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Statistical Review and Evaluation	
Application Type	BLA (efficacy supplement)
STN	125614/398
CBER Received Date	9/24/2020
PDUFA Goal Date	7/25/2021
Division / Office	Division of Vaccines and Related Product Applications (DVRPA) / Office of Vaccines Research and Review (OVRR)
Committee Chair	Ramachandra Naik
Clinical Reviewer	Darcie Everett
Project Managers	Laura Gottschalk
Priority Review	No
Reviewer Name(s)	Sang Ahnn, VEB/DB/OBE
Concurrence	Lei Huang, Concurring Reviewer, VEB/DB/OBE Tsai-Lien Lin, Branch Chief, VEB/DB/OBE
Applicant	GlaxoSmithKline Biologicals
Established Name	Zoster Vaccine Recombinant, Adjuvanted
Trade Name	Shingrix
Pharmacologic Class	Vaccine
Formulation	50 µg gE per 0.5 mL of reconstituted vaccine + MPL, QS21 and liposome (50 µg MPL and 50 µg QS21) per 0.5 mL of reconstituted vaccine
Dosage Form(s) and Route(s) of Administration	Two 0.5-mL doses into the deltoid muscle
Indication(s) and Intended Population(s)	Prevention of herpes zoster in adults 18 years of age and older who are at increased risk due to immunodeficiency or immunosuppression caused by disease or therapy

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1. Executive Summary

Shingrix is a recombinant adjuvanted Herpes zoster (HZ) vaccine approved in the United States on October 2017 and indicated for prevention of HZ (shingles) in adults aged 50 years and older. Shingrix consists of recombinant subunit Varicella zoster virus (VZV) glycoprotein E (gE) (50 µg/dose) and the $AS01_B$ Adjuvant System [MPL, QS21 and liposome (50 µg MPL and 50 µg QS21)], and is to be administered according to a 2-dose schedule given 2 to 6 months apart.

This submission includes the applicant's clinical study reports (CSRs) of four studies conducted in immunocompromised (IC, immunodeficient or immunosuppressed) adults with autologous hematopoietic stem cell transplant (auHSCT) (ZOSTER-002), hematologic malignancy (ZOSTER-039), renal transplants (ZOSTER-041) and solid tumor (ZOSTER-028). In addition, CSRs of two supporting studies in IC adults with auHSCT (ZOSTER-001) and HIV infection (ZOSTER-015) are also included in this submission. Clinical efficacy was assessed only in study ZOSTER-002. The applicant is seeking an expansion of indication to include adults aged 18 years and older who are at increased risk of HZ due to immunodeficiency or immunosuppression caused by disease or therapy with this submission. The focus of this review is on ZOSTER-002 and ZOSTER-039.

ZOSTER-002

ZOSTER-002 was a randomized, observer-blind, placebo-controlled, multi-center (167 centers in 28 countries including US), phase 3 clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' Shingrix (herpes zoster gE/$AS01_B$ vaccine) when administered intramuscularly on a two-dose schedule to adults with autologous haematopoietic stem cell transplant (auHSCT). The study was conducted between July 2012 and February 2017.

Subjects 18 years of age and older who had undergone auHSCT in the previous 50 to 70 days were eligible. A total of 1865 subjects were randomized in 1:1 ratio to receive either Shingrix or placebo. Of them, 1846 subjects (922 in the vaccine group and 924 in the placebo group) were vaccinated with the first dose; 1735 subjects received both doses (873 in the vaccine group and 862 in the placebo group).

Randomization based on a minimization procedure was used to achieve balance between study groups with respect to 6 factors: age, underlying diagnosis, post-transplantation antineoplastic maintenance therapy, anticipated duration of post-transplantation antiviral prophylaxis, center, and sex. Two 0.5-mL doses of either Shingrix or placebo were administered into the deltoid muscle: the first dose 50 to 70 days after auHSCT and the second dose 1 to 2 months after the first dose.

The primary efficacy endpoint was (first) occurrence of confirmed HZ cases, and the primary objective of the study was to evaluate vaccine efficacy (VE) of Shingrix in the prevention of HZ. The primary efficacy analysis (Table 1) was based on the modified Total Vaccinated Cohort (mTVC), which included all subjects who received 2 doses of the same investigational product (Subjects who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the mTVC).

