Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From:	Ravi Goud MD, MPH Medical Officer, Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
To:	Carmen Collazo PhD Chair of the Review Committee
Through:	Deepa Arya MD, MPH, MBA Branch Chief, Analytic Epidemiology Branch Scott Proestel MD Director Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Glaxo Smith Kline (GSK)
Product:	Shingrix® (Zoster Vaccine Non-Live, Recombinant) is a sterile, non-live vaccine for intramuscular injection.
Application Type/Number:	BLA/ STN 125614/0.0
Proposed Indication:	Shingrix® is a non-live, recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.
Submission Date:	October 21, 2016
Action Due Date:	October 21, 2017

1 Objective

The purpose of this review is to assess the adequacy of the pharmacovigilance plan (PVP) based on the safety profile of Shingrix®.

2 Product Information

2.1 Product description

Shingrix® (Zoster Vaccine Non-Live, Recombinant) is a sterile, non-live vaccine for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant varicella zoster virus surface glycoprotein E antigen (VZV gE) which is reconstituted at the time of use with the accompanying vial of AS01B adjuvant suspension. The antigen is a truncate of the VZV gE expressed in Chinese Hamster Ovary cells.

The Adjuvant System, AS01B, is composed of 3-*O*-desacyl-238 4'-monophosphoryl lipid A (MPL) from *Salmonella Minnesota* and a saponin molecule (QS-21) purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation.

2.2 Proposed dosing regimen(s) and formulation(s)

Two doses (0.5-mL each) by intramuscular injection according to the following schedule: 0 and anytime between 2 and 6 months.

Suspension for injection supplied as a single-dose vial of lyophilized antigen to be reconstituted with the accompanying vial of adjuvant suspension. A single dose after reconstitution is 0.5 mL.

3 Materials Reviewed

Table 1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
10/21/2016	Glaxo Smith Kline	BLA Sequence 0000	Modules: 2.7.4, Summary of clinical safety, 5.3.5.3, Integrated summary of safety 1.16, Risk management plans
7/26/2017	Glaxo Smith Kline	BLA Sequence 0031	Module 1.11.3, Question 1 (response to FDA request to update PVP)
8/11/17	Glaxo Smith Kline	Sent via email	Proposed plan for PVP update
9/6/2017	Glaxo Smith Kline	BLA Sequence 0040	Module 16.1, Risk management plans (includes PVP)
9/26/2017	Glaxo Smith Kline	BLA Sequence 0047	Module 1.11.3 Responses to CBER IR (Questions 1,2,3,4, and Outline for HZ study)

Date	Source	Document Type	Document(s) Reviewed
10/6/2017	Glaxo Smith Kline	BLA Sequence 0051	Module 1.11.3 Responses to CBER IR of 29 Sept 2017
10/12/2017	Glaxo Smith Kline	BLA Sequence 0052	Module 1.16 Risk Management Plan – version 0.2
10/21/2016	Glaxo Smith Kline	BLA Sequence 0000	Module 1.14.1.3 Draft PI

4 Summary of Prior Marketed Experience

Not applicable. Product does not have a history of regulatory approval and general use outside the US.

5 Brief description of Safety Database

The safety database included data from 7 clinical studies, and included 15,493 HZ/su recipients, who are included in the broader safety pool. The preponderance of data was from two pivotal Phase III studies, ZOSTER-006 (7,695 subjects ≥ 50 years of age [YOA] received HZ/su) and ZOSTER-022 (6,950 subjects ≥70 YOA received HZ/su) which were randomized, double-blind, placebo-controlled studies (total 14,645 HZ/su). These subjects are included in the main safety pool (MSP), and were compared to 14,660 subjects in the placebo group.

The studies assessed the prophylactic efficacy, safety, and immunogenicity of HZ/su when administered according to a 0, 2-month schedule. ZOSTER-006 enrolled subjects in the age ranges 50-59 YOA, 60-69 YOA, 70-79 YOA and greater than 80 YOA in approximately an 8:5:3:1 ratio. ZOSTER-022 enrolled subjects in the age ranges 70-79 YOA and greater than 80 YOA in approximately a 3:1 ratio. Eligible subjects 70-79 YOA and greater than 80 YOA were randomly assigned to ZOSTER- 006 or ZOSTER-022. Subjects were randomized 1:1 to receive either HZ/su or a saline placebo.

