Summary Basis for Regulatory Action

Date: October 20, 2017

From: Carmen M. Collazo-Custodio, Ph.D., Chair of the Review Committee

BLA STN#: 125614/0

Applicant Name: GlaxoSmithKline Biologicals, S. A.

Date of Submission: October 21, 2016

Goal Date: October 21, 2017

Proprietary Name: SHINGRIX

Established Name: Zoster Vaccine Recombinant, Adjuvanted

Indication: SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority:
Marion F. Gruber, Ph.D., Director, Office of Vaccine Research and Review

- **X I concur with the summary review.**
- □ **I concur with the summary review and include a separate review to add further analysis.**
- □ **I do not concur with the summary review and include a separate review.**

The table below indicates the materials reviewed when developing the Summary Basis of Regulatory Action (SBRA).

Document title	**Reviewer name - document date**
CMC Reviews • *CMC* • *Inspection waiver memo* • *Facilities review*	Shuang Tang, Ph.D. (Antigen CMC review, OVRR/DVP) - October 17, 2017 Marina Zaitseva, Ph.D. (Adjuvant CMC review, OVRR/DVP) - October 17, 2017 Hang Xie, Ph.D. (CMC, Consult assay reviewer, OVRR/DVP) - July 17, 2017 Jeremy Wally, Ph.D. (Inspection waiver memo, OCBQ/DMPQ) - August 14, 2017; Jeremy Wally, Ph.D. (Facilities review, OCBQ/DMPQ) - October 16, 2017
Clinical Reviews • *Clinical (OVRR/DVRPA)* • *Postmarketing safety epidemiological review* • *BIMO*	Paula Agger, M.D., M.P.H., and Rebecca Reindel, M.D. (Clinical, OVRR/DVRPA) - October 20, 2017 Ravi Goud, M.D., M.P.H. (OBE/DE) - October 13, 2017 Haecin Chun, M.S. (BIMO, OCBQ/DIS) - September 26, 2017
Statistical Reviews • *Clinical data* • *Clinical assays* • *Non-clinical assays*	 Rong Fu, Ph.D. (OBE/DB) - October 16, 2017 Rong Fu, Ph.D. (OBE/DB) - August 31, 2017 Rong Fu, Ph.D. (OBE/DB) - August 31, 2017
Toxicology Review	Nabil Al-Humadi, Ph.D., and Claudia Wrzesinski, Ph.D. (OVRR/DVRPA) - August 30, 2017
Labeling Reviews • *APLB* • *Other*	Oluchi Elekwachi, PharmD, M.P.H. (PNR Memo, OCBQ/APLB) - November 22, 2016; Oluchi Elekwachi, PharmD, M.P.H. (Labeling review, OCBQ/APLB) - May 17, 2017 Daphne D. Stewart (Labeling review, OVRR/DVRPA) - September 22, 2017 Ramachandra Naik, Ph.D. (Labeling review, OVRR/DVRPA) - October 20, 2017
Other Reviews • *Analytical methods and product testing*	Simleen Kaur, M.Sc. (OCBQ/DBSQC) - January 4, 2017 Tao Pan, Ph.D. (OCBQ/DBSQC) - September 19, 2017 Alfred Del-Grosso (OCBQ/DBSQC) Ph.D. - October 13, 2017 Noel Baichoo, Ph.D. (OCBQ/DBSQC) - October 12, 2017 Marie Anderson (OCBQ/DBSQC) - October 12, 2017
Advisory Committee Meeting	September 13, 2017

1. INTRODUCTION

GlaxoSmithKline Biologicals (GSK) submitted Biologics License Application (BLA) 125614 for licensure of Zoster Vaccine Recombinant, Adjuvanted. The proprietary name of the vaccine is SHINGRIX. SHINGRIX is indicated for prevention of herpes zoster (HZ) or shingles in adults aged 50 years and older. The vaccine is administered intramuscularly (IM) in two doses (0.5 mL each) according to the following schedule: a first dose at month 0 followed by a second dose given anytime between 2 and 6 months later.

SHINGRIX is a subunit vaccine consisting of a recombinant varicella zoster virus (VZV) envelope glycoprotein E (gE) antigen lyophilized component that is reconstituted at the time of use with $AS01_B$, GSK's proprietary adjuvant suspension component.

The $AS01_B$ adjuvant suspension component contains 3-O-desacyl-4'-monophosphoryl lipid A (MPL), a chemically detoxified form of the lipopolysaccharide derived from the Gram-negative bacterium *Salmonella minnesota* (b) (4), and QS-21, a saponin (triterpene glycoside) purified from the (b) (4) of the South American tree *Quillaja saponaria* Molina. MPL and QS-21 are combined in a liposomal formulation consisting of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered saline solution.

SHINGRIX is supplied as two components: a single-dose vial of VZV gE antigen lyophilized component and a single-dose vial of $AS01_B$ adjuvant suspension component. The antigen component must be reconstituted with the adjuvant component to form SHINGRIX before use. After reconstitution, each 0.5 mL dose contains:

- 50 micrograms (µg) of the recombinant VZV gE antigen
- 50 µg of MPL
- 50 µg of QS-21

Each dose also contains 20 mg of sucrose (as a stabilizer), 4.385 mg of sodium chloride, 1 mg of DOPC, 0.54 mg of potassium dihydrogen phosphate, 0.25 mg of cholesterol, 0.160 mg of sodium dihydrogen phosphate dihydrate, 0.15 mg of disodium phosphate anhydrous, 0.116 mg of dipotassium phosphate, and 0.08 mg of polysorbate 80. After reconstitution, SHINGRIX is a sterile, opalescent, colorless to pale brownish liquid.

The dating period for the VZV gE antigen lyophilized component and the $AS01_B$ adjuvant component of SHINGRIX is 36 months from the date of manufacture when stored at 2-8° C. The dates of manufacture of the VZV gE antigen and the $AS01_B$ adjuvant components are defined as the dates of filling into final containers. The expiration date for the packaged product, the VZV gE antigen component and the $AS01_B$ adjuvant component, is dependent on the shortest expiration date of any component.

