from the first dose up to 30 days post last vaccination period.

From first dose up to 365 days post last vaccination period, 113 (0.8%) and 132 (0.9%) subjects who received HZ/su and Placebo respectively in the TVC of the main pooling analysis died. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each

treatment group during this time period were in the Cardiac disorders, Infections and infestations and Neoplasms SOCs. The most commonly reported fatal SAEs reported during this time period by PT were myocardial infarction [reported by 9 (0.1%) subjects in both groups], acute myocardial infarction [reported by 7 (0.0%) and 10 (0.1%) of subjects in the HZ/su and Placebo groups, respectively], pneumonia [reported by 11 (0.1%) and 4 (0.0%) of subjects in the HZ/su and Placebo groups, respectively], cardiac failure [reported by 4 (0.0%) and 11 (0.1%) of subjects in the HZ/su and Placebo groups, respectively] and cerebrovascular accident [reported by 7 (0.0%) and 6 (0.0%) of subjects in the HZ/su and Placebo groups, respectively].

From first vaccination through the whole post-vaccination follow-up period, 634 (4.3%) and 682 (4.7%) subjects who received HZ/su and Placebo respectively in the TVC of the main pooling analysis died. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Neoplasms and Cardiac disorders SOCs. The fatal events by PT reported with a frequency of > 0.2% of subjects in either treatment group were the following: cardiac failure (0.3% in the HZ/su group and 0.4% in the Placebo group), myocardial infarction (0.3% in both treatment groups), death (0.2% in the HZ/su group and 0.3% in the Placebo group) and pneumonia (0.3% in both treatment groups).

Fatal SAEs by age strata and region – For the main safety pooling, the proportions of subjects who died in each age stratum (50 – 69 and ≥ 70 YOA) were comparable between treatment groups for each time period, with the proportions of subjects who died in the older (≥ 70 YOA) age strata consistently higher during each time period than the proportions of subjects who died in the younger (50 – 69 YOA) age group. By region, the proportions of subjects who died from first dose to 30 days after last dose, from 30 days to 365 days after last dose and during the whole post-vaccination period were generally comparable between treatment groups. Additionally, no clinically significant differences were found between treatment groups in the proportions of North American subjects who died in the TVC of the main pooling analysis during the whole post-vaccination period, the 365-day post last vaccination period, or the 30-day post-vaccination period.

Reviewer's comment – No clinically significant difference was seen between treatment groups in the proportions of subjects with fatal SAEs overall, by SOC by PT or by age, or within regions during the whole post-vaccination period.

Fatal SAEs in the broader pooling analysis
In the broader safety pooling, no subjects died between the day of administration of Dose 1 to 30 days post last vaccination. From Dose 1 until 365 days following administration of the last vaccination, five subjects died; the most commonly reported PT recorded as a cause of death was coded as the PT of "death" (two subjects). An additional four subjects (nine subjects total) in the broader pooling died during whole post-vaccination period. The SOC with the most PTs recorded as a cause of death for this period was the Neoplasms SOC. The most commonly reported PT as a cause of death during this period was "death" (3 subjects reporting); other causes of death by PT were reported once and were typical of that expected of an older population. None of the deaths were considered causally related to study product.

Reviewer's comment – Following review, this reviewer agrees that the additional deaths do not appear causally related to the investigational product. No safety signals were identified regarding deaths that occurred in the broader pooled analysis.

8.4.2 Serious Adverse Events

SAEs in the main pooling analysis

The Applicant's SAE analysis was performed on all SAEs, including fatal SAEs. The numbers and proportions of subjects reporting at least one SAE by age group and overall during specified time periods is below.

Table 84 – Number and percentage of subjects reporting at least one SAE by time window (TVC - main pooling analysis)

	HZ/su 50 – 69 YOA N = 5887	Placebo 50 – 69 YOA N = 5887	HZ/su **≥ 70 YOA** N = 8758	Placebo **≥ 70 YOA** N = 8773	HZ/su All N = 14645	Placebo All N = 14660
Subjects with at least one serious adverse event from the first dose up to 30 days post last vaccination period	81 (1.4%)	79 (1.3%)	261 (3.0%)	248 (2.8%)	342 (2.3%)	327 (2.2%)
Subjects with at least one serious adverse event from the first dose up to 365 days post last vaccination period	367 (6.2%)	359 (6.1%)	1115 (12.7%)	1166 (13.3%)	1482 (10.1%)	1525 (10.4%)

Source: Adapted from 125614/25 Table 219, p. 420

From first administered dose up to 30 days post last vaccination SAEs were reported by 2.3% (342) and 2.2% (327) of subjects receiving HZ/su and Placebo, respectively. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Cardiac disorders, Infections and infestations, Neoplasms and Injury, poisoning and procedural complications SOCs. No single SAE by PT was reported by more than 0.1% of either treatment group. The most frequently reported SAEs by PT reported by at least 0.1% in the HZ/su group were atrial fibrillation [reported by 10 (0.1%) and 12 (0.1%) of subjects in the HZ/su and Placebo groups, respectively] and pneumonia [reported by 14 (0.1%) and 11 (0.1%) of subjects in the HZ/su and Placebo groups, respectively], osteoarthritis and coronary artery disease (reported by 0.1% of subjects in the HZ/su group). The proportions of subjects reporting SAEs during this time period increased with increasing age in both treatment groups; in the 50 – 59, 60 – 69 and 70 – 79 and ≥ 80 YOA groups, the proportions of subjects reporting SAEs during this time period in the HZ/su and Placebo groups, respectively, were 1.3% and 1.2%, 1.5% and 1.6%, 2.9% and 2.5% and 3.3% and 4.0%.

From first administered dose up to 365 days post last vaccination period, SAEs were reported by 10.1% (1482) of subjects in the HZ/su group and 10.4% (1525) of subjects in the Placebo group in the TVC of the main pooling. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Infections and infestations and Cardiac disorders SOCs; no clinically significant imbalances were observed between treatment groups for the proportions of subjects reporting SAEs by SOC. The most frequently reported SAEs were pneumonia, atrial fibrillation, myocardial infarction, cerebrovascular accident, coronary artery disease, cardiac failure and urinary tract infection. The number and proportion of subjects with these events in each treatment group is below; there were no clinically significant differences between treatment groups in the occurrence of these events.

Table 85 – Subjects reporting the most common SAEs overall and by PT from first administered dose up to 365 days post last vaccination period (TVC – main pooling)

	HZ/su N = 14645 n (%)	Placebo N = 14660 n (%)
Overall	1482 (10.1%)	1525 (10.4%)
Pneumonia	83 (0.6%)	66 (0.5%)
Atrial fibrillation	55 (0.4%)	58 (0.4%)
Myocardial infarction	40 (0.3%)	42 (0.3%)
Coronary artery disease	37 (0.3%)	38 (0.3%)
Cerebrovascular accident	39 (0.3%)	27 (0.2%)
Cardiac failure	34 (0.2%)	43 (0.3%)
Urinary tract infection	36 (0.2%)	27 (0.2%)

Source: Adapted from 125614/0 ISS Table 53, p. 470 – 495

One event by PT, supraventricular tachycardia, was reported significantly more frequently by the HZ/su recipients (6 subjects) as compared to Placebo recipients (0 subjects). See Section 8.5 for a discussion regarding cardiac arrhythmias and supraventricular tachyarrhythmias.

Reviewer's comment – The most commonly reported SAEs by PT were reported by comparable proportions of subjects in each treatment group from first dose up to 365 days post last vaccination period.

Although the difference was small, the numbers of subjects in the HZ/su group reporting the specific PTs of cerebrovascular accident and pneumonia was higher in the HZ/su group as compared to the Placebo group. CBER analyzed the proportions of subjects in each treatment group reporting MAEs at select time periods in the narrow CNS vascular disorders supraordinate SMQ and sub-SMQs as well as the proportions reporting MAEs contained in the Higher level term (HLT) of Lower respiratory tract and lung infections which contains the PT of pneumonia (as there is no SMQ for pneumonia). Evaluation of MAEs was selected as some reports of transient ischemic attacks (included in the CNS vascular disorders supraordinate SMQ and Ischemic CNS vascular disorders sub-SMQ) and pneumonia in the dataset were not recorded as SAEs.

Table 86 – Proportions of subjects reporting MAEs during the 30-day post-vaccination period and from M0 – M8 (D0 – D244) in the CNS Vascular disorders SMQ and the Lower Respiratory Tract and Lung Infections Higher Level Term grouping (TVC – main pooling)

MedDRA search terms	HZ/su N = 14645	Placebo N = 14660
CNS vascular disorders SMQ (Level1) – 30-day post vaccination period	23 (0.16%)	25 (0.17%)
Ischemic CNS vascular disorders (Level 3) – 30-day post vaccination period	18 (0.12%)	23 (0.16%)
Hemorrhagic CNS vascular disorders (Level 3) – 30-day post vaccination period	10 (0.07%)	13 (0.09%)
CNS vascular disorders SMQ (Level 1) – D0 to D244	92 (0.63%)	90 (0.61%)
Ischemic CNS vascular disorders (Level 3) – D0 to D244	80 (0.55%)	73 (0.50%)
Hemorrhagic CNS vascular disorders (Level 3) – D0 to D244	37 (0.25%)	34 (0.23%)
Lower respiratory tract and lung infections (HLT) – 30-day post vaccination period	148 (1.0%)	139 (1.0%)
Lower respiratory tract and lung infections (HLT) – D0 to D244	429 (2.3%)	428 (2.3%)

Source: CBER analysis derived from ISS Table 44, p. 316 and Table 46, p. 366

Reviewer's comment – There was no clinically significant differences between treatment groups for the proportions of subjects reporting events in the narrow CNS Vascular disorders SMQ and sub-SMQs and Lower Respiratory tract and lung infections HLT during the 30-day post-vaccination period or from M0 to M8.

By age group (50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA), the proportions of subjects reporting SAEs from first dose to 365-day post vaccination in the HZ/su group and Placebo groups, respectively, were 5.6% and 5.3%, 7.2% and 7.4%, 11.2% and 11.8%, and 18.0% and 18.5%.

SAEs by region - The proportions of subjects reporting at least one SAE during the time periods from first dose to 30 days and 365 days post last vaccination period were relatively consistent between regions and within regions, similar between treatment groups.

SAEs in North American subjects
From first dose up to 30 days post last vaccination, at least one SAE was reported by 57 (2.1%) and 62 (2.3%) subjects in the HZ/su and Placebo groups, respectively. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each treatment group during this time period was in the Cardiac disorders SOC.

From first dose to 365 days post last vaccination at least one SAE was reported by 289 (10.8%) and 301 (11.2%) subjects in the HZ/su and Placebo groups, respectively. The most commonly reported SAEs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Infections and infestations and Cardiac disorders SOC.

Reviewer's comment – There were no clinically significant differences between treatment groups in the proportions of North American subjects reporting at least one SAE during the 30-day post last vaccination time point overall or 365-day post last vaccination time point, or for the proportions of subjects reporting SAEs by PT and SOC during these time periods. The proportions of North American subjects reporting at least one SAE during these time periods were also consistent with that of the TVC of the main pooling, as were the types of events reported by PT.

SAEs in the broader pooling analysis
From first dose up to 30 days after last vaccination, 24/848 (2.8%) of subjects in the broader pooling (excluding subjects in Zoster-006 and Zoster-022) reported at least one SAE. The SOC with the most subjects reporting events was the Gastrointestinal disorders SOC (7 subjects reporting) and the most commonly reported events by PT were atrial fibrillation, ulcerative colitis and hypertension (reported by 2 subjects each)

From first dose up to 1 year after last vaccination, an additional 71 of 848 subjects (7.1%) in the broader pooling (excluding subjects in Zoster-006 and Zoster-022) reported SAEs.

Of these subjects, 71 reported 99 SAEs within 365 days of last vaccination. The SOC with the greatest number of events was the Gastrointestinal disorders SOC with 15 subjects reporting, and the Cardiac disorders SOC with 12 subjects reporting. The most commonly reported events by PT overall were atrial fibrillation, osteoarthritis and hypertension, each reported by 3 subjects. The majority of events were reported by subjects ≥ 70 YOA.

Reviewer's comment -There were no unusual patterns or clustering of SAEs temporally associated with vaccination occurring in subjects in the broader pooling who were not in the

main pooling, and the events were typical of that expected in an older population of subjects and similar to those in main pooled analysis.

Related SAEs

During the whole post-vaccination follow-up period, 15 (0.1%) HZ/su recipients (3 in Zoster-006 and 12 in Zoster-022) and 15 (0.1%) Placebo recipients reported SAEs that were considered related to study product by the investigators. The Applicant did not consider any of these events related to vaccination.

Two events judged related to HZ/su by the investigators were considered by CBER as likely related to HZ/su administration due to temporal association with vaccination, biologic plausibility and no satisfactory alternative etiology. These events are as follows:

- Lymphadenitis – An 82 YO male reported axillary lymphadenopathy temporally associated with both vaccinations which resulted in surgical resection to rule out a malignant process.
- IS pain, IS erythema, chills, pyrexia – A 73 YO female reported fever up to 40˚ C (104˚ F), and moderate IS erythema, chills and IS pain one day after receipt of Dose 1 of HZ/su. No treatment was necessary and the reported events lasted up to three days.

The following additional SAEs were judged related to HZ/su by the investigators. For some of these events, CBER could not completely rule out the potential for causal association, however, there were either alternative etiologies for the event, no clinically significant imbalance in the incidence of the events between vaccination groups for a similar time period or there was lack of temporal association or clustering of like events associated with vaccination.