The clinical trials collected the following safety data: solicited general and local symptoms 7 days post vaccination, unsolicited adverse events (AEs) 30 days post vaccination, serious AEs (SAEs), and potential immune-mediated disease (pIMD) in the whole post vaccination period (maximum median follow up of 4.4 years).

6 Sponsor's Pharmacovigilance Plan

Table 2: Pharmacovigilance Plan from Sponsor Risk Management Plan – version 0.2 (page 50, BLA sequence 52)

Safety concern (important potential risk) : Risk of hypersensitivity reactions (including anaphylaxis)		
Areas requiring confirmation or further investigation	**Proposed routine* and additional Pharmacovigilance activities**	**Objectives**
To evaluate any possible association between *HZ/su candidate vaccine* and hypersensitivity reactions (including anaphylaxis).	Post marketing surveillance - routine pharmacovigilance through spontaneous reporting (PBRER cycles).	To evaluate signals in a timely fashion.

*routine pharmacovigilance in accordance with established guidelines (ICH E2E)

Safety concern (important potential risk) : Risk of potential Immune Mediated Disorders (pIMDs) following HZ/su vaccination		
Areas requiring confirmation or further investigation	**Proposed routine* and additional Pharmacovigilance activities**	**Objectives**
To evaluate any possible association between *HZ/su candidate vaccine* and pIMDs	Routine: Close monitoring of pIMDs in clinical studies. Post marketing surveillance - routine pharmacovigilance through spontaneous reporting (Periodic Benefit-Risk Evaluation Report (PBRER) cycles). **Enhanced surveillance:** Generation of background incidence rates for selected pIMDs: polymyalgia rheumatica, rheumatoid arthritis, psoriasis, autoimmune thyroiditis, multiple sclerosis, Guillan-Barré syndrome, idiopathic thrombocytopenia,	To monitor severity, changes in pattern and risk factors of the safety concern. To evaluate signals in a timely fashion. Further analysis of pIMD data generated through the spontaneous reporting process and in clinical trials

Safety concern (important potential risk) : Risk of potential Immune Mediated Disorders (pIMDs) following HZ/su vaccination		
	optic neuritis, inflammatory bowel diseases, Still's disease adult onset, leukocytoclastic vasculitis, and gout. Quantitative analyses should a signal arise, such as observed-to-expected analyses. Targeted follow-up questionnaires for above pre-selected pIMDs. <u>Active surveillance:</u> Targeted safety study: EPI-ZOSTER-030 VS	

*routine pharmacovigilance in accordance with established guidelines (ICH E2E)

Safety concern (important potential risk) : Risk of serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.		
Areas requiring confirmation or further investigation	**Proposed routine* and additional Pharmacovigilance activities**	**Objectives**
To evaluate any possible association between HZ/su *candidate vaccine* and serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.	<u>Routine</u>: Close monitoring of serious ocular complications that may be due to vasculitis or inflammation in clinical studies. Post marketing surveillance - routine pharmacovigilance through spontaneous reporting (Periodic Benefit-Risk Evaluation Report (PBRER) cycles). <u>Enhanced surveillance:</u> Generation of background incidence rates for: temporal arteritis and optic ischemic neuropathy (arteritic and non-	To monitor severity, changes in pattern and risk factors of the safety concern. To evaluate signals in a timely fashion. Further analysis of data generated through the spontaneous reporting process and in clinical trials with focus in identifying serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.

Safety concern (important potential risk) : Risk of serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.		
	arteritic types). Quantitative analyses should a signal arise, such as observed-to-expected analyses. Targeted follow-up questionnaires for: temporal arteritis, and serious ocular complications that may be due to vasculitis or inflammation, i.e. optic ischemic neuropathy and inflammatory (non-infective) ocular disease. <u>Active surveillance:</u> Targeted safety study: EPI-ZOSTER-030 VS.	

