Application Type	Original BLA
STN	125614/0
CBER Received Date	October 21, 2016
PDUFA Goal Date	October 20, 2017
Division / Office	DVRPA/OVRR
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	GlaxoSmithKline Biologicals
Established Name	Zoster Vaccine Recombinant, Adjuvanted
(Proposed) Trade Name	Shingrix
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	After reconstitution, each 0.5 mL dose contains 50 mcg of gE recombinant protein, 50 mcg of MPL, and 50 mcg of QS-21.
Dosage Form(s) and Route(s) of Administration	Two doses (0.5-mL each) administered intramuscularly
Dosing Regimen	Administer 2 doses at 0 and 2 to 6 months
Indication(s) and Intended Population(s)	Prevention of herpes zoster (shingles) in adults aged 50 years and older.

Table of Contents

GLOSSARY

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATPc	According to Protocol Cohort
CI	Confidence Interval
CMI	Cell-Mediated Immunogenicity
CSR	Clinical Study Report
DLP	Data Lock Point
EOS	End of Study
GCP	Good Clinical Practice
GMC/T	Geometric Mean Concentration/Titer
HI	Hemagglutination Inhibition
HZ	Herpes Zoster
HZAC	Herpes Zoster Adjudication Committee
IM	Intramuscular/Intramuscularly
ISS	Integrated Summary of Safety
IR	Information Request
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
mTVc	Modified Total Vaccinated Cohort
PCR	Polymerase Chain Reaction
PHN	Postherpetic Neuralgia
PIMD	Potential Immune-Mediated Disease
RR	Relative Risk
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TVc	Total Vaccinated Cohort
VE	Vaccine Efficacy
VRR	Vaccine Response Rate
VZV	Varicella-Zoster Virus
YOA	Year of Age
ZBPI	Zoster Brief Pain Inventory

1. EXECUTIVE SUMMARY

GSK is seeking licensure of the herpes zoster (HZ) vaccine Shingrix (referred to as HZ/su in this review), indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. The application is mainly supported by the efficacy and safety data from two pivotal studies ZOSTER-006 and ZOSTER-022, where study subjects received two doses of HZ/su or placebo on a 0, 2-month schedule. The application is also supported by three other pivotal phase 3 immunogenicity studies in subjects ≥50 years of age (YOA).

ZOSTER-006 and ZOSTER-022 (Efficacy): The primary efficacy objectives in each individual efficacy study and in the pooled efficacy analysis were all met.

- The primary objective to demonstrate the vaccine efficacy (VE) of HZ/su in prevention of HZ compared to placebo in adults ≥50 YOA was met in ZOSTER-006

(success criterion: lower limit of the two-sided 95% confidence interval [CI] of VE >25%). The estimated HZ VE in adults ≥50 was 97.16% (95% CI: 93.72% to 98.97%).

- The primary objective to demonstrate the VE of HZ/su in prevention of HZ compared to placebo in adults ≥70 YOA was also met in ZOSTER-022 (success criterion: lower limit of the two-sided 95% CI of VE >10%). The estimated HZ VE in adults ≥70 was 89.79% (95% CI: 84.29% to 93.66%).
- The primary objective to demonstrate the VE of HZ/su in prevention of postherpetic neuralgia (PHN) compared to placebo in adults ≥70 YOA was met in the pooled analysis of ZOSTER-006 and ZOSTER-022 (success criterion: lower limit of the two-sided 95% CI of VE >0%). The estimated PHN VE in adults ≥70 was 88.78% (95% CI: 68.70% to 97.10%).

ZOSTER-006 and ZOSTER-022 (Safety): HZ/su showed higher risk of local and general reactogenicity (any grade and grade 3) and unsolicited adverse events (AEs) (within 30 days post-vaccination) compared to placebo. No apparent imbalance was observed in the incidence rate of deaths, serious adverse events (SAEs), or potential immune-mediated diseases (pIMDs) between the HZ/su and placebo groups.

ZOSTER-007: The primary objective of lot-to-lot consistency in terms of geometric mean concentration (GMC) of anti-gE ELISA antibody at one month post the second dose of HZ/su (referred to as post-vaccination anti-gE ELISA hereafter in the Executive Summary) was met.

ZOSTER-004: This study was to assess the immunogenicity of HZ/su when co-administered with a quadrivalent influenza vaccine (Co-Ad) versus separate administration of the two vaccines (Control) in adults ≥50 YOA. Three co-primary objectives were evaluated based on the vaccine response rate (VRR) of post-vaccination anti-gE ELISA in the Co-Ad group, and non-inferiority of the Co-Ad group compared to the Control group in terms of post-vaccination anti-gE ELISA GMC and Hemagglutination Inhibition (HI) geometric mean titer (GMT) 21 days post influenza vaccination. All three co-primary objectives were met.

ZOSTER-026: This study was a dosing schedule comparison study that evaluated the post-vaccination anti-gE ELISA (0, 6-month and 0,12-month versus 0, 2-month) in adults ≥50 YOA. The co-primary objectives based on evaluations of VRR and non-inferiority in terms of GMC compared to the 0, 2-month schedule were met for the 0, 6-month schedule, but not met for the 0,12-month schedule (the non-inferiority criterion was not met).

2. CLINICAL AND REGULATORY BACKGROUND

Shingrix is a sub-unit vaccine consisting of recombinant Varicella-Zoster Virus (VZV) glycoprotein gE as antigen, combined with GSK's proprietary Adjuvant System AS01B. The content of the AS01B vial is used to reconstitute the content of the gE vial immediately prior to intramuscular injection of HZ/su. The purpose of this application is to obtain approval for the following indication: "Shingrix is a non-live, recombinant

vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, Shingrix reduces the overall incidence of postherpetic neuralgia."

2.1 Disease or Health-Related Condition(s) Studied

Please refer to the clinical review.

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

Please refer to the clinical review.

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

Please refer to the clinical review.

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

NA

2.6 Other Relevant Background Information

NA

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring reviews.

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

Please refer to each corresponding discipline review.

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

5.1 Review Strategy

This review focuses on five pivotal clinical studies as listed in Section 5.3.

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

The following sections in STN 125614/0.0 were reviewed in detail:

- Module 1.14: Labeling

- Module 2.7.4: Summary of Clinical Safety
- Module 5.3.5.1: Clinical study reports (CSRs) and protocols: ZOSTER-006, ZOSTER-022, ZOSTER-004, and ZOSTER-026
- Module 5.3.5.2: CSR and protocol: ZOSTER-007
- Module 5.3.5.3: Integrated Summary of Safety (ISS)

In addition, I reviewed the information submitted in response to information requests (IRs) in amendments to the original BLA submission:

- Amendment 6: module 5.3.5: Statistical Analysis Plans (SAPs) for five pivotal clinical studies and the ISS
- Amendment 16: module 1.11.3: GSK's clarification regarding the eligibility criterion on age for enrolled subjects in ZOSTER-006 and ZOSTER-022
- Amendment 20: module 1.11.3: GSK's response regarding the IR on efficacy analyses for ZOSTER-006 and ZOSTER-022
- Amendment 21: module 1.11.3: Subgroup efficacy analyses for ZOSTER-006, ZOSTER-022, and pooled analysis of ZOSTER-006 and ZOSTER-022
- Amendment 22: module 1.11.3: Revised safety analyses on death
- Amendment 25: module 1.11.3: Revised safety analyses on SAE and pIMD

5.3 Table of Studies/Clinical Trials

There are five pivotal studies included in this submission to support the licensure application.

Table 1: Overview of pivotal clinical studies in the application

Study	Study population	Study countries	Study design	Treatment groups	Number of total subjects enrolled	Duration of follow-up planned	Primary objectives
Zoster-006	Adults (≥50 YOA) stratified: 50-59, 60-69, 70-79, and ≥80 YOA in a 8:5:3:1 ratio	18 countries[a]	Phase III, randomized, observer-blind, pivotal efficacy study	1:1 to HZ/su or placebo 2 doses at Months 0 and 2	16161	Follow-up driven by case accrual was at least 30 months[b].	VE in the prevention of HZ in adults ≥50 YOA
Zoster-022	Adults (≥70 YOA) stratified: 70-79 and ≥80 YOA in a 3:1 ratio	Identical to Zoster-006	Phase III, randomized, observer-blind, pivotal efficacy study	1:1 to HZ/su or placebo 2 doses at Months 0 and 2	14816	Follow-up driven by case accrual was at least 30 months[b].	VE in the prevention of HZ in adults ≥70 YOA (Co-primary objectives for Pooled Zoster-002 and Zoster-006: • VE in the prevention of PHN in subjects ≥ 70 YOA • VE in the prevention of HZ in subjects ≥70 YOA)
Zoster-007	Adults (≥50 YOA)	Belgium, Canada, US	Phase III, randomized, double-blind, lot-to-lot consistency study	1:1:1 to three HZ/su lots	651	12 months post last vaccination[c]	Lot-to-lot consistency in terms of anti-gE Abs GMC at Month 3 between 3 HZ/su production lots
Zoster-004	Adults (≥50 YOA)	Canada, Germany, US	Phase III, randomized, open-label, co-administration of HZ/su with quadrivalent seasonal influenza vaccine (FLU-D-QIV)	1:1 to Co-Ad or Control Co-Ad: 2 doses HZ/su at Months 0 and 2 & 1 dose FLU-D-QIV at Month 0 Control: 1 dose FLU-D-QIV at Month 0 & 2 doses HZ/su at Months 2 and 4	828	12 months post last vaccination	Co-primary objectives: • VRR to HZ/su (anti-gE Abs) in Co-Ad group at Month 3 • Non-inferiority in terms of anti-gE Ab GMC one month post the 2nd dose of HZ/su • Non-inferiority in terms of HI antibody GMT against 4 influenza vaccine strains at Day 21 post vaccination
Zoster-026	Adults (≥50 YOA)	Estonia, US	Phase III, randomized, open-label, schedule comparison study	1:1:1 to three dose schedule groups (0,2-month; 0,6-month; 0,12-month)	354	12 months post last vaccination	Co-primary objectives: • VRR to HZ/su (anti-gE Abs) at 1 month post Dose 2 in the 0,6-month and 0,12-month schedule groups. • If the 0,6-month schedule VRR objective was met: non-inferiority of 0,6-month to 0,2-month in terms of anti-gE Ab GMC ratio at 1 month post Dose 2. • If the 0,12-month schedule VRR objective was met: non-inferiority of 0,12-month to 0,2-month in terms of anti-gE Ab GMC ratio at 1 month post Dose 2.

[a]Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, China-Hong Kong, Italy, Japan, Mexico, South Korea, Spain, Sweden, Taiwan, UK, US
[b]The median follow-up time was 4.1 years for ZOSTER-006 and 3.9 years for ZOSTER-022 at the End of Study analysis.
[c]The CSR submitted to this BLA included data for the Month 3 analysis.
Ab: Antibody
Source: Table 2 of Module 2.5 Clinical Overview

5.4 Consultations

NA

5.5 Literature Reviewed (if applicable)

NA

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Zoster-006

Title: A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.

6.1.1 Objectives (Primary, Secondary, etc.)

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.
    - Success criterion: To demonstrate clinically meaningful overall HZ VE, the lower limit of the two-sided 95% CI of VE should be above 25%.

Secondary objectives

- To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59, 60-69, and ≥70 YOA, as measured by the 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, 60-69, 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, 60-69, and ≥70 YOA, with confirmed HZ;
- To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥50 YOA and in subjects within each of the following age ranges: 50-59, 60-69, 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, 60-69, 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, 60-69, and ≥70 YOA, with confirmed HZ;
- To evaluate vaccine safety and reactogenicity.

6.1.2 Design Overview

This study was an observer-blinded trial. Eligible subjects 50-69 YOA were assigned to ZOSTER-006, and eligible subjects 70-79 YOA and ≥80 YOA were randomly assigned through a central randomization system on the internet to ZOSTER-006 or ZOSTER-022. In study ZOSTER-006, eligible subjects were randomized 1:1 to receive HZ/su or placebo at Month 0 and Month 2, stratified by age (50-59, 60-69, 70-79, and ≥80 YOA in approximately an 8:5:3:1 ratio to achieve similar numbers of HZ cases in three main age strata [70-79 and ≥80 YOA combined]). The randomization algorithm used stratification and minimization techniques for each parameter (see below) to determine the treatment number to be used for each subject:

- by region: stratification;
- by age cohort within each region: stratification;
- by country within each region: minimization;
- by site within each country: minimization.

Follow up of HZ

Data were collected on all suspected HZ cases that occurred from administration of the first vaccination until the cut-off date for End of Study (EOS) analysis. For each suspected case of HZ that the investigator concluded was clinically consistent with HZ, data on HZ-associated pain (using Zoster Brief Pain Inventory [ZBPI] questionnaires completed by the subject) were collected daily from Day HZ-1 (the day after Visit HZ-1 when the subject came to the study site for the first evaluation of the suspected case of HZ) up to Day-HZ-28, and weekly from Day HZ-29 until:1) the subject had no HZ-associated pain for 4 consecutive weeks; or 2) the cut-off date for EOS analysis (for all subjects with ongoing HZ-associated pain at the time of cut-off date for EOS analysis, ZBPI data were collected until a 4-week pain-free period was documented or until at least Day HZ-90). If a 4-week pain-free period was achieved and the HZ rash resolved, subsequent follow-up visits or contacts related to this case of HZ were cancelled. If pain reappeared in the same area after a 4-week pain-free period and was not accompanied by a new HZ rash, it was assigned to the previous HZ-episode. The completion of ZBPI resumed based upon the weekly schedule established at the start of the assigned episode.

A suspected case of HZ could be confirmed in two ways: by Polymerase Chain Reaction (PCR) or by the herpes zoster adjudication committee (HZAC). The HZAC classified all referred cases as either “HZ,” “not HZ,” or “not able to decide.” However, the HZAC classification served as the final case definition only when the case could not be confirmed or excluded by PCR (e.g., when all samples from a given subject were inadequate or when both the VZV and β-actin PCR results were negative or when no samples were available for a given subject). If the final outcome was “not able to decide” based on HZAC, for analysis it was considered as not HZ.

PHN was defined by the presence of HZ-associated severe “worst” pain persisting or appearing more than 90 days after onset of the HZ rash. Severe “worst” pain was defined as HZ-associated pain rated as 3 or greater on the “worst pain” ZBPI question. The presence of the following HZ complications was documented in the electronic case report

form: HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke.