- Acute myocardial infarction (MI) – A 75 YO male had an acute MI within 24 hours after vaccination. The subject did not receive a second vaccination. *CBER assessment – Causality for this particular event cannot be ruled out, but this subject had a potential alternative etiology for his SAE (occlusion of the left anterior descending artery on angiography). No imbalances were noted between treatment groups for the proportions of subjects in the main pooling reporting events contained in the narrow SMQ of ischemic heart disease and narrow sub-SMQ of ischemic heart disease – MI as unsolicited AEs or MAEs within 30 days post-vaccination.*Herpes zoster oticus – A 72 YO male reported herpes zoster oticus one day after receipt of Dose 1. *CBER assessment – This event was not likely due to receipt of HZ/su, given the natural history of HZ with regard to the duration of prodromal symptoms prior to HZ rash onset.*
- Ulcerative colitis (serious pIMD) – A 75 YO male developed UC beginning 8 days after Dose 2; it is not clear from the two narratives provided whether there was a pre-existing history of inflammatory bowel disease. *CBER assessment – While this event was temporally associated with vaccination, subjects with IBD experience periodic exacerbations and remissions. CBER did not detect a difference between treatment groups in the proportions of subjects in the main pooling reporting unsolicited AEs included in the HLT "colitis (excluding infective)" during the 30 –day post vaccination period or as MAEs from M0 – M8.*
- Erysipelas – A 72 YO female was diagnosed with possible erysipelas 6 days after Dose 1. Erythema nodosum was mentioned in the narrative. *CBER assessment – It is unclear from the narrative as to the final diagnosis of this event. It is plausible that the event of erysipelas could have occurred due to the vaccination procedure and not the product. It is also biologically plausible that erythema nodosum, a panniculitis thought to be due to a delayed type hypersensitivity reaction associated with a variety of antigens (Schwartz, 2007), could be associated with receipt of HZ/su. However, as erythema nodosum is*

associated with many other conditions, causality cannot be ascribed. There were no other reports of erythema nodosum temporally associated with HZ/su vaccination.

- Eczema (serious pIMD) – An 86 YO male with a past medical history of eczema was diagnosed with an exacerbation of eczema 3 days after administration of Dose 1. *CBER assessment – CBER did not detect imbalances between treatment groups in the proportions of subjects in the main pooling reporting serious and non-serious exacerbations of eczema reported as AEs within the 30-day post-vaccination period or reported as MAES during M0 – M8.*
- Musculoskeletal chest pain – A 55 YO male reported pain in the left arm and on the left side of the chest and feeling feverish one day after administration of HZ/su Dose 1 in the left arm. *CBER assessment – This event was possibly associated with HZ/su administration but had potential alternative etiologies such as administration of infliximab on the day of the SAE.*
- Immune thrombocytopenic purpura (serious pIMD) – A 54 YO female subject with a prior medical history of idiopathic thrombocytopenia diagnosed approximately 11 months prior to Dose 1 developed an exacerbation of immune thrombocytopenia 108 days after Dose 2. *CBER assessment – The day of onset of the subject's thrombocytopenia is unclear, as she reported having symptoms consistent with thrombocytopenia (bleeding gingiva and bruising) for 6 months prior to the full physical. Therefore, a causal association with vaccination cannot be ruled out. See Section 8.5 for an accounting of immune-mediated thrombocytopenia by treatment group.*
- Pancreatitis acute (serious pIMD as judged by investigator) – An 83 YO female subject reported acute pancreatitis 34 days after Dose 2 which resolved 71 days after onset. The subject did not have any risk factors for pancreatitis. The PI considered this a pIMD due to lack of evidence of infection. The Applicant did not consider this a pIMD. *CBER assessment – CBER did not detect a difference between treatment groups in the proportions of subjects experiencing the PTs of "pancreatitis" or "pancreatitis acute" reported by subjects in the main pooling as an unsolicited AE within 30 days of vaccination or MAE from M0 – M8. There is also a lack of clustering of similar events temporally associated with vaccination of HZ/su.*
- Allergic granulomatous angiitis (serious pIMD) – An 80 YO male developed respiratory symptoms typical of the allergic phase of this condition beginning 320 days after Dose 2. Results of subsequent electromyogram and muscle biopsy led to a diagnosis of allergic granulomatous angiitis (Churg-Strauss syndrome or eosinophilic granulomatosis with polyangiitis), an ANCA associated vasculitis. *CBER assessment – Allergic granulomatous angiitis is an uncommon cause of vasculitis in people over 65 years of age; the mean age at diagnosis is 40 years. One Japanese study estimated the prevalence at 17.8/1,000,000 (Sada, 2014). Causality cannot be determined, but the time period from vaccination to onset makes a causal relationship less likely. No other granulomatous angiopathies were reported in the main pooling of the HZ/SU group.*
- Arthritis bacterial – A 73 YO female developed pyogenic arthritis due to *H. influenzae* in the L shoulder region 67 days after Dose 2. *CBER assessment – The event is likely not associated with receipt of HZ/su.*
- Neutropenic sepsis and acute myeloid leukemia – A ≥ 90 YO male with a concurrent medical history of stable immune thrombocytopenic purpura since February 2000) was found to be pancytopenic 72 days after receipt of his first and only dose of HZ/su (on 02-MAR-2011) and was diagnosed with acute myeloid leukemia shortly thereafter, and died (b) (6) days later, (b) (6) after presenting with neutropenic sepsis. *CBER assessment – The SAE of neutropenic sepsis is likely due to the subjects' current medical condition and therapies. CBER evaluation of the supraordinate Hematopoietic cytopenias narrow*

SMQ and narrow sub-SMQ of hematopoietic leukopenia and the Toxic-septic shock conditions SMQ reported as medically attended events by subjects in the main pooling during M0 – M8 did not reveal clinically imbalances between treatment groups.

- Guillain-Barré syndrome (GBS) (serious pIMD) – An 81 YO male reported worsening of weakness, slurred speech and dysphagia 181 days after Dose 2. The event as assessed Brighton Level 4 of Diagnostic Certainty (insufficient evidence to meet case definition) by the Applicant. *CBER assessment – Onset of this SAE was relatively distant from vaccination. See the assessment of Guillain-Barré and acute polyneuropathies in Section 8.5.*
- Nervous system disorder – A 65 YO male with recurrent pre-syncope reported a "nervous system disorder (cerebral seizures)", syncope and a cranial contusion on 28-MAR-2011, 32 days after Dose 2 of HZ/su. EEG showed paroxysmal activity/irritative focus in the left temporal region. *CBER assessment – This subject had episodes of pre-syncope which pre-dated vaccination, which may have been an alternative presentation of focal seizures. Causality with regard to HZ/su cannot be determined. During the 30-day post vaccination period, eight subjects in the HZ/su group and 1 in the placebo group of the main pooling reported unsolicited events in the narrow SMQ of convulsions. See Section 8.5.*

8.4.4 Common Adverse Events

Unsolicited AEs in the main pooling analysis

The following table contains the proportions of subjects in the TVC of the main pooling by treatment group overall and by age group who reported unsolicited AEs within the 30-day post vaccination period.

Table 87 - Proportions of subjects reporting at least one unsolicited (serious or non-serious symptom within the 30-day post-vaccination period (TVC – Main pooling analysis)

	HZ/su 50 – 69 N = 5887 n (%)	HZ/su **≥ 70** N = 8758 n (%)	Placebo 50 – 69 N = 5887 n (%)	Placebo **≥ 70** N = 8773 n (%)	Overall HZ/su N = 14645 n (%)	Overall Placebo N = 14660 n (%)
Subjects reporting occurrence of at least one unsolicited symptom	3027 (51.4%)	4366 (49.9%)	1957 (33.2%)	2732 (31.1%)	7393 (50.5%)	4689 (32.0%)

Source: Adapted from 125614/0 ISS Tables 98 (p. 1537 - 1581) and 212 (p. 3004 – 3050)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

The proportion of subjects reporting at least one unsolicited AE in the 30-day post-vaccination period was higher in the HZ/su group due to the reporting of reactogenicity events in subjects who had not been randomized to the 7-day diary card subset.

The events by PT most commonly reported as unsolicited AEs during the 30-day post vaccination were those that had been included on the 7-day diary card; these were reported more frequently in the HZ/su group as compared to the Placebo group as follows: IS pain (23.0% vs. 1.7%), IS erythema (9.7% vs. 0.3%), pyrexia/fever (7.1% vs. 0.5%), IS swelling (6.9% vs. 0.2%), fatigue (3.6% vs. 1.0%), chills/shivering (3.5% vs. 0.2%), headache (6.5% vs. 3.0%), myalgia (3.3% vs. 0.7%). Of note, while nausea, vomiting and diarrhea were included on

the 7-day diary card as "GI symptoms", nausea, but not diarrhea or vomiting, was reported more frequently by subjects in the HZ/su group (1.35%) than the Placebo group (0.47%). The table below includes the PTs not appearing on the 7-day diary card for which the proportion of subjects reporting the events was higher in the HZ/su group and reported with a frequency of ≥ 1.0%.

Table 88 – Relative risk (RR) between groups of subject reporting the occurrence of unsolicited AEs during the 30-day post-vaccination period [incidence ≥ 1.0% of HZ/su subjects, RR and LB of RR > 1.0 (HZ/su over Placebo)] (TVC – main pooling analysis)

	HZ/su N = 14645 n (%)	Placebo N = 14660 n (%)
IS pruritus	317 (2.2%)	35 (0.2%)
Malaise	254 (1.7%)	43 (0.3%)
Pain	204 (1.4%)	34 (0.2%)
IS warmth	149 (1.0%)	5 (0.0%)
Dizziness	182 (1.2%)	113 (0.8%)
Upper respiratory tract infection	231 (1.6%)	182 (1.2%)
Arthralgia	252 (1.7%)	171 (1.2%)
Pain in extremity	155 (1.1%)	107 (0.7%)

Source: Adapted from 125614/0 SCS Table 25, p. 99
At least one symptom = at least one symptom reported (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

The following non-localized unsolicited events by PT occurred in less than 1.0% of subjects in the HZ/su group, but were reported by higher proportions of subjects in the HZ/su group; flushing, feeling hot, feeling cold, decreased appetite, asthenia, influenza like illness, lethargy, somnolence, gout, insomnia, hyperhidrosis, dyslipidemia, dysgeusia, respiratory tract infection, asthenopia, bone pain, and upper respiratory tract infection.

Reviewer's comment – Some of these events (e.g., dizziness, arthralgia, malaise) were biologically plausible constitutional symptoms consistent with general reactogenicity. See Section 8.5 for a discussion regarding the PTs of respiratory infection, upper respiratory infection and dyslipidemia.

During the 30-day post-vaccination period, gout was reported by 26 and 7 subjects in the HZ/su and Placebo groups respectively, and gouty arthritis reported by 1 subject in each group.

For the HZ/su and Placebo groups respectively, in the main safety pooling analysis, 18.8% and 18.9% of subjects had an unsolicited AE within the 30-day post-vaccination period that was medically attended. The proportions of subjects within each age group (50 – 69 YOA and ≥ 70 YOA) with medically attended visits during this time period were comparable between treatment groups.

Unsolicited AEs during the 30 day post-vaccination period in the North American cohort
The unsolicited AEs reported by more than ≥ 1.0% of the North American cohort HZ/su recipients during the 30-day post-vaccination period were similar to that reported by the TVC in the table above.

8.4.8 Adverse Events of Special Interest

pIMDs in the main pooling analysis

The numbers and proportions of subjects by age group in each treatment group in the TVC of the main pooling analysis who reported a new onset or exacerbation of a pIMD at selected time points are presented in the table below.

Table 89 - Number and percentage of subjects reporting the occurrence of a pIMD by time window (TVC - main pooling analysis)

	HZ/su 50 – 69 N = 5887 n (%)	HZ/su **≥ 70** N = 8758 n (%)	Placebo 50 – 69 N = 5887 n (%)	Placebo **≥ 70** N = 8773 n (%)	Overall HZ/su 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 125614/25. Annex 3, Table 321, p. 120

From first administered dose up to 30 days post last vaccination pIMDs were reported by 0.2% of subjects in both treatment groups. The most commonly reported pIMDs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Musculoskeletal and connective tissue disorders SOC. The most commonly reported events by PT were PMR and rheumatoid arthritis, each reported by 3 subjects in the HZ/su group and 4 subjects in the Placebo group.

From first administered dose up to 365 days post last vaccination, pIMDs were reported for 0.6% and 0.7% of subjects in the HZ/su and Placebo groups, respectively. The most commonly reported pIMDs by SOC, reported by comparable proportions of subjects in each treatment group during this time period, were in the Musculoskeletal and connective tissue disorders SOC. Of the 68 discrete PTs reported, the most commonly reported events were PMR [reported by 17 (0.1%) and 12 subjects (0.1%) in the HZ/su and Placebo groups, respectively], rheumatoid arthritis [reported by 7 (0.0%) and 15 (0.1%) subjects in the HZ/su and Placebo groups, respectively], psoriasis [reported by 8 (0.1%) subjects in each group] and autoimmune thyroiditis [reported by 7 (0.0%) and 6 (0.0%) subjects in the HZ/su and Placebo groups, respectively]. However, no single PT was reported by more than 0.1% of subjects in either group.

Reviewer's comment – In the 365-day post last vaccination time period, there were three cases of Giant cell/temporal arteritis (14, 204 and 235 days after second vaccination) reported in the HZ/su group and none in the Placebo group. Overall, there were 6 and 3 cases of Giant cell/temporal arteritis (9 subjects total) collected as pIMDs in the HZ/su and Placebo groups respectively during the whole post-vaccination time period. VZV antigens have been identified in some pathologically confirmed cases of Giant cell/temporal arteritis (Gilden, 2015).