2. BACKGROUND

VZV is an alpha herpesvirus that can cause two diseases: varicella (chickenpox) and HZ.[1-2] HZ, also known as zoster or shingles, is caused by the reactivation of latent VZV following primary VZV infection manifested as varicella (chickenpox).[1-3] During the primary infection, VZV migrates to the central nervous system, where it establishes latency in sensory neurons of cranial and dorsal root ganglia. HZ generally presents as a unilateral, vesicular rash in a single dermatome accompanied by pain, which may be severe and persistent.[2-3] Other symptoms such as fever, malaise, and headache may be present. The rash typically heals in 2-4 weeks but it may leave scaring and pigmentation changes. Post-herpetic neuralgia (PHN) is a HZ-related complication often defined as pain persisting for 90 days or more after the onset of the rash.[2-3] PHN develops as a consequence of the nerve damage caused by the reactivation of VZV in the ganglia. PHN is the third most common cause of chronic neuropathic pain in the United States (U.S.), with a point estimate of 500,000 cases yearly.[2]

Evidence indicates that HZ occurs due to a decline in VZV-specific immunity.[2] Thus, the elderly and those individuals immunocompromised from disease or immune suppressive therapy are at an increased risk for HZ and for greater disease severity.[3] Annually, it is estimated that approximately 1 million new cases of HZ are diagnosed in the U.S, with an estimated rate of 4.6 cases per 1,000 person-years among immunocompetent individuals.[4] HZ causes substantial morbidity which can interfere with activities of daily living and reduce the quality of life.

Antiviral therapy is available for the treatment of individuals with HZ complications. In addition, ZOSTAVAX, a live, attenuated VZV vaccine, is licensed in the U.S. for the prevention of HZ (shingles) in individuals 50 years of age and older.[5]

3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Manufacturing Overview

SHINGRIX consists of the VZV gE antigen lyophilized component and the $AS01_B$ adjuvant suspension component. The liquid $AS01_B$ adjuvant component is used to reconstitute the VZV gE antigen lyophilized component extemporaneously prior to administration. Manufacturing of both the VZV gE antigen and the $Aso1_B$ adjuvant components takes place in (b) (4), Belgium. Labeling and packaging operations for both the VZV gE final container vial and the $AS01_B$ liquid vial are conducted at the facilities located in (b) (4) Belgium (b) (4) .

VZV gE Antigen Lyophilized Component of SHINGRIX

VZV gE is the most abundant envelope glycoprotein, predominantly expressed on the surface of virus-infected cells. The VZV gE protein plays a critical role in virus infectivity since it is involved in virus entry and cell-to-cell spread. Evidence also indicates that the gE protein induces both neutralizing antibodies and T-cell responses.

The gE antigen component of SHINGRIX is derived from a VZV strain that was isolated from a patient with severe varicella disease. This antigen is a recombinant truncated form of VZV gE that lacks the (b) (4) and the (b) (4) of the native protein. The recombinant protein is produced in Chinese Hamster Ovary (b) (4) (CHO(b) (4)) cells that were genetically modified to express the VZV gE gene. The expression of the truncated protein is controlled by the human (b) (4). Removal of the (b) (4) facilitates the secretion of the VZV gE recombinant protein into the (b) (4). The resulting product is a purified glycosylated protein of (b) (4). Its molecular mass ranges between (b) (4) due to (b) (4)

The integrity and stability of the VZV gE gene integrated into CHO(b) (4) cells was demonstrated by the applicant. A (b) (4) have been established and carefully characterized to demonstrate that they are genetically stable, ensuring consistent quality for future production. The (b) (4) were extensively tested using comprehensive *in vitro* and *in vivo* analytical methods and no viral, bacterial, or fungal adventitious agents were detected.

VZV gE Antigen (b) (4)

The process for the manufacture of the (b) (4) consists of the following steps:

(b) (4)

VZV gE Antigen Lyophilized Drug Product (DP)

The process for the formulation of the DP involves two main steps:

- (b) (4).
- A filling step to produce gE final container (FC) through aseptic filling of the (b) (4) into 3 mL type (b) glass containers followed by lyophilization. The lyophilized gE containers are capped and inspected.

Composition

The composition of the VZV gE antigen FC component and the function of the ingredients are provided in Table 1.

Table 1. Composition of the VZV gE Antigen FC Component

Ingredients	**Quantity (per 0.5 mL dose)** [1]	**Function**
gE	50 µg	Antigen
Sucrose	20 mg	Stabilizer (b) (4)
Polysorbate 80	0.08 mg	(b) (4)
Sodium dihydrogen phosphate dihydrate	0.160 mg	Buffering agent
Dipotassium phosphate	0.116 mg	Buffering agent

[1] (b) (4)

Specifications and Methods

The tests and specifications applied for routine release of the VZV gE antigen component FC are shown in Table 2.

Table 2. Control of VZV gE Antigen FC: Tests and Specifications

Test	**Acceptance criteria**
Description	White cake or powder. Clear to opalescent, colorless liquid after reconstitution with water for injection
	(b) (4)
pH	(b) (4)
(b) (4)	(b) (4)
Identity gE by (b) (4)	(b) (4)
Protein content by (b) (4)	(b) (4)
Endotoxin content by (b) (4)	(b) (4)
Water content by (b) (4)	(b) (4)
Polysorbate 80 content by (b) (4)	(b) (4)
Sucrose content by (b) (4)	(b) (4)
Potency gE by (b) (4)	(b) (4)
Sterility test (b) (4)	
Sterility test (b) (4)	

(b) (4)

The gE potency by (b) (4) for the FC is expressed as a ratio between the gE (b) (4) The specification of gE potency by (b) (4) . It was agreed that GSK will (b) (4) provided in the original BLA to "*between* (b) (4) *after reconstitution with* (b) (4) This change will be (b) (4) . In the meantime, GSK committed to provide for release final container lots to the U.S. market that meet the (b) (4) of "*between* (b) (4) *after reconstitution with* (b) (4) " until the (b) (4)

Stability

The parameters tested throughout the stability evaluation of the gE antigen FC are: description, sterility test (b) (4) sterility test (b) (4) , endotoxin content by (b) (4) , pH, (b) (4) , gE content by (b) (4) and container closure integrity test. The stability data provided in the submission support a dating period of 36 months from the date of manufacture (i.e., filling date) when stored at 2-8 °C for the gE antigen FC lots filled in 3 mL glass vials.

During release and stability testing, it was observed that (b) (4) (b) (4) levels of the gE protein were higher for the commercial consistency lots than for the clinical lots. An investigation revealed that the (b) (4) in the commercial lots was due to the use of (b) (4) to (b) (4) (b) (4) prior to the filling of vials (the clinical lots were filled in a different facility that does not have (b) (4) (b) (4) . Product impact studies concluded that the higher levels of (b) (4) of the gE antigen do not significantly impact the immunogenicity, antigenicity, and secondary and tertiary structures of the protein. To minimize the level of (b) (4) in the vials and to reduce the level of gE protein (b) (4)

The $AS01_B$ Adjuvant Component of SHINGRIX

Mechanism of Action of $AS01_B$ Adjuvant

The $AS01_B$ adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: MPL, which signals through Toll-like Receptor 4, and QS-21, which acts through as yet unknown receptor(s). Studies have shown that QS-21 signaling involves activation of the NLRP3 inflammasome complex. MPL and QS-21 activate antigen presenting cells loaded with antigen in the draining lymph node enabling recruitment of naive CD4+ T cells. Studies conducted by GSK indicate that

both MPL and QS-21 are required to induce the maximal frequencies of gE-specific cytokine-producing CD4+ T cells and the highest titers of gE-specific antibodies.