Blood samples collection for immunogenicity

- Blood samples were collected from all subjects at Month 0 and Month 3, to contribute to the correlate of protection assessment should the subject experience a HZ episode or be selected as a case control;
- Blood samples were collected from a subset of subjects at Months 14, 26, and 38 to assess persistence of humoral immune response. In these subjects, the blood samples from Months 0 and 3 were also assessed for humoral immune response;
- Blood samples were collected from a subset of subjects at Months 0, 3, 14, 26, and 38 to assess cell-mediated immune (CMI) response (CMI component of immunogenicity subset);

Subjects were randomly allocated to be part of the immunogenicity subset according to a provisional sample size by country: Czech Republic, Japan, and US were to have approximately 156 subjects per country, equally distributed over the 50-59, 60-69, and ≥70 YOA age strata and treatment groups; other countries were to have approximately 138 subjects per country, equally distributed over the 50-59, 60-69, and ≥70 YOA age strata and treatment groups. This resulted in a provisional number of 2538 subjects in total for the immunogenicity subset. The CMI component for immunogenicity subset consisted of three countries (Czech Republic, Japan, and US) at designated sites that had access to a peripheral blood mononuclear cells processing facility within the acceptable time window from sample collection to processing.

Safety data collection

A random subset of subjects from the 50-59 and 60-69 YOA strata and all subjects from the 70-79 and ≥80 YOA strata were to be allocated to the 7-day diary card subset. The provisional number of subjects in the 7-day diary card subset was 1410 per treatment group for the 50-59, 60-69, and 70-79 YOA age strata, and 470 per treatment group for the ≥80 YOA age stratum. Solicited AEs were evaluated only in subjects who were part of the 7-day diary card subset from Day 0 to Day 6 after each vaccination. Unsolicited AEs and any concomitant medication and vaccination were evaluated in all subjects from Day 0 to Day 29 after each vaccination. SAEs were evaluated in all subjects; the standard time period for collecting and recording SAEs began at Day 0 and continued until Month 14. Follow-up for the occurrence of SAEs related to an HZ complication, study participation, a concurrent GSK medication/vaccine, or any fatal SAE continued until study conclusion. Follow-up for the occurrence of pIMDs began at Day 0 and continued until study conclusion. Medically attended visits were evaluated in all subjects from Day 0 until Month 8.

Duration of the study

All subjects were followed at least until the cut-off date for EOS analysis, regardless of their date of enrollment. Study end took place when the conditions for EOS analysis were met and, for each HZ case that occurred up to the cut-off date for EOS analysis, a minimum 90 days follow-up was completed or four consecutive weeks of HZ-associated

pain-free was documented and rash resolved. The maximum duration for each subject was expected to be approximately four to five years.

6.1.3 Population

The study included subjects aged 50 years and older without a history of HZ, previous vaccination against varicella or HZ, or confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or therapy.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study vaccine HZ/su was supplied in 2 vials, one containing the VZV gE antigen and the other containing Adjuvant System $AS01_B$. After reconstitution, each 0.5 mL dose of study vaccine contained 50 µg of gE recombinant protein, 50 µg of MPL (3-*O*-desacyl-4'-monophosphoryl lipid A), 50 µg of QS-21 (Quillaja saponaria Molina, fraction 21), and liposomes. The (b) (4) solution used as placebo was provided in monodose vials (0.5 mL/dose) containing (b) (4) per 0.5 mL dose. The route of vaccination was intramuscular (IM) injection.

6.1.6 Sites and Centers

The study was conducted at sites in 18 countries: Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, China-Hong Kong, Italy, Japan, Mexico, South Korea, Spain, Sweden, Taiwan, United Kingdom, and US.

6.1.7 Surveillance/Monitoring

NA

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint

- Confirmed HZ cases during the study in the modified total vaccinated cohort (mTVc).

Secondary efficacy endpoints

- Incidence of PHN calculated using 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 overall and HZ-related mortality during the study;
- Incidence of HZ complications during the study in subjects with confirmed HZ;
- Incidence of overall and HZ-related hospitalizations during the study;
- Duration of pain medication administered for HZ during the study in subjects with confirmed HZ.

Secondary safety endpoints

- Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;

- Occurrence, intensity, and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
- Occurrence, intensity, and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, in all subjects;
- Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
- Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
- Occurrence of any fatal SAEs during the entire study period in all subjects;
- Occurrence and relationship to vaccination of any pIMDs during the entire study period in all subjects;
- Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits, or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in all subjects.

Reviewer's comments:
The secondary objective on pain medication was to evaluate the VE in reduction in "use" of pain medication (as a binary variable Yes/No), whereas the secondary endpoint on pain medication was defined as the "duration" of pain medication. Since the success criterion and statistical analysis method specified in the SAP were both for "use" of pain medication, "use" of pain medication is considered as a pre-specified endpoint. This issue also applies to ZOSTER-022.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Scope of analyses, ZOSTER-006, ZOSTER-022, and pooling of ZOSTER-006 and ZOSTER-022

Study ZOSTER-006 (enrolling subjects ≥50 YOA) and study ZOSTER-022 (enrolling subjects ≥70 YOA) were similar studies conducted concurrently at the same sites to evaluate efficacy of the HZ/su vaccine. The primary objective for study ZOSTER-006 was to evaluate HZ VE in subjects ≥50 YOA. The primary objective for study ZOSTER-022 was to evaluate HZ VE in subjects ≥70 YOA. The evaluation of VE in reduction of PHN in subjects ≥70 YOA was a primary objective for the pooled analysis of ZOSTER-006 and ZOSTER-022.

Sequence of analyses

It was predicted that study ZOSTER-006 would reach conditions required for triggering the final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore, GSK decided to disassociate the two studies in terms of timing of the analysis of each study. The protocol was therefore amended to allow for a two-step approach (final analysis of HZ efficacy, then PHN efficacy) for the analysis of each study. Both studies ended concurrently for the pooled analysis. In study ZOSTER-006, the planned analysis steps were:

1. Final HZ efficacy analysis (step 1), which was to include analyses of all HZ VE objectives, and all reactogenicity/safety and immunogenicity objectives. The cut-off date for this step was defined when the following conditions were met and occurred on July 1, 2014:
   - at least 196 confirmed HZ cases were accrued in the mTVc;
   - approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA were accrued in the mTVc;
   - approximately 75% of subjects in each stratum had completed at least 36 months follow-up after Dose 2, and the remaining subjects had completed at least 30 months follow-up after Dose 2.

   The ZOSTER-006 study continued until an adequate number of HZ cases were accrued in ZOSTER-022 and an adequate number of PHN cases were accrued in both ZOSTER-006 and ZOSTER-022.

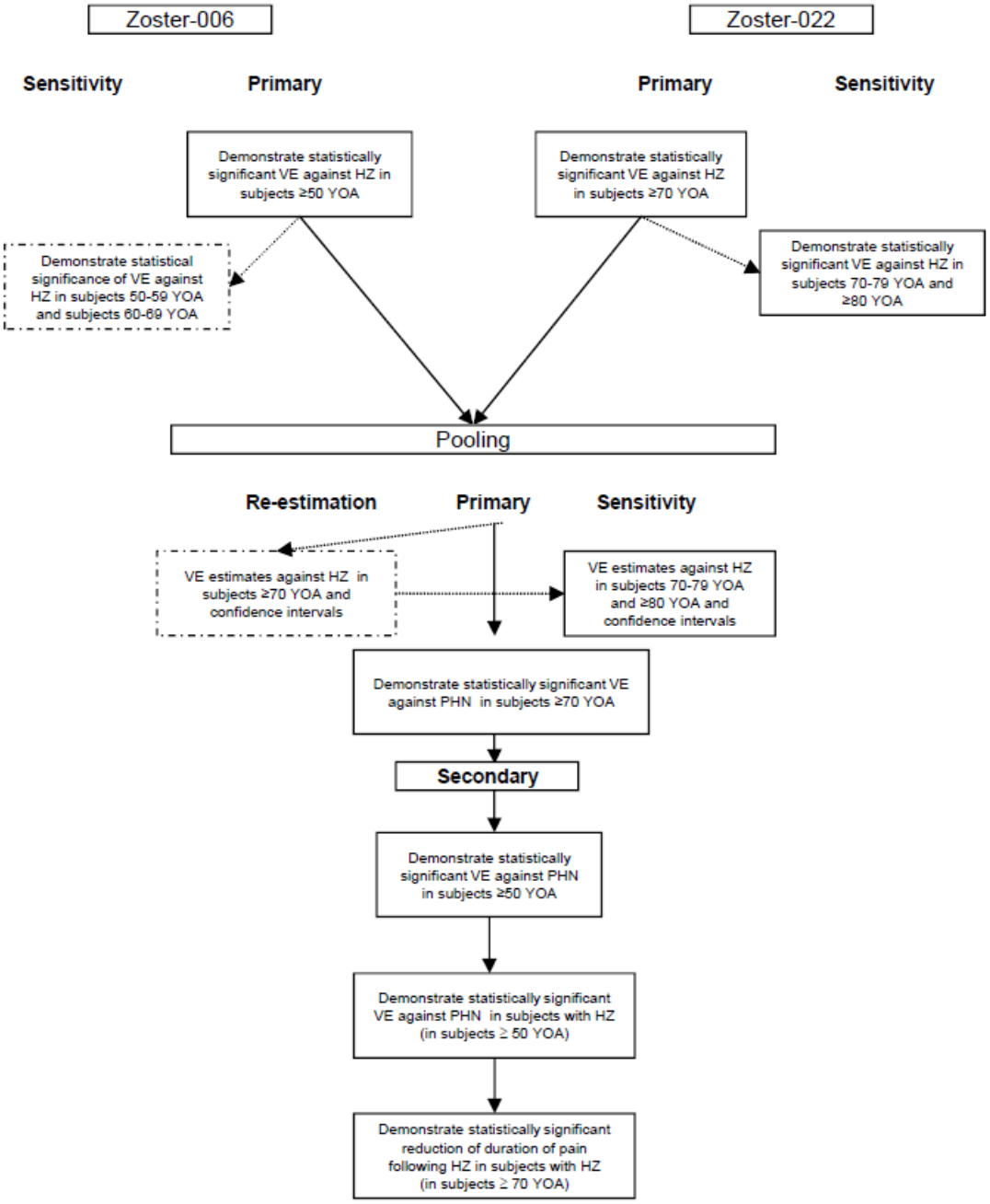
2. EOS analysis (step 2). All objectives of study ZOSTER-006 were to be analyzed. Objectives already analyzed at step 1 were re-analyzed (as descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise). The cut-off date for EOS analysis occurred on April 21, 2015 given the following:
   - all conditions were met for final HZ efficacy analysis in study ZOSTER-022;
   - at least 35 PHN cases in subjects ≥70 YOA were accrued in the mTVc when pooling studies ZOSTER-006 and ZOSTER-022.

Pooled analysis of studies ZOSTER-006 and ZOSTER-022 was planned if the primary objectives of both study ZOSTER-006 and study ZOSTER-022 were demonstrated.

Significance level

The statistical testing for each study proceeded sequentially using a gatekeeping procedure defined prospectively (Figure 1). All secondary objectives in ZOSTER-006 and ZOSTER-022 were evaluated within each report. However, the overall type 1 error of 5% two-sided can only be fully controlled for those objectives that were mentioned sequentially in the gatekeeping strategy. If a gatekeeping family failed to be demonstrated, the remaining planned tests were performed, but the type 1 error of the following families is not fully controlled.

Figure 1: Gatekeeping strategy (ZOSTER-006, ZOSTER-022, and pooling of ZOSTER-006 and ZOSTER-022)



Source: Figure 1 of Zoster-006 protocol Amendment 4

Sample size

It was estimated that 196 confirmed HZ cases would provide ~97% power to demonstrate an overall HZ VE of at least 40%, assuming a true HZ VE of 68% and a HZ VE of at least 10% for the 50-59 and 60-69 YOA age strata with power of 99% and 98%, respectively. A total sample size of 15,980 was selected to provide the required number of HZ cases within a follow-up time of ~3 years.

Efficacy analyses

The primary analysis for efficacy was based on the mTVc. For the primary objective of HZ VE, the analysis method considered the exact inference on the relative risk (RR) stratified for age (three main age levels: 50-59, 60-69, and ≥70 YOA) and regions, assuming a Poisson distribution for the number of HZ cases and conditioning on the total number of events observed and time at risk. StatXact 9.0 was used to calculate the RR. The VE was calculated as 1-RR (vaccine group versus placebo group). The HZ incidence rate was determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject. The number of person-years at risk over an interval of time was the sum of the confirmed HZ-free time 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.

Regarding the analyses of secondary efficacy objectives:

- For the VE in reduction in PHN risk and HZ-related mortality and hospitalization , the RR was evaluated using the exact Poisson method similar to that for the HZ VE;
- The VE in reduction of duration of severe "worst" pain was analyzed primarily using the Cox-proportional hazards model (with the time to event calculated as being the inverse of duration of pain or 1 if censored);
- For the VE in reduction in use of pain medication and HZ associated complications in subjects with confirmed HZ, the RR was evaluated using the asymptotic standardized unconditional binomial test, stratified by age stratum.

In addition, the SAP specified for each of the above secondary efficacy objectives that the VE was to be demonstrated if the lower limit of the two-sided 95% CI of VE was above 0%.

Reviewer's comments:

Although a success criterion was pre-defined for each of the secondary efficacy objectives, no appropriate Type I error control strategies appear to be pre-specified within study ZOSTER-006. Also, a summary of analyses in the SAP indicated that the PHN VE was to be analyzed as a descriptive objective instead of an inferential objective at the EOS analysis step in ZOSTER-006.

Immunogenicity analyses

The primary analysis of immunogenicity was based on the According to Protocol cohort (ATPc) for immunogenicity. Subjects with missing or non-evaluable measurements were excluded. The following parameters (with 95% CIs) were tabulated for anti-gE ELISA antibody titers, for each treatment group by age stratum and by region: GMCs, seropositivity rate (cut-off: 97 mIU/mL), and VRR. The VRR for anti-gE ELISA titers was defined as the percentage of subjects who had at least:

- a 4-fold increase in the post-dose 2 anti-gE antibody titers as compared to the pre-vaccination titers, for subjects who were seropositive at baseline, or,
- a 4-fold increase in the post dose 2 anti-gE antibody titers as compared to the cut-off value for seropositivity, for subjects who were seronegative at baseline.

Safety analyses

The primary analysis of safety was based on the Total Vaccinated cohort (TVc). The analysis of solicited symptoms only included subjects/doses with documented safety data (i.e., symptom screen/sheet completed) for subjects belonging to the 7-day diary card subset.