From first vaccination through the whole post-vaccination follow-up period, pIMDs were reported for 179 (1.2%) and 202 (1.4%) of subjects of HZ/su and placebo recipients respectively in the TVC of the main pooling analysis. The most commonly reported pIMDs by SOC, reported by comparable proportions of subjects in each treatment group during this time period were in the Musculoskeletal and connective tissue disorders SOC. Of the 95 discrete PTs reported, two

discrete PTs, PMR (reported by 0.2% of subjects in both treatment groups) and rheumatoid arthritis (reported by 0.1% of subjects in the HZ/su group and 0.2% of subjects in the Placebo group), were reported by more than 0.1% of subjects in either treatment group. Another commonly reported event was psoriasis [reported by 15 (0.1%) and 18 (0.1%) subjects in the HZ/su and Placebo groups, respectively].

Similar proportions of pIMDs by age group (50 – 69 and ≥ 70 YOA) were reported for the time points in the tabulations above.

Reviewer's comment –The Applicant noted that "about half of the pIMDs had a time to onset longer than 1 year post last vaccination", which was confirmed by CBER dataset review. CBER analysis of the proportions of subjects reporting pIMDs by year (see below) indicated that proportions of subjects reporting pIMDs were highest in the first year post-vaccination, and were lower, but consistent, in subsequent years. One interpretation of this finding may be that pIMD reporting may have been less consistent after the first year post-vaccination.

Table 90 – Incidence of pIMDs by year (TVC – Main pooling analysis)

Time relative to last dose	HZ/su n	HZ/su N	HZ/su Time (year)	HZ/su n/N (%)	HZ/su n/time per 1000 (95% CI)	Placebo n	Placebo N	Placebo Time (year)	Placebo n/N (%)	Placebo n/time per 1000 (95% CI)
Year 1	80	14645	14181	0.55	5.64 (4.47, 7.02)	98	14660	14235	0.67	6.88 (5.59, 8.39)
Year 2	41	14040	13780	0.29	2.98 (2.14, 4.04)	44	14110	13821	0.31	3.18 (2.31, 4.27)
Year 3	36	13656	13385	0.26	2.69 (1.88, 3.72)	37	13676	13433	0.27	2.75 (1.94, 3.80)
Year 4	18	13232	12851	0.14	1.40 (0.83, 2.21)	28	13269	12891	0.21	2.17 (1.44, 3.14)

Source: CBER analysis of 125614/0 datasets
n = number reporting
N = number of subjects that had follow-up at least up to the indicated year

Related pIMDs (main pooling)

pIMDs considered related to vaccination were reported by 16 (0.1%) of the subjects in the HZ/su group and 18 (0.1%) of subjects in the Placebo group. Serious pIMDs were reviewed in the SAE section above. The non-serious pIMDs judged related to HZ/su vaccination by the investigator are presented below; none were considered related by the Applicant.

- Rheumatoid arthritis – A 70 YO female was diagnosed with rheumatoid arthritis and fatigue one day after Dose 2. The narrative lacks information about the time of onset and nature of symptoms. *CBER assessment – The time between vaccination and diagnosis is unusually short, making causal association less likely. There was no difference was noted between treatment groups for the proportions of subjects reporting rheumatoid arthritis in the main pooling during select time periods relative to vaccination and overall.*
- Reactive arthritis – A 73 YO female with a past medical history of an unspecified inflammatory reaction in the year prior to vaccination (fever of unknown origin with elevated complement components 3 and 4) reported reactive arthritis 2 years and 194 day after Dose 2. *CBER assessment – The long delay of onset post-vaccination makes causal association unlikely.*
- Psoriasis (exacerbation) – A 72 YO male with a 50+ year history of psoriasis with exacerbations triggered by stress, sun and salt reported psoriasis four days after Dose 1. *CBER assessment – The narrative lacks information about the presence of known triggers at the time of this subjects' psoriasis. This event appears temporally associated with vaccination and causal association cannot be ruled out. No difference was noted*

between treatment groups for the proportions of subjects in the main pooling reporting psoriasis during select time periods relative to vaccination and overall.

- Psoriasis (exacerbation) – A 76 YO male with a prior history of exacerbation of psoriasis after influenza vaccine reported a mild exacerbation of psoriasis 23 days after Dose 2 (location of exacerbation was not specified). The subject refused treatment. The rash was diagnosed as Koebner's phenomenon by a dermatologist. *CBER assessment – This event was temporally associated with vaccination and causal association cannot be ruled out. No difference was noted between treatment groups for the proportions of subjects in the main pooling reporting psoriasis during select time periods relative to vaccination and overall*.
- Myasthenic syndrome – A 65 YO male with a history of hyperthyroidism reported right lid ptosis 47 days after Dose 1. No other symptoms were reported. Laboratory testing and electromyography confirmed the diagnosis of myasthenia gravis. *CBER assessment – This event was temporally associated with vaccination and although causal association cannot be ruled out, no other reports of myasthenic events were reported in the HZ/su group in temporal association with vaccination. There were four events in the Placebo group, only one in the first year post-vaccination.*
- Thrombocytopenia – A 68 YO female with no pertinent medical history was noted to have mild thrombocytopenia on routine blood examination 105 days after Dose 2. Further examination showed immune thrombocytopenia with a positive result for oligo-specific antibodies. Bone marrow biopsy was not performed and immunosuppressive therapy was not indicated. *CBER assessment – It is unclear as to whether this event was temporally associated with vaccination since the thrombocytopenia was detected on routine exam and there were no associated symptoms reported, the recorded date of onset may not be the actual date of onset. See Section 8.5 for the reports of immune mediated thrombocytopenia by vaccination group.*
- Exfoliative dermatitis – A 64 YO female with hypothyroidism reported exfoliative dermatitis "10 x 5 cm on the lower medial area of left brachium" four days after Dose 1. Biopsy revealed non-specific lymphocyte-dominant perivascular dermatitis. The subject was treated with mometasone furoate and the event resolved 745 days after onset. The subject did not receive Dose 2. *CBER assessment – This event was temporally associated with vaccination. No other events of exfoliative dermatitis were reported in either vaccination group.*
- Polymyalgia rheumatica – A 66 YO male with no significant medical history reported polymyalgia rheumatica approximately nine months after Dose 2. Treatment included prednisolone. The event resolved 814 days after onset. *CBER assessment – The event did not occur temporally associated with vaccination and no difference was noted between vaccination groups for the proportions of subjects reporting psoriasis in the main pooling during select time periods relative to vaccination and overall.*
- Rheumatoid arthritis – A 68 YO female with many co-morbid conditions including a 37 year history of rheumatoid arthritis with exacerbations three times per year, reported aggravated rheumatoid arthritis 13 days after Dose 1. After treatment with steroids, the event resolved 9 days after onset. The subject received a second dose without incident. *CBER assessment – This event was temporally associated with vaccination, but the subject had a history of exacerbations of RA and received the second dose without incident. Additionally, no difference was noted between vaccination groups for the proportions of subjects reporting psoriasis in the main pooling during select time periods relative to vaccination and overall.*
- Alopecia areata – A 68 YO female with a non-contributory medical history except for enalapril use reported alopecia areata on her head 16 days after Dose 2. Treatment

included biotin and minoxidil and the event resolved 196 days after onset. *CBER assessment – This event was temporally associated with HZ/SU vaccination and causality cannot be ruled out. One other event of alopecia areata was reported in the Placebo group more than 3 years after Dose 2. Alopecia is listed as an adverse reaction to enalapril in the PI.*

- Hypersensitivity vasculitis – A 56 YO male with a concurrent medical history of eczema and hepatitis B reported right thigh purpuric rash 11 days after Dose 2. A skin biopsy was performed which showed vasculitis (suspected leukocytoclastic vasculitis. The subject was treated with paracetamol, cephalexin, and chloramphenicol and the event resolved 9 days after onset. The Applicant noted that while the event was temporally associated with vaccination, alternative etiologies existed for the event. *CBER assessment – The event was temporally associated with HZ/su vaccination and causality cannot be ruled out. However, there were no other reports of leukocytoclastic vasculitis in the main pooling temporally associated with vaccination, nor did the subject report a similar event in temporal association with Dose 1. There did not appear to be a difference between vaccination groups for the proportions of subjects in the main pooling reporting pIMDs in the Vascular disorders SOC during select time periods relative to vaccination or overall and CBER analysis did not detect a difference between vaccination groups for the proportions of subjects in the main pooling reporting events in the narrow SMQ of vasculitis captured as a MAE from M0 – M8.*

pIMDs in North American subjects

Similar frequencies of subjects in the vaccination groups reported the occurrence of pIMDs during the 30 days post last vaccination, 365 days post last vaccination and whole post-vaccination period as indicated below.

Table 91 - Subjects reporting the occurrence of pIMDs during select time periods (TVC – main pooling of North American subjects)

	HZ/su N = 2680	Placebo N = 2683
Subjects with ≥ 1 pIMD reported during the whole post-vaccination follow-up period	32 (1.2%)	34 (1.3%)
Subjects with ≥ 1 pIMD reported from first vaccination up to 365 days post last vaccination	17 (0.6%)	20 (0.7%)
Subjects with ≥ 1 pIMD reported from first vaccination up to 30 days post last vaccination	3 (0.1%)	6 (0.2%)

Source: Adapted from 125614/25, Annex 3, Table 339, p. 150
n/% = number/percentage of subjects reporting symptom at least once during the time period
Note: this analysis is conducted on the pooled data from studies ZOSTER-006 and -022 for North American subjects

The SOC with the most subjects reporting pIMDs for each time period was the Musculoskeletal and connective tissue disorders SOC and the most commonly reported event by PT was PMR during the 30-day post last vaccination period, PMR and autoimmune thyroiditis during the 365-day post last vaccination period, and PMR, autoimmune thyroiditis and rheumatoid arthritis during the whole post-vaccination period.

Reviewer's comment - No overall imbalances were noted between vaccination groups in terms of the proportions of subjects reporting pIMDs by PT or SOC during the specified time periods. See Section 8.5 for a discussion of discrete pIMDs of interest.

pIMDs in the broader pooling analysis

Five additional HZ/su recipients reported pIMDs in the broader pooling analysis during the whole post-vaccination period. Three subjects reported events within 365 days following the last vaccination; two subjects reported exacerbations of ulcerative colitis, occurring 5 days after

Dose 2 and 27 days after Dose 1 and one subject reported vocal cord paralysis 268 days after the last dose of study product. The other 3 events (exacerbation of UC, PMR and psoriasis) occurred more than two years after last vaccination. None were considered related to vaccination by the investigator or Applicant.

Reviewer's comment – No difference was detected between treatment groups in the proportions of subjects in the TVC of the main pooling reporting events during the 30-day post-vaccination period in the HLT "colitis (excluding infective)" which contains the specific PT ulcerative colitis.

The overall proportions of subjects reporting pIMDs during different time periods, as well the proportions of subjects reporting the most commonly reported pIMDs during different time periods appear comparable between treatment groups. Since pIMDs are uncommon events, a larger sample size might be required to detect a small effect size if a true difference existed between treatment groups.

8.5 Additional Safety Evaluations

CBER conducted exploratory descriptive and comparative analyses of the proportions of subjects in the TVC of the main pooling (HZ/su N = 14645, Placebo N = 14660) reporting AEs. These data were analyzed using MedDRA version 18.0. It should be noted that Zoster-006 and Zoster-022 were not powered for the evaluation of safety, and the analyses are not adjusted for the multiplicity of safety endpoints. Additionally, as adverse event data are often collected with no pre-determined case definitions, there may be issues with regard to misclassification, ascertainment and other possible biases. For the purposes of these analyses the M0 – M8 time period included events from Day 0 up to Day 244 and the M0 – M14 time period included events from Day 0 up to Day 427.

Some of the most common AEs by PT reported in the study were contained in the SMQs of Ischemic heart disease (and the sub-SMQ of Ischemic heart disease – MI), Cardiac failure, Central nervous system vascular disorders (and sub-SMQs), Cardiac arrhythmias (and sub-SMQs) and Cardiomyopathy. CBER analysis included evaluation of the proportions of subjects reporting PTs in these narrow SMQs as unsolicited AEs during the 30-day post-vaccination period, as MAEs from M0 – M8 and as SAEs from M0 – M14. No clinically significant difference was noted between treatment groups for the proportions of subjects who reported events by these SMQs during the specified time periods.

Inclusion of the events below does not imply causal association with HZ/su; 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.

Dyslipidemia - The proportions of subjects reporting dyslipidemia during the 30-day post-vaccination period was higher in the HZ/su as compared to the Placebo group. However, there was no difference between treatment groups for the proportions of subjects who reported the specific PTs of hyperlipidemia, hypercholesterolemia, or hypertriglyceridemia, nor were there differences between treatment groups for the proportions of subject reporting events within the 30-day post-vaccination period in the MedDRA Higher Level Group Term (HLGT) of Lipid metabolism disorders, which contains PTs including hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia and investigations such as lipids increased, blood cholesterol increased and blood triglycerides increased.

Reviewer's comment – When considering the HLGT of MedDRA terminology that is used to code lipid metabolism disorders, there did not appear to be excess risk of dyslipidemias for HZ/su recipients.

Gout
During the 30-day post-vaccination period, gout was reported by 26 and 7 subjects in the HZ/su and Placebo groups respectively, and gouty arthritis reported by 1 subject in each group. Of the subjects reporting gout in that time period, 19 in the HZ/su group and 3 in the Placebo group were reporting gout for the first time.

Reviewer's comment – The proposed pharmacovigilance plan addresses the occurrence of gout with routine pharmacovigilance, enhanced pharmacovigilance and by inclusion in a proposed active surveillance study.

Osteonecrosis - There were five subjects in the HZ/su group who reported six events of osteonecrosis during the first year post-vaccination. No cases of osteonecrosis were reported in the Placebo group. The cases occurred 4 days after Dose 1, and 72, 95, 132 (two events in one subject) and 178 days after Dose 2.

Reviewer's comment – CBER review of the narratives indicated that all but one of the subjects may have had symptoms and/or a history of osteonecrosis prior to vaccination.