Composition

The $AS01_B$ adjuvant component consists of QS-21 and MPL, using liposomes as a vehicle. The bilayers of the liposomal membrane are composed of DOPC and cholesterol. DOPC is a semi-synthetic phospholipid produced from a (b) (4) Cholesterol is a (b) (4) cholesterol obtained from an (b) (4) . Cholesterol (b) (4) . The use of QS-21 in the $AS01_B$ adjuvant has been contractually authorized to GSK by (b) (4) , a wholly owned subsidiary of (b) (4) The composition of the $AS01_B$ adjuvant FC component and the function of the ingredients are provided in Table 3.

Table 3. Composition of the $AS01_B$ Adjuvant FC Component

Ingredients	**Quantity (per 0.5 mL dose)** [1]	**Function**
MPL	50 µg	Immune enhancer
QS-21[2]	50 µg	Immune enhancer
DOPC	1 mg	Liposomes membrane constituent
Cholesterol	0.25 mg	Liposomes membrane constituent (b) (4)
Disodium phosphate anhydrous	0.15 mg	Buffering agent
Potassium dihydrogen phosphate	0.54 mg	Buffering agent
Sodium chloride	4.385 mg	Tonicity agent
Water for injection	(b) (4)	Solvent

[1] (b) (4)
[2] Purified *Quillaja* Saponin, fraction 21 is the full name of QS-21
[3] (b) (4)

Manufacturing

Manufacturing of the $AS01_B$ adjuvant component involves two intermediates: the (b) (4) containing MPL, DOPC, and cholesterol in the form of liposomes, and the QS-21 (b) (4) These intermediates are used to formulate the $AS01_B$ (b) (4) that is subsequently filled into the FC.

Overall, the manufacturing process of the $AS01_B$ adjuvant component consists of the following steps:

- (b) (4)

- (b) (4)

Except for (b) (4), no other materials from human or animal origin are used in the manufacture of the $AS01_B$ adjuvant. (b) (4) are used during the production process of MPL; specifically, they are part of the (b) (4) used in the production of the (b) (4) strain of *Salmonella minnesota*. (b) (4) are derived from (b) (4). The countries of origin of the (b) (4). According to the applicant, the (b) (4) is exclusively sourced from animals deemed fit for human consumption and the source of (b) (4) is compliant with current (b) (4) guidelines.

An evaluation of extractables and leachables was performed on the container/closure systems used for the (b) (4), QS-21 (b) (4) and $AS01_B$ adjuvant. After careful evaluation, the applicant concluded that the levels of extractables and leachables are not expected to present significant toxicological concerns.

Specifications and Methods

The tests and specifications applied for routine release of the $AS01_B$ adjuvant component FC are presented in Table 4.

Table 4. Control of $AS01_B$ Adjuvant FC: Tests and Specifications

Test	Acceptance criteria
Description	Opalescent, colorless to pale brownish liquid (b) (4)
pH	(b) (4)
Volume	
MPL content by (b) (4)	
QS-21 content by (b) (4)	
DOPC content by (b) (4)	
Cholesterol content by (b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	

Test	Acceptance criteria
(b) (4)	
(b) (4)	
(b) (4)	
Sterility test (b) (4)	
Sterility test (b) (4)	

(b) (4)

The specification of the MPL content by (b) (4). GSK informed CBER that some errors were found in the MPL content data used to define the specification. The applicant proposed to (b) (4) This change will be (b) (4) 2017 to update the relevant sections of the BLA. In the meantime, GSK committed to provide $AS01_B$ adjuvant lots to the U.S. market that meet the proposed (b) (4)

Stability

The parameters tested throughout the stability evaluation of the $AS01_B$ adjuvant FC are: description, sterility test (b) (4) sterility test (b) (4) pH, QS-21 content by (b) (4) cholesterol content by (b) (4) DOPC content by (b) (4) and container closure integrity test. The stability data generated support a dating period of 36 months from the date of manufacture (i.e., filling date) when stored at 2-8 °C for the $AS01_B$ adjuvant filled in 3 mL glass vials.

The SHINGRIX Vaccine

Product Composition

As previously described, SHINGRIX consists of a VZV gE antigen lyophilized component that is reconstituted at the time of use with the $AS01_B$ adjuvant component. A single dose of SHINGRIX is 0.5 mL and it does not contain preservatives. The composition of the reconstituted vaccine and the function of the ingredients are provided in Table 5.

Table 5. Composition of the SHINGRIX Vaccine

Ingredients	Quantity (per 0.5 mL dose)	Function
VZV gE	50 µg	Antigen
MPL	50 µg	Immune enhancer
QS-21	50 µg	Immune enhancer
Sucrose	20 mg	Stabilizer (b) (4)
Polysorbate 80	0.08 mg	(b) (4)
DOPC	1 mg	Liposomes membrane constituent
Cholesterol	0.25 mg	Liposomes membrane constituent (b) (4)
Sodium chloride	4.385 mg	Tonicity agent
Sodium dihydrogen phosphate dihydrate	0.160 mg	Buffering agent
Dipotassium phosphate	0.116 mg	Buffering agent
Disodium phosphate anhydrous	0.15 mg	Buffering agent
Potassium dihydrogen phosphate	0.54 mg	Buffering agent
Water for injection	(b) (4)	Solvent

Presentation and Packaging System

SHINGRIX is supplied as two components: A single-dose vial of VZV gE antigen lyophilized component and a single-dose vial of VZV gE antigen suspension component. The vials are co-packaged without syringes or needles using two separate packaging configurations: Antigen Vial + Adjuvant Vial (x10) and Antigen Vial + Adjuvant Vial (x1). In the Antigen Vial + Adjuvant Vial (x10) configuration, the carton box contains 20 vials: 10 vials of antigen and 10 vials of adjuvant. In the Antigen Vial + Adjuvant Vial (x1) configuration, the carton box contains one clear plastic blister. The blister contains 2 vials: 1 vial of antigen and 1 vial of adjuvant. In both configurations, the vial caps are color-coded: brown caps for the antigen vials and blue-green caps for the adjuvant vials.