Major changes in the conduct of study or planned analyses from the protocol

- The cut-off date used for ZOSTER-006 (and ZOSTER-022) EOS efficacy analysis was April 21, 2015. Following GSK's decision on April 16, 2015 to end the ZOSTER-006 and ZOSTER-022 trials, the investigators were asked to stop the collection of suspected HZ cases in both studies on April 23, 2015. By error, April 21 instead of April 23 was applied as the cut-off date for the analysis of efficacy. The impact was very low. No suspected HZ cases were collected from April 21 to April 23. As a sensitivity analysis, primary and secondary VE objectives for HZ and PHN were assessed using both cut-off dates (April 21 and 23, 2015); the results showed no differences regarding VE , 95% CI, and p-value;
- According to the protocol, a suspected case of HZ was considered as "HZ" if the HZAC members concurred unanimously; otherwise, it was to be classified as "not HZ." GSK clarified that the final HZAC assignment of a suspected case of HZ could also be categorized by HZAC as "not able to decide." If the HZAC final outcome was "not able to decide" and the case could not be confirmed or excluded by PCR, the overall final outcome was "No possible classification." For analysis, the categories "not HZ" and "No possible classification" were considered as "not HZ."
- Regarding the evaluation of VE in use of pain medication, a more adapted method (i.e., binomial test instead of the SAP specified Poisson procedure) was used, in consideration that the objective was to be evaluated in subjects with confirmed HZ.
- Evaluation of VE in the reduction of overall mortality and hospitalization was not performed, but descriptive safety tables and SAE listings were generated.
- Given the anticipated timing of availability of immunogenicity test results, in alignment with the SAP, a second database freeze pertaining to the final HZ efficacy analysis step was planned for immunogenicity data. However, given GSK's decision to terminate ZOSTER-006 earlier than initially anticipated, the second database freeze pertaining to the final HZ efficacy analysis step did not occur, and assessments of the immunogenicity objectives occurred at the time of EOS.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

- The TVc included all vaccinated subjects (at least one dose) with respect to the vaccine actually administered.
- The mTVc excluded subjects in the TVc for efficacy analysis who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination, or for whom one of the following criteria applied:
    - site or route of study vaccine administration was wrong or unknown; study vaccine administration was not according to protocol for reason (other than

site and 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 ATPc for immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. ATPc for immunogenicity-Humoral and ATPc for immunogenicity-CMI were defined separately depending on the availability of respective immune response.

6.1.10.1.1 Demographics

The summary of demographic characteristics for the mTVc at the final HZ efficacy analysis step is presented in Table 2. The distribution of demographic characteristics for EOS analysis TVc and mTVc are very similar to that for the final HZ efficacy analysis.

Table 2: Summary of demographic characteristics for ZOSTER-006 (mTVc - Final HZ efficacy analysis)

Characteristics	Parameters or Categories	HZ/su N=7344		Placebo N=7415		Total N=14759	
		Value or n	%	Value or n	%	Value or n	%
Age (years) at dose 1	Mean	62.3	-	62.2	-	62.3	-
	Range	50 – 96	-	48 – 95	-	48 – 96	-
Gender	Female	4483	61.0	4544	61.3	9027	61.2
	Male	2861	39.0	2871	38.7	5732	38.8
Ethnicity	American Hispanic or Latino	780	10.6	808	10.9	1588	10.8
	Not American Hispanic or Latino	6564	89.4	6607	89.1	13171	89.2
Geographic Ancestry	African Heritage / African American	126	1.7	123	1.7	249	1.7
	American Indian or Alaskan Native	8	0.1	5	0.1	13	0.1
	Asian - Central/South Asian Heritage	4	0.1	4	0.1	8	0.1
	Asian - East Asian Heritage	1080	14.7	1080	14.6	2160	14.6
	Asian - Japanese Heritage	299	4.1	304	4.1	603	4.1
	Asian - South East Asian Heritage	7	0.1	17	0.2	24	0.2
	Native Hawaiian or Other Pacific Islander	1	0.0	3	0.0	4	0.0
	White - Arabic / North African Heritage	43	0.6	41	0.6	84	0.6
	White - Caucasian / European Heritage	5278	71.9	5313	71.7	10591	71.8
	Other	498	6.8	525	7.1	1023	6.9

Source: Table 28 of Zoster-006 CSR

Reviewer's comments:

The study was designed to enroll subjects ≥50 YOA, but actually included one subject (in the placebo group) who was 48 YOA. This inclusion appears acceptable, as the clinical reviewer considered this subject to be close to 50 and at a similar risk level.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

NA

6.1.10.1.3 Subject Disposition

A total of 16161 subjects were enrolled in the study. At the final HZ efficacy analysis step, 16160 subjects were encoded in the clinical dataset as enrolled in the study. Among

them, 726 (4.5%) were eliminated from all statistical analyses. These subjects included all subjects (N=671) from Center 74895 in Mexico due to significant deviations from Good Clinical Practice (GCP) compliance, 9 subjects from Centers 75780 and 75783 in Mexico because of incorrectly applied informed consent process, all subjects (N=46) from Center 80997 in the US due to center closure in August 2014 for business reasons. The number of subjects included in the TVc and the number of subjects excluded from the mTVc with reasons for exclusion are presented for the final HZ efficacy analysis step in Table 3.

At the EOS analysis step, 6 additional subjects (3 subjects in each treatment group) were excluded from all statistical analyses (2 subjects in Center 80157 in the US whose data were not endorsed by the investigator and 4 subjects in Center 75783 in Mexico whose source documentation [medical charts] was lost). (Of note, one of the 6 subjects did not receive dose 2 and was finally excluded from the mTVc at the final HZ efficacy analysis step.) Therefore, 732 (4.5%) of 16161 subjects were eliminated from all statistical analyses. A subject who was entered in the clinical database after the final HZ efficacy analysis step did not receive the study vaccine and was eliminated from the TVc. As a result, after excluding additional subjects who did not receive any administration, the number of subjects included in the TVc was 15405 (7695 and 7710 in HZ/su group and placebo group, respectively). Compared to the final HZ efficacy analysis step, it was confirmed that one additional subject in the HZ/su group from the TVc did not receive dose 2 (this subject did not have a confirmed HZ episode). For subjects in the TVc, 14753 were included in the mTVc (7340 [95.4%] in HZ/su and 7413 [96.1%] in placebo).

Table 3: Number of subjects enrolled into study ZOSTER-006 as well as the number excluded from mTVc with reasons for exclusion (Final HZ efficacy analysis)

	Total			**HZ/su**		**Placebo**		**No Group**	
Title	**n**	**s**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total cohort	16160		-	8068	-	8077		15	-
Subjects excluded from all stat analysis	726	726	-	363	-	362		1	-
Total effective cohort	15434		-	7705	-	7715		14	-
Study vaccine dose not administrated but subject number allocate	23	24	-	7	-	2		14	-
Total vaccinated cohort	15411		100	7698	100	7713	100	0	-
Study vaccine dose not administered according to protocol	6	6	0.0	4	0.1	2	0.0	0	-
Wrong replacement or study vaccine administered	14	15	0.1	9	0.1	5	0.1	0	-
Subjects who did not receive two doses	614	654	4.0	337	4.4	277	3.6	0	-
Subjects having an episode of HZ prior than 30 days after the dose 2	18	18	0.1	4	0.1	14	0.2	0	-
Modified Total Vaccinated Cohort	14759		95.8	7344	94.5	7415	96.1	0	-

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 TVc
s = number of subjects with the elimination code assigned
% = percentage of subjects relative to the TVc
Source: Table 25 (revised) of IR response submitted to STN 125614/0.9

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The analysis of the primary objective of HZ VE in subjects ≥50 YOA occurred at the final HZ efficacy analysis step. This included HZ cases that were confirmed before or on

the cutoff date of July 1, 2014. The follow-up time ended at the last visit for subjects who completed the study and did not have a confirmed HZ episode, and at the cutoff date for subjects who did not yet complete the study at the time of analysis and did not have a confirmed HZ episode (IR response submitted to STN 125614/0.20). Results are summarized in Table 4. The acceptance criterion of lower bound of the 95% CI of VE >25% was met.

Table 4: Vaccine efficacy: First or only episode of HZ during the entire study period in subjects ≥50 YOA using Poisson method (mTVc - Final HZ efficacy analysis) – ZOSTER-006

	HZ/su				Placebo				VE	
Age	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	95% CI
≥50 YOA	7344	6	23297.0	0.3	7415	210	23170.5	9.1	97.16	(93.72, 98.97)

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
Source: Table 33 of Zoster-006 CSR

Reviewer's comments:
I conducted the following sensitivity analyses:

1. *Four subjects had their HZ episode confirmed after the final HZ efficacy analysis cutoff date. At the time of final HZ efficacy analysis, they had the HZAC decision available but PCR result pending (therefore considered as "Not HZ" for the primary analysis). A sensitivity analysis was performed by determining their HZ outcomes using the HZAC decisions.*
2. *A second sensitivity analysis was performed by setting the end of follow-up time for non-HZ cases at the last contact before the cut-off date.*
3. *The third sensitivity analysis was performed by excluding the 6 subjects (see Section 6.1.10.1.3) who were included in the mTVc at the final HZ efficacy analysis step but excluded at the EOS analysis step.*

The VE results from the above sensitivity analyses were very similar to those presented in Table 4 and Table 5, with point estimates and lower 95% CI bounds differing by no more than 0.03%.

6.1.11.2 Analyses of Secondary Endpoints

The HZ VE was consistent across all age strata as shown in Table 5.

Table 5: Vaccine efficacy: First or only episode of HZ during the entire study period by age stratum using Poisson method (mTVc - Final HZ efficacy analysis) – ZOSTER-006

	HZ/su				Placebo				VE	
Age	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	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)

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
Source: Table 33 of Zoster-006 CSR

The PHN VEs overall and by age stratum in subjects ≥50 YOA were analyzed at the EOS analysis step in study ZOSTER-006. Overall, no PHN episode was reported in the HZ/su

group and at least one PHN episode was reported in 18 subjects in the placebo group. The overall PHN VE in subjects ≥50 YOA was estimated as 100.00% (95% CI: 77.11% to 100.00%). The main evaluation of PHN VE in subjects ≥70 YOA was conducted as a co-primary objective in the pooled analysis of studies ZOSTER-006 and ZOSTER-022, and the PHN VE in subjects ≥50 YOA was re-estimated as a secondary objective in the pooled analysis. Please refer to Section 7.14 and Section 7.15.

No HZ-related mortality or HZ-related hospitalization was reported during this study. No evaluations of the corresponding VE were performed.

For the remaining secondary endpoints which were to be evaluated in subjects with a confirmed HZ episode, no meaningful statistical analysis on VE could be performed, given the low number of HZ cases in the HZ/su group. As a brief descriptive summary, at the EOS analysis step, 263 subjects had at least one confirmed HZ episode (9 in the HZ/su group and 254 in the placebo group). Among them, HZ-related complications (other than PHN) were reported in 6 (2.4%) HZ cases who received placebo and 0 (0%) HZ cases who received HZ/su, and the use of pain medication was reported in 190 (74.8%) HZ cases who received placebo and 6 (66.7%) HZ cases who received HZ/su.

Reviewer's comments:
The objectives to evaluate VE in reduction of HZ-associated complications, the use of pain medication, and duration of "worst" severe pain were defined for subjects with a confirmed HZ episode. The applicant's analyses for these objectives were to calculate VE using only the subset of subjects who had confirmed HZ. However, such analyses by simply subsetting the data based on a post-treatment outcome variable could bias the estimate of causal treatment effect. VE results obtained by this approach may provide insight into vaccine efficacy but lack causal interpretation. This issue also applies to study ZOSTER-022.

6.1.11.3 Subpopulation Analyses

Subgroup analyses were performed by sex, race (African American, Asian, White, and Other), ethnicity ("American Hispanic or Latino" and "Not American Hispanic or Latino"), and region (Australasia, Europe, Latin America, and North America). The subgroup analysis results were presented for the final HZ efficacy analysis step by main age stratum (50-59, 60-69, and ≥70 YOA) and overall (≥50 YOA).

- By sex: The HZ VE estimates were similar between females and males overall.
- By race: The African American subgroup had a sample size too small to support a meaningful statistical analysis. White subjects tended to have slightly higher VE than Asian and Other race groups (99% versus 93%-94%). In the White subgroup, which comprised around 72% of subjects, the HZ VE was consistently high across all age strata.
- By ethnicity: The Not Hispanic subgroup tended to have slightly higher VE than the Hispanic subgroup (98% versus 92%). In the Not Hispanic subgroup, which comprised around 89% of subjects, the HZ VE was consistently high across all age strata.

- By region: The European, Australasian, North American, and Latin American subgroups comprised 52%, 21%, 17%, and 10% of study subjects in the mTVc, respectively. The overall HZ VE was high in all four regions (95%-99%). In the European and North American subgroups, the HZ VE was consistently high across all age strata. The HZ VE in the Australasian ≥70 YOA subgroup tended to be slightly lower (88%).

6.1.11.4 Dropouts and/or Discontinuations

Up to the final HZ efficacy analysis, 749 subjects (9.7%) in the HZ/su group and 682 (8.8%) subjects in the placebo group from the TVc were withdrawn. The most common reason for withdrawal was consent withdrawal (4.1% in the HZ/su group and 3.8% in the placebo group). The second most common reason for withdrawal was SAE, with 2.4% of subjects in the HZ/su group and 2.5% of subjects in the placebo group. A non-serious AE was a reason for withdrawal for 0.4% subjects in the HZ/su group and 0.2% subjects in the placebo group.

Up to the EOS efficacy analysis, 922 (12.0%) subjects in the HZ/su group and 902 (11.7%) subjects in the placebo group from the TVc were withdrawn. An SAE was a reason for withdrawal for 2.9% subjects in the HZ/su group and 3.0% subjects in the placebo group; a non-serious AE was a reason for withdrawal for 0.4% subjects in the HZ/su group and 0.2% subjects in the placebo group.

6.1.11.5 Exploratory and Post Hoc Analyses

Please refer to Section 7.1.6 for descriptive analyses on anti-gE ELISA antibody titers on the ATPc for immunogenicity-Humoral in pooled analysis of ZOSTER-006 and ZOSTER-022.

6.1.12 Safety Analyses

Please refer to Section 8 for an integrated overview of safety pooling ZOSTER-006 and ZOSTER-022.

6.2 Zoster-022

Title: A phase III, randomized, observer-blind, placebo-controlled, multicenter, clinical vaccination trial to assess the prophylactic efficacy, safety and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older.

6.2.1 Objectives (Primary, Secondary, etc.)

<u>Primary objective</u>

- To evaluate VE in the prevention of HZ compared to placebo in adults ≥70 YOA, as measured by the reduction in HZ risk.
    - Success criterion: To demonstrate a clinically meaningful HZ VE in subjects ≥70 YOA, the lower limit of the two-sided 95% CI of VE should be above 10%.