*routine pharmacovigilance in accordance with established guidelines (ICH E2E)

Safety concern (missing information) : Long term efficacy and need for a booster dose		
Areas requiring confirmation or further investigation	**Proposed routine and additional Pharmacovigilance activities**	**Objectives**
Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older.	Clinical study – ZOSTER-049 (201190): A phase IIIb, open-label, multi-country, multi-centre, long-term follow-up study (ZOE-LTFU) of studies ZOSTER-006 and 022 to assess the prophylactic efficacy, safety, and immunogenicity persistence of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine and assessment of 1 or 2 additional doses on a 0 or 0, 2-month schedule in two subgroups of adults50 years of age and older. Long-term follow-up: including 5, 6, 7, 8, 9 and 10 years post-vaccination.	<u>Primary objective</u>: To assess the VE in the prevention of HZ over the total duration of the ZOSTER-049 study overall as measured by the reduction in HZ risk in subjects ≥ 50 YOA at the time of first vaccination in the ZOSTER-006/022 studies <u>Secondary objectives</u>: VE for HZ by age groups and by year of follow-up, VE for PHN, persistence of humoral and cell-mediated immune responses after primary vaccination course; safety; humoral and cell-mediated

Safety concern (missing information) : Long term efficacy and need for a booster dose		
		immune responses 1 month after each additional dose and at Years 1, 2, 3, 4, 5 and 6 after additional dose(s) and reactogenicity and safety after additional dose(s).

Safety concern (missing information): Long term immunogenicity in adults 50 years of age and older		
Areas requiring confirmation or further investigation	**Proposed routine and additional Pharmacovigilance activities**	**Objectives**
Long-term immunogenicity in adults 50 years of age and older	Clinical study –ZOSTER-060 (204926): A phase IIIb, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A, at Months 108 and 120 post-vaccination and the assessment of re-vaccination with two additional doses administered at 10 years after the initial vaccination in study Zoster-003 in healthy subjects aged 60 years of age and older. Long-term follow-up: 9 and 10 years post-vaccination	Primary objective: persistence of humoral and cell-mediated immune responses at 108 and 120 months post first dose of initial vaccination course in ZOSTER-003. Secondary objectives: Persistence of humoral and cell-mediated immune responses by age cohorts at Months 108 and 120 post dose 1 of initial vaccination course, safety from Months 108 to 120 For re-vaccination phase: humoral and cell-mediated immune responses one month after each dose and 12 months after last dose , safety and reactogenicity after re-vaccination,

7 Analysis of Sponsor's Pharmacovigilance Plan

7.1 Important potential risk: Hypersensitivity reactions (including anaphylaxis)

The sponsor used narrow anaphylactic reaction and hypersensitivity standardized MedDRA queries (SMQ) to find cases during the 30-day post-vaccination period in the safety database. The hypersensitivity query identified 380 cases (2.6%) in the HZ/su group compared to 349 cases (2.6%) in the placebo arm. The cases most frequently described disorders of the skin such as rash and eczema.

The anaphylaxis query identified one case in the HZ/su group, but after review and adjudication using the Brighton Collaboration case definition, this case was adjudicated as not anaphylaxis (level 5).

Reviewer comment: Hypersensitivity and anaphylaxis are well-recognized potential risks associated with vaccines. No marked imbalance in hypersensitivity cases was observed across trial groups, and cases did not describe severe symptoms. In addition, no cases of anaphylaxis were observed, so the sponsor-recommended plan for routine pharmacovigilance is adequate.

7.2 Important potential risk: Potential Immune Mediated Disorders following HZ/su vaccination.

7.2.1 pIMDs

The sponsor identified cases of pIMDs according to a company defined list of disorders with autoimmune and inflammatory pathology, which it uses in study protocols for the clinical development of vaccines with adjuvant systems. This list contains more than 50 disorders, and includes diseases such as Guillain-Barré syndrome, inflammatory bowel disease, and Graves disease.