Table 1: Vaccine Efficacy (VE) of Shingrix among autologous haematopoietic stem cell transplant (auHSCT) recipients 18 years of age and older
[Shingrix vs. Placebo in modified Total Vaccinated Cohort (mTVC)]

	# of subjects	# of HZ cases	Sum of follow-up in years[@]	HZ incidence rate[&]	VE (95% CI)
Shingrix	870	49	1633.1	30.0	68.2 % (55.6, 77.5)
Placebo	851	135	1431.9	94.3	

@ sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years
& Per 1000 person years
Source: Based on the applicant's Table 31 in the CSR of ZOSTER-002.

As shown in Table 1 above, the point estimate of VE is 68.2% with the lower bound of the 95% confidence interval (CI) of VE being 55.6%. The median (mean) follow-up time was 22.0 (22.5) months for Shingrix group, and 19.9 (20.2) months for Placebo group. The pre-specified efficacy success criterion was that the lower bound of the 95% confidence interval (CI) of VE should be greater than 0%.

As a sensitivity analysis, the primary efficacy analysis was also performed in the Total Vaccinated Cohort (TVC), which included 1846 subjects (922 in the vaccine group and 924 in the placebo group) who received at least the first study dose. The point estimate of VE is 63.7% with the lower bound of the 95% confidence interval (CI) of VE being 51.8%.

Among 1846 subjects who received at least the first study dose (Total Vaccinated Cohort (TVC); 922 in Shingrix group and 924 in Placebo group), 68 subjects (7.4%) in Shingrix group and 64 subjects (6.9%) in Placebo group experienced SAEs from first vaccination up to 30 days post-vaccination. From first vaccination up to 1-year post-vaccination, 261 (28.3%) in Shingrix group and 231 (25.0%) in Placebo group experienced SAEs. From first vaccination up to 1-year post-vaccination, 51 (5.5%) in Shingrix group and 49 (5.3%) in Placebo group died.

ZOSTER-039

ZOSTER-039 was a randomized, observer-blind, placebo-controlled, multi-center (77 centers in 21 countries including US), phase 3 clinical trial to assess the safety, and immunogenicity of GSK Biologicals' Shingrix (herpes zoster gE/AS01$_B$ vaccine) when administered intramuscularly on a two-dose schedule to adults with hematologic malignancies. The study was conducted between March 2013 and January 2017.

Subjects 18 years of age and older, diagnosed with at least one hematologic malignancy, were eligible if they had a life expectancy of 12 months or longer and were receiving or had just finished immunosuppressive cancer treatments. A total of 569 subjects were randomized in 1:1 ratio to receive either Shingrix (n=286) or placebo (n=283); 562 subjects (283 in the vaccine group and 279 in the placebo group) were vaccinated with the first dose; 516 subjects received both doses (259 in the vaccine group and 257 in the placebo group).

Subjects were stratified based on their underlying disease (non-Hodgkin B-cell lymphoma,

chronic lymphocytic leukemia, and all others). Within each stratum, randomization was based on a minimization procedure to account for underlying disease, age, sex, locality, and timing of study vaccination. Two 0.5-mL doses of either Shingrix or placebo were administered into the deltoid muscle: the first dose at Visit 1 and the second dose 1 to 2 months after the first dose.

The primary immunogenicity endpoints were (1) vaccine response rate (VRR) for anti-glycoprotein E (gE) humoral immune responses at Month 2 following a two-dose administration of the vaccine in subjects with hematologic malignancies *excluding* subjects with Non-Hodgkin B-cell Lymphoma (NHBCL) and Chronic Lymphocytic Leukemia (CLL), and (2) anti-gE humoral immune responses at Month 2 following a two-dose administration of the vaccine, as compared to placebo (GMT ratio) in subjects with hematologic malignancies *excluding* subjects with NHBCL and CLL. The primary immunogenicity analyses were based on the according-to-protocol (ATP) cohort for the humoral immunogenicity. VRR was defined as: for initially seronegative subjects, antibody concentrations at Month 2 being ≥ 4-fold the cut-off for anti-gE (i.e. 4x97 mIU/mL), and for initially seropositive subjects, antibody concentrations at Month 2 being ≥ 4-fold the pre-vaccination antibody concentration.

VRR in the Shingrix group was 80.4% (73.1, 86.5) and GMT ratio (Shingrix over Placebo) was 29.8 (21.1, 42.0). The immunogenicity success criteria were (1) the lower limit (LL) of the 95% confidence interval (CI) of the VRR in the Shingrix group > 60%, (2) the LL of the 95% CI of the Geometric Mean Titer (GMT) ratio (Shingrix over placebo) for anti-gE ELISA antibody concentrations at Month 2 > 3.0.

