Summary Basis for Regulatory Action

Date: April 18, 2018

From: Luba Vujcic, Chair of the Review Committee

***BLA* STN#:** 125123/2058

Applicant Name: Merck Sharp & Dohme Corp

Date of Submission: June 22, 2017

Goal Date: April 22, 2018

Proprietary Name/Established Name: ZOSTAVAX®/Zoster Vaccine Live

Indication: Prevention of herpes zoster (shingles) in individuals 50 years of age and older.

Recommended Action:
The Review Committee recommends approval of this efficacy supplement, to include data from an interim analysis of an observational study that support longer-term effectiveness of ZOSTAVAX® in individuals 50 years of age and older. The applicant should complete this ongoing postmarketing observational study as planned to collect additional data.

Review Office(s) Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

☐ **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 material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
CMC Review • *Facilities review (OCBQ/DMPQ)*	Jeremy Wally, January 31, 2018
Clinical Review(s) • *Clinical (product office)*	Edna Termilus, April 18, 2018

Document title	Reviewer name, Document date
• *Postmarketing safety epidemiological review (OBE/DE)*	Jaspal Ahluwalia, March 22, 2018
Statistical Review • *Clinical data*	Elizabeth Teeple, March 29, 2018
Labeling Review • *APLB (OCBQ/APLB)*	Oluchi Elekwachi, February 16, 2018

1. Introduction

ZOSTAVAX® is a lyophilized preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). ZOSTAVAX was initially approved by the FDA in May 2006 for the prevention of HZ in individuals 60 years of age or older, and in March 2011 the indication was expanded to include use in individuals 50 to 59 years of age.

As a postmarketing commitment under the approval for individuals 50 to 59 years of age (STN 125123/734), Merck agreed to conduct an observational study (Protocol 024) to assess the duration of protection against HZ in this age range. Under this supplement, Merck is requesting to update the Clinical Studies section of the ZOSTAVAX US Prescribing Information (PI) with the data from the first interim study report for Protocol 024.

2. Background

ZOSTAVAX is a live, attenuated VZV vaccine administered as a single dose to protect against HZ in individuals 50 years of age and older. Protocol 024 is an ongoing observational study of the long-term effectiveness of ZOSTAVAX that is being conducted as a post-marketing commitment to the U.S. FDA, the European Medicines Agency (EMA), and other health authorities that requested additional data to assess the duration of protection of the vaccine, especially in individuals 50 to 59 years of age.

The efficacy and safety of ZOSTAVAX were established through several clinical studies, which included a large scale, placebo-controlled clinical trial known as the Shingles Prevention Study (SPS, more than 38,000 adults 60 years of age and older), and a placebo controlled trial known as ZOSTAVAX Efficacy and Safety Trial (ZEST, more than 22,000 adults 50 to 59 years of age). The SPS study had a median follow up period of 3.1 years, and the vaccine was shown to reduce the incidence of HZ by 51% and the incidence of PHN by 67%. The Short Term Persistence Study (STPS) extended the study follow-up period to 7 years post-vaccination for a subset of the cohort enrolled in the SPS study and the Long Term Persistence Study (LTPS) extended the follow-up time for an additional 5 years in a subset of the vaccine cohort. The ZEST study had a median follow-up period of 1.3 years, and the vaccine efficacy on HZ incidence was 70%. The study provided no data on the duration of protection of the vaccine against HZ in adults between 50 and 59 years of age.

Protocol 024 is a large-scale prospective observational cohort study run by Kaiser Permanente Northern California (KPNC) designed to evaluate the effectiveness and

assess the persistence of protection elicited by ZOSTAVAX in vaccinated individuals 50 years of age or older. Data on approximately 1.3 million members of the KPNC network were included in the interim study report, with 100,000 individuals with more than 5 years of follow-up post-vaccination. The study is still ongoing, and the second interim study report will be submitted December 2020. The study will continue until June 2023, or until data are accrued from 5,000 individuals ages 50-59 years vaccinated with ZOSTAVAX and followed for at least 10 years post-vaccination.

In a Type C meeting held on October 4, 2016, CBER concurred that the first interim report from Protocol 024 could be used to update the ZOSTAVAX US PI. Merck submitted this sBLA to include data from the first interim report from Protocol 024 in the ZOSTAVAX US PI. Revisions were proposed to the text in Section 14 CLINICAL STUDIES by adding a paragraph entitled "Long-term effectiveness study in individuals 50 years of age or older."