The main safety pooling analysis identified 179 pIMD cases (1.2%) in the HZ/su group, vs. 202 (1.4%) in the placebo group. The most frequent pIMD were polymyalgia rheumatica (32 HZ/su vs. 29 placebo), rheumatoid arthritis (20 HZ/su vs. 26 placebo), psoriasis (15 HZ/su vs. 18 placebo), and autoimmune thyroiditis (13 HZ/su vs. 10 placebo). In both the intervention and placebo groups, 30 subjects reported a pIMD within 30 days after vaccination. During the whole post vaccination period, 16 subjects in HZ/su group and 18 in the placebo group had pIMDs that investigators reported as related to vaccination. The sponsor reviewed these cases and did not identify a causal relationship with vaccination.

Other than pIMD identified in following sections of this document, or in the sponsor's PVP, there were no significant imbalances, or clustering of pIMDs that suggested a possible association with HZ/su vaccination.

7.2.1.1 Arthralgia and gout

Review of clinical trial data submitted by the sponsor identified imbalances in arthralgia (252 HZ/su vs. 171 placebo, RR = 1.48 [95% CI: 1.21-1.80], p= 0.00009) and gout and gouty arthritis (27 HZ/su vs. 8 placebo, RR = 3.38 [95% CI: 1.49-8.60], p = 0.0019) occurring within 30 days of vaccination.

Gout was an unsolicited AE, and the rate of a pre-existing gout diagnosis was equivalent in the vaccination and placebo groups (369 or 2.5% HZ/su vs. 379 or 2.6% placebo). Of the new gout cases identified in the clinical trial, 7 cases in HZ/su group had a prior history of gout compared to 5 in the placebo group.

CBER communicated concern about these imbalances to the sponsor, and they agreed to add gout to the list of disorders in the pIMD risk category. In addition, CBER communicated feedback to GSK requesting the inclusion of gout and arthralgia clinical trial data in the product insert (PI).

7.2.2 Sponsor's proposed plan for pIMD

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

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

Active surveillance will occur through a Targeted Safety Study (TSS), which will be a postmarketing commitment (PMC). This study will monitor the 12 pIMDs identified for enhanced surveillance, and medically-attended or serious AEs utilizing a medical database. Specifics of the study protocol are being developed, and the sponsor is planning a feasibility assessment, but the primary objective will be to assess the risk of gout, polymyalgia rheumatica, and temporal arteritis 12 months post-vaccination, and the study will utilize an appropriate comparator for signal generation and detection. The sponsor anticipates gathering data from 60-70,000 Shingrix® vaccinees, and a 60-70,000 patient comparator cohort.

The sponsor also agreed to include sub-analyses of post-marketing safety data in periodic safety reports such as the periodic benefit-risk evaluation report (PBRER) that analyze case reports of gout and other pIMDs with primarily arthritic pathology or presentations.

Reviewer comment: The combination of routine pharmacovigilance, enhanced surveillance as defined by the sponsor, and the active surveillance TSS, is adequate for monitoring the potential risk of pIMD.

7.3 Important potential risk: Serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease

7.3.1 Optic ischemic neuropathy and temporal arteritis

Review of clinical trial data submitted by the sponsor identified imbalances in optic ischemic neuropathy (OIN) (3 HZ/su vs. 0 placebo) within 60 days post-vaccination, and temporal arteritis (3 HZ/su vs. 0 placebo) within 1 year post-vaccination. In addition, polymyalgia rheumatica, a condition considered to share etiologies with temporal arteritis, but having a different presentation, had an imbalance of 17 HZ/su to 12 placebo one year post-vaccination. These are non-overlapping cases, so the total imbalance in these potentially related disease processes is 23 HZ/su to 12 placebo.

There is biological plausibility for the possible association of herpes zoster (HZ), or herpes zoster vaccination with these diseases, as the zoster virus remains latent in nerve cells, and an immune response towards latent virus could cause neurological complications.[1] In addition, retrospective observational studies in healthcare databases have found an association of temporal arteritis with both HZ and vaccination with Zostavax®.[2,3]

CBER communicated concern about these imbalances to the sponsor, and they agreed to add "Serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g., optic ischemic neuropathy and inflammatory (non-infective) ocular disease" as a potential risk to the PVP. CBER also communicated feedback to GSK requesting the inclusion of OIN data in the PI.