Based on a *post-hoc* efficacy analysis, the incidence of herpes zoster was 8.5 per 1000 person-years in the vaccine group and 66.2 per 1000 person-years in the placebo group (VE = 87.2% with 95% CI of (44.3, 98.6)). The median follow-up was 11.1 months from 30 days after dose 2. This post-hoc efficacy analysis was performed on the modified Total Vaccinated Cohort (mTVC), which included 515 subjects (259 in the vaccine group and 256 in the placebo group) who received 2 doses of the same investigational product (Subjects who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the mTVC).

As a sensitivity analysis, efficacy analysis was also performed in Total Vaccinated Cohort (TVC), which included 562 subjects (283 in the vaccine group and 279 in the placebo group) who received at least the first study dose. The incidence of herpes zoster was 20.2 per 1000 person-years in the vaccine group and 70.9 per 1000 person-years in the placebo group (VE = 71.4% with 95% CI of (31.6, 88.1)).

Among 562 subjects who received at least the first study dose (Total Vaccinated Cohort (TVC); 283 in Shingrix group and 279 in Placebo group), 17 subjects (6.0%) in Shingrix group and 29 subjects (10.4%) in Placebo group experienced SAEs from first vaccination up to 30 days post-vaccination. During the entire study period, 66 (23.3%) in Shingrix group and 82 (29.4%) in Placebo group experience SAEs. During the entire study period, 29 (10.2%) in Shingrix group and 37 (13.3%) in Placebo group died.

Conclusion and Recommendation

The clinical efficacy of Shingrix was evaluated in ZOSTER-002 when administered to adults 18 years and older with autologous haematopoietic stem cell transplant (auHSCT). The point estimate of VE was 68.2% with the lower bound of the 95% confidence interval (CI) of VE being 55.6% when the analysis was performed on mTVC which included all subjects who received 2 doses of the same investigational product. The point estimate of VE was 63.7% with the lower bound of the 95% confidence interval (CI) of VE being 51.8% when the analysis was performed on TVC who received at least the first study dose.

A Post-hoc analysis of clinical efficacy of Shingrix was performed in ZOSTER-039 when administered to adults 18 years and older with hematologic malignancies. The point estimate of VE was 87.2% with the lower bound of the 95% confidence interval (CI) of VE being 44.3% when the analysis was performed on mTVC which included all subjects who received 2 doses of the same investigational product. The point estimate of VE was 71.4% with the lower bound of the 95% confidence interval (CI) of VE being 31.6% when the analysis was performed on TVC who received at least the first study dose.

Based on the safety analysis of SAEs, no safety concern has been identified.

2. Clinical and Regulatory Background

Please refer to this section in the clinical reviewer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The initial submissions (STN 125614/398.0 and STN 125614/398.1) were inadequately organized for conducting a complete statistical review (especially the location and contents of legacy analysis datasets). It was subsequently corrected by the applicant in response to the requests of the review team.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issue was found. However, numerous minor problems especially among legacy analysis datasets were found in the earlier submissions. The problems were subsequently corrected by the applicant in response to the requests of the review team.

5. Sources of Clinical data and Other Information Considered in the Review

5.1 Review Strategy

This submission includes the clinical study reports of ZOSTER-002, ZOSTER-028, ZOSTER-039, and ZOSTER-041. Statistical aspects of the efficacy, immunogenicity, and safety analyses of ZOSTER-002 and ZOSTER-039 were reviewed.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

The submission of this application (STN 125614/398) was completed on 10/2/2020 and is in the EDR. The Clinical Study Reports (CSRs), electronic datasets, and Case Report Forms (CRFs) for ZOSTER-002, ZOSTER-028, ZOSTER-039, and ZOSTER-041 are in Module 5.3.5.1 of this submission (STN 125614/398.0 and STN 125614/398.1).

6. Discussion of Individual Studies/Clinical Trials

6.1 ZOSTER-002

Title of the study: "A phase 3, randomized, observer-blind, placebo-controlled, multi-center, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01$_B$ candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients."

Study initiation date: 7/13/2012
Study completion date: 2/1/2017.

6.1.1 Objectives

The primary objective of this study was to evaluate the vaccine efficacy of two doses of herpes zoster gE/AS01$_B$ candidate vaccine in the prevention of HZ in autologous HCT recipients 18 years of age and older.