Optic ischemic neuropathy (OIN) – OIN is a cause of visual impairment or blindness. 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)].

Three events of optic ischemic neuropathy temporally associated with vaccination were reported in the HZ/su 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 Dose 1 of HZ/su. 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 HZ/su. 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 Dose 1, 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. A temporal artery biopsy 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 HZ/su. 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.

CBER analysis did not detect any clinically significant imbalances were noted between treatment groups with regard to other ocular inflammatory, ocular vascular or neurovascular events.

Reviewer's comment – The proposed pharmacovigilance plan addresses the occurrence of OIN with routine pharmacovigilance, enhanced pharmacovigilance and by inclusion in a proposed active surveillance study.

Temporal arteritis - Temporal arteritis was classified as a pIMD, and thus this event was collected throughout the study. Nine subjects in the main pooling reported temporal arteritis, 6 in the HZ/su group and 3 in the Placebo group. Of the 6 events in the HZ/su group, 3 occurred within the year following the last vaccination at 14, 204 and 235 days after Dose 2 and the other events occurred 484, 872 and 1538 days after Dose 2. The cases in the Placebo group were reported 723, 929 and 1084 days after Dose 2.

Reviewer's comment – The proposed pharmacovigilance plan addresses the occurrence of temporal arteritis with routine pharmacovigilance, enhanced pharmacovigilance and by inclusion in a proposed active surveillance study.

Immune mediated thrombocytopenia – There were five subjects in the main pooling of the HZ/su group and one in the Placebo reporting immune mediated thrombocytopenia during the whole post-vaccination period. Three subjects reported events during the first year post vaccination at 105 (reported as related by investigator - see Section 8.4.8), 108 (reported as related by investigator - see Section 8.4.2) and 230 days after Dose 2. The other two subjects reported the event more than one year post last vaccination (504 and 1418 days after Dose 2). One subject in the Placebo group reported immune mediated thrombocytopenia 38 days after Dose 2.

Reviewer's comment – Along with routine pharmacovigilance for pIMDs, the Applicant has proposed enhanced pharmacovigilance for several pIMDs including idiopathic thrombocytopenia.

Supraventricular tachyarrhythmias – There were numerical imbalances between treatment groups (HZ/su > Placebo) for the proportions of subjects reporting 1) the PTs of atrial fibrillation/flutter as unsolicited AEs during the 30-day post-vaccination period in Zoster-006, 2) MAEs by PT contained in the narrow sub-SMQ of supraventricular tachyarrhythmias during the 30-day post vaccination period in Zoster-006, 3) the SAE by PT of supraventricular tachycardia from first dose to 365-day post-vaccination period (main pooling). Using narrow SMQs for analysis, no imbalances were noted between treatment groups for the proportions of subjects reporting the occurrence of events in the Cardiac arrhythmias, tachyarrhythmias and supraventricular tachyarrhythmias narrow SMQs and sub-SMQs reported as unsolicited AEs during the 30-day post-vaccination time period or as MAEs during M0 – M14.

Reviewer's comment – Imbalances for the proportions of subjects reporting supraventricular tachyarrhythmias (HZ/su > Placebo) was noted in Zoster-006 but not Zoster-022 or the main pooling and therefore the occurrence of supraventricular tachyarrhythmias will not be recommended for enhanced pharmacovigilance.

GBS and acute polyneuropathies – There were five cases of GBS recorded during the whole post vaccination period; two in the HZ/su 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). There was also one case of Miller-Fisher syndrome reported in the Placebo group 419 days after Dose 2.

Reviewer's comment – There were no imbalances noted between treatment groups for the proportions of subjects reporting GBS, or the proportions of subjects reporting event in the SMQ of Peripheral neuropathy or the HLT of Acute polyneuropathies as MAEs from M0 – M8. Along with routine pharmacovigilance for pIMDs, the Applicant has proposed enhanced pharmacovigilance for several pIMDs including GBS.

Amyotrophic lateral sclerosis (ALS) – There were three subjects in the HZ/SU group reporting ALS in the 365-day post last vaccination period, at 80, 173 and 211 days post Dose 2, none judged to be related to vaccination. In the Placebo group, ALS was found as 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 person-years [Chio, 2013].

Reviewer's comment – The incidence of ALS in the HZ/su group appeared higher than expected given the background incidence rate.

Seizure/convulsions – During the 30-day post vaccination period, eight subjects in the HZ/su group and one in the Placebo group of the main pooling reported unsolicited events by PT included in the narrow SMQ of Convulsions. Only three events were judged serious and had available narratives.

Reviewer's comment – There was an imbalance in subjects in the main pooling (HZ/su > Placebo) reporting unsolicited events by PT contained in the narrow SMQ of Convulsions during the 30-day post-vaccination period. However, one and possibly two subjects had a prior history of epilepsy, two subjects had alternative etiologies for their convulsions and one subject may not have had a convulsion based on the verbatim term recorded; based on review of the available data the occurrence of convulsions will not be addressed with enhanced pharmacovigilance.

Infections and infestations – While there were differences between treatment groups for the proportions of subjects in the main pooling reporting the specific PTs of respiratory infection (HZ/su 0.29%, Placebo 0.24%) and upper respiratory tract infection (HZ/su 1.58%, Placebo 1.24%) during the 30-day post-vaccination periods, there was no difference in the proportions of subjects reporting similar events by PT (e.g., nasopharyngitis, rhinitis). Additionally, CBER analysis indicated no difference was noted between treatment groups for the proportions of subjects reporting events included in the HLT of Upper respiratory tract infections (which includes terms such as sinusitis, pharyngitis, and tonsillitis) during the 30-day post-vaccination periods or lower respiratory tract and lung infections (which includes the PT of pneumonia) reported as AEs during the 30-day post-vaccination periods or as MAEs during M0 – M8.

Reviewer's comment – There appeared to be no excess risk for subjects in the HZ/su group with regard to infectious respiratory diseases.

Anaphylaxis/hypersensitivity – CBER confirmed the Applicant's analysis of the proportions of subjects in the TVC of the main pooling reporting events by PT during the 30day post-vaccination period captured in the narrow Hypersensitivity SMQ [380 (2.6% of HZ/su subjects

reporting and 349 (2.4% of Placebo subjects reporting]. Review of the datasets also confirmed that the most frequently reported PTs captured under the SMQ included various types of rashes, with no safety concern identified.

There was one subject who had an event coded with the PT of anaphylaxis rated of mild intensity. A 54 YO female subject reported the AEs of mild injection site pain, severe pyrexia, severe fatigue, mild injection site erythema, severe chills, severe nausea and severe disorientation on Day 0. 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.

Reviewer's comment – CBER agrees with the Applicant's analysis of the event coded as anaphylaxis.

Post-hoc safety analysis for subjects from closed site in Mexico
The Applicant provided an analysis of safety (SAEs, fatal SAEs and pIMDs) for 1,536 subjects from the closed sites 74895 of Zoster-006 (671 subjects) and 75256 of Zoster-022 (865 subjects) under the auspices of a single investigator in Mexico, which were closed due to significant violations of GCP. Overall, an equal number of subjects (768) were in each treatment group. Similar proportions of subjects 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 HZ/su 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 those seen in the main pooling; acute myocardial infarction, cardio-respiratory arrest, and pneumonia, and no clinically significant imbalances were noted between treatment groups for these events by PT. Five subjects reported pIMDs, 2 (0.3%) in the HZ/su 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) 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.

Reviewer's comment – No safety signals were identified after review of safety data from the closed sites in Mexico, therefore, CBER's conclusions regarding safety are unchanged.

8.5.5 Product-Product Interactions
The safety and immunogenicity of HZ/su when concomitantly administered with QIV was compared to non-concomitant administration of the two vaccines in Zoster-004. See Section 9.2.

8.6 Safety Conclusions

Local and/or general solicited symptoms, generally of short duration, were reported by the majority of subjects evaluated in the HZ/su group. Severe reactogenicity was not uncommon, especially in the younger age strata. Overall, deaths, SAEs and pIMDs were reported in similar proportions of subjects in the HZ/su and Placebo groups. Routine pharmacovigilance and a proposed enhanced pharmacovigilance plan and active surveillance study will address observed imbalances (HZ/su group > Placebo group) and will surveil for other rare adverse

events including pIMDs which may not have been observed given the sample size evaluated in the clinical studies.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.3 Pediatric Use and PREA Considerations
The Applicant requested and will receive a full waiver for assessments in all pediatric age groups. See Section 5.4 for details.

9.1.4 Immunocompromised Patients
Zoster-015
Zoster-015 was a Phase 1/2a randomized, observer-blind, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of HZ/su in comparison to placebo when administered as 3 doses to adult human immunodeficiency virus (HIV)-infected subjects. The study, initiated on 30-SEP-2010 and completed on 14-MAY-2013, enrolled 123 subjects 18 years or older with HIV, stable on anti-retroviral therapy (ART) for at least one year with an undetectable viral load (VL) (<40 copies/mL) and a CD4 T cell count ≥50 cells/mm^3 at screening or ART naïve subjects with VL ≥1000 and ≤100000 copies/mL and CD4 T cell count ≥500 cells/mm^3 at screening. Three cohorts (ART-treated subjects with a CD4 T cell count ≥200 cells/mm^3 [ARTHCD4 cohort], ART-treated subjects with a CD4 T cell count 50-199 cells/mm^3 [ARTLCD4 cohort], and ART-naïve HIV-infected subjects with a CD4 T cell count of ≥500 cells/mm^3 [NARTHCD cohort]) of 45 subjects each were randomized 3:2 to receive 3 doses of HZ/su or saline placebo at Months 0, 2, and 6 (M0, M2, M6). Study subject participation was 7 months, followed by an extended follow up of 11 months. Co-primary objectives included the evaluation of the safety and reactogenicity of the HZ/su study vaccine in HIV-infected subjects by ART and CD4 count cohorts and overall as well as an estimation of the gE-specific humoral and cellular immune responses at M7 (one month post-final vaccination) in ART and non-ART cohorts presenting high CD4 counts at enrollment. Primary endpoints for immunogenicity included the frequency of gE-specific T cells as determined by intracellular cytokine staining (ICS), expressing at least two immunological activation markers at M7, and anti-gE antibody concentrations as determined by ELISA at M7. Primary safety endpoints included worsening of the HIV condition (significant change to ART, occurrence of an acquired immune deficiency syndrome-defining condition, and occurrence of pre-defined HIV related changes in VL and/or CD4 counts), occurrence of SAEs, pre-defined AEs (new onset of autoimmune diseases and other immune mediated inflammatory disorders), solicited local and general symptoms, unsolicited AEs, and hematological and biochemical parameters.

A total of 123 subjects were enrolled, vaccinated, and included in the TVC. Of the 74 subjects who received HZ/su, the mean age was 46.6 years and 93.2% were male. Of the 49 subjects who received placebo, the mean age was 45.1 years and 95.9% were male. Most subjects were white with a Caucasian/European heritage (89.2% of subjects who received HZ/su and 85.7% of subjects who received placebo). By HIV status, the mean age was higher in the ARTLCD4 group (51 years HZ/su group and 52.8 years Placebo group) and ARTHCD4 group (47.8 years HZ/su group and 46.3 years Placebo group) compared to the NARTHCD group (34.6 years HZ/su group and 31 years Placebo group). The remaining demographics were generally comparable between groups by HIV status. A total of 119 subjects completed the M7 visit and 112 completed the final Month 18 visit; one subject was withdrawn from the study due to two SAEs (esophageal varices hemorrhage and portal hypertension).

Overall, in ART subjects and non-ART subjects with high CD4 T cell count at enrollment, the gE-specific humoral immune response was higher in the HZ/su group, as measured by a GM ratio of gE-specific antibody concentrations (HZ/su group/Placebo group) of 46.22 (95% CI: 33.63; 63.53). Overall, in ART subjects and non-ART subjects with high CD4 T cell count at enrollment, the cell-mediated immune response was higher in the HZ/su group at M7, as measured by a GM ratio of gE-specific T cells expressing at least two immunological activation markers (HZ group/Placebo group) of 21.95 (95% CI: 12.67; 38.02) and a GM ratio of T cells expressing at least two immunological activation markers following induction with gE (HZ group/Placebo group) of 6.48 (95% CI: 5.52; 7.61).

Reviewer's comment: No correlate of protection has been established for HZ, and the relationship between humoral and cellular immune response to HZ/su vaccination and HZ/su VE is unknown.

Subjects in the HZ/su group reported more frequent solicited local AEs (pain in almost all subjects) and solicited general AEs (most frequently headache, fatigue, and myalgia) than subjects who received placebo. Overall per subject, the proportions of subjects reporting Grade 3 pain, fatigue, myalgia, and shivering were 16.4%, 16.4%, 13.7%, and 15.1%, respectively. A *post hoc* age-based analysis of reactogenicity demonstrated that, overall per subject, the proportions of vaccine recipients < 50 years of age reporting Grade 3 solicited general events, including fatigue, myalgia, and shivering (each reported by 21.7% of subjects), were higher compared to vaccine recipients ≥ 50 years of age (fatigue and shivering reported by 7.4% and 3.7% of subjects). The proportions of subjects reporting unsolicited AEs and Grade 3 unsolicited AEs during the 30-day post-vaccination period were comparable between vaccination groups. From the time of first vaccination through study end, 7 SAEs were reported by 6 subjects in the HZ/su group, all of which were unlikely to be related to the vaccine, and 2 SAEs were reported for 2 subjects in the placebo group. None of the SAEs were considered vaccine-related by the investigator. No trend of worsening of HIV condition after HZ/su was observed. One subject reported HZ 83 days after Dose 1 of HZ/su. There was no confirmatory PCR specimen; the case was determined by the sponsor responsible physician. No immune mediated inflammatory disorders were reported in any study group.