7.3.2 Sponsor's proposed plan for ocular complications

The sponsor proposes addressing the potential risks of ocular complications post-vaccination by supplementing routine pharmacovigilance with enhanced surveillance and active surveillance. Enhanced surveillance will occur for 2 ocular complications: optic ischemic neuropathy, and temporal arteritis, and will occur as described in section 7.2.2.

Active surveillance will occur through the TSS, a PMC. The protocol is under development, but basic elements of the study design are described in section 7.2.2, and will include studying the two ocular complications identified for enhanced surveillance.

Reviewer comment: The combination of routine pharmacovigilance, enhanced surveillance as defined by the sponsor, and the active surveillance TSS, is adequate for monitoring the potential risk of ocular complications.

7.4 Missing information: Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older and Long-term immunogenicity in adults 50 years of age and older.

The long-term efficacy and immunogenicity of the Shingrix® vaccine beyond the observed follow-up period in the premarket clinical trials are not known. To help address this knowledge gap the sponsor proposes two studies:

- ZOSTER-049 – A phase IIIb, open-label, multicountry, multi-centre, long-term follow-up study of studies ZOSTER-006 and 022 to assess the prophylactic efficacy, safety, and immunogenicity persistence of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine and assessment of 1 or 2 additional doses on a 0 or 0, 2- month schedule in two subgroups of adults50 years of age and older. Long-term follow-up: including 5, 6, 7, 8, 9 and 10 years post-vaccination.
- ZOSTER-060 – A phase IIIb, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine at Months 108 and 120 post-vaccination and the assessment of re-vaccination with two additional doses administered at 10 years after the initial vaccination in study Zoster-003 in healthy subjects aged 60 years of age and older. Long-term follow-up: 9 and 10 years post-vaccination.

Reviewer comment: The sponsor's proposal to address missing efficacy and immunogenicity information with the proposed studies is adequate.

8 Conclusions

The sponsor's PVP adequately reflects safety concerns based on the clinical trial experience. There are no identified risks. The potential risks of pIMD and ocular complications are adequately addressed with the addition of enhanced surveillance, and the active surveillance TSS. Missing information on long-term efficacy, the potential need for a booster dose, and long-term immunogenicity are adequately addressed through the two proposed studies.

9 Recommendations

Table 3: Summary of PVP

	Important Safety Concern	Pharmacovigilance Action
	Important identified safety concerns	
1	None identified	• No actions
	Important potential safety concerns	
2	Hypersensitivity reactions	• Routine pharmacovigilance as required under 21 CFR 600.80
	pIMD (including gout)	• Routine pharmacovigilance as required under 21 CFR 600.80 • Enhanced surveillance with follow-up questionnaires and observed to expected analysis with passive surveillance data • PMC Active surveillance study: the TSS
	Ocular complications	• Routine pharmacovigilance as required under 21 CFR 600.80 • Enhanced surveillance with follow-up

	Important Safety Concern	Pharmacovigilance Action
		questionnaires and observed to expected analysis with passive surveillance data • PMC Active surveillance study: the TSS
	Important missing information	
3	Long-term efficacy and immunogenicity	• 2 PMC studies addressing efficacy and immunogenicity

No additional actions recommended prior to approval. The sponsor's proposed PVP is adequate.

References

1. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. Clin Infect Dis. 2014 Jun;58(11):1497-503. doi: 10.1093/cid/ciu098. Epub 2014 Apr 2. PubMed PMID: 24700656; PubMed Central PMCID: PMC4017889.
2. England BR, Mikuls TR, Xie F, Yang S, Chen L, Curtis JR. Herpes Zoster as a Risk Factor for Incident Giant Cell Arteritis. Arthritis Rheumatol. 2017 Aug 29. doi: 10.1002/art.40236. [Epub ahead of print] PubMed PMID: 28853238.
3. Lotan I, Steiner I. Giant cell arteritis following varicella zoster vaccination. J Neurol Sci. 2017 Apr 15;375:158-159. doi: 10.1016/j.jns.2017.01.053. Epub 2017 Jan 18. PubMed PMID: 28320119.