The secondary objectives were to (1) evaluate VE in reducing the total duration of 'worst' HZ-associated pain over the entire pain reporting period, (2) evaluate VE in the reduction of confirmed HZ-associated complications, (3) evaluate VE in the prevention of post-herpetic neuralgia (PHN), (4) evaluate humoral immune responses to the study vaccine in a sub-cohort of subjects, and (5) evaluate vaccine safety and reactogenicity.

6.1.2 Design Overview

ZOSTER-002 was a randomized, observer-blind, placebo-controlled, multi-center (167 centers in 28 countries including US), phase 3 clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' Shingrix (herpes zoster gE/AS01$_B$ vaccine) when administered intramuscularly on a two-dose schedule to adults with autologous haematopoietic stem cell transplant (auHSCT).

Subjects 18 years of age and older who had undergone auHSCT in the previous 50 to 70 days were eligible. A total of 1865 subjects were randomized in 1:1 ratio to receive either Shingrix or placebo; 1846 subjects (922 in the vaccine group and 924 in the placebo group) were vaccinated with the first dose; 1735 subjects received both doses (873 in the vaccine group and 862 in the placebo group).

Randomization based on a minimization procedure was used to achieve balance between study groups with respect to 6 factors: age, underlying diagnosis, post-transplantation antineoplastic maintenance therapy, anticipated duration of post-transplantation antiviral prophylaxis, center, and sex.

6.1.3 Population

The primary efficacy analysis was performed on the modified Total Vaccinated Cohort (mTVC), which included all subjects who received 2 doses of the same investigational product. Subjects who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the mTVC. There were 1721 subjects (870 in the vaccine group and 851 in the placebo group) in the mTVC. As a sensitivity analysis, the primary efficacy analysis was also performed in Total Vaccinated Cohort (TVC), which included 1846 subjects (922 in the vaccine group and 924 in the placebo group) who received at least the first study dose.

The safety was evaluated in TVC.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Two 0.5-mL doses of either Shingrix or placebo were administered into the deltoid muscle: the first dose 50 to 70 days after auHSCT and the second dose 1 to 2 months after the first dose.

6.1.6 Sites and centers

This study was conducted at 167 centers in 28 countries. Among 1846 TVC subjects, 13.5% (250 subjects) were from US (21 centers).

6.1.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's review.

6.1.8 Endpoints and Criteria for Study Success

Efficacy endpoint: The primary efficacy endpoint was (first) occurrence of confirmed HZ cases. The pre-specified success criterion based on the primary efficacy endpoint was that the lower bound of the 95% confidence interval (CI) of VE is > 0%. The secondary endpoints were (1) duration of 'worst' HZ-associated pain, (2) occurrence of confirmed HZ-associated complications, (3) occurrence of PHN, and (4) antigen-specific antibody (anti- gE Ab) concentrations as determined by ELISA in a sub-cohort of subjects

Safety endpoints: The safety endpoints were (1) occurrence of solicited local and general AEs, (2) occurrence of unsolicited AEs, (3) occurrence of SAEs, and (4) occurrence of AEs of specific interest.

6.1.9 Statistical Considerations and Statistical Analysis Plan

The primary efficacy hypothesis tested was

H_0: VE = 0 vs. H_a: VE $\neq$ 0

where VE [Vaccine Efficacy against HZ] = 1 – RR = 1 - $IR_{SHINGRIX}/IR_{PLACEBO}$,
$IR_{SHINGRIX}$ = incidence rate of HZ for individuals in Shingrix group,
$IR_{PLACEBO}$ = incidence rate of HZ for individuals in Placebo group.

Calculation of VE and its CI was based on the exact inference on the relative risk (RR) conditionally on the number of HZ cases observed and time at risk.

6.1.10 Primary Efficacy Analyses

The primary efficacy analysis was based on the modified Total Vaccinated Cohort (mTVC), which included all subjects who received 2 doses of the same investigational product. Subjects who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the mTVC in consideration of the unknown period between (2^{nd}) vaccination and a vaccine-induced protective immune response (lag-period).