Secondary objectives

- 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 ≥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.

6.2.2 Design Overview

The overall study design was similar to that of ZOSTER-006, including treatment groups, randomization ratio (stratification and minimization strategies), inclusion and exclusion criteria (apart from the age of the subjects enrolled), subject evaluations (except that the CMI was not evaluated in study ZOSTER-022), case definitions, and definition of cohorts for analysis. Please refer to Section 6.1.2 for follow-up of HZ cases, collection of safety data, and collection of blood samples for immunogenicity. The selection of 7-day diary card subset and immunogenicity subset had different provisional sample sizes than ZOSTER-006:

- 7-day diary card subset: A random subset of subjects from the 70-79 and ≥80 YOA strata were allocated to the 7-day diary card subset, with a provisional number of subjects of 252 per treatment group for each age stratum.
- Immunogenicity subset: Subjects were randomized to the immunogenicity subset, with a provisional sample size of 46 per treatment group in each of the two countries, Japan and the US, and 23 per treatment group for each of the other participating countries.

6.2.3 Population

The study included subjects aged 70 years and older without a history of HZ, previous vaccination against varicella or HZ, or confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or therapy.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The same as in study ZOSTER-006 (Section 6.1.4).

6.2.6 Sites and Centers

The same as in study ZOSTER-006 (Section 6.1.6).

6.2.7 Surveillance/Monitoring

NA

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint

- Confirmed HZ cases during the study in the mTVc.

Secondary efficacy 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 overall and HZ-related mortality during the study;
- Incidence of HZ complications during the study in subjects with confirmed HZ;
- Incidence of overall and HZ-related hospitalizations during the study;
- Duration of pain medication administered for HZ during the study in subjects with confirmed HZ.

Secondary safety endpoints

The same as in study ZOSTER-006 (Section 6.1.8).

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sequence of analyses

Please refer to Section 6.1.9 for the overall scope of analyses for ZOSTER-006, ZOSTER-022, and pooling of these two studies. In ZOSTER-022, the planned analysis steps were:

1. Final HZ efficacy analysis (step 1), which was to analyze the HZ VE objective and all reactogenicity/safety and immunogenicity objectives. The cut-off date for final HZ efficacy analysis occurred when the following conditions were met:
   - at least 278 confirmed HZ cases were accrued in the mTVc;
   - approximately 75% of subjects in each stratum had completed at least 36 months follow-up after Dose 2, and the remaining subjects had completed at least 30 months follow-up after Dose 2.
2. EOS analysis (step 2), at which all objectives were to be analyzed. Objectives already analyzed at step 1 were to be re-analyzed (confirmatory descriptive in case of inferential analysis at step 1 or descriptive analysis otherwise). The cut-off date for the EOS analysis occurred given the following:
   - at least 35 PHN cases in subjects ≥70 YOA were accrued in the mTVc when pooling studies ZOSTER-006 and ZOSTER-022.

For study ZOSTER-022, step 1 occurred at the same time as step 2, on April 21, 2015. At the same time, the overall PHN VE in subjects ≥70 YOA and other pre-specified endpoints were analyzed in the pooled analyses of studies ZOSTER-006 and ZOSTER-022.

Sample size

The final HZ efficacy analysis for ZOSTER-022 was planned after the accumulation of at least 278 confirmed HZ cases, which would provide ~99% power to demonstrate an HZ

VE of at least 10% under certain assumptions. The EOS analyses of ZOSTER-006 and ZOSTER-022 were planned after the accumulation at least 35 PHN cases in subjects ≥70 YOA in the pooled ZOSTER-006 and ZOSTER-022. This number of PHN cases would provide ~90% power to demonstrate a PHN VE with a lower confidence bound above 0%. The sample size was selected as 7256 per treatment group in order to provide the required number of HZ and PHN cases within a follow-up time of ~3 years.

Statistical analysis

The statistical methods to analyze the efficacy, immunogenicity, and safety endpoints were similar to those in ZOSTER-006, except that for age stratification, levels of 70-79 and ≥80 YOA were used.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Please refer to Section 6.1.10.1 for the definitions of TVc, mTVc, and ATPc for immunogenicity.

6.2.10.1.1 Demographics

The summary of demographic characteristics for the mTVc is presented in Table 6. The distribution of demographic characteristics was similar between treatment groups.

Table 6: Summary of demographic characteristics for ZOSTER-022 (mTVc)

Characteristics	Parameters or Categories	HZ/su N=7344		Placebo N=7415		Total N=14759	
		Value or n	%	Value or n	%	Value or n	%
Age (years) at dose 1	Mean	75.5	-	75.5	-	75.5	-
	Range	70 – 96	-	62 – 95	-	62 – 96	-
Gender	Female	3564	54.5	3636	54.9	7200	54.7
	Male	2977	45.5	2986	45.1	5963	45.3
Ethnicity	American Hispanic or Latino	526	8.0	525	7.9	1051	8.0
	Not American Hispanic or Latino	6015	92.0	6097	92.1	12112	92.0
Geographic Ancestry	African Heritage / African American	74	1.1	61	0.9	135	1.0
	American Indian or Alaskan Native	1	0.0	8	0.1	9	0.1
	Asian - Central/South Asian Heritage	3	0.0	5	0.1	8	0.1
	Asian - East Asian Heritage	828	12.7	846	12.8	1674	12.7
	Asian - Japanese Heritage	276	4.2	287	4.3	563	4.3
	Asian - South East Asian Heritage	7	0.1	4	0.1	11	0.1
	Native Hawaiian or Other Pacific Islander	3	0.0	3	0.0	6	0.0
	White - Arabic / North African Heritage	36	0.6	44	0.7	80	0.6
	White - Caucasian / European Heritage	5045	77.1	5090	76.9	10135	77.0
	Other	268	4.1	274	4.1	542	4.1

Source: Table 22 of Zoster-022 CSR

Reviewer's comments:

The study was designed to enroll subjects ≥70 YOA, but actually included 3 subjects (2 in placebo and 1 in HZ/su) who were 69 years old and 1 subject who was 62 years old (in placebo). GSK explained that the enrolled subjects in violation of the eligibility criteria for age were not eliminated from the TVc in order to have the TVc best represent use of

the vaccine in a real-life setting. These subjects were eliminated from the ATPc. Such strategy was applied to all GSK ZOSTER studies.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.2.10.1.3 Subject Disposition
A total of 14816 subjects were enrolled in the study. Among them, 903 (6.1%) were eliminated from all statistical analyses. These subjects included all subjects (N=865) from Center 75265 in Mexico due to significant deviations from GCP compliance, all subjects (N=34) from Center 80998 in the US due to center closure in August 2014 for business reasons, 2 subjects with an informed consent form issue, and 2 subjects with lost source documentation. The number of subjects included in the TVc and the number of subjects excluded from the mTVc with reasons for exclusion are presented in Table 7.

Table 7: Number of subjects enrolled into study ZOSTER-022 as well as the number excluded from mTVc with reasons for exclusion

	Total			HZ/su		Placebo		No Group	
Title	n	s	%	n	%	n	%	n	%
Total enrolled cohort	14816			7408		7406		2	
Subjects excluded from all stat analysis	903	903		453		450		0	
Total effective cohort	13913			6955		6956		2	
Study vaccine dose not administrated but subject number allocated	13	13		5		6		2	
Total Vaccinated Cohort	13900		100	6950	100	6950	100	0	-
Study vaccine dose not administered according to protocol	7	7	0.1	3	0.0	4	0.1	0	-
Wrong replacement or study vaccine administered	20	20	0.1	12	0.2	8	0.1	0	-
Subjects who did not receive two doses	695	697	5.0	390	5.6	305	4.4	0	-
Subjects having an episode of HZ prior than 30 days after the dose 2	15	15	0.1	4	0.1	11	0.2	0	-
modified Total Vaccinated Cohort	13163		94.7	6541	94.1	6622	95.3	0	-

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 TVc
s = number of subjects with the elimination code assigned
% = percentage of subjects relative to the TVc
Source: Table 6.18 of Zoster-022 CSR

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The results for the primary objective of HZ VE in subjects ≥70 YOA are summarized in Table 8. The acceptance criterion of lower bound of the 95% CI of VE >10% was met.

Table 8: Vaccine efficacy: First or only episode of HZ during the entire study period in subjects ≥70 YOA using Poisson method (mTVc) – ZOSTER-022

	HZ/su				Placebo				VE	
Age	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	95% CI
≥70YOA	6541	23	24405.1	0.9	6622	223	24167.8	9.2	89.79	(84.29, 93.66)

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
Source: Table 23 of Zoster-022 CSR

6.2.11.2 Analyses of Secondary Endpoints

The main efficacy analysis of PHN VE in subjects ≥70 YOA was conducted in the pooled analysis. Please refer to Section 7.1.4. For study ZOSTER-022, the PHN VE was analyzed as a descriptive objective. There were 32 subjects (4 in the HZ/su group and 28 in the placebo group) having PHN, with a PHN VE of 85.49% (95% CI: 58.52% to 96.30%).

No HZ-related mortality was reported during this study. HZ-related hospitalization was reported in 5 (0.1%) subjects in the placebo group and 0 (0%) subjects in the HZ/su group. No meaningful statistical analysis on VE of HZ-related mortality or hospitalization could be performed given the low number of events.

For the remaining secondary objectives to be evaluated in subjects with a confirmed HZ episode, no meaningful statistical analysis on VE could be performed for HZ-associated complications (other than PHN) or duration of severe "worst" HZ-associated pain, given the low number of HZ cases in the HZ/su group (23 and 223 subjects had a confirmed HZ episode in HZ/su and placebo, respectively). As a brief descriptive summary, HZ-related complications (other than PHN) were reported in 10 (4.5%) HZ cases who received placebo and 1 (4.3%) HZ case who received HZ/su, and the use of pain medication was reported in 160 (71.7%) HZ cases who received placebo and 10 (43.5%) HZ cases who received HZ/su. The VE in reduction in use of pain medication calculated in subjects with a confirmed HZ episode was 39.60% (95% CI: 10.79% to 64.75%).

Reviewer's comments:
Like study ZOSTER-006, the applicant's method for VE evaluation in subjects with a confirmed HZ could bias the estimate of causal treatment effect by simply subsetting the data based on a post-treatment outcome variable. The obtained VE results lack direct causal interpretability.

6.2.11.3 Subpopulation Analyses

Subgroup analyses were performed by age, sex, race, ethnicity, and region similar to study ZOSTER-006. The subgroup analysis results were presented overall and by main age stratum (70-79 and ≥80 YOA).

- By age: The HZ VE was similar between the 70-79 YOA group (VE: 90.02%; 95% CI: 83.54% to 94.32%) and the ≥80 YOA group (VE: 89.08%; 95% CI: 74.65% to 96.16%).
- By sex: The HZ VE was similar between males and females across both age strata.
- By race: The African American subgroup had a sample size too small to support a meaningful statistical analysis. Asian subjects tended to have slightly higher overall HZ VE in subjects ≥70 YOA than the White and Other race subgroups (95% versus 87%-91%). In the Asian and White subgroups, which comprised around 17% and 77% of subjects, respectively, the HZ VE was consistent across age strata.
- By ethnicity: The Not Hispanic subgroup tended to have slightly higher VE than the Hispanic subgroup (90% versus 85%). In the Not Hispanic subgroup, which comprised around 92% of subjects, the HZ VE was consistent across age strata.

- By region: The European, Australasian, North American, and Latin American subgroups comprised 55%, 19%, 19%, and 7% of study subjects in the mTVc, respectively. The overall HZ VE in subjects ≥70 YOA tended to be higher in the Australasian region (96%) than other regions (83%-88%).

6.2.11.4 Dropouts and/or Discontinuations

A total of 1180 (17.0%) subjects in the HZ/su group and 1189 (17.1%) in the placebo group from the TVc were withdrawn. One subject in the placebo group had unknown completion status. The most common reason for withdrawal was SAE (6.6% in HZ/su and 7.0% in placebo). A non-serious AE was a reason for withdrawal in 0.7% subjects in the HZ/su group and 0.2% subjects in the placebo group.

Reviewer's comments:
Although no apparent imbalance was observed between two treatment groups regarding subjects withdrawn due to SAEs, the incidence of SAE tended to be higher in dropouts than in completers (48% versus 11%), suggesting there may be heterogeneity in underlying HZ infection risk between dropouts and completers. This heterogeneity may also include heterogeneity in VE for dropouts versus completers, and therefore this may be a source of bias in the VE point estimate for the indicated population.

6.2.11.5 Exploratory and Post Hoc Analyses

Please refer to Section 7.1.6 for descriptive analyses on anti-gE ELISA antibody titers on the ATPc for immunogenicity-humoral in pooled analysis of ZOSTER-006 and ZOSTER-022.

6.2.12 Safety Analyses

Please refer to Section 8 for an integrated overview of safety pooling of ZOSTER-006 and ZOSTER-22.

6.3 Zoster-007

Title: A phase III, randomized, double blind multicenter study, to evaluate consistency, immunogenicity, safety and reactogenicity of 3 lots of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0, 2 month schedule to adults ≥50 years of age.

6.3.1 Objectives (Primary, Secondary, etc.)

Primary objective

- 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 (Month 3).
    - Success criterion: One month after the second dose, the two-sided 95 % CI of the GMC ratio between all pairs of lots should be within [0.67, 1.5].

Secondary objectives

- To demonstrate the consistency of three manufacturing lots of HZ/su vaccine in terms of vaccine response rates one month after the second vaccine dose;
    - Success criterion: For each pair-wise comparison, the two-sided 95% CI on the lot difference in VRR to the HZ/su vaccine (in terms of the humoral anti-gE immune response) one month after the second vaccine dose should be within [-10%; 10%].
- To characterize anti-gE humoral immune responses for all study groups at Month 0 and Month 3;
- To evaluate the safety and reactogenicity following administration of HZ/su vaccine up to one month post last vaccination and until study end.

6.3.2 Design Overview

The study was a randomized, double-blind study with three parallel groups. Subjects aged ≥50 YOA (target enrollment was 217 subjects per lot group) were randomized 1:1:1 to receive one of three lots of HZ/su vaccine (hereafter referred to as HZ/su Lot A, HZ/su Lot B, and HZ/su Lot C), each composed of a unique randomized combination of antigen and adjuvant lots. The vaccination schedule was at Month 0 and Month 2. The randomization used a minimization procedure accounting for center, age (50-59, 60-69, and ≥70 YOA), and country. Blood samples to assess humoral immunogenicity were collected at Month 0 and Month 3. Each subject was followed for approximately 12 months after the second vaccine dose for safety follow-up. At each vaccination visit, diary cards were provided to subjects to record body (oral) temperature and any solicited local/general AEs on the day of vaccination and during the next 6 days, or any unsolicited AEs on the day of vaccination and during the next 29 days occurring after vaccination. The time period for collecting and recording SAEs, pregnancies, and pIMDs began at the first receipt of study vaccine and ended at approximately 12 months following administration of the last dose of study vaccine.