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

No CMC information/data was provided in the supplement.

b) CBER Lot Release (only applicable for BLAs)

N/A

c) Facilities review/inspection

No manufacturing or facilities- and equipment-related information/data was provided in the supplement.

d) Environmental Assessment

The PAS included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (a). The FDA concluded that this request is justified as this action will not increase the use of the active moiety and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

N/A

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

N/A

5. CLINICAL PHARMACOLOGY

N/A

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

(Extracted in part from the reviews of Drs. Edna Termilus and Elizabeth Teeple)

The applicant agreed to conduct a prospective observational study to assess the long-term effectiveness of the vaccine to better characterize the duration of protection against HZ. This observational study is being conducted by KPNC using electronic administrative data for KPNC members from outpatient, inpatient, and emergency department visits, prescription records, and laboratory results.

The applicant provided tabular and descriptive summaries of the study results. The provided results were reviewed by the clinical review team, in conjunction with the statistical and epidemiology reviewers. The submitted study was well designed and adequately adjusted for potential confounders including demographics, health-seeking behavior, and comorbidities.

The primary objective of this study was to describe the impact of ZOSTAVAX on the incidence of herpes zoster in individuals vaccinated at 50 years of age or older.

- To describe the incidence of HZ in vaccinated people overall, by age at vaccination (50-59, 60-69, 70-79, ≥ 80 years of age) and by time since vaccination.

- To assess vaccine effectiveness on HZ incidence in people vaccinated as compared to a group of unvaccinated people overall, by age at vaccination (50-59, 60-69, 70-79, ≥ 80 years of age) and by time since vaccination.

An incident HZ case was defined as a new HZ episode in an individual having no evidence of a prior HZ episode in the last 12 months.

The secondary objective of this study was to describe the impact of ZOSTAVAX on postherpetic neuralgia (PHN) in individuals vaccinated at 50 years of age or older.

- To describe the incidence of PHN in vaccinated people overall, by age at vaccination (50-59, 60-69, 70-79, ≥ 80 years of age) and by time since vaccination.

- To assess vaccine effectiveness on PHN in people vaccinated as compared to a group of unvaccinated people overall, by age at vaccination (50-59, 60-69, 70-79, ≥ 80 years of age) and by time since vaccination.

An incident PHN case was defined as zoster-associated pain (ZAP) reported ≥90 days and up to 1 year following an incident HZ diagnosis.

The inclusion and exclusion criteria were:

Inclusion criteria:

The study cohort was limited to KPNC members with continuous KPNC membership since becoming age-eligible for ZOSTAVAX and with 12 months of continuous enrollment in KPNC before their study start date.

Exclusion criteria:

- a HZ diagnosis in the baseline period
- receipt of ZOSTAVAX prior to study start date
- joining KPNC after age-eligibility (i.e., individuals ≥ 60 years of age who join KPNC after May 2006 and individuals ≥ 50 years of age who join KPNC after March 2011). Though the study did not start until January 2007, the earlier eligibility date is to ensure ZOSTAVAX was not received under a previous health plan.

Eligible individuals entered the study cohort as unvaccinated and contributed person-time to the unvaccinated cohort until vaccination. Vaccinated and unvaccinated study individuals were followed prospectively for the first occurrence of HZ and PHN, death, or discontinued enrollment in the KPNC network.

At the time of the interim analysis, data on 1,355,720 individuals were included in the study, with 392,677 of those individuals vaccinated with ZOSTAVAX. From 2007 to 2014, there were 48,616 cases of HZ. The incidence rate of HZ in the unvaccinated study cohort was 8.9 cases per 1,000 person-years (95% CI: 8.9, 9.0), and the incidence rate in the vaccinated cohort was 5.8 per 1,000 person-years (95% CI: 5.6, 5.9). The incidence rate remained higher in the unvaccinated cohort compared to the vaccinated cohort when stratified by age group, sex, and race.