Container Closure System

As mentioned above, SHINGRIX is supplied as a co-packaged VZV gE antigen component vial and an adjuvant component vial. The container closure system for both the antigen and adjuvant components consists of a 3 mL Type (b) (4) glass vial (supplied by (b) (4) closed with a (b) (4) Type (b) (4) rubber stopper (supplied by (b) (4) and an (b) (4) flip-off cap (supplied by (b) (4)). Container closure integrity testing was performed by GlaxoSmithKline Biologicals SA on container closures sealed at the Rixensart, Belgium facility employing the (b) (4) method; all acceptance criteria were met.

Stability

GSK conducted in-use stability studies to support the maximum temperature and time period that the reconstituted vaccine can retain its physicochemical properties. The tests used to monitor the stability of the reconstituted vaccine are: description, pH, gE potency in (b) (4), and gE potency by (b) (4). Based on the data generated, GSK concluded that SHINGRIX, once reconstituted, retains its quality attributes for up to (b) (4)

The carton labels and the Prescribing Information (PI) state that after reconstitution, SHINGRIX should be administered immediately or stored refrigerated between 2-8 °C (36-46 °F) and used within 6 hours. The reconstituted vaccine should be discarded if not used within 6 hours. GSK's rationale for this guidance is based on the following:

- The available in-use stability data supporting storage for up to (b) (4)
- The WHO multi-dose vial policy which recommends limiting the use of opened vials to within 6 hours of being opened to ensure sterility.
- The vaccine evaluated in the clinical studies was administered within 6 hours of reconstitution.

Comparability Protocols (CPs)

GSK submitted the following CPs in the BLA:

(b) (4)

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. CBER reviewed these CPs and agreed with the reporting category of annual report for the changes specified in CPs 1 and 2, listed above. In addition, CBER reviewed and agreed with the reporting category of CBE-30 for the change specified in CP 3.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of SHINGRIX

are listed in Table 6. In addition, the activities performed and inspectional histories are noted in Table 6 and are further described in the paragraph that follows.

Table 6. Manufacturing Facilities for SHINGRIX

Name/Address	Manufacturing Activities	FEI Number	DUNS Number	Inspection/ Waiver	Results/ Justification
GlaxoSmithKline Biologicals SA (b) (4) , Belgium	Drug Substance Manufacturing	(b) (4)		Waived	Team Biologics (b) (4) VAI
GlaxoSmithKline Biologicals SA (b) (4) Belgium	Drug Product and Co-Packaged Adjuvant Manufacturing, Labeling, Packaging and Release Testing	(b) (4)		Waived	Team Biologics (b) (4) VAI
(b) (4) GlaxoSmithKline Vaccines (b) (4)	Drug Product and Co-Packaged Adjuvant Labeling, Packaging and Release Testing	(b) (4)		Waived	Team Biologics (b) (4) VAI

VAI: Voluntary Action Indicated

Team Biologics conducted surveillance inspections of the GlaxoSmithKline Biologicals SA manufacturing facilities in (b) (4) Belgium from (b) (4) , and the (b) (4) GlaxoSmithKline Vaccines manufacturing facility in (b) (4) , (b) (4) from (b) (4) . These inspections were all classified as VAI and all inspectional issues were adequately resolved.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

SHINGRIX has been evaluated in two repeat dose toxicity studies in rabbits, one reproductive-developmental toxicity study in rats, one male fertility study in rats, two local tolerance studies in rabbits, and one safety pharmacology study in rats. In addition, the $AS01_B$ adjuvant or some of its components (i.e., MPL, QS21) were

evaluated in three safety pharmacology studies, ten general toxicology studies, ten genotoxicology studies, five reproductive toxicology studies, and three local tolerance studies.

In the repeat dose toxicity studies with SHINGRIX, the vaccine was well tolerated, but induced systemic as well as local reactogenicity. A transient but statistically significant increase in C-Reactive Protein (CRP) levels was observed in rabbits receiving SHINGRIX with levels up to 9 times (male animals) and 5 times (female animals) higher compared to control animals. These changes in CRP levels reflect an activation of the acute-phase response and indicate increasing levels of systemic inflammation, which potentially may be correlated with clinical adverse events such as malaise, fatigue, and nausea. In addition, increases in bilirubin (up to 2 times compared to control), popliteal lymph node weight (up to 50%), spleen weight (up to 17%), and thymus weight (up to 24%) were reported. Locally, mixed inflammatory cell infiltrate in the muscle and an enhanced activated appearance in the draining popliteal lymph nodes were observed. These are not unexpected or serious findings and are most likely related to the immune response to the vaccine.

SHINGRIX was evaluated in a male fertility study in rats, as well as in a reproductive developmental toxicity study in female rats. Treatment of male CD rats with SHINGRIX at 20% of the full human dose did not affect male mating performance, fertility or early embryonic development. Treatment of female CD rats with the candidate vaccine at 40% of the full human dose per occasion was well tolerated, did not lead to maternal toxicity, and did not adversely affect embryo-fetal or pre- and post-natal survival, growth or development of the offspring.

Genotoxicity studies evaluating $AS01_B$ adjuvant, MPL, and (b) (4) QS-21" (also denoted (b) (4))/QS21 did not reveal genotoxicity in the submitted *in vitro* or *in vivo* studies. Safety pharmacology studies evaluating the candidate vaccine formulation, $AS01_B$ adjuvant, and MPL did not report clinically relevant adverse findings.

Overall, based on the nonclinical toxicity assessments provided in the submission, CBER concluded that there are no significant safety issues.

5. CLINICAL PHARMACOLOGY

Pharmacodynamic data, comprised of humoral and cellular immune responses to SHINGRIX, were obtained in the clinical studies. The data demonstrated that SHINGRIX induces VZV-specific cell-mediated immune responses as well as VZV-specific humoral immunity. A measure of the immune response that confers protection against HZ is unknown.

6. CLINICAL/STATISTICAL

a) Clinical Program

Overview

The applicant included data from 19 clinical studies in the BLA. The pivotal clinical studies which will be discussed in this SBRA are shown in Table 7.

Table 7. Overview of Pivotal Clinical Studies

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

YOA: Years of age; **VE**: Vaccine efficacy; **QIV**: FLUARIX QUADRIVALENT; **IM**: Intramuscular; **M**: Month

‡ Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, South Korea, Spain, Sweden, Taiwan, United Kingdom, U.S., Mexico. GSK identified serious deviations from Good

Clinical Practice compliance for a study site in Mexico, resulting in the exclusion of 671 subjects in Zoster-006 and 865 subjects in Zoster-022 from all statistical analyses. These subjects were analyzed for safety separately.