Table 2 shows the results of primary efficacy analysis:

Table 2: Vaccine Efficacy (VE) of Shingrix among autologous haematopoietic stem cell transplant (auHSCT) recipients 18 years of age and older
[Shingrix vs. Placebo in modified Total Vaccinated Cohort (mTVC)]

	# of subjects	# of HZ cases	Sum of follow-up in years[@]	HZ incidence rate[&]	VE* (95% CI)
Shingrix	870	49	1633.1	30.0	68.2 % (55.6, 77.5)
Placebo	851	135	1431.9	94.3	

@ sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) in years
& Per 1000 person years
* Calculation of VE and its CI was based on the exact inference on the relative risk (RR) conditionally on the number of HZ cases observed and time at risk. If the calculation of VE and its CI was based on cumulative incidence where RR=(49/870)/(135/851) and VE=1-RR, then VE=64.5% with 95% CI of (51.6, 74.0).
Source: Based on the applicant's Table 31 in the CSR of ZOSTER-002.

As shown in Table 2 above, the point estimate of VE is 68.2% with the lower bound of the 95% confidence interval (CI) of VE being 55.6%. The median (mean) follow-up time was 22.0 (22.5) months for Shingrix group, and 19.9 (20.2) months for Placebo group. The pre-specified efficacy success criterion (the lower bound of the 95% confidence interval (CI) of VE > 0%) was met.

As a sensitivity analysis, Table 3 shows the results of efficacy analysis in Total Vaccinated Cohort (TVC):

Table 3: Vaccine Efficacy (VE) of Shingrix among autologous haematopoietic stem cell transplant (auHSCT) recipients 18 years of age and older
[Shingrix vs. Placebo in Total Vaccinated Cohort (TVC)]

	# of subjects	# of HZ cases	Sum of follow-up in years[@]	HZ incidence rate[&]	VE* (95% CI)
Shingrix	922	70	2017.5	34.7	63.7 % (51.8, 72.9)
Placebo	924	172	1798.8	95.6	

@ sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) in years
& Per 1000 person years
* Calculation of VE and its CI was based on the exact inference on the relative risk (RR) conditionally on the number of HZ cases observed and time at risk. If the calculation of VE and its CI was based on cumulative incidence where RR=(70/922)/(172/924) and VE=1-RR, then VE=59.2% with 95% CI of (47.1, 68.6).
Source: Based on the applicant's Table 7.26 in the CSR of ZOSTER-002.

6.1.11 Secondary Efficacy Analyses

The applicant proposed four secondary efficacy/effectiveness/immunogenicity endpoints as described in 6.1.8. However, multiplicity adjustment was not performed for the analyses of these four secondary endpoints. One of the secondary endpoints which could be considered for inclusion in the package insert was the occurrence of PHN.

Among all subjects aged 18 years and older in the mTVC, 1 case of PHN were reported in the vaccine group and 9 cases of PHN were reported in the placebo group (Table 4).

Table 4: Vaccine Efficacy (VE) of Shingrix against PHN*
[Shingrix vs. Placebo in modified Total Vaccinated Cohort (mTVC)]

SHINGRIX				Placebo				
# of subjects	# of HZ cases	# of PHN cases	% of HZ cases with PHN	# of subjects	# of HZ cases	# of PHN cases	% of HZ cases with PHN	VE against PHN among all subjects
870	49	1	2.0%	851	135	9	6.7%	89.3% (22.5%, 99.8%)

* PHN was defined as HZ-associated pain rated as ≥3 (on a 0-10 scale), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory (ZBPI).
Source: Reviewer's analysis.

6.1.12 Safety Analyses

Among 1846 subjects who received at least the first study dose (Total Vaccinated Cohort (TVC); 922 in Shingrix group and 924 in Placebo group), 68 subjects (7.4%) in Shingrix group and 64 subjects (6.9%) in Placebo group experienced SAEs from first vaccination up to 30 days post-vaccination. From first vaccination up to 1-year post-vaccination, 261 (28.3%) in Shingrix group and 231 (25.0%) in Placebo group experience SAEs. From first vaccination up to 1-year post-vaccination, 51 (5.5%) in Shingrix group and 49 (5.3%) in Placebo group died.

6.1.13 Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses of efficacy were performed by age (18-49 years and 50+ years), underlying diseases (multiple myeloma and others), gender (female and male) and ethnicity (White, Asian and others). Subgroup analyses of efficacy by age and underlying diseases were generally shown to be consistent with overall efficacy results. However, VE in female subjects was slightly higher compared to male. Also, VE in Asians was substantially higher compared to Whites as shown in Table 5.

Table 5. Vaccine Efficacy (VE) of Shingrix by gender and ethnicity
(Subgroup Analyses in mTVC)

Subgroup (n)	VE (95% CI)
Total (1721)	68.2 % (55.6, 77.5)
Female (640)	77.6% (60.7, 87.9)
Male (1081)	60.3% (39.4, 74.5)
White (1333)	56.1% (38.7, 68.6)
Asian (277)	93.1% (74.5, 98.2)
Other (111)	69.8% (-21.6, 92.7)

Source: Reviewer's analysis.