6.3.3 Population

Subjects enrolled in this study were 50 years or older males and females who had no history of HZ, previous vaccination against varicella or HZ, or confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or therapy.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Please refer to Section 6.1.4 for information on dosage and administration of the HZ/su vaccine. The 3 production lots of the HZ/su vaccine were randomly assigned unique combinations of 3 adjuvant lots (DA01A056A, DA01A058A, and DA01A059B) with the 3 gE lots (DVZVA009, DVZVA010, and DVZVA011).

6.3.6 Sites and Centers

This study was conducted in 8 centers: 2 in Belgium, 3 in Canada, and 3 in the US.

6.3.7 Surveillance/Monitoring

NA

6.3.8 Endpoints and Criteria for Study Success

Primary endpoint

- Anti-gE antibody concentrations, as determined by ELISA, at Month 3.

Secondary immunogenicity endpoints

- Anti-gE antibody concentrations, as determined by ELISA, at Month 0 and Month 3;
- Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, at Month 3.

Secondary safety endpoints

- Occurrence, intensity and duration of each solicited local symptom within 7 days (Days 0-6) after each vaccination;
- Occurrence, intensity, duration, and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination;
- Occurrence, intensity, and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the MedDRA classification;
- Occurrence and relationship to vaccination of all SAEs from first vaccination up to 30 days post last vaccination;
- Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination until study end;
- Occurrence of any pIMDs from first vaccination up to 30 days post last vaccination;
- Occurrence of any pIMDs during the period starting after 30 days post last vaccination until study end.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity analyses

The primary analysis was based on the ATPc for immunogenicity.

- Primary objective of lot-to-lot consistency in terms of GMC: The GMC ratios and 95% CIs were obtained using an Analysis of Covariance (ANCOVA) model on the logarithm-transformed titers. The ANCOVA model included the vaccine group as the fixed effect and the pre-vaccination log-transformed titer as a covariate.
- Secondary objective of lot-to-lot consistency in terms of VRR: The asymptotic standardized 95% CIs for the pairwise VRR differences were computed using Proc StatXact 8.1. Please refer to Section 6.1.9 for the definition of VRR for anti-gE ELISA antibody titers.
- To control the type I error, a hierarchical procedure was used for the primary and secondary (immunogenicity) objectives. Each objective can only be reached if all the associated criteria were met and all previous objectives had been reached.
- The main analysis of the immunogenicity, reactogenicity, and safety data were to be performed when all data up to and including Month 3 were available.

Reviewer's comments:

For the submitted CSR, subjects were followed until the data lock point (DLP) for the Month 3 analysis.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The TVc included all vaccinated subjects with respect to the vaccine actually administered.

The ATPc for immunogenicity included all evaluable subjects:

- who had received at least one dose of study vaccine according to their random assignment;
- for whom administration site of study vaccine was known/correct;
- who had not received other vaccine(s) forbidden in the protocol;
- who met all eligibility criteria;
- who complied with the procedures and intervals defined in the protocol for the active phase (till Month 3);
- who did not meet any of the criteria for elimination from an ATP analysis during the active phase (till Month 3);
- who did not receive a product leading to elimination from an ATP analysis during the active phase (till Month 3);
- who did not present with a medical condition leading to elimination from an ATP analysis during the active phase (till Month 3);
- for whom data concerning immunogenicity endpoint measures were available during the active phase (till Month 3).

6.3.10.1.1 Demographics

For the 651 subjects included in the TVc, the age range was from 49 to 91 years and the mean age was 64.5 years at the time of the first vaccination. There were 55.3% females, 93.7% Caucasians. The majority of subjects (98.9%) were not American Hispanic or Latino. The demographic characteristics were similar for the ATPc for immunogenicity and balanced across 3 vaccine lot groups, with the exception that there were slightly more females in Lot B relative to the other lots (60% in the Lot B group versus 53% in the Lot A and Lot C groups).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

NA

6.3.10.1.3 Subject Disposition

A total of 651 subjects were included in the TVc, with approximately equal numbers of subjects in each of the three lot groups (218, 217, and 216 in Lot A, Lot B, and Lot C, respectively). Among them, 622 (95.5%) were included in the ATPc for immunogenicity (210 [96.3%], 210 [96.8%], and 202 [93.5%] in each of the three lot groups, respectively). The most common reason for a subject to be excluded from the ATPc for immunogenicity was incomplete vaccination course (2.3%, 0.5%, and 3.2% of TVc subjects in each of the three lot groups, respectively).

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The adjusted anti-gE ELISA antibody GMC ratios of Lot A/Lot B, Lot A/Lot C, and Lot B/Lot C at one month post-dose 2 are presented in Table 9. The lot-to-lot consistency in terms of anti-gE ELISA antibody GMC between the 3 manufacturing lots of the HZ/su vaccine was demonstrated as the 95% CI of the GMC ratio between each pair of lots was within [0.67, 1.5].

Table 9: Primary objective: lot-to-lot consistency in terms of anti-gE ELISA antibody GMC - ZOSTER-007

Adjusted GMC ratio Lot A/ Lot B		Adjusted GMC ratio Lot A/ Lot C		Adjusted GMC ratio Lot B/ Lot C	
Value	95% CI	Value	95% CI	Value	95% CI
0.97	(0.86, 1.09)	0.96	(0.85, 1.08)	0.99	(0.88, 1.10)

Source: Tables 17-19 of Zoster-007 CSR

6.3.11.2 Analyses of Secondary Endpoints

The VRR differences in anti-gE ELISA antibody between lot groups (Lot A-Lot B, Lot A-Lot C, and Lot B-Lot C) at one month post-dose 2 are presented in Table 10. The VRRs for all three lot groups at one month post-dose 2 were above 95%. The consistency of the 3 manufacturing lots of HZ/su vaccine in terms of anti-gE ELISA antibody VRR one month post-dose 2 was demonstrated as for each pair-wise comparison, the 2-sided 95% CI on the VRR difference was within [-10%, 10%].

Table 10: Secondary objective: lot-to-lot consistency in terms of anti-gE ELISA antibody VRR - ZOSTER-007

Difference in VRR Lot A - Lot B		Difference in VRR Lot A - Lot C		Difference in VRR Lot B - Lot C	
%	95% CI	%	95% CI	%	95% CI
-1.90	(-5.86, 1.72)	-1.81	(-5.79, 1.92)	0.09	(-3.30, 3.58)

Source: Tables 20-22 of Zoster-007 CSR

6.3.11.3 Subpopulation Analyses

No subgroup analyses were performed for the primary objective of lot-to-lot consistency.

6.3.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.3.12.7.

6.3.11.5 Exploratory and Post Hoc Analyses

NA

6.3.12 Safety Analyses

6.3.12.1 Methods

The primary analysis for safety was based on the TVc. Safety endpoints were tabulated descriptively.

6.3.12.3 Deaths

One subject (0.2%) in the TVc, 77 year old White Caucasian female, died (b) (6) days post first vaccination (Lot A) following an acute myocardial infarction. The investigator considered this SAE to be not related to vaccination.

6.3.12.4 Nonfatal Serious Adverse Events

A total of 44 SAEs were reported by 29 (4.5%) subjects up to the DLP in the TVc, similarly distributed across three lot groups. None of the SAEs was considered related to the vaccination by the investigator. During the period up to 30 days post last vaccination, 26 SAEs were reported by 13 (2.0%) subjects in the TVc.

6.3.12.5 Adverse Events of Special Interest (AESI)

A total of 7 pIMDs were reported by 6 (0.9%) subjects up to the DLP in the TVc, with 4 (1.8%) and 2 (0.9%) subjects in the Lot A and Lot C groups, respectively. Among them, 5 pIMDs were reported by 4 (0.6%) subjects during the period up to 30 days post the last vaccination. Of the 7 pIMDs, 3 cases reported in 3 (0.5%) subjects were considered related to the vaccination by the investigator (Raynaud's phenomenon [in Lot A], rheumatic polymyalgia [in Lot A], and rheumatoid arthritis [in Lot C]). In addition, one subject (0.2%) in the TVc was clinically diagnosed with the HZ which began 4 days post dose 2 and resolved after 31 days. This case was considered related to vaccination by the investigator.

6.3.12.6 Clinical Test Results

NA

6.3.12.7 Dropouts and/or Discontinuations

Among 651 subjects in the TVc, 6 (0.9%) subjects dropped out of the study up to DLP, 3 (1.4%) from group Lot A, 1 (0.5%) from group Lot B, and 2 (0.9%) from group Lot C. One subject in each group withdrew due to AEs (serious or non-serious).

6.4 Zoster-004

Title: A phase III, randomized, open-label, multicenter clinical trial to assess the immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with GSK Biologicals' quadrivalent influenza vaccine FLU D-QIV (GSK2321138A) versus separate administration of the two vaccines in adults aged 50 years and older.

6.4.1 Objectives (Primary, Secondary, etc)

Co-primary objectives

- To evaluate the VRR to the HZ/su vaccine (based on the humoral immune response) one month after the last vaccine dose in the HZ/su-FLUD-QIV co-administration group.
    - Success criterion: The lower limit of the 95% CI of the VRR for anti-gE antibody concentrations in the HZ/su-FLU-D-QIV co-administration group should be at least 60%.

- To demonstrate non-inferiority in terms of humoral immune response of two doses of the HZ/su vaccine when FLU-D-QIV vaccine is co-administered with the first HZ/su vaccine dose compared to two doses of HZ/su vaccine given alone, one month after the last vaccine dose.
    - Non-inferiority criterion: One month after the second vaccine dose, the upper limit of the 95% CI for the GMC ratio for anti-gE antibodies of the control group over the HZ/su-FLU-D-QIV co-administration group should be below 1.5.
- To demonstrate non-inferiority in terms of HI antibody of one dose of FLUD-QIV vaccine when co-administered with the first HZ/su vaccine dose compared to one dose of FLU-D-QIV vaccine given alone, for the four strains included in FLUD-QIV vaccine, at Day 21 post vaccination.
    - Non-inferiority criterion: At Day 21 post vaccination, the upper limit of the two-sided 95% CI for the HI titer GMT ratio of the control group over the HZ/su-FLU-D-QIV co-administration group should be below 1.5 for each strain included in the FLU-D-QIV vaccine.

6.4.2 Design Overview

This study was an open-label, randomized, controlled, multi-center, multi-country study with two parallel groups. Subjects aged ≥50 years (targeted at ~414 subjects per group) were randomized 1:1 to the Co-Ad group or Control group. The randomization was stratified by age (50-59, 60-69, and ≥70 YOA with approximate distribution: 155, 155, and 104 subjects, respectively). Within each age stratum, a minimization procedure was used, accounting for the center and influenza pre-vaccination history for the previous season (2012-2013). The schedules for vaccination and immunogenicity blood sample collection are summarized in Table 11. The follow-up for safety was similar to that in study Zoster-007 (see Section 6.3.2).

Table 11: Study design - ZOSTER-004

Group	Vaccination schedule	Blood sample collected for immunogenicity
Co-Ad group	Day 0: 1st dose of HZ/su and one dose of FLU-D-QIV Month 2: 2nd dose of HZ/su	Day 0: pre-vaccination HI titer and ant-gE ELISA antibody concentration Day 21: post-vaccination HI titer Month 3: post-dose 2 anti-gE ELISA antibody concentration
Control group	Day 0: one dose of FLU-D-QIV Month 2: 1st dose of HZ/su Month 4: 2nd dose of HZ/su	Day 0: pre-vaccination HI titer Day 21: post-vaccination HI titer Month 2: pre-vaccination ant-gE ELISA antibody concentration Month 5: post-dose 2 anti-gE ELISA antibody concentration

Source: Section 3 of Zoster-004 protocol Amendment 2

6.4.3 Population

Subjects enrolled in this study were 50 years or older males and females who had no history of HZ, previous vaccination against varicella or HZ, or confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or therapy.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Each 0.5 mL dose of the FLU-D-QIV vaccine used in this study contained 15 µg of hemagglutinin from each of the following four influenza strains (in accordance with the WHO recommendations issued for the Northern Hemisphere season 2013-2014):

A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata), B/Brisbane/60/2008 (Victoria). Please refer to Section 6.1.4 for information on the study vaccine HZ/su. The preferred site of IM injection was deltoid muscle of the upper non-dominant arm for HZ/su and deltoid muscle of the upper dominant arm for FLU-D-QIV.

6.4.6 Sites and Centers

The study was conducted in 20 centers, with 2 in Canada, 3 in the US, and 15 in Germany.

6.4.7 Surveillance/Monitoring

NA

6.4.8 Endpoints and Criteria for Study Success

Co-primary endpoints

- HZ/su humoral immunogenicity:
    - Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, in subjects from the HZ/su-FLUD-QIV Co-Ad group, at one month post-dose 2 (Month 3);
    - Anti-gE antibody concentrations as determined by ELISA, at one month post dose 2 (Month 3 for the Co-Ad group and Month 5 for the Control group).
- FLU-D-QIV humoral immunogenicity:
    - GMTs of HI antibody titers against the four influenza vaccine strains at Day 21.

6.4.9 Statistical Considerations & Statistical Analysis Plan

- The primary analysis was based on the ATPc for immunogenicity. The study was to be considered a success if all three co-primary objectives were achieved.
- Co-primary objective in terms of anti-gE ELISA in the Co-Ad group: The VRR in the Co-Ad group at one month after the last dose of HZ/su was calculated with exact 95% CI. Please refer to Section 6.1.9 for the definition of VRR for anti-gE ELISA antibody.
- Co-primary objective in terms of anti-gE ELISA GMC ratio between the Co-Ad group and the Control group: The ANCOVA model was used to analyze post-vaccination log-transformed concentrations of anti-gE (one month after the last dose of HZ/su), with treatment group, age cohort, and log-transformed pre-vaccination anti-gE concentrations included in the model. Adjusted Least Squares (LS) means and difference of LS means between treatment groups were calculated together with 2-sided 95% CIs and back-transformed to provide GMC ratios.
- Co-primary objective in terms of HI titer GMT ratio between the Co-Ad group and the Control group: For each strain, the GMT ratio of HI at Day 21 was calculated similarly to the anti-gE ELISA using the ANCOVA model.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

- The TVc included all vaccinated subjects with respect to the vaccine actually administered.
- The ATPc for immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available.