Summary – Low numbers of subjects in the ARTLCD4 and NARTHCD groups preclude any conclusive analysis of the comparisons of immune responses between the HIV groups. As efficacy was not evaluated in this study and there is no established immune correlate of protection for HZ, it remains unclear whether the immune response to HZ/su observed in the study subjects reflects protection from HZ. The incidence of Grade 3 solicited events in the HZ/su group was high, with an overall/subject incidence of 16.4% for pain, 16.4% for fatigue, 13.7% for myalgia, and 15.1% for shivering. In a post-hoc analysis, the incidence of Grade 3 solicited local and systemic symptoms was higher in HZ/su recipients < 50 years of age than those ≥ 50 years of age, with rates of Grade 3 local symptoms, fatigue, myalgia, and shivering reported by > 20% of subjects < 50 years of age. Due to the small numbers of subjects in the study, safety data are insufficient to characterize risk.

Zoster-001
Zoster-001 was a Phase 1/2a, randomized, observer-blind, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of HZ/su in comparison to gE combined with 1/2 dose $AS01_B$ adjuvant (gE/$AS01_E$) and to saline (placebo) when administered as 2 doses or 3 doses to autologous hematopoietic stem cell transplantation (HCT) recipients. The study, initiated on 14-JUL-2009 and completed on 21-MAR-2012, enrolled 120 subjects 18 years or

older with autologous HCT within the previous 50-70 days for treatment of Hodgkin lymphoma, non-Hodgkin lymphoma (T or B cell), myeloma, or acute myelogenous leukemia. Study subject participation was 15 months. Co-primary objectives included assessment of safety and reactogenicity of HZ/su and gE/AS01$_E$ study vaccines in adult autologous HCT recipients (primary cohort for analysis - TVC) and gE-specific humoral and cellular immune responses at M4. Primary endpoints for immunogenicity included the frequency of gE-specific T cells expressing at least two immunological activation markers as determined by ICS at M4 and anti-gE antibody concentrations as determined by ELISA at M4.

A total of 120 subjects were enrolled, vaccinated, and included in the TVC. For all subjects in the study, the mean age was 56.1 years, and the majority of subjects were White/Caucasian (83.3%) and male (65.0%). The demographics of the four treatment groups were generally comparable, with a mean age ranging from 53.1 to 57.8 years, male subjects ranging from 60-69%, and White/Caucasian subjects ranging from 73.3% - 96.8%. Between 96.7% - 100% of subjects in each group received a standard autologous HCT, most of which (90% - 100%) were derived from peripheral blood cells. The most common diagnosis in each group was myeloma (60% to 65.5%) followed by non-Hodgkin lymphoma (20.0% to 26.7%). A total of 110 subjects completed the M4 visit and 98 subjects completed the study; 10 subjects were withdrawn from the study prior to the M4 visit, with transplant failure/recurrence of underlying malignancy as the most common reason for withdrawal, and 12 subjects were withdrawn from the study after the M4 visit, with SAEs as the most common reason for withdrawal.

Efficacy was not evaluated. Immunogenicity analyses were performed but are not presented here.

Reviewer's comment: No correlate of protection has been established for HZ, and the relationship between humoral and cellular immune response to HZ/su or gE/AS01$_E$ vaccination and VE is unknown.

Solicited local symptoms were more frequent after administration of HZ/su or gE/AS01$_E$ than after placebo; overall per subject, the proportions of subjects reporting Grade 3 pain were 3.6% - 10% of subjects after HZ/su, 17.2% of subjects after gE/AS01$_E$, and no subjects after placebo. Solicited general symptoms were more frequent after HZ/su or gE/AS01$_E$ administration than after placebo, including overall per subject reports of Grade 3 symptoms of myalgia, fatigue, and headache. The proportions of subjects reporting unsolicited AEs during the 30-day post-vaccination period were comparable between vaccination groups, although more Grade 3 unsolicited events were reported by subjects receiving a 3-dose regimen. Most reported unsolicited AEs were consistent with expected adverse events in this subject population, including hematologic abnormalities. During the study, a total of 54 SAEs were reported in 33 subjects, including 9 subjects who died. Two fatalities had an unknown cause of death and seven fatalities were due to progression of the underlying disease and did not appear to be associated with a specific treatment group. An alternative etiology was present for 29 non-fatal SAEs (infectious, traumatic, intentional overdose, and occurrence after placebo administration). Of the remaining 14 non-fatal SAEs, a causal relationship with vaccine was unlikely due to limited information, confounding factors, temporal implausibility, and/or lack of a biologically plausible mechanism. Two episodes of HZ were reported in subjects who received active vaccine, both of whom reported a recurrence of the underlying malignancy approximately 60 days prior to the onset of HZ. Transplant failure/recurrence of underlying malignancy was most frequently observed in subjects with myeloma. A relationship between vaccination with HZ/su or gE/AS01$_E$ and disease recurrence was not observed.

Summary – As there is no clinical efficacy endpoint in this study and no established correlate of protection for HZ, it remains unclear whether the immune response to active vaccination observed in the study translates into protection from disease. Hematologic adverse events, including serious adverse events, were noted in this population, consistent with the underlying diagnoses and expected concomitant medications for this subject population. Due to the small numbers of subjects in the study, safety data are insufficient to characterize risk.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Zoster-026

Zoster-026 was a Phase 3, randomized, open-label, multi-center (one center in the US, one in Estonia) study designed to assess the safety and immunogenicity of HZ/su when administered IM as two doses on a M0/M2 (Gr0-2), M0/M6 (Gr0-6) or M0/M12 (Gr0-12) schedule to subjects ≥ 50 YOA. The study, initiated on 12-MAR-2013 and completed on 08-APR-2015, enrolled 354 generally healthy subjects without a history of HZ or vaccination against HZ or varicella who were randomized 1:1:1 to one of the three groups and followed for safety and evaluation of immune response to vaccination up to one year after Dose 2. There were three primary objectives, evaluated on the ATPc for immunogenicity, which consisted of subjects who did not meet elimination criteria and for whom immunogenicity assessment were available; acceptability of the VRR (defined in Section 6.1.9) for anti-gE humoral response at one month post-Dose 2 in all groups (criterion to be used: the LB of the 97.5% CI of the VRR for anti-gE ELISA Ab concentrations at one month post-Dose 2 in the M0/M6 or M0/M12 schedule groups is at least 60%) and demonstration of the non-inferiority of the anti-gE humoral response at M3 for the M0/M6 and M0/M12 schedule as compared to M0/M2 schedule (criterion for non-inferiority: the UB of the 97.5% CI for the anti-gE ELISA GMC ratio M0/M2 schedule over M0/M6 and M0/M12 schedule at one month post-Dose 2 is below 1.5).

The median age of subjects in the TVC was 63.0 years and was comparable between vaccination groups. Over 95% of subjects in each group were non-Hispanic or Latino and Caucasian and the proportions of females (ranging from 65% – 76% per group) were higher than males. Of 354 subjects vaccinated and included in the TVC, 8 (2 in Gr0-2 and 3 each in Gr0-6 and Gr0-12) withdrew (did not complete study/return for last visit). Of these 8 subjects, 4 withdrew due to an SAE: one (Gr0-12 group) withdrew consent not due to an AE, one (Gr0-2 group) was lost to follow-up with an incomplete vaccination course and two (one each in Gr-06 and Gr0-12 groups) were lost to follow-up with a complete vaccination course. There were 11 subjects excluded from the ATPc for immunogenicity for the following reasons; administration of medication forbidden by the protocol (3 subjects), non-compliance with blood sampling schedule (2 subjects), serologic data missing (4 subjects) and subjects did not receive 2 doses (2 subjects).

The VRR one month post-Dose 2 was 96.5% (97.5% CI: 90.4%, 99.2%) for the Gr0-6 group and 94.5% (97.5% CI: 87.6%, 98.3%) for the Gr0-12 group, and thus the VRR objective (LB of the 97.5% CI ≥ 60%) was met for both groups. The non-inferiority endpoint was met for the Gr0-6 schedule, as the UB of the adjusted GMC ratio (Gr0-2/Gr0-6) at one month post-Dose 2 was < 1.5 [adjusted GMC ratio 44352.6/38137.8 = 1.16 (97.5% CI: 0.98, 1.39)], while the non-inferiority objective was not met for the Gr0-12 schedule [adjusted GMC ratio (Gr0-2/Gr0-12) = 44201.0/37019.9 or 1.19 (97.5% CI: 0.93, 1.53)] as the UB of the adjusted GMC ratio was ≥ 1.5.

Overall per subject during the 7-day post-vaccination period, the proportions of subjects reporting solicited symptoms and the duration of solicited symptoms were comparable between vaccination groups and similar to the proportions reported in the pivotal studies. There

appeared to a be a trend toward higher proportions of subjects reporting any solicited, any solicited local and any solicited general symptom after Dose 2 as compared to Dose 1 for the Gr0-12 group. Reports of Grade 3 solicited symptoms were also marginally higher for the Gr0-12 group as compared to the other groups with a trend toward increasing solicited symptom reporting after Dose 2 as compared to Dose 1. The proportions of subjects reporting unsolicited AEs and Grade 3 unsolicited AEs during the 30-day post-vaccination period were comparable between vaccination groups. Twelve subjects [4 (3.4%) in the Gr0-6 and 8 (6.9%) in the Gr0-12 group] reported 18 SAEs from first vaccination through 30 days post last vaccination, and from first vaccination to study end 5 (4.2%), 9 (7.6%) and 12 (10.3%) of subjects in the Gr0-2, Gr0-6 and Gr0-12 reported SAEs. Two subjects died during the study; a 79 YO female in the Gr0-2 group with a history of TIA and heart disease had a cerebral hemorrhage (b) (6) months after Dose 2 and a 77 YO female in Gr0-12 with a history of heart disease died of a cerebrovascular disorder (b) (6) months after Dose 1. None of the fatal and non-fatal SAEs were considered vaccine-related by the investigator or Applicant. No pIMDs, pregnancies or HZ episodes were reported during the study.

Summary – The humoral immune response to HZ/su as measured by anti-gE antibody concentrations when evaluated at one month after Dose 2 on the M0/M6 schedule was acceptable and non-inferior to the humoral immune response to HZ/su when evaluated one month after Dose 2 on a M0/M2 schedule. The non-inferiority of the humoral immune response to HZ/su when measured one month after Dose 2 on a M0/M12 schedule was not demonstrated. Although higher proportions of subjects in the Gr0-6 and Gr0-12 reported SAEs during the entire study period, this was due to the longer intervals for safety follow-up for these groups. The safety profile of HZ/su when administered on a M0/M6 schedule was comparable to that of administration on a M0/M2 schedule.

Zoster-004

Zoster-004 was a Phase 3, open-label, randomized, controlled, multicenter, multi-country study to evaluate the evaluate the safety and immunogenicity of concomitant or separate administration of HZ/su and the quadrivalent, inactivated seasonal influenza vaccine FLU D-QIV. The study, initiated on 03-OCT-2013 and completed on 20-MAR-2015, enrolled a total of 829 generally healthy subjects ≥ 50 YOA without a history of HZ or previous vaccination against HZ or varicella stratified by age in each of the two groups (55 subjects 50-59 YOA, 155 subjects 60-69 YOA, and 104 subjects ≥ 70 YOA) and randomized 1:1 to receive either one dose of HZ/su and one dose of FLU D-QIV vaccine at M0 and one dose of HZ/su vaccine at M2 (Co-Ad group) or one dose of FLU D-QIV vaccine at M0 and one dose of HZ/su at M2 and M4 (Control group). Study subject participation was approximately 14 months for subjects in the Co-Ad group and approximately 16 months for subjects in the Control group. Co-primary objectives included evaluation of the VRR to the HZ/su vaccine (based on the humoral immune response) one month after Dose 2 of HZ/su in the Co-Ad group, demonstration of non-inferiority of the humoral immune response in the Co-Ad group compared to the Control group, and demonstration of the non-inferiority (in terms of haemagglutinin inhibition [HI] antibody GMTs for the four strains included in FLU D-QIV vaccine) of one dose of FLU D-QIV vaccine in the Co-Ad group compared to the Control group at Day 21 post vaccination. The co-primary endpoints for HZ/su humoral immunogenicity included the VRR (Co-Ad group) and GMC ratios (Co-Ad and Control groups) of anti-gE antibody concentrations as determined by ELISA, as well as the GMTs of serum HI antibody titers against the four influenza vaccine strains.

A total of 829 subjects were enrolled in the study and 828 subjects were vaccinated and included in the TVC; one subject who was enrolled withdrew consent before being assigned to a group. Of the subjects in the TVC, the mean and median ages of subjects were 63.4 and 63.0,

51.8% were female, and 92% were of White-Caucasian/European heritage. The demographic characteristics were generally comparable between the groups. A total of 796 subjects completed the study; eight subjects were withdrawn from the study due to fatal SAEs (four from the Co-Ad group and five from the Control group), one subject was withdrawn from the study due to an SAE of cerebrovascular accident (Co-Ad group), and three subjects were withdrawn from the study due to non-serious AEs (one from the Co-Ad group and two from the Control group).

The pre-specified success criteria for the primary objectives were met for humoral immune responses to HZ/su in the Co-Ad group compared to the Control group. Humoral immune responses to HZ/su in the Co-Ad group were non-inferior to those in the Control group (the lower limit of the 95% CI of the VRR for anti-gE antibody concentrations in the HZ/su-FLU D-QIV Co-Ad group was >60% and the UL of the 95% CI for the GMC ratio for anti-gE antibodies of the Control group over the Co-Ad group was below 1.5) and humoral immune responses to FLU D-QIV in the Co-Ad group were non-inferior to those in the Control group (the UL of the two-sided 95% CI for the GMT ratio of the Control group to the Co-Ad group was below 1.5 for each FLU D-QIV strain). The pre-specified success criteria for the secondary objective of FLU D-QIV vaccine seroprotection rates were met. The success criteria for the secondary objective of HI antibody seroconversion rates for were met for only both age groups and in both treatment groups for the A/H1N1 strain, but the success criteria for non-inferiority of HI antibody seroconversion rates of the Co-Ad group compared to the Control group were met for three of the four influenza strains.