6.2 ZOSTER-039

Title of the study: "A Phase 3, randomized, observer-blind, placebo-controlled, multi-center study to assess the safety and immunogenicity of GSK Biologicals' Herpes Zoster HZ/su (gE/AS01$_B$) candidate vaccine when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with hematologic malignancies."

Study start date: 3/1/2013
Study completion date: 1/6/2017

6.2.1 Objectives

The primary (immunogenicity) objectives of this study were:

(1) to evaluate vaccine response rate (VRR) for anti-glycoprotein E (gE) humoral immune responses at Month 2 following a two-dose administration of Shingrix in subjects with hematologic malignancies excluding subjects with Non-Hodgkin B-cell Lymphoma (NHBCL) and Chronic Lymphocytic Leukemia (CLL) [VRR was defined as: for initially seronegative subjects, antibody concentrations at Month 2 being $\geqslant$ 4-fold the cut-off for anti-gE (4x97 mIU/mL), and for initially seropositive subjects, antibody concentrations at Month 2 being $\geqslant$ 4-fold the pre-vaccination antibody concentration.], and

(2) to evaluate anti-gE humoral immune responses at Month 2 following a two-dose administration of Shingrix, as compared to placebo, in subjects with hematologic malignancies excluding subjects with NHBCL and CLL.

The safety objectives included the evaluation of the safety and reactogenicity following administration of Shingrix compared to placebo from the first vaccination up to 30 days post last vaccination in subjects with hematologic malignancies, aged 18 years and older.

6.2.2 Design Overview

ZOSTER-039 was a randomized, observer-blind, placebo-controlled, multi-center (77 centers in 21 countries including US), phase 3 clinical trial to assess the safety, and immunogenicity of GSK Biologicals' Shingrix (herpes zoster gE/AS01$_B$ vaccine) when administered intramuscularly on a two-dose schedule to adults with hematologic malignancies.

Subjects 18 years of age and older, diagnosed with at least one hematologic malignancy, were eligible if they had a life expectancy of 12 months or longer and were receiving or had just finished immunosuppressive cancer treatments. A total of 569 subjects were randomized in 1:1 ratio to receive either Shingrix (n=286) or placebo (n=283); 562 subjects (283 in the vaccine group and 279 in the placebo group) were vaccinated with the first dose; 516 subjects received both doses (259 in the vaccine group and 257 in the placebo group).

Subjects were stratified based on their underlying disease (non-Hodgkin B-cell lymphoma, chronic lymphocytic leukemia, and all others). Within each stratum, randomization was based on a minimization procedure to account for underlying disease, age, sex, locality, and timing of

study vaccination.

6.2.3 Population

The primary immunogenicity analyses were based on the according-to-protocol (ATP) cohort for the humoral immunogenicity, which included all subjects who received 2 doses of the same investigational product according to protocol *excluding* those with non-Hodgkin B-cell lymphoma (NHBCL) and chronic lymphocytic leukemia (CLL). There were 278 subjects (148 in the vaccine group and 130 in the placebo group).

The safety was evaluated in Total Vaccinated Cohort (TVC), which included 562 subjects (283 in the vaccine group and 279 in the placebo group) who received at least the first study dose.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Two 0.5-mL doses of either Shingrix or placebo were administered into the deltoid muscle: the first dose at Visit 1 and the second dose 1 to 2 months after the first dose.

6.2.6 Sites and centers

This study was conducted at 77 centers in 21 countries. Among 562 TVC subjects, 4.1% (23 subjects) were from US (4 centers).

6.2.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's review.

6.2.8 Endpoints and Criteria for Study Success

Immunogenicity endpoints: The primary immunogenicity endpoints were

(1) vaccine response rate (VRR) for anti-glycoprotein E (gE) humoral immune responses at Month 2 following a two-dose administration of the vaccine in subjects with hematologic malignancies *excluding* subjects with Non-Hodgkin B-cell Lymphoma (NHBCL) and Chronic Lymphocytic Leukemia (CLL) [VRR was defined as: for initially seronegative subjects, antibody concentrations at Month 2 being ≥ 4-fold the cut-off for anti-gE (4x97 mIU/mL), and for initially seropositive subjects, antibody concentrations at Month 2 being ≥ 4-fold the pre-vaccination antibody concentration], and
(2) anti-gE humoral immune responses at Month 2 following a two-dose administration of the vaccine, as compared to placebo (GMT ratio) in subjects with hematologic malignancies *excluding* subjects with NHBCL and CLL.