6.4.10.1.1 Demographics

For the 828 subjects in the TVc, the mean age was 63.4 years (range: 50 to 92 years) at the time of the first vaccination. There were 51.8% females. Most of the subjects (92.0%) were Caucasians. The demographic characteristics were balanced between treatment groups. The ATPc for immunogenicity had a similar distribution of demographic characteristics.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

NA

6.4.10.1.3 Subject Disposition

A total of 829 subjects were enrolled in the study. One enrolled subject withdrew consent before being assigned to a group; therefore, the TVc included 828 subjects (413 in the Co-Ad group and 415 in the Control group). Of subjects in the TVc, 386 (93.5%) subjects in the Co-Ad group and 395 (95.2%) subjects in the Control group were included in the ATPc for immunogenicity. The most common reason for a subject in the TVc to be excluded from the ATPc for immunogenicity was non-compliance with blood sampling schedule, including wrong and unknown dates (for 3.1% of subjects in the TVc).

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

Co-primary objective in terms of anti-gE ELISA VRR in Co-Ad group

In the Co-Ad group, among 382 subjects in the ATPc for immunogenicity who had both pre- and post-vaccination anti-gE ELISA results available, 366 had vaccine response, resulting in a VRR of 95.8% (95% CI: 93.3% to 97.6%). The corresponding success criterion (lower limit of the 95% CI for VRR ≥60%) was met.

Co-primary objective in terms of anti-gE ELISA GMC ratio between Co-Ad group and Control group

One month after the second dose of HZ/su, the adjusted GMC of anti-gE ELISA antibody titers was (b) (4) mIU/mL for the Control group and the Co-Ad group, respectively. The GMC ratio (Control/Co-Ad) was 1.08 (95% CI: 0.97 to 1.20) on ATPc for immunogenicity. The non-inferiority criterion that the upper limit of the 95% CI for the GMC ratio (Control/Co-Ad) should be <1.5 was met.

Co-primary objective in terms of HI GMT ratio between Co-Ad group and Control group
Although the study vaccine strain used was A/Christchurch/16/2010 (H1N1), an HI test against A/California/7/2009 (H1N1) strain was performed, because these two strains were considered antigenically equivalent. The GMT ratios for HI titers (Control/Co-Ad) at Day 21 post vaccination of FLU-D-QIV are summarized in Table 12. The non-inferiority criterion was met, as the upper limit of the two-sided 95% CI for the GMT ratio (Control/Co-Ad) was <1.5 for each strain included in the FLU-D-QIV vaccine.

Table 12: Co-primary objective: GMT ratios (Control over Co-Ad) in HI antibodies at Day 21(ATPc for immunogenicity) – Zoster-004

	Control		Co-Ad		Control/Co-Ad	
Strain	N	Adjusted GMT	N	Adjusted GMT	GMT ratio	95% CI
A/California/7/2009 (H1N1)	394	194.3	384	187.5	1.04	(0.88, 1.22)
A/Texas/50/2012 (H3N2)	394	65.9	384	63.7	1.03	(0.91, 1.17)
B/Brisbane/60/2008 (Victoria)	394	181.6	384	170.2	1.07	(0.95, 1.20)
B/Massachusetts/2/2012 (Yamagata)	394	413.9	384	423.5	0.98	(0.88, 1.09)

Source: Table 19 of Zoster-004 CSR

6.4.11.2 Analyses of Secondary Endpoints

NA

6.4.11.3 Subpopulation Analyses

No subgroup analyses were performed for the evaluations of co-primary objectives.

6.4.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.4.12.7.

6.4.11.5 Exploratory and Post Hoc Analyses

NA

6.4.12 Safety Analyses

6.4.12.1 Methods

Safety data were analyzed descriptively for the TVc. Overall, during the 7-day post-vaccination period after dose 1, more subjects in the Co-Ad group (with HZ/su-FLU-D-QIV co-administration) than in the Control group (with FLU-D-QIV only) reported at least one solicited local or general symptom (general: 60.9% versus 33.6%; local: 79.3% versus 30.6%). Overall, no apparent imbalance was observed for the incidence rate of solicited local or general symptoms between the two groups during the 7-day post-vaccination period, regardless of dose.

Within 30 days after vaccination, fewer subjects in the Co-Ad group reported at least one unsolicited AE (26.6% versus 39.0%) and at least one Grade 3 unsolicited AE (4.1% versus 7.0%), as compared to the Control group.

6.4.12.3 Deaths

During the entire study period, death was reported in 8 (1.0%) subjects (3 [0.7%] in the Co-Ad group and 5 [1.2%] in the Control group). None of the deaths was considered related to vaccination by the investigator.

6.4.12.4 Nonfatal Serious Adverse Events

A total of 123 SAEs were reported by 81 (9.8%) subjects in the TVc during the entire follow up, similarly distributed between the Co-ad and Control groups (10.2% and 9.4%, respectively). None of the SAEs was considered to be related to vaccination by the investigator.

6.4.12.5 Adverse Events of Special Interest (AESI)

A total of 6 pIMDs were reported by 6 (0.7%) subjects during the entire follow up in the TVc, with 4 (1.0%) and 2 (0.5%) subjects in the Co-ad and Control groups, respectively. None of the pIMDs was considered related to the vaccination by the investigator. A total of 3 (0.4%) subjects (1 [0.2%] in the Co-Ad group and 2 [0.5%] in the Control group) reported a HZ infection during the course of the study. The two suspected HZ cases in the Control group occurred after the injection of influenza vaccine and then were withdrawn before the planned HZ/su administration.

6.4.12.6 Clinical Test Results

NA

6.4.12.7 Dropouts and/or Discontinuations

Of the 828 subjects in the TVc, 32 (3.9%) did not complete the study (13 [3.1%] in the Co-Ad group and 19 [4.6%] in the Control group). A non-serious AE was a reason of withdrawal for 1 (0.2%) and 2 (0.5%) subjects in the Co-Ad and Control groups, respectively, and an SAE was a reason of withdrawal for 4 (1.0%) and 5 (1.2%) subjects in the Co-Ad and Control groups, respectively.

6.5 Zoster-026

Title: A phase III, randomized, open-label, multicenter clinical trial to assess the safety and immunogenicity of GSK Biologicals' HZ/su vaccine when administered intramuscularly according to a 0, 2-month schedule, a 0, 6-month schedule or a 0,12-month schedule in adults aged 50 years or older.

6.5.1 Objectives (Primary, Secondary, etc.)

<u>Co-primary objectives</u>

- To evaluate VRR for anti-gE humoral immune responses at one month post-dose 2 in the 0, 6-month and 0,12-month schedule groups.
  - Success criterion: The lower limit of the 97.5% CI of the VRR for anti-gE ELISA antibody concentrations at one month post-dose 2 in the 0, 6-month or 0,12-month schedule group should be at least 60%.

- If the VRR objective was met for the 0, 6-month schedule, the following objective was to be evaluated: To demonstrate non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 given according to a 0, 6-month schedule compared to a 0, 2-month schedule.
  - Criterion for non-inferiority: The upper limit of the 97.5% CI for the anti-gE ELISA GMC ratio (0, 2-month schedule over 0, 6-month schedule) at one month post-dose 2 should be below 1.5.
- If the VRR objective was met for the 0,12-month schedule, the following objective was to be evaluated: To demonstrate non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 given according to a 0,12-month schedule compared to a 0, 2-month schedule.
  - Criterion for non-inferiority: The upper limit of the 97.5% CI for the anti-gE ELISA GMC ratio (0, 2-month schedule over 0,12-month schedule) at one month post-dose 2 should be below 1.5.

6.5.2 Design Overview

This study was an open-label, randomized, uncontrolled, multi-centric study with three parallel groups. Subjects aged ≥50 years (targeted at ~118 subjects per group) were randomized 1:1:1 to receive two doses of HZ/su vaccine at one of the three schedules: 0, 2-month, 0, 6-month, or 0,12-month (hereafter referred to as Gr0-2, Gr0-6, and Gr0-12, respectively). Randomization was stratified by age with a minimum of 35 subjects in each age stratum (50-59, 60-69, and ≥70 YOA). The blood samples for anti-gE ELISA antibodies were collected at Month 0 (pre-vaccination), 1 month after dose 2, and 12 months after dose 2 for all subjects. The follow-up of safety was similar to that in study ZOSTER 007 (see Section 6.3.2).

6.5.3 Population

Subjects enrolled in this study were 50 years or older males and females who had no history of HZ, previous vaccination against varicella or HZ, or confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or therapy.

6.5.4 Study Treatments or Agents Mandated by the Protocol

Please refer to Section 6.1.4 for the information on dosage and administration of the HZ/su vaccine.

6.5.6 Sites and Centers

The study was conducted at 4 centers, 3 in the US and 1 in Estonia.

6.5.7 Surveillance/Monitoring

NA

6.5.8 Endpoints and Criteria for Study Success

<u>Primary endpoints</u>

- Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, at one month post-dose 2;
- Anti-gE antibody concentrations, as determined by ELISA in all subjects at one month post-dose 2.

6.5.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis was based on the ATPc for immunogenicity. The calculation of VRR (with exact CI) and GMC ratio of anti-gE ELISA antibody concentrations was based on the same methods as those used in study ZOSTER-004 where HZ/su was co-administered with FLU-D-QIV (see Section 6.4.9).

A hierarchical procedure was used to control the overall type I error. The co-primary objective on VRR for the 0, 6-month schedule (co-primary objective 1) and on VRR for the 0,12-month schedule (co-primary objective 2) were evaluated first. Co-primary objective 3 on non-inferiority in terms of GMC of 0, 6-month schedule to 0, 2-month schedule could be reached only if co-primary objective 1 had been reached and the criterion for objective 3 was met. Similarly, co-primary objective 4 on non-inferiority in terms of GMC of 0,12- month schedule could be reached only if co-primary objective 2 had been reached and the criterion for objective 4 was met. The study was to be declared successful if the criteria associated with co-primary objectives 1 and 3 were met or the criteria associated with co-primary objectives 2 and 4 were met. To conclude independently on co-primary objectives 1, 3 and co-primary objectives 2, 4, a Bonferroni correction was used, i.e., 1.25% type I error one-sided per objective.

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

- The TVc included all subjects with at least one vaccine administration documented.
- The ATPc for immunogenicity included all evaluable subjects:
    - who had received at least one dose of study vaccine according to their random assignment;
    - for whom administration site of study vaccine was known/correct;
    - who had not received other vaccine(s) forbidden in the protocol;
    - who met all eligibility criteria;
    - who complied with the procedures and intervals defined in the protocol;
    - who did not meet any of the criteria for elimination during the study;
    - for whom data concerning immunogenicity endpoint measures were available.

6.5.10.1.1 Demographics

For the 354 subjects in the TVc, the mean age was 64.2 years (range 50 to 86 years) at the time of first vaccination, and there were 69.5% females. Most of the subjects (98.9%) were Caucasians. The demographic characteristics were balanced across treatment groups, with the exception that there were slightly more females in Gr0-2 relative to the other groups (75.6% versus 65%-68%). The ATPc had a similar distribution of demographic characteristics.

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.5.10.1.3 Subject Disposition
A total of 354 subjects (119, 119, and 116 in each of the 0, 2-month, 0, 6-month, and 0,12-month vaccination schedule groups, respectively) received at least one dose of vaccination and therefore were included in the TVc. Eleven (3.1%) subjects in the TVc were excluded from the ATPc for immunogenicity, resulting in 343 subjects in the ATPc for immunogenicity (118, 114, and 111 subjects in each of the 0, 2-month, 0, 6-month, and 0,12-month vaccination groups, respectively).

6.5.11 Efficacy Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

Co-primary objectives in terms of anti-gE ELISA antibody VRR in 0, 6-month and 0,12-month vaccination schedule groups

- In the 0, 6-month group, all 114 subjects in the ATPc for immunogenicity had both pre- and post-vaccination anti-gE ELISA results available to evaluate the vaccine response rate. Among them, 110 subjects had vaccine response one month after the second dose, resulting in a VRR of 96.5% (97.5% CI: 90.4% to 99.2%).
- In the 0,12-month group, 110 of 111 subjects in the ATPc for immunogenicity had both pre- and post-vaccination anti-gE ELISA results available to evaluate the vaccine response rate. Among them, 104 subjects had vaccine response one month after the second dose, resulting in a VRR of 94.5% (97.5% CI: 87.6% to 98.3%).

As both the 0, 6-month and 0,12-month schedules met the success criterion that the lower limit of the 97.5% CI of the VRR should be ≥60%, the following two non-inferiority co-primary objectives were evaluated.

Co-primary objectives of non-inferiority in terms of anti-gE ELISA antibody GMC ratio for the 0, 6-month group to the 0,2-group, and for the 0,12-month group to the 0, 2-month group

- One month after the second dose of vaccination, the GMC ratio for anti-gE ELISA antibodies (0, 2-month/0, 6-month) was 1.16 (97.5% CI: 0.98 to 1.39). The non-inferiority criterion that the upper limit of the 97.5% CI for the GMC ratio (0, 2-month/0, 6-month) should be <1.5 was met.
- One month after the second dose of vaccination, the GMC ratio for anti-gE ELISA antibodies (0, 2-month/0, 12-month) was 1.19 (97.5% CI: 0.93 to 1.53). The non-inferiority criterion that the upper limit of the 97.5% CI for the GMC ratio (0, 2-month/0,12-month) should be <1.5 was not technically met; the upper limit, 1.53, was just beyond the 1.5 criterion.

6.5.11.2 Analyses of Secondary Endpoints
NA

6.5.11.3 Subpopulation Analyses
No subgroup analyses were performed for evaluation of the co-primary objectives.

6.5.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.5.12.7.

6.5.11.5 Exploratory and Post Hoc Analyses

NA

6.5.12 Safety Analyses

6.5.12.1 Methods

Safety data were analyzed descriptively on the TVc. Overall, during the 7-day post-vaccination period, no apparent imbalance was observed across the three schedule groups regarding the proportion of subjects who reported at least one solicited local or general symptom (general: 70%-78%; local: 84%-86%). Within 30 days after vaccination, similar proportions of subjects in the three treatment groups reported at least one unsolicited AE (20%-23%) and at least one Grade 3 unsolicited AE (3.4%).

6.5.12.3 Deaths

During the entire study period, death was reported in 2 (0.6%) subjects in the TVc (one in Gr0-2 and one in Gr0-12). The investigator assessed neither death to be causally related to vaccination.