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

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

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

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

€ For the mTVC at the Zoster-022 analysis

Zoster-006 and **Zoster-022** had similar designs and were conducted in parallel. Subjects ≥ 70 years of age (YOA) were randomized to Zoster-006 or Zoster-022 prior to randomization to treatment group. These studies were performed at the same study sites in eighteen countries (including the U.S.) with a treatment group randomization ratio of 1:1 (SHINGRIX:saline Placebo). Subjects in Zoster-006 were stratified 8:5:3:1 by age as follows: 50–59, 60–69, 70–79 and ≥ 80 YOA. Subjects in Zoster-022 were stratified 3:1 by age as follows: 70–79 and ≥ 80 YOA. The primary objectives of Zoster-006 and Zoster-022 were to evaluate SHINGRIX vaccine efficacy (VE) in the prevention of HZ compared to Placebo as measured by the reduction in HZ risk. The primary endpoint of Zoster-006 and Zoster-022 was incidence of confirmed HZ cases during the study in the modified Total Vaccinated Cohort (mTVC). The mTVC is defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or Placebo and did not develop a confirmed case of HZ within 1 month after the second dose. In Zoster-006, overall efficacy of SHINGRIX against HZ in subjects ≥ 50 YOA was demonstrated if the lower limit (LL) of the 95% confidence interval (CI) of vaccine efficacy (VE) was above 25%. In Zoster-022, overall HZ VE was demonstrated in subjects ≥ 70 YOA if the LL of the 95% CI was above 10%.

Secondary objectives in both studies included evaluation of SHINGRIX VE in the prevention of overall PHN (evaluated in all subjects, not only in subjects with confirmed HZ), and SHINGRIX safety and reactogenicity. The immune responses and persistence of these responses to SHINGRIX vaccination were exploratory objectives. The conditions for the analyses of Zoster-006 and Zoster-022 were in part event-driven, based on the number of confirmed HZ and PHN cases as well as a minimum follow-up period to ensure adequate safety and efficacy data collection.

The co-primary objectives for the pooled analysis for both studies were to consolidate HZ VE in subjects ≥ 70 YOA across both studies, and to evaluate SHINGRIX VE in the prevention of "overall" post-herpetic neuralgia (overall reduction in PHN risk independent of the occurrence of HZ) compared to Placebo in subjects ≥ 70 YOA across both studies.

Zoster-006 results: As shown in Table 8, at the Final HZ efficacy analysis, there were 6 cases of confirmed HZ recorded in the mTVC of the SHINGRIX group (N= 7,344) and 210 cases of confirmed HZ recorded in the mTVC of the Placebo group (N= 7,415). The breakdown of HZ case confirmation was 89.4% by PCR and 10.6% by the Herpes Zoster Adjudication Committee (HZAC). The HZ incidence rates in the SHINGRIX and Placebo groups were 0.3 and 9.1 per 1,000 person-years (PY), respectively. The overall VE against HZ in subjects ≥ 50 YOA was 97.16% (95% CI:

93.72 to 98.97). Therefore, the primary study objective regarding HZ VE in subjects ≥ 50 YOA was met as the lower bound of the 95% CI was above 25%.

Table 8. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Zoster-006[a] (mTVC[b])

Age Group	SHINGRIX N (n)	SHINGRIX Incidence Rate of HZ per 1,000 Person-Years	Placebo N (n)	Placebo Incidence Rate of HZ per 1,000 Person-Years	% Efficacy (95% CI)
Overall (≥ 50)[c]	7,344 (6)	0.3	7,415 (210)	9.1	97.16 (93.72, 98.97)
50-59	3,492 (3)	0.3	3,525 (87)	7.8	96.57 (89.62, 99.31)
60-69	2,141 (2)	0.3	2,166 (75)	10.8	97.36 (90.14, 99.69)
≥ 70	1,711 (1)	0.2	1,724 (48)	9.4	97.93 (87.91, 99.95)

N = Number of subjects included in each group; **n** = Number of subjects having at least 1 confirmed HZ case; **HZ** = Herpes zoster; **CI** = Confidence Interval.

[a] Zoster-006 (NCT01165177)

[b] mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or Placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

[c] Primary study endpoint was based on confirmed HZ cases in subjects 50 years of age and older.

A secondary objective of Zoster-006 was to evaluate HZ VE by age strata. The study was powered to demonstrate HZ VE for the age strata 50–59 and 60–69 YOA and the objective met if the LL of the 95% CI for the point estimate of HZ VE for these strata was > 10%. The objective was met for the 50–59 YOA and 60–69 YOA age strata.

Suspected HZ cases were followed prospectively for the development of PHN, an HZ-related complication defined as HZ-associated pain (rated as 3 or greater on a 0- to 10-point scale by the study subject) occurring or persisting at least 90 days following the onset of rash in confirmed cases of HZ. Among all subjects 50 years of age or older in the mTVC, there were 18 cases of PHN reported in the Placebo group and none reported in the SHINGRIX group.

Zoster-022 results: As shown in Table 9, at the end of study analysis, there were 23 cases of confirmed HZ recorded in the mTVC of the SHINGRIX group (N = 6,541) and 223 cases in the mTVC of the Placebo group (N = 6,622). The breakdown of HZ case confirmation was 92.3% by PCR and 7.7% by the HZAC. The HZ incidence rates in the SHINGRIX and Placebo groups were 0.9 and 9.2 per 1,000 PY, respectively. The overall VE against HZ in subjects ≥ 70 YOA was 89.79% (95% CI: 84.29 to 93.66). Therefore, the primary study objective regarding HZ VE in subjects ≥ 70 YOA was met as the lower bound of the 95% CI of the point estimate of VE was above 10%.

Table 9. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Zoster-022[a] (mTVC[b])

Age Group	SHINGRIX N (n)	SHINGRIX Incidence Rate of HZ per 1,000 Person-Years	Placebo N (n)	Placebo Incidence Rate of HZ per 1,000 Person-Years	% Efficacy (95% CI)
≥ 70	6,541 (23)	0.9	6,622 (223)	9.2	89.79 (84.29, 93.66)

N = Number of subjects included in each group; **n** = Number of subjects having at least 1 confirmed HZ case; **HZ** = Herpes zoster; **CI** = Confidence Interval.

[a] Zoster-022 (NCT01165229)

[b] mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or Placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

Among all subjects 70 years of age or older in the mTVC, there were 28 cases of PHN reported in the Placebo group and 4 cases reported in the SHINGRIX group for an overall PHN VE of 85.49% (95% CI: 58.52 to 96.30).