Overall per subject, the proportions of subjects reporting any local or general solicited symptom were comparable in the Co-Ad and Control groups (69.9% - 79.3% and 52.1% - 64.2% of subjects, respectively). The proportions of subjects reporting any Grade 3 local solicited symptom were comparable in the Co-Ad and Control groups (7.4% -10% of subjects), but was numerically higher in the Co-Ad group. The proportions of subjects reporting any general solicited symptom was numerically highest after a second dose of HZ/su in both groups (63.7% - 64.2% of subjects). In the Co-Ad group, with the exception of GI symptoms, solicited general symptoms were more frequently reported after Dose 2 (HZ/su alone) than Dose 1 (HZ/su with FLU D-QIV). With the exception of fever and myalgia, the proportions of subjects reporting specific solicited general symptoms was lowest for a first dose of HZ/su given alone (Control group Dose 2) than for any other HZ/su dose. The proportions of subjects reporting unsolicited AEs and Grade 3 unsolicited AEs during the 30-day post-vaccination period were comparable between vaccination groups.

A total of 42 subjects (10.2%) in the Co-Ad group and 39 subjects (9.4%) in the Control group reported at least one SAE from the first vaccination up to study end. None of the SAEs were assessed as causally related by the Investigator. A total of 8 subjects reported SAEs with a fatal outcome, including a fatal event of cerebrovascular disorder occurring 91 days after Dose 2 of HZ/su in the Co-Ad group. SAEs of coronary artery related events and other potentially thrombotic/thromboembolic events were more commonly reported in the Co-Ad group than the Control group. A total of 7 (1.69%) subjects in the Co-Ad group reported coronary artery related events as compared to 2 (0.48%) subjects in the Control group. The minimum time to onset of these events was 24 days after Dose 2 of HZ/su. A total of 5 (1.45%) subjects in the Co-Ad group reported other potentially thrombotic/thromboembolic events as compared to 1 (0.24%) subject in the Control group. An event of cerebrovascular accident occurred 17 days after co-administered HZ/su and FLU D-QIV; the remaining events had a minimum time to onset of 29 days after Dose 2 of HZ/su. A total of 6 subjects (4 in Co-Ad group and 2 in Control group) reported pIMDs. One subject in the Control group with a history of colitis reported a pIMD of

ulcerative colitis with an onset 5 days after Dose 1 of HZ/su. One subject in the Co-Ad group reported HZ following Dose 2 of HZ/su.

Summary – The humoral immune response to HZ/su at one month post Dose 2 when co-administered with FLU D-QIV schedule was acceptable and non-inferior to that of the control schedule. The HI antibody immune response after co-administration of the FLU D-QIV dose with HZ/su was non-inferior to that of the control schedule. More coronary artery related and thromboembolic SAEs were reported in the Co-Ad group than the Control group. These events were varied in nature. With the exception of one event of cerebrovascular accident 17 days after the co-administered HZ/su and FLU D-QIV, these events all occurred with a minimum time to onset of 24 days after Dose 2 of HZ/su in both groups. There was an imbalance in the occurrence of vascular SAEs (Co-Ad > Control); considering the available safety profile of each vaccine and the timing of the events, causal association due to co-administration appears less likely. Imbalances between treatment groups for coronary artery related and other thromboembolic SAEs were not observed in the pooled safety data from Zoster-006 and Zoster-022.

Zoster-032

Zoster-032 was a Phase 3, randomized, open-label clinical trial designed to assess the safety and immunogenicity of HZ/su in adults ≥ 50 YOA when administered SC as compared to IM. The study, initiated on 17-JUN-2013 and completed on 11-NOV-2014, was conducted in a single center in Japan and enrolled 60 generally healthy subjects of Japanese ethnic origin (JEO) ≥ 50 YOA without a history of HZ or previous vaccination against HZ or varicella. Subjects were evaluated for safety and immune response to HZ/su for 1 year after last vaccination. The Applicant's rationale for evaluation of the SC route of administration was that this is the preferred route of administration of some vaccines in the elderly in Japan and other select populations. The objectives of the study were to evaluate the VRR and GMCs (based on anti-gE antibody responses as determined by ELISA) at M3 when HZ/su was administered SC as compared to IM as well as to compare the safety and reactogenicity of the SC and IM routes of administration.

The mean and median ages of subjects in the TVC were 61.9 and 63.0 and there were 15 males and 15 females in each vaccination group. Within each vaccination group, there were 12 subjects 50 – 59 YOA, 12 subjects 60 – 69 YOA and 6 subjects ≥ 70. All were of JEO. Fifty nine of the sixty subjects enrolled and included in the TVC completed the study. One subject in the IM group who received a dose at M0 withdrew consent at M1 not due to an AE and did not receive Dose 2; this subject was eliminated from the ATPc for immunogenicity at M3 and the EOS analysis. Two more subjects were eliminated from immunogenicity analyses for deviations from sampling collection timelines and for use of a medication forbidden by the protocol.

At M3, the GMCs (95% CI) for the SC and IM groups were 44126.1 IU/mL (36326.1, 53601.0) and 45521.5 IU/mL (37549.5, 55185.9), respectively and 100% of subjects in both treatment groups were vaccine responders. While similar proportions of subjects in each group reported any grade pain following vaccination, other solicited local symptoms were reported by higher proportions of subjects in the SC as compared to the IM group; overall by subject redness, swelling, pruritus and impaired arm movement were reported by 86.7% vs. 50%, 80.0% vs. 40.0%, 70.0% vs. 33.3% and 60.0% vs. 40.0% of subjects in the SC as compared to the IM group respectively. Specific solicited general symptoms of any grade were comparable between vaccination groups. Grade 3 solicited general symptoms were reported by similar proportions of subjects in each vaccination group, but Grade 3 solicited local symptoms were reported by 56.7% of subjects in the SC group as compared to 6.7% of subject 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 (defined as preventing daily activity) limitation of arm movement. Overall per dose, the median duration of solicited local symptoms ranged from 2.0 – 3.0 days in the IM group as compared to 3.0 – 5.0 days in the SC group. None of the solicited local or general symptoms reported resulted in a medically attended visit. No clinically significant imbalances were noted between vaccination groups regarding the type of unsolicited events reported or proportions of subjects reporting unsolicited events within the 30-day post-vaccination period. Three subjects, two in the SC and one in the IM group reported SAEs; none were reported as vaccine-related. There were no pIMDs, HZ episodes or deaths reported during the study.

Summary – Although humoral immune responses were comparable at M3 following IM and SC administration of HZ/su, higher proportions of subjects reported Grade 3 swelling and redness post-vaccination in the SC group as compared to the IM group, precluding further development of the SC route of administration of HZ/su.

Zoster-007

Zoster-007 was a Phase 3, randomized, double-blind, multicenter study to evaluate the consistency, immunogenicity, safety, and reactogenicity of 3 lots of HZ/su when administered intramuscularly on a 0 and 2-month schedule to adults ≥ 50 YOA. The study was initiated on 13-AUG-2014, had a study completion date for the Active Phase (up to M3) of 29-APR- 2015, and a database lock for the interim M3 analysis of 13-AUG-2015. This study enrolled 651 subjects randomized 1:1:1 to receive two doses from one of three lots of HZ/su vaccine (HZ/su Lot A, HZ/su Lot B and HZ/su Lot C groups), each composed of unique randomized combinations of 50 µg of gE antigen and $AS01_B$ adjuvant lots. Study subject participation was approximately 14 months. The primary objective of the study was to demonstrate lot-to-lot consistency in terms of anti-gE humoral immunogenicity between three production lots of the HZ/su vaccine one month after the second dose (M3) and the primary endpoint was anti-gE antibody concentrations, as determined by ELISA, at M3.

A total of 651 subjects were enrolled, vaccinated, and included in the TVC, including 218 subjects in the Lot A group, 217 subjects in the Lot B group, and 216 subjects in the Lot C group. Of subjects in the TVC, the mean and median ages of subjects were 64.5 and 65.0, 55.3% of subjects were female, and 93.7% of the subjects were of White-Caucasian/ European Heritage. The demographic characteristics were generally comparable across the 3 vaccine lot groups; however, there were more females in Lot B (59.9%) relative to the other lots (52.8% - 53.2%). A total of 645 subjects completed the M3 visit; one subject in the Lot A group was withdrawn due to a fatal SAE of acute myocardial infarction, one subject in the Lot B group withdrew due to a non-serious adverse event (redness, left outer aspect of orbit), and one subject in the Lot C group withdrew due to an SAE of breast carcinoma.

Analyses of immunogenicity at M3 included assessments of humoral responses as measured by anti-gE antibody concentrations, with a success criterion for consistency of 2-sided 95% CI of the GMC ratio between all pairs of lots within 0.67 and 1.5. The adjusted ratios of Lot A/Lot B, Lot A/Lot C and Lot B/Lot C anti-gE antibody ELISA GMCs at M3 were all within the prespecified CI range.

Solicited local symptoms were reported overall per subject by 86.5% - 90.8% of subjects in each group. Pain was the most common solicited local event with comparable proportions of subjects reporting events across all lot groups. Grade 3 solicited local pain was reported by 6% - 10.1%

of subjects in each group. Solicited general symptoms were reported by 73.6% - 77.4% of subjects in each group. Myalgia, fatigue and headache were the most commonly reported general symptoms. Grade 3 solicited symptoms were reported by 18.6% of subjects in the TVC and were more common after the second dose of vaccine.

A total of 29 subjects reported SAEs, most of which had a plausible alternative etiology, such as a mechanical injury or obstruction, infectious source, or a tumor that was unlikely to be temporally related to vaccination. None were reported to be vaccine-related by the investigator. Two subjects (2/651, 0.3% of TVC) reported myocardial infarction within 30 days of vaccination, including the only fatal event of the study, a 78 year old with a history of arterial hypertension and five days of symptoms prior to a fatal myocardial infarction (b) (6) days after Dose 1 of vaccine and a 68 year old with a history of hypertension and hyperlipidemia who reported a myocardial infarction (b) (6) days after Dose 2. One event of aortic dissection occurred (b) (6) days after Dose 2. One subject reported HZ 4 days after Dose 2. Six pIMDs were reported in the study. The nature of the pIMDs was diverse and no given pIMD was seen in more than one subject.

Summary – The primary and secondary confirmatory objectives for the lot-to-lot consistency in terms of anti-gE humoral immunogenicity between the three manufacturing lots of the HZ/su vaccine one month post-dose 2 were met. Two subjects reported myocardial infarction within 30 days of vaccination with HZ/su. Imbalances in myocardial infarction were not observed in the pooled safety data from Zoster-006 and Zoster-022.

<u>Zoster-010</u>
Zoster-010 was a Phase 2, randomized, placebo-controlled, adjuvant dose selection, multi-center (12 sites in 3 countries; Czech Republic, Spain and the US) clinical trial designed to assess the safety and immunogenicity of HZ/su as compared to gE/AS01$_E$ (antigen with half dose AS01$_B$), unadjuvanted gE (gE/saline) and saline placebo. The study, initiated on 12-JAN-2009 and completed on 02-JUL-2010, with a planned enrollment of 395 generally healthy subjects ≥ 50 YOA (with age stratification 4:4:3:1 for subjects 50 – 59, 60 – 69 70 – 79 and ≥ 80 YOA) without a history of HZ or vaccination against HZ or varicella who were randomized 4:4:2:1 to one of 4 groups (HZ/su, gE/AS01$_E$, gE/saline or saline) to receive two doses of study product on a M0/M2 schedule. Study subject participation was for approximately 8 months, or 14 months if additional consent for further participation was obtained. The primary objective of the study was to compare gE and VZV-specific T-cell mediated and humoral immune responses to HZ/su, gE/AS01$_E$ and gE/saline at M3 in subjects ≥ 50 YOA and the primary endpoints were frequencies of gE and VZV-specific T cells as determined by *in vitro* intracellular cytokine staining, expressing at least two immunological activation markers at M3 and anti-gE and anti-VZV Ab concentrations as determined by ELISA at M3. As anti-gE concentrations were the primary immunologic read-out for the CDP, anti-VZV results will not be presented.

Of the 410 subjects vaccinated and included in the TVC there were 150 in the HZ/su group, 149 in the gE/AS01$_E$ group, 73 in the gE/saline group and 38 in the saline group. The mean (SD) and median age in the TVC was 65.0 years (9.2) and 64.0 years with a maximum age of 95 years. The majority of subjects in each treatment group (≥ 94.0%) were White of Caucasian/European heritage and the proportion of females was 56.6%. Demographic characteristics of the TVC were comparable to the ATP cohort for immunogenicity, and were generally comparable between treatment groups. Up to M8, 20 subjects withdrew from the study; 15 up to M3, and 5 from M3 – M8. Of these subjects, 9 were in the HZ/su group, 8 were in the gE/AS01$_E$ group, and 3 in the gE/saline group; 2 withdrawals were due to a fatal SAE (MI (b) (6) days after Dose 1 in the HZ/su group and cardiac failure (b) (6) months after Dose 2 in the gE/saline group), one due to a non-fatal SAE (GI hemorrhage 38 days after Dose 1 in the

gE/AS01$_E$ group) and 2 to an AE (1 subjects each with malaise in HZ/su group and IS redness in gE/AS01$_E$ group). Four subjects withdrew from M8 – M14, and 55 subjects total did not participate in the safety follow-up from M8 to the EOS contact at M14.