6.5.12.4 Nonfatal Serious Adverse Events

During the period from the first vaccination to 30 days post last vaccination, 18 SAEs were reported by 12 (3.4%) subjects, with slightly more subjects in the treatment group with a longer vaccination schedule (0 [0%], 4 [3.4%], and 8 [6.9%] for Gr0-2, Gr0-6, and Gr0-12, respectively). During the period from the first vaccination to one year after the second dose, 38 SAEs were reported by 26 (7.3%) subjects, with 4.2%, 7.6%, and 10.3% subjects in Gr0-2, Gr0-6, and Gr0-12 groups, respectively. None of the SAEs was assessed by the investigator to be causally related to vaccination.

6.5.12.5 Adverse Events of Special Interest (AESI)

No pIMDs or HZ cases were reported during the entire study.

6.5.12.6 Clinical Test Results

NA

6.5.12.7 Dropouts and/or Discontinuations

Of the 354 subjects in the TVc, 8 did not complete the study, (2 [1.7%], 3 [2.5%], and 3 [2.6%] subjects from Gr0-2, Gr0-6, and Gr0-12, respectively). Among subjects who withdrew, SAE was a reason for withdrawal for 1 (0.8%), 2 (1.7%), and 1 (0.9%) subjects from Gr0-2, Gr0-6, and Gr0-12, respectively. No subjects discontinued early because of a non-serious AE.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 ZOSTER 006-022

7.1.1 Methods of Integration

Integrated analysis of efficacy was performed combining the data from studies ZOSTER-006 and ZOSTER-022. The efficacy data from the two studies were pooled together and analyzed using similar statistical methods as in individual studies. This was justified based on similarity in study design, including treatment groups, randomization ratio, inclusion and exclusion criteria (except for the age of subjects enrolled), study endpoints, subject evaluations (except that CMI was only evaluated in ZOSTER-006), case definitions, and definition of cohorts for analysis. The pooled analysis (using the EOS analysis dataset for both studies) was intended to formally assess the VE in PHN in subjects ≥70 YOA. Specifically, the following primary and key secondary objectives were evaluated in the pooled analysis, using statistical methods similar to those in each individual study.

Reviewer's comments:
Because of the similarities in protocols, study designs, and subject characteristics, I have no concerns about Simpson's Paradox being an issue due to the method of combining the data from the two studies.

Primary objectives

- To evaluate VE in the prevention of PHN compared to placebo in subjects ≥70 YOA across both phase III studies;
    - Success criterion: To demonstrate a clinically meaningful overall PHN VE in all subjects ≥70 YOA, the lower limit of the 95% CI of VE should be above 0%.
- To consolidate VE estimation in the prevention of HZ compared to placebo in subjects ≥70 YOA across both phase III studies.

Key secondary efficacy objective

- To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥50 YOA.

7.1.2 Demographics and Baseline Characteristics

For subjects aged ≥70 years in the pooled mTVc analysis set who received HZ/su: the mean age was 75.5 years; 54.7% of subjects were female; and most of the subjects were Caucasian (77.3%) or Asian (17.1%). For overall subjects aged ≥50 years in the pooled mTVc analysis set who received HZ/su: the mean age was 68.5 years; 57.9% of subjects were female; and most of the subjects were Caucasian (74.4%) or Asian (18.0%). The placebo group had a distribution of baseline characteristics similar to the HZ/su group.

7.1.4 Analysis of Primary Endpoint(s)

The pooled analysis of VE in the prevention of PHN compared to placebo in subjects ≥70 YOA is summarized in Table 13.The primary objective of the pooled analysis regarding the PHN VE in subjects ≥70 YOA was met, as the lower limit of the 95% CI of the VE against PHN was above 0%.

Table 13: Vaccine efficacy: First or only episode of PHN during the entire study period in subjects ≥70 YOA using Poisson method (mTVc, ZOSTER 006-022 pooled)

	HZ/su				Placebo				VE	
Age	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	95% CI
≥ 70YOA	8250	4	30760.3	0.1	8346	36	30942.0	1.2	88.78	(68.70, 97.10)

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
Source: Table 85 of Zoster-022 CSR

The pooled analysis of VE in the prevention of HZ compared to placebo in subjects ≥70 YOA is summarized in Table 14.

Table 14: Vaccine efficacy: First or only episode of HZ during the entire study period in subjects ≥70 YOA using Poisson method (mTVc, ZOSTER 006-022 pooled)

	HZ/su				Placebo				VE	
Age	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	95% CI
≥ 70YOA	8250	25	30725.5	0.8	8346	284	30414.7	9.3	91.30	(86.88, 94.46)

n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
Source: Table 83 of Zoster-022 CSR

Reviewer's comments:
The evaluation of HZ VE in subjects ≥70 YOA in the pooled analysis was to consolidate the VE evaluation across both phase 3 trials (and was considered as a descriptive objective according to the protocol). The corresponding HZ VE estimate obtained in ZOSTER-022 was 89.79% (95% CI: 84.29% to 93.66%), and was 97.93% (95% CI: 87.91% to 99.95%) in ZOSTER-006 ≥70 YOA stratum.

7.1.5 Analysis of Secondary Endpoint(s)

The VE of HZ/su in the prevention of PHN compared to placebo in subjects ≥50 YOA in the pooled analysis was estimated as 91.22% (95% CI: 75.95% to 97.70%). This analysis consolidated the PHN VE estimated across both phase 3 trials.

7.1.6 Other Endpoints

Descriptive analyses were performed regarding the exploratory endpoints of anti-gE ELISA antibody response on the ATPc for immunogenicity-Humoral. The anti-gE ELISA antibody VRR induced by HZ/su was above 96% and 70% at Month 3 and Month 38, respectively, compared to 2%-3% in the placebo group (see Table 15).

Table 15: Vaccine response rate, geometric mean concentration, and mean geometric mean increase of anti-gE ELISA antibody at Month 3 and Month 38 (ATPc for immunogenicity-Humoral, ZOSTER 006-022 pooled)

Age	Group	Time	N	GMC (95% CI)	N'	VRR (%) (95% CI)	MGI (95% CI)
≥50 YOA	HZ/su	Month 3	1457	52020.4 (50236.7, 53867.4)	1455	97.8 (96.9, 98.5)	39.4 (37.2, 41.7)
		Month 38	1301	11524.3 (11050.0, 12019.0)	1279	77.1 (74.7, 79.4)	8.8 (8.2, 9.3)
	Placebo	Month 3	1479	1295.0 (1228.0, 1365.6)	1477	2.0 (1.3, 2.8)	0.9 0.9, 1.0)
		Month 38	1289	1301.1 (1230.3, 1376.1)	1270	3.4 (2.5, 4.5)	1.0 (0.9, 1.0)
≥70 YOA	HZ/su	Month 3	742	49691.5 (47250.8, 52258.2)	741	96.6 (95.1, 97.8)	34.2 (31.5, 37.2)
		Month 38	648	10507.7 (9899.2, 11153.6)	637	70.5 (66.8, 74.0)	7.1 (6.5, 7.7)
	Placebo	Month 3	768	1410.7 (1311.4, 1517.5)	768	2.5 (1.5, 3.8)	1.0 (0.9, 1.0)
		Month 38	640	1317.1 (1216.1, 1426.6)	631	2.4 (1.3, 3.9)	0.9 (0.9, 1.0)

N = Number of subjects with available results (for the GMC); N' = Number of subjects with pre- and post-vaccination results available
MGI: Mean geometric mean increase (over pre-vaccination at Month 0)
Source: Tables 88, 89, 91, 92, 15.3, and 15.7 of ZOSTER-022 CSR

7.1.7 Subpopulations

Please refer to Section 6.1.11.3 and Section 6.2.11.3 for the subgroup analysis on HZ VE in subjects ≥50 YOA and ≥70 YOA, respectively. This section summarizes the subgroup analysis on the evaluation of VE in reduction of PHN in subjects ≥70 YOA, using pooled mTVc of ZOSTER-006 and ZOSTER-022. The subgroup analysis was performed by age, sex, race, ethnicity, and region.

- By age: The PHN VE tended to be higher in the 70-79 YOA group (VE: 93.04%; 95% CI: 72.47% to 99.19%) than in the ≥80 YOA group (VE: 71.16%; 95% CI: -51.51% to 97.08%).
- By sex: Overall, the PHN VE tended to be higher in females than in males (92% versus 83%).
- By race: The African American subgroup had a sample size too small to support a meaningful statistical analysis. The PHN VE estimates were similar among White and Asian subjects (VE: 87%-90%).
- By ethnicity: Subjects were predominantly Not Hispanic, and the PHN VE in that ethnicity subgroup was similar to what was observed in the overall study population.
- By region: The European, North American, Australasian, and Latin American subgroups compromised 54%, 20%, 19%, and 7% of study subjects ≥70 YOA in the pooled mTVc, respectively. The Latin American subgroup had a sample size too small to support a meaningful statistical analysis. For the other three region subgroups, the PHN VE was generally high (86%-100%).

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

The pooled analysis of efficacy demonstrated that the HZ/su had a VE of 88.78% (95% CI: 68.70% to 97.10%) in prevention of PHN as compared to placebo in subjects ≥70 YOA. The success criterion that the lower limit of the 95% CI of VE against PHN should be above 0% was met. The pooled analysis also provided a consolidated VE estimate in reduction of HZ of HZ/su compared to placebo in subjects ≥70 YOA: 91.30% (95% CI: 86.88% to 94.46%). The anti-gE ELISA antibody VRRs at Month 3 and Month 38 induced by HZ/su were high (above 96% and 70%, respectively) as compared to the placebo group (2%-3%).

8. INTEGRATED OVERVIEW OF SAFETY

The main safety pooling analysis was conducted on the combined safety data from studies ZOSTER-006 and ZOSTER-022 in the TVc of subjects ≥50 YOA. In addition, a broader safety pooling was conducted combining subjects from 7 clinical studies (including ZOSTER-006 and ZOSTER-022) who received IM administration of the final HZ/su vaccine formulation (i.e., 50 μg gE/$AS01_B$) at the 0, 2-month schedule, and completed at least 1 year follow-up post last vaccination at the time of DLP for the safety pooling (October 21, 2015). The broader safety pooling consisted of 15493 subjects, and among them 94.5% were from ZOSTER-006 or ZOSTER-022. Subjects in the broader safety pooling who were from studies other than ZOSTER-006 and ZOSTER-022 showed consistent incidence rates of deaths, SAEs, and pIMDs as compared to subjects in ZOSTER-006 and ZOSTER-022. No SAEs or pIMDs were considered to be related to vaccination by the investigator, in the broader pooling excluding ZOSTER-006 and ZOSTER-022. Therefore, the integrated overview of safety focused only on the main pooling of ZOSTER-006 and ZOSTER-022.

8.1 Safety Assessment Methods

Reactogenicity (solicited AEs) within 7 days post-vaccination was assessed based on the 7-day diary cards of TVc subjects who had documented safety data (i.e., symptom screen completed). For analysis of unsolicited AEs within 30 days post-vaccination, SAEs (note the standard follow-up of SAEs was from the first vaccination until Month 14), and pIMDs, all vaccinated subjects were considered. Subjects who did not report the event were considered as without the event. Integrated safety analyses were performed by tabulating the incidence rates of safety endpoints according to the treatment subjects actually received, and by calculating the relative risk and 95% CI (based on the exact Poisson method conditional on the total number of events observed) for unsolicited AEs and SAEs (note the CIs were interpreted as descriptive flagging devices rather than as hypothesis tests). The median safety follow-up time for both treatment groups was 4.4 years; approximately 79% and 90% of the study subjects had a follow-up time more than 4 years and 3 years, respectively.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The integrated safety analyses were based on safety data from studies ZOSTER-006 and ZOSTER-022.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The TVc for integrated safety analyses included 14645 subjects who received HZ/su and 14660 subjects who received placebo. Of the subjects who received HZ/su, 5887 were 50-69 YOA and 8785 were ≥70 YOA. Overall, in the HZ/su group, the mean age was 68.6 years, 58.3% were female, and most of the subjects were Caucasian (73.7%) or Asian (18.3%). The placebo group had a similar demographic distribution.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

ZOSTER-006 and ZOSTER-022 were both placebo-controlled clinical trials (randomization ratio: 1:1) with similar protocols, dose administered, duration of safety endpoint follow-up, and methods of safety data collection. These two studies were conducted at the same sites where subjects 50-69 YOA were assigned to ZOSTER-006 and subjects ≥70 YOA were randomly assigned to either ZOSTER-006 or ZOSTER-022. Safety data were evaluated overall, as well as by age stratum. Therefore, I have no concerns regarding pooling the safety data from these two clinical studies.

8.4 Safety Results

8.4.1 Deaths

Table 16 summarizes the number of deaths in the integrated safety analysis set. No apparent imbalance was observed between the two treatment groups. One of the deaths was considered by the investigator to be related to vaccination, which occurred in a 90-year-old male approximately 3 months after he received the first dose of HZ/su vaccine. This subject developed acute myeloid leukemia 75 days after receiving the first dose of HZ/su, developed neutropenic sepsis 97 days after receiving the first dose of HZ/su, and then died (b) (6) later.

Table 16: Number and percentage of subjects who died during selected time periods by age stratum (TVc, ZOSTER 006-022 pooled)

	Aged 50 - 69 Years		Aged ≥70 Years		Overall ≥50 Years	
	HZ/su N=5887 n (%)	Placebo N=5887 n (%)	HZ/su N=8758 n (%)	Placebo N=8773 n (%)	HZ/su N=14645 n (%)	Placebo N=14660 n (%)
Death during up to 30 days post last vaccination	1 (0.0)	1 (0.0)	5 (0.1)	7 (0.1)	6 (0.0)	8 (0.1)
Death during up to 365 days post last vaccination	22 (0.4)	23 (0.4)	91 (1.0)	109 (1.2)	113 (0.8)	132 (0.9)
Death during the whole post-vaccination follow-up	95 (1.6)	100 (1.7)	539 (6.2)	582 (6.6)	634 (4.3)	682 (4.7)

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects died during the indicated time period
Source: Table 98 of Annex 1 submitted to STN 125614/0.22

8.4.2 Nonfatal Serious Adverse Events

Table 17 summarizes the number of subjects reporting at least one SAE during different follow-up periods. In both age strata, SAEs occurred at a similar rate between subjects who received HZ/su and who received placebo up to 30 days after the last vaccination, and up to 365 days after the last vaccination. For the 10 most frequently reported SAEs by Preferred Term (PT) up to 365 days post the last vaccination in the HZ/su group (incidence rate >0.2%; including osteoarthritis, cerebrovascular accident, pneumonia, urinary tract infection, chest pain, myocardial infarction, cardiac failure congestive, atrial fibrillation, coronary artery disease, and cardiac failure), no apparent imbalance between the two treatment groups was noted. In both treatment groups, the incidence rate of SAEs was higher in subjects aged ≥70 years compared to subjects aged 50-69 years. Up to 365 days after the last vaccination, 15 (0.1%) and 13 (0.1%) subjects in the HZ/su and placebo groups, respectively, reported at least one SAE with causal relationship with vaccination assessed by the investigator. During the entire follow-up period, 15 (0.1%) subjects in each treatment group reported at least one SAE that was considered related to vaccination by the investigator.