Pooled Efficacy Analyses

Analyses on the efficacy of SHINGRIX to prevent HZ and PHN in subjects 70 years and older was conducted by pooling the data from studies Zoster-006 and Zoster-022 in the mTVC. The primary endpoints of the pooled analysis were the occurrence of overall PHN (incidence of PHN calculated using the mTVC during the entire study period in subjects ≥ 70 YOA) and the occurrence of confirmed HZ during the entire study period in subjects ≥ 70 YOA.

As presented in Table 10, of the 309 subjects with confirmed HZ episodes in the mTVC for the pooled analysis, 284 subjects were in the Placebo group and 25 were in the SHINGRIX group. The overall HZ VE was 91.30 (95% CI: 86.88 to 94.46), and was similar for all age strata. Thus, the HZ VE on the pooled analysis in subjects ≥ 70 YOA across both studies was consistent with the HZ VE results in subjects ≥ 70 YOA in Zoster-022.

Table 10. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Zoster-006 and Zoster-022 (Pooled Data[a]) (mTVC[b])*

Age Group	SHINGRIX N (n)	SHINGRIX Incidence Rate of HZ per 1,000 Person-Years	Placebo N (n)	Placebo Incidence Rate of HZ per 1,000 Person-Years	% Efficacy (95% CI)
Overall (≥70)[c]	8,250 (25)	0.8	8,346 (284)	9.3	91.30 (86.88, 94.46)
70-79	6,468 (19)	0.8	6,554 (216)	8.9	91.27 (86.04, 94.85)
≥ 80	1,782 (6)	1.0	1,792 (68)	11.1	91.37 (80.22, 96.94)

N = Number of subjects included in each group; **n** = Number of subjects having at least 1 confirmed HZ case; **HZ** = Herpes zoster; **CI** = Confidence Interval.

[a] Pooled data from Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229).

[b] mTVC = Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or Placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

[c] Co-Primary endpoint of pooled analysis was based on confirmed HZ cases in subjects 70 years of age and older.

The pooled analysis for the co-primary endpoint of VE in the prevention of overall PHN in subjects ≥ 70 YOA compared to Placebo is presented in Table 11. The success criterion for the pooled analysis was to demonstrate statistically significant PHN VE in subjects ≥ 70 YOA if the LB of the 95% CI was above 0%.

Table 11. Efficacy of SHINGRIX on Overall Incidence of Postherpetic Neuralgia Compared with Placebo in Zoster-006 and Zoster-022 (Pooled Data[a]) (mTVC[b])*

Age Group	SHINGRIX N (n)	SHINGRIX Incidence Rate of PHN[c] per 1,000 Person-Years	Placebo N (n)	Placebo Incidence Rate of PHN per 1,000 Person-Years	% Efficacy (95% CI)
Overall (≥ 70)[d]	8,250 (4)	0.1	8,346 (36)	1.2	88.78 (68.70, 97.10)
70-79	6,468 (2)	0.1	6,554 (29)	1.2	93.04 (72.47, 99.19)
≥ 80	1,782 (2)	0.3	1,792 (7)	1.1	71.16 (-51.51, 97.08)

N = Number of subjects included in each group; **n** = Number of subjects having at least 1 PHN; **CI** = Confidence Interval.

[a] Pooled data from Zoster-006: NCT01165177 (subjects ≥50 years of age) and Zoster-022: NCT01165229 (subjects ≥70 years of age).

[b] mTVC: Modified Total Vaccinated Cohort defined as subjects who received 2 doses (0 and 2 months) of either SHINGRIX or Placebo and did not develop a confirmed case of HZ within 1 month after the second dose.

[c] PHN: Postherpetic neuralgia defined as HZ-associated pain rated as 3 or greater (on a 0- to 10-point scale) occurring or persisting at least 90 days following the onset of rash using Zoster Brief Pain Inventory questionnaire.

[d] Co-primary endpoint of pooled analysis was based on incidence of the PHN in subjects 70 years of age and older.

Of the 40 subjects reporting PHN in the pooled analysis of subjects 70 years of age and older, 4 were in the SHINGRIX group and 36 were in the Placebo group. The incidence

of overall PHN in the SHINGRIX group was 0.1 per 1000 PY and the incidence in the Placebo group was 1.2 per 1000 PY, for an overall PHN VE of 88.78% (95% CI: 68.70 to 97.10). The co-primary objective regarding SHINGRIX VE against overall PHN for subjects ≥ 70 YOA in the pooled analysis was met as the LB of the 95% CI > 0%.

A secondary endpoint of the pooled analyses was the occurrence of PHN in subjects ≥ 50 YOA with confirmed HZ over the entire study period. In subjects with a confirmed HZ episode, PHN was reported in 4 out of 32 subjects (12.5%) in the SHINGRIX group and in 46 out of 477 subjects (9.6%) in the Placebo group. No conclusions could be drawn regarding VE for reduction in PHN incidence in subjects ≥ 50 with confirmed HZ [0.29% (95% CI: -161.53, 65.57)].

The benefit of SHINGRIX in the prevention of PHN can be attributed to the effect of the vaccine on the prevention of HZ.

Concomitant Administration with Influenza Vaccine

Zoster-004 was an open-label clinical study designed to assess the safety and immunogenicity of SHINGRIX when co-administered with FLUARIX QUADRIVALENT (QIV). In this study, subjects 50 years of age and older received 1 dose each of SHINGRIX and QIV at 0 month and 1 dose of SHINGRIX at 2 months (co-administration group) or 1 dose of QIV at 0 month and 1 dose of SHINGRIX at 2 and 4 months (control group). There was no evidence of interference in the immune response to any of the antigens contained in SHINGRIX or the co-administered vaccine. Given the totality of the submitted data, no safety signals were identified in this study.

Lot Consistency

Zoster-007 was a phase 3, randomized, double blind multicenter study to evaluate consistency, immunogenicity, safety and reactogenicity of three lots of SHINGRIX when administered intramuscularly (IM) to adults 50 years of age and older. A clinical study interim report was provided in the BLA and presents immunogenicity results for the active phase, which was up to the 1 month post-dose 2 assessment. The safety data provided was collected for approximately 3.5 months after completion of the active phase.

The study enrolled 651 subjects randomized 1:1:1 to receive two doses from one of three lots of SHINGRIX (Lots A, B, and C groups), each consisting of unique randomized combinations of 50 μg of gE antigen and $AS01_B$ adjuvant lots. The primary objective of lot-to-lot consistency in terms of GMC of anti-gE ELISA antibody at one month post second dose of SHINGRIX was met as 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]. No safety signals were identified in the interim report included in the BLA.