Geometric mean gE-specific frequencies were higher at M3 after 2 doses of gE/AS01$_E$ or HZ/su (1580.65 and 2048.74 respectively) as compared to responses at M2 after 1 dose (378.43 and 387.35 respectively). CMI response in the gE/saline group at M2 and M3 was 166.50 and 392.88, respectively). At M3, the fold increase in frequency of gE-specific CD4 T cells (HZ/su over gE/AS01$_E$) was 1.30 (1.07, 1.58). Geometric mean gE-specific Ab concentrations were higher at M3 after 2 doses of gE/AS01$_E$ or HZ/su (48973.99 and 68689.13 respectively) as compared to at M2 after 1 dose (19349.33 and 24516.93 respectively). At M3, the fold increase in gE-specific Ab concentrations (HZ/su over gE/AS01$_E$) was 1.40 (1.17, 1.68).

Solicited symptoms were reported by higher proportions of subjects in the HZ/su as compared to other groups, but overall/subject, severe reactogenicity by solicited symptom was reported by ≤ 5.0% of subjects in the HZ/su group (except for severe fatigue, reported by 6.0%). Overall per dose, the number of days with solicited symptoms was comparable between the HZ/su and AS01$_E$ groups. The proportions of subjects reporting unsolicited AEs during the 30-day post-vaccination period in the HZ/su, gE/AS01$_E$, gE/saline and saline groups were 31%, 25%, 25% and 16% respectively, but the rates of Grade 3 unsolicited AEs were comparable between groups. No immune mediated inflammatory disorders or HZ cases were reported during the study. SAEs were reported by 13 subjects from M0 – M3 [HZ/su group (4 subjects), gE/AS01$_E$ group (4 subjects), gE/saline group (3 subjects) and saline group (2 subjects)]. One fatal SAE (MI in a 69 YO male with a history of hypertension, HZ/su group) was reported on Day (b) (6) after Dose 1. SAEs were reported by 8 subjects from M3 – M8 [HZ/su (2 subjects), gE/AS01$_E$ (2 subjects), gE/saline (4 subjects)]. One fatal SAE (cardiac failure in an 82 YO female (b) (6) months after Dose 2, gE/saline group) was reported during this period. The SAEs reported were typical of those expected in an older population, none were considered related to investigational product by the investigator, and no clinically significant imbalances were noted between groups with regard to the nature and incidence of the SAEs.

Reviewer's comment – Cellular and humoral immune responses after two doses of HZ/su and gE/AS01$_E$ were higher than after one dose of either study product and immune responses after two doses of HZ/su were higher than after two doses of gE/AS01$_E$. The clinical significance of the differences in immune response after one as compared to two doses of HZ/su or two doses of gE/AS01$_E$ as compared to two doses of HZ/su are not known, as the efficacy of 1-dose HZ/su or 2-dose gE/AS01$_E$ has not been evaluated in the CDP and there is no known immune correlate of protection against HZ.

<u>EXPLO CRD-004, Zoster-018, Zoster-019</u>
EXPLO CRD-004 was an exploratory, Phase 1/2, open, randomized, study conducted in Belgium to evaluate the safety and immunogenicity of concomitant or separate administration of HZ/su and a live attenuated OKA VZV vaccine (Varilrix). The study, initiated on 14-DEC-2004 and completed on 03-FEB-2006, enrolled 155 generally healthy adult subjects 18 - 30 and 50 - 70 years of age without prior VZV vaccination or history of HZ in the previous 5 years. Zoster-018 and Zoster-019 were exploratory, Phase 1/2, open, extension studies of EXPLO CRD-004 to evaluate the persistence of CMI at Months 30 and 42 to gE and VZV in recipients of HZ/su without Varilrix. Study subject participation was approximately 12 months for EXPLO CRD-004. Co-primary objectives of EXPLO CRD-004 included assessment of the safety and reactogenicity of HZ/su with or without Varilrix and a comparison of vaccine strategies to induce the optimum CD4 and/or CD8 T cell responses by ICS. The primary objective of Zoster-018 and

-019 was to evaluate the persistence of the CMI response to gE and VZV in HZ/su recipients at M30 and M42. Primary endpoints for immunogenicity included the frequency of cytokine-positive CD4/CD8 cells per 10^6 cells at M3 in cells expressing at least two immunological activation markers after stimulation by VZV lysate in EXPLO CRD-004 and the frequencies of gE- and VZV-specific CD4 T cells expressing at least two immunological activation markers at M30 and M42 after the first vaccination in the HZ/su only study vaccine groups in Zoster-018 and Zoster-019.

A total of 155 subjects were enrolled, vaccinated, and included in the TVC, and all subjects completed the study. Of the subjects in the TVC, the mean and median ages of subjects were 22.4 and 21.0 for the young adults and 56.1 and 55.0 for the older adults. The majority of subjects were female (64.5%) and most subjects were Caucasian (99.4%). Zoster-018 and 019: In the extension studies, the mean and median ages were 22.3 and 21.0 (Zoster-018) and 22.7 and 21.0 (Zoster-019) for the young adults and 54.9 and 54.0 (Zoster-018) and 56.0 and 57.5 (Zoster-019) for the older adults. In both studies most subjects (~ 80%) were female. Within age strata, the demographic characteristics of each group were comparable.

Humoral and CMI responses among elderly subjects were significantly higher in subjects who received HZ/su or HZ/su coadministered with Varilrix as compared to subjects who received Varilrix alone. A second dose of vaccine induced a better CD4 cytokine response and higher antibody levels than those seen after only one vaccination for all subjects except those who received Varilrix alone. CMI responses at M30 and M42 demonstrated waning immune responses over time, although 96.6% and 85% of subjects met vaccine response criteria (at least four-fold increase in antibody concentration compared to baseline) at M30 and M42, respectively.

In EXPLO-004, subjects who received vaccine regimens containing HZ/su reported more frequent solicited local AEs (pain in almost all subjects) and solicited general AEs (most frequently headache, fatigue, and myalgia) than subjects who received Varilrix alone. Overall per subject, Grade 3 solicited AEs were less frequently reported by subjects who received Varilrix alone. The proportions of subjects reporting unsolicited events and Grade 3 unsolicited events within the 30-day post-vaccination period were higher in subjects who received HZ/su. In EXPLO-004, nine subjects reported 10 SAEs; none were reported as vaccine-related by the Investigator and none appeared likely to be related to HZ/su. No SAEs were reported in ZOSTER-018, or ZOSTER-019. No deaths or events of HZ were reported in EXPLO-004, ZOSTER-018, or ZOSTER-019.

Summary - EXPLO-004, ZOSTER-018, and ZOSTER-019 demonstrated that administration of HZ/su with or without Varilrix induced higher cell-mediated and humoral antibody responses than were seen with Varilrix alone in elderly subjects, that cell-mediated and humoral antibody responses increased after a second dose of vaccine in all age groups, and that while immunity waned over time, humoral and cellular immunity remained higher than pre-vaccination 42 months after the first vaccination in elderly subjects. Solicited local and general AEs were more frequently reported by subjects who received vaccine regimens containing HZ/su compared to those who received Varilrix alone.

<u>Zoster-003, Zoster-011, Zoster-012, Zoster-013, Zoster-024</u>
Zoster-003 was a Phase 2, single-blind, randomized, controlled, multicenter vaccination study to evaluate the safety and immunogenicity of HZ/su and to compare several vaccination regimens of gE with $AS01_B$ in healthy elderly subjects 60 to 69 years of age and 70 years of age and above. The study treatments explored two varying two dose regimens of gE (25, 50, and 100 µg

per dose) with $AS01_B$, a two dose regimen of gE (100 µg per dose) without adjuvant, and a single dose regimen of 100 µg gE with $AS01_B$. Zoster-011, Zoster-012, and Zoster-013 were single-blind extension studies to evaluate the persistence of immune responses at Months 12, 24 and 36, respectively, and safety from study start until M36. Zoster-024 was an open, Phase 2 long term extension study to evaluate the immune responses to and safety of the HZ/su two-dose vaccine regimen at Months 48, 60 and 72 post-vaccination in healthy subjects ≥ 60 YOA. The studies, initiated on 14-FEB-2007 and completed on 20-JUNE-2013, enrolled 715 generally healthy subjects 60 years or older, including 166 subjects who received the final formulation and schedule (two doses of 50 µg gE/$AS01_B$). The primary objective of Zoster-003 was a comparison of the CD4 T cell response to HZ/su in healthy elderly subjects ≥ 70 years of age, with a primary endpoint of the frequencies of gE-specific CD4 T cells expressing at least two immunological activation markers at M3. The primary objective of Zoster-024 was the evaluation of humoral and cell mediated immune responses to HZ/su in healthy elderly adults (overall and within each age cohort) at Months 48, 60, and 72, with primary endpoints of the frequencies of antigen-specific CD4 T cells and CD4 T cells with antigen-specific IFN-γ and/or IL-2 and/or TNF-α and/or CD40L secretion/expression to gE and VZV as determined by ICS, as well as anti-gE and anti-VZV antibody concentrations as determined by ELISA.

A total of 715 subjects were enrolled, including 714 subjects who were vaccinated and included in the TVC. The mean age of subjects in the TVC was 72.9 years, and most subjects were White/Caucasian (99.2%) and female (56.6%). The demographics of the five treatment groups were generally comparable. A total of 701 subjects completed the M3 visit. Thirteen subjects were withdrawn from the study, including six who withdrew consent, two due to AEs (each of whom reported generalized weakness and nausea after the Dose 1), one due to a fatal SAE of drowning, two who were lost to follow up, and two with protocol deviations. Twenty eight subjects from Zoster-003 did not participate in study Zoster-011, 21 subjects from Zoster-011 did not participate in Zoster-012, and 20 subjects from Zoster-012 did not participate in Zoster-013.

M3 CMI measures were generally higher in all age groups and for subjects ≥ 70 years of age following all of the two dose adjuvanted regimens compared to the other regimens (but comparable between gE antigen doses when administered with adjuvant). Cellular and humoral responses in the two-dose 50 µg gE/$AS01_B$ remained generally stable or decreased slightly from M48 through M72.

Solicited local and general symptoms, including Grade 3 symptoms, were more frequently reported after gE/$AS01_B$ regimens than gE/saline regimens. The proportions of subjects reporting solicited local and general symptoms was generally comparable across the gE dose range, and no dose-related increase in symptoms was noted. Unsolicited adverse events were more commonly reported in the two-dose gE/$AS01_B$ treatment groups, including events in the Nervous system disorder SOC, which were only reported after doses of gE/$AS01_B$; these events were varied and none occurred after more than 1% of doses in any group. A total of 18 subjects reported 21 SAEs during Zoster-003. None of these SAEs were considered related to study vaccine by the Investigator. Two subjects died, one of whom drowned and one of whom reported bronchial carcinoma. A total of 54 subjects reported 61 SAEs during Zoster-011, none of which were considered causally related by the Investigator. The percentage of subjects experiencing at least one SAE was comparable between groups. One subject died of diabetic gangrene. In the 0 - 36 month time period after vaccination, no pattern of SAEs suggesting a relationship with gE dose was noted. Certain SAEs (coronary artery related SAEs, neoplasms, and stroke related SAEs) were more frequent in the $AS01_B$ groups as compared to the 100 µg gE/Saline group.

Reviewer's comment - Limited numbers of subjects in the 100 µg gE/Saline group complicate an interpretation of these differences in the frequency of events between the groups; imbalances in these events were not observed in the pooled safety data from Zoster-006 and Zoster-022. Eleven fatal SAEs occurring within 12 months of vaccination were not included in summary tabulations of SAEs as they occurred after ZOSTER-003 and the subjects did not participate in subsequent extension studies. Of the 129 subjects in the total cohort of persistence for ZOSTER-024, only 3 subjects reported SAEs over a 3 year time period, which was proportionately fewer than expected as compared to Zoster-012 and 013.

Summary - At M3, cell mediated immune responses in subjects ≥ 70 YOA demonstrated comparable immunogenicity between the three 2-dose gE/AS01$_B$ regimens, which were all significantly more immunogenic than the 1-dose gE/AS01$_B$ regimen and the 2-dose gE/saline regimen. Cellular and humoral responses in the 2-dose 50 µg gE/AS01$_B$ regimen group remained generally stable or decreased slightly from M48 through M72.
Coronary artery related SAEs, neoplasms, and stroke related SAEs were more frequently observed in the AS01$_B$ groups compared to the 100 µg gE/Saline group; however limited numbers of subjects in the 100 µg gE/Saline group complicate an interpretation of these differences and imbalances in these events were not observed in the pooled safety data from Zoster-006 and Zoster-022.

The 50 µg gE/AS01$_B$ formulation was selected for use in subsequent clinical studies with the rationale that it was the lowest dose that induced a high level of CMI and humoral immune responses with an acceptable reactogenicity profile.

Zoster-023
Zoster-023 was a Phase 1, open label study conducted in Australia in subjects of JEO to evaluate the safety and immunogenicity of two doses of HZ/su administered at M0 and M2. The study, initiated on 04-MAR-2010 and completed on 25-NOV-2010, enrolled 20 healthy subjects of JEO 18 – 30 YOA (N = 10) and 50 - 69 YOA (N = 10) without a history of HZ or VZV vaccination. Immunogenicity assessments included humoral responses as measured by anti-gE antibody concentrations.

GMCs as measured by anti-gE ELISA rose after successive doses of the vaccine, which were evaluated post-vaccination at M1 and M3.

Solicited local and systemic symptoms were reported by 100% of subjects; Grade 3 solicited local and systemic symptoms were reported in both age groups, and were common and more frequently reported in the younger as compared to the older age group. Related unsolicited AEs included chills, feeling hot, arthralgia, back pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, and dizziness. There were no SAEs, deaths, withdrawals due to SAEs or AEs, or new onset autoimmune disease observed during the study, and no suspected cases of HZ were reported. One subject became pregnant and delivered a healthy infant at term 12 months after the second dose of vaccine.