Table 17: Number and percentage of subjects reporting the occurrence of serious adverse events by time period and age stratum (TVc, ZOSTER 006-022 pooled)

	Aged 50 - 69 Years		Aged ≥70 Years		Overall ≥50 Years	
	HZ/su N=5887 n (%)	Placebo N=5887 n (%)	HZ/su N=8758 n (%)	Placebo N=8773 n (%)	HZ/su N=14645 n (%)	Placebo N=14660 n (%)
SAE up to 30 days post last vaccination	81 (1.4)	79 (1.3)	261 (3.0)	248 (2.8)	342 (2.3)	327 (2.2)
SAE up to 365 days post last vaccination	367 (6.2)	359 (6.1)	1115 (12.7)	1166 (13.3)	1482 (10.1)	1525 (10.4)

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least one SAE during the indicated period
Source: Table 219 of Annex 2 submitted to STN 125614/0.25

8.4.3 Study Dropouts/Discontinuations

Among subjects who received at least one dose of treatment, 2102 (14.4%) subjects who received HZ/su and 2091 (14.3%) subjects who received placebo did not complete the study, with relatively more subjects aged ≥70 years than subjects aged 50–69 years (17% versus 10%) in both treatment groups. An SAE was a reason for withdrawal in 4.7% HZ/su recipients and 4.9% placebo recipients, and a non-serious AE was a reason for withdrawal for 0.5% HZ/su recipients and 0.2% placebo recipients. SAE was the most common reason for withdrawal in subjects ≥70 YOA.

8.4.4 Common Adverse Events

Please refer to Section 8.4.6 and Section 8.4.7.

8.4.5 Clinical Test Results

NA

8.4.6 Systemic Adverse Events

The 7-day diary card subset included 57.9% subjects (approximately 3:3:4 for the 50-59, 60-69, and ≥70 YOA strata) in study ZOSTER-006 and 7.4% subjects in study ZOSTER-

022. Table 18 summarizes the incidence rate of solicited general symptoms during the 7-day post-vaccination period by age stratum. The HZ/su group had notably higher incidence rate of general solicited AEs (any grade and Grade 3) compared to the placebo group. For subjects who received HZ/su, the younger age stratum tended to have a higher percentage of subjects reporting solicited general AEs (any grade and Grade 3). The most frequent solicited general symptoms (any grade and Grade 3) reported in the HZ/su group were myalgia (35%-57%) and fatigue (37%-57%) across the three age strata.

Table 18: Number and percentage of subjects reporting solicited general symptoms during the 7-day post-vaccination period (TVc with 7-day diary card, ZOSTER 006-022 pooled)

	Aged 50 - 59 Years		Aged 60 - 69 Years		Aged ≥70 Years	
	HZ/su N=1315 n (%)	Placebo N=1312 n (%)	HZ/su N=1309 n (%)	Placebo N=1305 n (%)	HZ/su N=2252 n (%)	Placebo N=2264 n (%)
Myalgia	748 (56.9)	199 (15.2)	642 (49.0)	146 (11.2)	790 (35.1)	225 (9.9)
Myalgia, Grade 3	117 (8.9)	12 (0.9)	69 (5.3)	11 (0.8)	62 (2.8)	10 (0.4)
Fatigue	749 (57.0)	260 (19.8)	598 (45.7)	219 (16.8)	825 (36.6)	326 (14.4)
Fatigue, Grade 3	112 (8.5)	23 (1.8)	66 (5.0)	10 (0.8)	79 (3.5)	17 (0.8)
Headache	666 (50.6)	283 (21.6)	519 (39.6)	204 (15.6)	653 (29.0)	268 (11.8)
Headache, Grade 3	79 (6.0)	22 (1.7)	49 (3.7)	2 (0.2)	34 (1.5)	10 (0.4)
Shivering	471 (35.8)	97 (7.4)	397 (30.3)	74 (5.7)	439 (19.5)	110 (4.9)
Shivering, Grade 3	90 (6.8)	3 (0.2)	59 (4.5)	4 (0.3)	49 (2.2)	6 (0.3)
Fever	366 (27.8)	40 (3.0)	313 (23.9)	44 (3.4)	323 (14.3)	61 (2.7)
Fever, Grade 3	5 (0.4)	2 (0.2)	6 (0.5)	3 (0.2)	3 (0.1)	3 (0.1)
Gastrointestinal	319 (24.3)	141 (10.7)	219 (16.7)	113 (8.7)	304 (13.5)	172 (7.6)
Gastrointestinal, Grade 3	28 (2.1)	9 (0.7)	12 (0.9)	8 (0.6)	26 (1.2)	10 (0.4)

N = number of subjects with at least one documented safety data
n/% = number/percentage of subjects reporting the symptom at least once
Fever defined as ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°F.
Source: Tables 74 and 399 of ISS

8.4.7 Local Reactogenicity

Table 19 summarizes the incidence rate of solicited local symptoms during the 7-day post-vaccination period by age stratum. The HZ/su group had notably higher incidence rate of local solicited AEs (any grade and Grade 3) compared to the placebo group. The most frequent solicited local symptom (any grade and Grade 3) reported in the HZ/su group was pain (69%-88%) across three age strata.

Table 19: Number and percentage of subjects reporting solicited local symptoms during the 7-day post-vaccination period (TVc with 7-day diary card, ZOSTER 006-022 pooled)

	Aged 50 - 59 Years		Aged 60 - 69 Years		Aged ≥70 Years	
	HZ/su N=1315 n (%)	Placebo N=1312 n (%)	HZ/su N=1311 n (%)	Placebo N=1305 n (%)	HZ/su N=2258 n (%)	Placebo N=2263 n (%)
Pain	1162 (88.4)	189 (14.4)	1086 (82.8)	145 (11.1)	1562 (69.2)	199 (8.8)
Pain, Grade 3	135 (10.3)	7 (0.5)	90 (6.9)	6 (0.5)	90 (4.0)	4 (0.2)
Redness	509 (38.7)	16 (1.2)	503 (38.4)	21 (1.6)	851 (37.7)	27 (1.2)
Redness, >100 mm	37 (2.8)	0 (0.0)	34 (2.6)	0 (0.0)	70 (3.1)	0 (0.0)
Swelling	401 (30.5)	10 (0.8)	347 (26.5)	13 (1.0)	519 (23.0)	25 (1.1)
Swelling, >100 mm	14 (1.1)	0 (0.0)	7 (0.5)	0 (0.0)	30 (1.3)	0 (0.0)

N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
Source: Tables 73 and 397 of ISS

8.4.8 Adverse Events of Special Interest

Table 20 summarizes the percentage of subjects reporting at least one pIMD during different follow-up periods. The percentages were similar between treatment groups and between the two age strata. There were 16 (0.1%) and 18 (0.1%) of subjects in HZ/su and placebo groups, respectively, reporting at least one pIMD that was considered causally related to vaccination by the investigator during the entire follow-up period.

Table 20: Number and percentage of subjects reporting potential immune-mediated disease by time period and age stratum (TVc, ZOSTER 006-022 pooled)

	Aged 50 - 69 Years		Aged ≥70 Years		Overall ≥50 Years	
	HZ/su N=5887 n (%)	Placebo N=5887 n (%)	HZ/su N=8758 n (%)	Placebo N=8773 n (%)	HZ/su N=14645 n (%)	Placebo N=14660 n (%)
pIMD up to 30 days post last vaccination	13 (0.2)	14 (0.2)	17 (0.2)	16 (0.2)	30 (0.2)	30 (0.2)
pIMD up to 365 days post last vaccination	33 (0.6)	44 (0.7)	57 (0.7)	61 (0.7)	90 (0.6)	105 (0.7)
pIMD over the entire period	69 (1.2)	84 (1.4)	110 (1.3)	118 (1.3)	179 (1.2)	202 (1.4)

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least one pIMD
Source: Tables 317 and 321of Annex 3 submitted STN 125614/0.25

Reviewer's comments:
The incidence rate of pIMD up to one year post last vaccination appears to be similar to that during the rest of the follow-up period.

8.5 Additional Safety Evaluations

Within 30 days post-vaccination, a higher percentage of unsolicited AEs occurred in the HZ/su group than in the placebo group (50.5% versus 32.0%) overall in subjects ≥50 YOA. Unsolicited AEs causally related to vaccination were reported in more subjects from the HZ/su group compared to the placebo group (34.5% versus 6.6%). This trend was also observed within each of the age strata (50-69 YOA and ≥70 YOA). Most unsolicited AEs reported in more than 1.0% HZ/su recipients and with a relative risk >2 as compared to placebo were under the MedDRA Primary System Organ Class of "General disorders and administration site conditions" or associated with Preferred Terms (PT) covering the local and general symptoms recorded as solicited on the 7-day diary

card by subjects who were part of the 7-day diary card subset (including injection site pain/swelling/redness, fever, headache, fatigue, chills [PT covering the solicited general symptom of shivering], myalgia, and nausea). Other unsolicited AEs reported with an incidence rate ≥1.0% in HZ/su recipients and a relative risk >2 compared to placebo include injection site pruritus (RR: 9.07%; 95% CI: 6.38% to 13.25%), malaise (RR: 5.91%; 95% CI: 4.27% to 8.37%), pain (RR: 6.01%; 95% CI: 4.16% to 8.91%), and injection site warmth (RR: 29.83%; 95% CI: 12.50% to 93.22%). The incidence rates of these four AEs in the HZ/su group were between 1.0% and 2.2%. Within the 7-day diary card subset, the percentage of subjects reporting at least one unsolicited AE within 30 days post-vaccination was similar between the HZ/su and placebo groups (29.2% versus 27.5%).

8.6 Safety Conclusions

The HZ/su showed apparently higher risk of local and general reactogenicity and unsolicited AEs (within 30 days post-vaccination) compared to placebo. No obvious imbalance was observed in the incidence rate of deaths, SAEs, or pIMDs between the HZ/su and placebo groups. In addition, the younger age stratum tended to have a higher percentage of subjects reporting solicited general AEs, and lower percentage of subjects reporting SAEs.

9. ADDITIONAL STATISTICAL ISSUES

NA

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The application was mainly supported by the efficacy and safety data from two placebo-controlled pivotal studies, ZOSTER-006 and ZOSTER-022. Three other phase 3 immunogenicity studies were also conducted to support the license application.

<u>ZOSTER-006 and ZOSTER-022 (Efficacy):</u>

- The primary objective to demonstrate the VE of HZ/su in prevention of HZ in adults ≥50 YOA compared to placebo was met in ZOSTER-006 (success criterion: lower limit of the two-sided 95% CI of VE >25%). The estimated HZ VE in adults ≥50 YOA was 97.16% (95% CI: 93.72% to 98.97%).
- The primary objective to demonstrate the VE of HZ/su in prevention of HZ in adults ≥70 YOA compared to placebo was also met in ZOSTER-022 (success criterion: lower limit of the two-sided 95% CI of VE >10%). The estimated HZ VE in adults ≥70 YOA was 89.79% (95% CI: 84.29% to 93.66%).
- The primary objective to demonstrate the VE of HZ/su in prevention of PHN in adults ≥70 YOA compared to placebo was met in the pooled analysis of ZOSTER-006 and ZOSTER-022 (success criterion: lower limit of the two-sided 95% CI of VE >0%). The estimated PHN VE in adults ≥70 YOA was 88.78% (95% CI: 68.70% to 97.10%).

ZOSTER-006 and ZOSTER-022 (Safety): HZ/su showed higher risk of local and general reactogenicity and unsolicited AEs (within 30 days post-vaccination) compared to placebo. No apparent imbalance was observed in the incidence rate of deaths, SAEs, or pIMDs between the HZ/su and placebo groups.

ZOSTER-007: The primary objective of lot-to-lot consistency in terms of GMC of anti-gE ELISA antibody at one month post second dose of HZ/su was met. The two-sided 95% CIs of GMC ratio between all three pairs of lots were within the pre-specified criterion of [0.67, 1.5].

ZOSTER-004: This study was to assess the immunogenicity of HZ/su when co-administered with GSK's quadrivalent influenza vaccine (Co-Ad) versus separate administration of the two vaccines (Control) in adults ≥50 YOA. All three co-primary objectives were met: 1) the VRR to HZ/su in terms of anti-gE ELISA antibodies at one month after the second dose in the Co-Ad group was 95.8% (95% CI: 93.3% to 97.6%), with the lower confidence limit above the criterion of 60%; 2) non-inferiority of the Co-Ad group compared to the Control group in terms of anti-gE ELISA antibodies at one month post second dose was demonstrated with the upper limit of the 95% CI of the GMC ratio (Control/Co-Ad) below the criterion of 1.5; 3) non-inferiority of the Co-Ad group compared to the Control group in terms of HI titers 21 days post vaccination was demonstrated with the upper limit of the 95% CI of the GMT ratio (Control/Co-Ad) below the criterion of 1.5 for each influenza vaccine strain.

ZOSTER-026: This study was a dosing schedule comparison study (0, 6-momth and 0,12 month versus 0, 2-month). The co-primary objectives for the 0, 6 month schedule were met: 1) the VRR for the 0, 6-month schedule in terms of anti-gE ELISA antibodies at one month after the second dose was 96.5% (97.5% CI: 90.4% to 99.2%), with the lower confidence limit above the criterion of 60%; 2) non-inferiority of the 0, 6-month schedule compared to the 0, 2-month schedule in terms of anti-gE ELISA antibodies at one month after the second dose was demonstrated (success criterion: the upper limit of the 97.5% CI of GMC ratio [0, 2-month/0, 6-month] <1.5). However, the co-primary objectives for the 0,12 month schedule were not met because the non-inferiority criterion was not met: the upper confidence limit of the GMC ratio [0, 2-month/0, 12-month] was 1.53, just above the 1.5 criterion.

10.2 Conclusions and Recommendations

All primary efficacy objectives in each individual efficacy study and in the pooled efficacy analysis were met. Regarding safety, no apparent imbalance was observed in the incidence rate of deaths, SAEs, or pIMDs between the HZ/su and placebo groups. HZ/su showed higher risk of local and general reactogenicity and unsolicited AEs (within 30 days post-vaccination) compared to placebo in pooled analysis of ZOSTER-006 and ZOSTER-022. The reviewer defers to the clinical reviewer for detailed review of adverse events and further considerations on the acceptability of the safety profile of HZ/su.