Dosing Schedule

Zoster-026 was a phase 3, randomized, open-label, multicenter clinical study designed to assess the safety and immunogenicity of SHINGRIX when administered IM as two doses. SHINGRIX was given to adults 50 years of age and older randomized in a 1:1:1

ratio on one of three schedules: 0, 2-month (original schedule), 0, 6-month or 0, 12-month. The co-primary objectives for the 0, 6-month schedule were met: (1) the Vaccine Response Rate at one month after the second dose was 96.5% (97.5% CI: 90.4 to 99.2), with LL of the 97.5% CI ≥60%; and (2) the anti-gE GMC ratio (0, 2-month/0, 6-month) at one month after the second dose was 1.16 (97.5% CI: 0.98; 1.39), meeting the non-inferiority criterion of UL of the 97.5% CI < 1.5. However, the non-inferiority of the 0, 12-month schedule as compared to the 0, 2-month schedule was not demonstrated. Safety was comparable between the groups. Based on the results of study Zoster-26, the applicant proposed and CBER agreed with a dosing schedule described in the PI of "a first dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later."

Dose Selection

Zoster-003, a phase 2 clinical study, defined the optimal dose of the gE antigen in the SHINGRIX vaccine. Three different concentrations of gE antigen were evaluated: 25 μg, 50 μg, and 100 μg. Based on adequate immunogenicity and safety profiles, the 50 μg dose was selected for manufacturing and clinical development. In addition, the applicant conducted **Zoster-10**, a phase 2 adjuvant dose selection study designed to evaluate the immunogenicity and safety of 50 μg of gE antigen adjuvanted with different doses of AS01: $AS01_B$ (full dose), ½ dose of $AS01_B$ (i.e., $AS01_E$), or without adjuvant. The results of study **Zoster-10** justify the selection of the $AS01_B$ adjuvant for the final vaccine formulation, since it induced the highest level of cell-mediated immunity (CMI) and humoral immune responses with an acceptable reactogenicity profile.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were issued for five foreign clinical sites that participated in the conduct of study Protocols 110390 (Zoster-006) and 113077 (Zoster-022). The inspections did not reveal significant issues that impact the data submitted in this application.

b) Pediatrics

A presentation of GSK's Pediatric Plan was made to the FDA Pediatric Review Committee (PeRC) on June 28, 2017. The committee agreed with the applicant's request for a full waiver of studies of SHINGRIX in all pediatric age groups as it is impossible or highly impracticable to conduct clinical endpoint studies in the U.S. pediatric population because the estimated annual number of pediatric HZ cases is low and widely dispersed.

7. SAFETY/PHARMACOVIGILANCE

Safety monitoring for Zoster-006 and Zoster-022 included recording solicited local (injection site pain, swelling and redness) and general (fever, headache, myalgia, gastrointestinal symptoms, shivering, and fatigue) symptoms on standardized diary cards by a subset of subjects for seven days (Days 0–6) following each vaccination. The safety evaluation also consisted of recording unsolicited adverse events (AEs) on a diary

card by all subjects for 30 days following each vaccination; collecting serious adverse events (SAEs) on all subjects from month 0–month 14; and collecting deaths, potential immune-mediated inflammatory diseases (pIMDs), and SAEs for the duration of the studies. Safety results were analyzed on the Total Vaccinated Cohort, which consisted of subjects receiving at least one dose of study product, by product received.

The reported frequencies of solicited local adverse reactions and general adverse events (overall per subject), by age group, are presented in Table 12.

Table 12. Percentage of Subjects with Solicited Local Adverse Reactions and General Adverse Events within 7 Days[a] of Vaccination in Adults 50 to 59 Years of Age, 60 to 69 Years of Age, and 70 Years of Age and Older[b] (Total Vaccinated Cohort with 7-Day Diary Card)

	SHINGRIX 50-59 YOA %	Placebo[c] 50-59 YOA %	SHINGRIX 60-69 YOA %	Placebo 60-69 YOA %	SHINGRIX ≥ 70 YOA %	Placebo ≥ 70 YOA %
Local Adverse Reactions	**n = 1,315**	**n = 1,312**	**n = 1,311**	**n = 1,305**	**n = 2,258**	**n = 2,263**
Pain	88.4	14.4	82.8	11.1	69.2	8.8
Pain, Grade 3[d]	10.3	0.5	6.9	0.5	4.0	0.2
Redness	38.7	1.2	38.4	1.6	37.7	1.2
Redness, > 100 mm	2.8	0.0	2.6	0.0	3.1	0.0
Swelling	30.5	0.8	26.5	1.0	23.0	1.1
Swelling, > 100 mm	1.1	0.0	0.5	0.0	1.3	0.0
General Adverse Events	**n = 1,315**	**n = 1,312**	**n = 1,309**	**n = 1,305**	**n =2,252**	**n = 2,264**
Myalgia	56.9	15.2	49.0	11.2	35.1	9.9
Myalgia, Grade 3[e]	8.9	0.9	5.3	0.8	2.8	0.4
Fatigue	57.0	19.8	45.7	16.8	36.6	14.4
Fatigue, Grade 3[e]	8.5	1.8	5.0	0.8	3.5	0.8
Headache	50.6	21.6	39.6	15.6	29.0	11.8
Headache, Grade 3[e]	6.0	1.7	3.7	0.2	1.5	0.4
Shivering	35.8	7.4	30.3	5.7	19.5	4.9
Shivering, Grade 3[e]	6.8	0.2	4.5	0.3	2.2	0.3
Fever	27.8	3.0	23.9	3.4	14.3	2.7
Fever, Grade 3[f]	0.4	0.2	0.5	0.2	0.1	0.1
GI[g]	24.3	10.7	16.7	8.7	13.5	7.6
GI, Grade 3[e]	2.1	0.7	0.9	0.6	1.2	0.4

YOA: Years of age; **n** = Total vaccinated cohort for safety included all subjects with at least 1 documented dose.

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Data for subjects 50 to 59 YOA and 60 to 69 YOA are based on Zoster-006. Data for subjects 70 years of age and older are based on pooled data from Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229).

[c] Placebo was a saline solution.

[d] Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

[e] Grade 3 myalgia, fatigue, headache, shivering, GI: Defined as preventing normal activity.

[f] 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.