Summary - Humoral immune responses to HZ/su were observed in subjects of JEO.

Zoster-033
Zoster-033 was a Phase 3, non-randomized, open-label, multicenter, single arm clinical trial to evaluate the immunogenicity and safety of HZ/su when administered to adults ≥ 50 years of age with a prior episode of herpes zoster (HZ). The study, initiated on 10-JUNE-2013 and completed

on 25-NOV-2014, enrolled 96 subjects stratified 1:1:1 by age: 50- 59 YOA; 60-69 YOA and ≥ 70 YOA to receive gE-AS01$_B$ at M0 and M2. The majority of subjects in the study were female, and nearly all subjects were Caucasian. A total of 93 subjects completed the study; three subjects were withdrawn from the study, one due to a non-serious adverse event and two due to consent withdrawal.

Immunogenicity assessments at M3 (one month after completion of study vaccinations) included humoral responses as measured by anti-gE antibody concentrations. Humoral immune responses were generally comparable across the age strata, and the VRR was 90.2% (95% CI: 81.7%; 95.7%), which met the pre-specified success criterion of a lower limit of the 95% CI of at least 60%.

The reactogenicity profile of gE-AS01$_B$ containing regimens was similar to that observed in other studies submitted to the application. Five SAEs were reported by 3 subjects, all of which were unlikely to be related to the vaccine. A total of 6 subjects, all of whom were located in Canada, reported 9 suspected HZ episodes during the study period. Three subjects reported HZ after a Dose 2, with a time to onset ranging from Day 131 - 288. The remaining 3 subjects reported HZ after one dose of vaccine, with a time to onset ranging from Day 28 - 430. None of the episodes were verified with laboratory testing, but five of the subjects were treated with antiviral medication, suggesting that the clinical presentation was consistent with HZ. All subjects with suspected HZ episodes with available M3 anti-gE antibody titers demonstrated increases from baseline, and those who received a second vaccination, were vaccine responders (i.e., had at least a 4-fold increase in anti-gE antibody titers from baseline to M3). Of the 6 subjects reporting HZ episodes, four reported the post-vaccination episode of HZ within 5 years of a previous episode. Two of these 6 subjects had a medical history of more than one previous episode of HZ. Of the 3 additional subjects who reported AEs of PHN and facial neuralgia in the absence of a diagnosis of HZ, limited available information precluded conclusive diagnosis, although one subject had a clinical history that suggested HZ.

Summary -The pre-specified success criterion for VRR was met, although it is unclear that vaccine response following administration of HZ/su in the study population predicts protection against HZ. An additional limitation to interpreting the data from this study is that episodes of HZ in this study were reported with an incidence rate higher than that noted both expected in unvaccinated individuals with or without a prior history of HZ. To formally evaluate the incidence of HZ in subjects with prior HZ, the Applicant has proposed study Zoster-062, a randomized, observer-blind, placebo controlled, multicenter clinical trial to assess the safety, reactogenicity and immunogenicity of HZ/su when administered intramuscularly on a 0 and 2 month schedule to adults ≥ 50 years of age with a prior episode of HZ, which includes a secondary objective of the evaluation of the incidence of confirmed recurrent HZ episodes during the entire study period.

10. CONCLUSIONS

In Zoster-006 and Zoster-022, local and/or general solicited symptoms, generally of short duration, were reported in the majority of subjects evaluated in the HZ/su group. Severe reactogenicity was not uncommon, especially in the younger age strata. Overall, deaths, SAEs and pIMDs were reported in similar proportions of subjects in the HZ/su and Placebo groups. Routine pharmacovigilance and a proposed enhanced pharmacovigilance plan and active surveillance study will address observed imbalances (HZ/su group > Placebo group) and will surveil for other rare adverse events including pIMDs which may not have been observed given the sample size evaluated in the clinical efficacy studies.

HZ VE was confirmed in Zoster-006 (subjects ≥ 50 YOA) and Zoster-022 (subjects ≥ 70 YOA) and on the pooled analysis on subjects ≥ 70 YOA across both studies. Efficacy appears comparable in all age strata evaluated and durable up to 4 years post-vaccination. The benefit of HZ/su with regard to prevention of PHN appears attributable to VE against HZ.

Additional studies submitted to the BLA provided initial assessments of safety and immunogenicity (EXPLO-CRD-004 and extension studies, Zoster-023, Zoster-003 and extension studies), demonstrated that immune responses after administration of two doses of HZ/su were higher than after administration of gE/AS01$_E$ or gE/saline (Zoster-010), established the non-inferiority and safety of HZ/su when administered on a M0/M6 as compared to a M0/M2 schedule (Zoster-026), confirmed that the route of HZ/su administration would be IM (Zoster-032), confirmed the lot-to-lot consistency of HZ/su (Zoster-007), and evaluated the safety and immunogenicity of concomitant administration of HZ/su and QIV (Zoster-004).

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 92 – Risk Benefit Table

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Most individuals in developed countries have latent VZV infection. • Immunosenescence, immunosuppression or immunocompromise are major risk factors for HZ and HZ-related complications. • Acute HZ-associated pain can be severe and debilitating. • The complications of HZ are serious, and include acute pain, persistent neuropathic pain (PHN), viral dissemination, stroke, encephalitis and visual impairment including blindness.	• Older adults are at risk for HZ and HZ-related complications. • HZ is associated with substantial morbidity, which can be acute and/or chronic. • Based on the debilitating impact on physical and psychological well-being, HZ is a serious condition.
Unmet Medical Need	• Available preventive therapy for HZ in the U.S. is vaccination with a live attenuated virus vaccine (Zostavax). • The treatment of HZ includes time-sensitive administration of antiviral medications and therapeutics for pain control, including opioids. • PHN, the most common HZ-associated complication, can be refractory to treatment.	• HZ/su VE was high for all age strata evaluated. • Effective preventive vaccines obviate the need for time-sensitive antiviral medication and use of medications for adequate pain control, some with a narrow toxicity to therapeutic ratio in elderly individuals at high risk of HZ.
Clinical Benefit	• Two randomized, placebo-controlled, clinical endpoint efficacy trials were submitted, one in subjects ≥ 50 YOA (Zoster-006) and one in subjects ≥ 70 YOA (Zoster-022). • Point estimates of HZ VE were 97.16% [95% CI: (93.72, 98.97)] and 89.79% [95% CI: (84.29, 93.66)] in Zoster-006 and Zoster-022, respectively. • HZ VE was comparable in the pre-specified age strata (50 – 59, 60 – 69 and ≥ 70 YOA), and across genders, ethnicities, regions and most racial groups – HZ VE could not be demonstrated in subjects of African/African-American heritage. • HZ VE was not evaluated in immunodeficient/immunocompromised individuals, individuals with prior HZ, or in individuals with prior vaccination against HZ or VZV who were ineligible for enrollment in the clinical endpoint trials. • Data regarding immune response following concomitant administration with quadrivalent influenza vaccine (QIV) were included in this BLA, and immune responses when HZ/su was given alone were similar to those observed when HZ/su was co-administered with QIV. • HZ VE appeared durable up to year 4, but is unknown thereafter. • The need for and timing of a booster dose or re-vaccination is not known. • PHN VE appears attributable to VE against HZ.	• The clinical benefit of HZ/su was demonstrated, with high VE in all pre-specified age strata. • Although the study was not powered to evaluate HZ VE among racial or ethnic subgroups, the trend was that HZ VE was similar between the groups evaluated. • HZ VE in several sub-populations who were excluded from participation in the clinical endpoint studies is not known. • Efficacy of HZ/su when co-administered with any vaccine, including QIV, has not been evaluated. • HZ/su VE is being evaluated in a long-term follow-up study (Zoster-049), which enrolled subjects vaccinated in Zoster-006 and Zoster-022, with duration of follow-up ≈ 6 years. A small sub-population of subjects will receive 1 dose (booster) or 2 doses (re-vaccination) in the study.

Risk	• Reactogenicity was commonly reported and severe reactogenicity observed, and some general solicited symptoms were marginally higher after Dose 2 as compared to Dose 1. However, most reactogenicity events were mild or moderate and of short duration. • Imbalances (HZ/su > Placebo) in the occurrence of some AEs were observed. • In general, the occurrence of SAEs, pIMDs and deaths were comparable between vaccination groups in Zoster-006 and Zoster-022. • There is either no or insufficient safety information to assess the risk of vaccination in subjects who were excluded from the clinical endpoint studies but are not excluded from vaccination given the proposed indication, including immunodeficient/immunocompromised individuals, individuals with prior HZ, and individuals with prior vaccination against HZ or VZV. • As the immunogenicity results were only provided on a small subset of subjects, and the majority of individuals evaluated in Zoster-006 and Zoster-022 were seropositive at baseline, there are insufficient data in seronegative individuals to inform the safety of the vaccine in this population. • Ocular inflammatory events (e.g., keratitis, uveitis) have been reported in temporal association with vaccination against HZ (with the currently licensed live vaccine) in subjects with prior HZO; while causality has not been ascribed, a proposed mechanism for these events is that vaccination enhances the VZV-specific immune response targeting retained viral antigens in ocular tissues [(Hwang, 2013), (Khalifa, 2010)]. • Data regarding the safety and reactogenicity of the vaccine when co-administered with vaccines other than QIV were not included in the licensure application. • The safety and reactogenicity of re-vaccination with HZ/su is not known. • Although the database was adequate for the assessment of safety, a larger safety database may elucidate the risks, if any, for imbalances observed, and imbalances of rare events or events for which the effect size may be small.	• It is unknown whether the observed reactogenicity may increase health care utilization among HZ/su vaccinees or result in subjects not returning for a second vaccination in routine clinical practice. • Despite high overall reactogenicity of short duration, the overall safety profile supports licensure of HZ/su in adults ≥ 50 YOA. • The safety database submitted for immunocompromised subjects ≥ 50 YOA in Zoster-001 and Zoster-015 was insufficient to assess risk. • The Applicant has proposed study Zoster-062 to evaluate the safety, reactogenicity, and immunogenicity) of HZ/su in subjects with prior HZ. • Zoster-049 will evaluate the safety of revaccination with HZ/su.
Risk Management	The proposed pharmacovigilance plan includes routine pharmacovigilance as well as enhanced pharmacovigilance and a targeted safety study for 14 conditions based on their frequency in the clinical studies, the prevalence of the condition in the target population, or because they are events of interest.	• As proposed, the pharmacovigilance plan is adequate to manage the risk of HZ/su vaccination.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA establishes a substantial likelihood of benefit of vaccination with HZ/su in individuals ≥ 50 YOA due to VE in the prevention of HZ. The prevention of PHN is appears to be attributable to VE against HZ. Reactogenicity of short duration was commonly reported after HZ/su administration, and severe reactogenicity was reported, both higher in the younger age strata. While there were some imbalances in adverse events noted between the HZ/su and Placebo groups (HZ/su > Placebo), the proportions of subjects reporting SAEs, pIMDs and death were generally comparable between treatment groups. The risk-benefit profile of HZ/su supports approval in individuals ≥ 50 YOA.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval of HZ/su in individuals 50 YOA and older.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of HZ/su for the prevention of HZ in individuals 50 YOA and older.

11.5 Labeling Review and Recommendations

CBER requested that the Applicant delete reference to PHN in the proposed indication. The Highlights should contain a concise statement of each of the product's indications [21 CFR 201.57(a)(6)], and all indications in the full prescribing information must be supported by substantial evidence of effectiveness [21 CFR 201.57(c)(2)(v)].

Reviewer's comment – As proposed by the Applicant, the indication is not concise, and since it did not appear that additional benefit in terms of prevention of PHN could be demonstrated beyond that conferred by VE against HZ, vaccine effect on PHN incidence can be adequately described in the body of the PI.

11.6 Recommendations on Post-marketing Actions

CBER recommends that the following planned studies be post-marketing commitments; Zoster-062, Zoster-049 and a Targeted Safety Study to evaluate the safety of HZ/su in adults aged 50 years and older in a real time setting in the U.S.

Reviewer's comment – CBER concurs with the post-marketing commitments as proposed by the Applicant. Please refer to Section 4.6 and the OBE review for further details regarding post-marketing activities and pharmacovigilance.

APPENDIX

Table 93 List of Potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) Multiple sclerosis (including variants) Transverse myelitis Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) Other demyelinating diseases (including acute disseminated encephalomyelitis) Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) Non-infectious encephalitis/ encephalomyelitis Neuritis (including peripheral neuropathies) Narcolepsy	Systemic lupus erythematosus Scleroderma (including, CREST syndrome and morphoea) Systemic sclerosis Dermatomyositis Polymyositis Antisynthetase syndrome Rheumatoid arthritis, Juvenile chronic arthritis, (including Still's disease) Polymyalgia rheumatica Reactive arthritis Psoriatic arthropathy Ankylosing spondylitis Relapsing polychondritis Mixed connective tissue disorder	Psoriasis Vitiligo Raynaud's phenomenon Erythema nodosum Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) Cutaneous lupus erythematosus Alopecia areata Lichen planus Sweet's syndrome
Liver disorders	**Gastrointestinal disorders**	**Metabolic diseases**
Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis.	Crohn's disease Ulcerative colitis Ulcerative proctitis Celiac disease	Autoimmune thyroiditis (including Hashimoto thyroiditis) Grave's or Basedow's disease Diabetes mellitus type I Addison's disease
Vasculitides		**Others**
Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis. Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.		Autoimmune hemolytic anemia Autoimmune thrombocytopenias Antiphospholipid syndrome Pernicious anemia Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) Uveitis Autoimmune myocarditis/cardiomyopathy Sarcoidosis Stevens-johnson syndrome Sjögren's syndrome Idiopathic pulmonary fibrosis Goodpasture syndrome

Source: 125614/0 Zoster-006 Clinical Study Report Page 99 Table 16

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