The immunogenicity success criteria were (1) the lower limit (LL) of the 95% confidence interval (CI) of the VRR in the Shingrix group > 60%, (2) the LL of the 95% CI of the Geometric Mean Titer (GMT) ratio (Shingrix over placebo) for anti-gE ELISA antibody

concentrations at Month 2 > 3.0.

Safety endpoints: The safety endpoints were the occurrences of

(1) solicited local and general AEs,
(2) unsolicited AEs,
(3) SAEs, and
(4) AEs of specific interest.

6.2.9 Statistical Considerations and Statistical Analysis Plan

The primary immunogenicity hypotheses tested were

H_0: VRR $\leq$ 60% vs H_1: VRR > 60% in Shingrix group, and

H_0: $GMT_S/GMT_P \leq 3.0$ vs H_1: $GMT_S/GMT_P > 3$,
where GMT_S is the geometric mean titer of anti-gE humoral immune responses at Month 2 in Shingrix group, and GMT_P is the geometric mean titer of anti-gE humoral immune responses at Month 2 in Placebo group.

To demonstrate study success, both hypotheses need to be rejected.

6.2.10 Primary Immunogenicity Analyses

The primary immunogenicity analyses were based on the according-to-protocol (ATP) cohort for the humoral immunogenicity *excluding* subjects with Non-Hodgkin B-cell Lymphoma (NHBCL) and Chronic Lymphocytic Leukemia (CLL).

VRR in the Shingrix group was 80.4% (73.1, 86.5) and GMT ratio (Shingrix over Placebo) was 29.8 (21.1, 42.0), hence meeting the immunogenicity success criteria for both VRR and GMT ratio.

The success criteria were also met for both co-primary immunogenicity objectives when evaluated in the total vaccinated cohort (TVC), which included all subjects who received at least the first study dose *including* those with non-Hodgkin B-cell lymphoma (NHBCL) and chronic lymphocytic leukemia (CLL).

6.2.11 *Post-hoc* analysis of clinical efficacy

The applicant performed a post-hoc efficacy analysis based on the modified Total Vaccinated Cohort (mTVC), which included all subjects who received 2 doses of the same investigational product. Subjects who developed an episode of herpes zoster less than 1 month after receiving the second study dose were excluded from the mTVC in consideration of the unknown period between (2^{nd}) vaccination and a vaccine-induced protective immune response (lag-period).

Table 6 shows the results of post-hoc efficacy analysis:

Table 6: Vaccine Efficacy (VE) of Shingrix among adults aged 18 years and older with hematologic malignancies
[Shingrix vs. Placebo in modified Total Vaccinated Cohort (mTVC)]

	# of subjects	# of HZ cases	Sum of follow-up in years[@]	HZ incidence rate[&]	VE* (95% CI)
Shingrix	259	2	236.1	8.5	87.2 % (44.3, 98.6)
Placebo	256	14	211.6	66.2	

@ sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) in years
& Per 1000 person years
* Calculation of VE and its CI was based on the exact inference on the relative risk (RR) conditionally on the number of HZ cases observed and time at risk. If the calculation of VE and its CI was based on cumulative incidence where RR=(2/259)/(14/256) and VE=1-RR, then VE=85.9% with 95% CI of (45.1, 96.4).
Source: Based on the applicant's Table 8.9 in the CSR of ZOSTER-039.

As a sensitivity analysis, Table 7 shows the results of efficacy analysis in Total Vaccinated Cohort (TVC):

Table 7: Vaccine Efficacy (VE) of Shingrix among adults aged 18 years and older with hematologic malignancies
[Shingrix vs. Placebo in Total Vaccinated Cohort (TVC)]

	# of subjects	# of HZ cases	Sum of follow-up in years[@]	HZ incidence rate[&]	VE* (95% CI)
Shingrix	283	6	296.4	20.2	71.4 % (31.6, 88.1)
Placebo	279	19	268.1	70.9	

@ sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) in years
& Per 1000 person years
* Calculation of VE and its CI was based on the exact inference on the relative risk (RR) conditionally on the number of HZ cases observed and time at risk. If the calculation of VE and its CI was based on cumulative incidence where RR=(6/283)/(19/279) and VE=1-RR, then VE=68.9% with 95% CI of (25.6, 87.1).
Source: Based on the applicant's Table 8.9 in the CSR of ZOSTER-039.