[g] GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

As shown in Table 12, local and general reactogenicity events were higher in SHINGRIX when compared to the Placebo (saline) control group. Pain (any grade and Grade 3) was the most commonly solicited local event reported by SHINGRIX recipients of all age groups, with the percentage of subjects reporting pain decreasing with increasing age. The most commonly reported solicited general events of any grade following SHINGRIX administration were myalgia, fatigue, and headache.

In the main pooling analyses, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and Placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥ 1% of recipients of SHINGRIX and at a rate at least 1.5-fold higher than Placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

In addition, imbalances noted and targeted as part of the pharmacovigilance activities proposed by GSK include gout and gouty arthritis (SHINGRIX n = 27 subjects versus Placebo n = 8 subjects), reported within 30 days post-vaccination; and optic ischemic neuropathy (SHINGRIX n =3 subjects versus Placebo n = 0 subjects), reported within 50 days post-vaccination.

There were no notable differences observed between treatment groups for the proportions of subjects in the main pooling reporting SAEs (SHINGRIX 10.1% versus Placebo 10.4%), deaths (SHINGRIX 0.8% versus Placebo 0.9%), or pIMDs (SHINGRIX 0.6% versus Placebo 0.7 %) within 365 days post-last vaccination.

Evaluation of SHINGRIX in Subjects with Prior HZ

In **Zoster-033**, a one arm, uncontrolled non-IND study in which subjects with prior HZ received SHINGRIX, the immune response induced in adults 50 years of age and older with a history of previous HZ was consistent with the immune response observed in individuals with no history of HZ. However, the overall incidence of HZ in subjects with a prior history of HZ was higher than expected. Six subjects (6.25%) reported 9 events of HZ over the 14-month study duration of the study, although none of the cases included laboratory confirmation of disease and the incidence of HZ was not a pre-specified study endpoint. Of the 3 additional subjects who reported AEs of postherpetic neuralgia and facial neuralgia in the absence of a diagnosis of HZ, limited available information precluded conclusive diagnosis, although one subject had a clinical history that suggested HZ. Thus, the results of Zoster-033 are insufficient to evaluate the safety of SHINGRIX in subjects with prior HZ. The applicant proposed to conduct Zoster-062, a study to evaluate the safety and immunogenicity of SHINGRIX in subjects with a prior episode HZ, which will be a postmarketing commitment (PMC).

Pharmacovigilance Plan (PVP)

GSK submitted a PVP to monitor safety concerns that could be associated with the administration of SHINGRIX. The applicant will address the potential risks of pIMDs

and ocular complications post-vaccination by supplementing routine pharmacovigilance with enhanced and active surveillance activities.

Enhanced surveillance will monitor the following pIMDs: polymyalgia rheumatica, rheumatoid arthritis, psoriasis, autoimmune thyroiditis, multiple sclerosis, Guillain-Barré syndrome, idiopathic thrombocytopenia, optic neuritis, inflammatory bowel diseases, Still's disease adult onset, leukocytoclastic vasculitis, gout, and two ocular complications: optic ischemic neuropathy and temporal arteritis. GSK identified these conditions for enhanced surveillance based on their frequency in the two pivotal studies, the prevalence of the pIMD in the vaccine target population, or as events of medical interest. Enhanced surveillance consists of generating background rates for the conditions of interest, conducting observed to expected rate analyses using passive surveillance data from routine pharmacovigilance, and utilizing follow-up questionnaires to gather data systematically for reported cases.

Active surveillance will occur through a Targeted Safety Study (TSS), which will be a PMC. This study will monitor for the conditions identified for enhanced surveillance, and medically-attended or serious adverse events (AEs) utilizing a medical database. Specifics of the study protocol are being developed, but the primary objective will be to assess the risk of gout, polymyalgia rheumatica, and temporal arteritis 12 months following vaccination with SHINGRIX. The study will utilize an appropriate comparator, and GSK estimates gathering data from 60,000-70,000 in each cohort (SHINGRIX vaccinees and an unvaccinated comparator cohort).

Conclusion and Plans for Postmarketing Commitments

SHINGRIX, when compared to Placebo, exhibited higher unsolicited AEs (within 30 days post-vaccination) and increased reactogenicity that was generally of short duration. Some imbalances in AEs were noted in SHINGRIX recipients, but the proportions of subjects reporting SAEs, pIMDs, and death were generally comparable between treatment groups. The pharmacovigilance activities proposed by the applicant will continue to monitor the safety of SHINGRIX post-licensure. Furthermore, GSK will conduct a study to evaluate the safety and immunogenicity of SHINGRIX in subjects with prior HZ (Zoster-062) and a long-term efficacy follow-up study (Zoster-049) as PMCs. For additional details on these PMCs, refer to Section 11: RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT.

8. ADVISORY COMMITTEE MEETING

A Vaccines and Related Biological Products Committee (VRBPAC) meeting was convened on September 13, 2017. The Committee voted unanimously (11 votes) that the efficacy and safety data supported the licensure of SHINGRIX for prevention of HZ in individuals 50 years of age and older.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable.

10. LABELING

The proprietary name, SHINGRIX, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on November 22, 2016, and found to be acceptable. CBER communicated this decision to GSK on January 23, 2017. The APLB found the PI and carton/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "Zoster Vaccine Non-Live" to "Zoster Vaccine Recombinant, Adjuvanted" and deleting reference to PHN in the proposed indication, as CBER considers the prevention of PHN attributable to VE against HZ. All labeling issues were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of the SHINGRIX vaccine for the proposed indication and usage.

b) Risk/Benefit Assessment

Considering the data submitted to support the safety and efficacy of the SHINGRIX vaccine that have been presented and discussed in this document, as well as the seriousness of HZ disease, the Review Committee is in agreement that the risk/benefit profile for SHINGRIX is favorable and supports approval in individuals 50 years of age and older.

c) Recommendation for Postmarketing Activities

GSK has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

1. Study Zoster-062 to assess the safety, reactogenicity, and immunogenicity of SHINGRIX in adults ≥50 years of age with a prior episode of Herpes Zoster.

   Final Protocol Submission: June 30, 2018

   Study Completion: November 30, 2020

   Final Report Submission: November 30, 2021

2. A targeted safety study, EPI-ZOSTER-030 VS, to evaluate the safety of SHINGRIX in adults ≥50 years of age in the United States.

   Final Protocol Submission: January 30, 2019

   Study Completion: June 30, 2024

   Final Report Submission: March 30, 2025

3. Study Zoster-049 to assess the long-term efficacy, immunogenicity, and safety of SHINGRIX in adults ≥50 years of age.

   Final Protocol Submission: December 18, 2015

   Study Completion: July 28, 2023

   Final Report Submission: May 25, 2024

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