6.2.12 Safety Analyses

Among 562 subjects who received at least the first study dose (Total Vaccinated Cohort (TVC); 283 in Shingrix group and 279 in Placebo group), 17 subjects (6.0%) in Shingrix group and 29 subjects (10.4%) in Placebo group experienced SAEs from first vaccination up to 30 days post-vaccination. During the entire study period, 66 (23.3%) in Shingrix group and 82 (29.4%) in Placebo group experience SAEs. During the entire study period, 29 (10.2%) in Shingrix group and 37 (13.3%) in Placebo group died.

For the further analyses of safety endpoints, please refer to this section in the clinical reviewer's review.

6.2.13 Subgroup Analyses of *Post-hoc* clinical efficacy endpoint

Since there were only 2 HZ occurrences in Shingrix group (mTVC) observed, it is not possible to perform a meaningful subgroup analysis in mTVC. The reviewer performed the following subgroup analyses in TVC.

Subgroup analyses of efficacy were performed by age (18-49 years and 50+ years), underlying diseases (CLL, NHBCL, and multiple myeloma & others), gender (female and male) and ethnicity (White, Asian and others). The subgroup analysis of efficacy by underlying diseases was generally shown to be consistent with overall efficacy results. However, statistically meaningful subgroup analyses were not possible due to the small sample size as shown in Table 8.

Table 8. Vaccine Efficacy (VE) of Shingrix by age, underlying diseases, gender and ethnicity (Subgroup Analyses in TVC)

Subgroup (n)	VE (95% CI)
Total (562)	71.4 % (31.6, 88.1)
18-49 years (147)	31.5% (-166.4, 82.5)
50+ years (415)	81.9% (42.8, 94.4)
MM & others* (399)	72.1% (20.2, 90.3)
CLL (83)	69.6% (-105.9, 95.6)
NHBCL (80)	70.4% (-100.3, 95.7)
Female (228)	50.0% (-78.3, 86.1)
Male (334)	77.5% (27.9, 93.0)
White (385)	58.0% (-26.3, 86.1)
Asian (133)	77.4% (11.5, 94.4)
Other (44)	100.0% (-396.3, 100.0)

*multiple myeloma, non-Hodgkin T-cell lymphoma, Hodgkin lymphoma, and other hematologic Malignancies

Source: Reviewer's analysis.

7. Integrated Overview of Efficacy

Clinical efficacy was assessed only in study ZOSTER-002. A post-hoc analysis of clinical efficacy was performed in ZOSTER-039. The integrated efficacy analysis of these two studies does not appear to be informative, since (1) the nature of the study population of these two studies were totally different, (2) ZOSTER-002 was much bigger than ZOSTER-039 in size, and (3) the efficacy analysis for ZOSTER-002 was pre-specified, while the efficacy analysis of ZOSTER-039 was post-hoc.

8. Integrated Overview of Safety

The integrated safety analysis of the studies does not appear to be informative, since the nature of study population in each study was different, and one study (ZOSTER-002) dominated other studies in size.

For further discussion of safety overview, please refer to this section in the clinical reviewer's review.

10. Conclusions

1. (a) The clinical efficacy of Shingrix was evaluated in ZOSTER-002 when administered to adults 18 years and older with autologous haematopoietic stem cell transplant (auHSCT). The point estimate of VE was 68.2% with the lower bound of the 95% confidence interval (CI) of VE being 55.6% when the analysis was performed on mTVC, which included all subjects who received 2 doses of the same investigational product.
   (b) As a sensitivity analysis, when the analysis was performed on TVC (who received at least the first study dose), the point estimate of VE was 63.7% with the lower bound of the 95% confidence interval (CI) of VE being 51.8%.

2. (a) A *post-hoc* analysis of clinical efficacy of Shingrix was performed in ZOSTER-039 when administered to adults 18 years and older with hematologic malignancies. The point estimate of VE was 87.2% with the lower bound of the 95% confidence interval (CI) of VE being 44.3% when the analysis was performed on mTVC which included all subjects who received 2 doses of the same investigational product.
   (b) As a sensitivity analysis, when the analysis was performed on TVC (who received at least the first study dose), the point estimate of VE was 71.4% with the lower bound of the 95% confidence interval (CI) of VE being 31.6%.

3. Based on the safety analysis of SAEs, no safety concern has been identified.