The overall vaccine effectiveness during the time period covered by the first interim analysis was 49.1% (95% CI: 48%, 51%) among all age groups combined. Vaccine effectiveness against HZ declined with increasing time since vaccination and age at vaccination. For individuals 50-59 years of age at the time of vaccination, the average VE against HZ over the first 3 years following vaccination was 60% (95% CI: 52, 66), with VE against HZ of 36% (95% CI: -55, 73) in the third year post-vaccination. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against HZ over the first 5 years following vaccination was 49% (95% CI: 47, 52), 46% (95% CI: 43, 48), and 44% (95% CI: 38, 49), respectively, with VE against HZ of 34% (95% CI: 25, 42), 29% (95% CI: 18, 38), and 36% (95% CI: 12, 53), respectively, in the fifth year post-vaccination.

Among those with an incident HZ episode, there were 3,297 cases that developed PHN. Of the PHN cases, 322 cases occurred in the vaccinated cohort and 2,975 cases in the unvaccinated cohort. The overall risk ratio for development of PHN in vaccinated individuals with HZ compared to unvaccinated individuals with HZ was 0.80 (95% CI: 0.72, 0.90). The overall incidence rate of PHN among the unvaccinated cohort was 62.1 cases per 100,000 person-years (95% CI: 59.8, 64.3), and the overall incidence rate of

PHN among the vaccinated cohort was 32.2 cases per 100,000 person-years (95% CI: 28.8, 36.0). The incidence rate remained higher in the unvaccinated cohort compared to the vaccinated cohort when stratified by age group, sex, and race.

The overall effectiveness of ZOSTAVAX® in preventing PHN during the time period covered by the first interim analysis was 69% (95% CI: 65%, 72%) among all age groups combined. Insufficient data were available at the time of the interim analysis to assess the outcome of PHN in individuals 50-59 years of age. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against PHN over the first 5 years following vaccination was 72% (95% CI: 65, 77), 69% (95% CI: 62, 75), and 61% (95% CI: 47, 71), respectively, with VE against PHN of 61% (95% CI: 33, 77), 69% (95% CI: 44, 82), and 34% (95% CI: -49, 71), respectively, in the fifth year post-vaccination.

b) Pediatrics

ZOSTAVAX is currently licensed for individuals 50 years of age or older. This submission does not trigger PeRC.

c) Other Special Populations

No other special populations were evaluated. This product is only intended for use in adults 50 years of age and older.

7. SAFETY

There are no safety concerns with the interim data in this supplement.

8. ADVISORY COMMITTEE MEETING

A Vaccines and Related Biologics Products Advisory Committee meeting was not held for this supplement as there were no issues or concerns that presented during the review of the supplement that required consult from the advisory committee.

9. OTHER RELEVANT REGULATORY ISSUES

There are no additional relevant regulatory issues.

10. LABELING

To present the data in the label for both HZ and PHN, two main issues were recognized.

- The average VE calculated for the first 3 year and 5 year intervals post-vaccination largely reflected VE during the first year post-vaccination and did not effectively communicate the decrease in effectiveness over subsequent years. The review committee agreed that the PI could describe average VE estimates if accompanied by VE estimates for the final year of the averaged time period.

- The calculation of VE based on incidence rates of PHN included all individuals enrolled in the study, which reflects both prevention of HZ and prevention of PHN following HZ; however, in the Shingles Prevention Study, VE for PHN was calculated as a rate ratio in individuals with incident HZ, which is a better indicator of whether vaccination prevents PHN in individuals who have HZ. However, due to the observational study design it was not possible to calculate with proper adjustment for potential confounders estimates of VE for PHN using rate ratios in individuals with incident HZ and stratified by time since vaccination. Therefore, the review committee agreed that the PI could describe VE for PHN based on PHN incidence rates.

The review committee negotiated revisions to the PI, including format and presentation of the long-term efficacy data for both HZ and PHN. Merck agreed with our suggested revisions.

An interim analysis of a prospective observational cohort study conducted in a US integrated healthcare system database estimated vaccine effectiveness against HZ and PHN among 1,355,720 individuals 50 years of age and older, including 392,677 who received ZOSTAVAX. Age eligible individuals contributed person-time to the unvaccinated group and, once vaccinated with ZOSTAVAX, contributed person-time to the vaccinated group for the remainder of the study. Vaccine effectiveness (VE) against HZ and PHN was calculated using the incidence rates of protocol-defined first episode of HZ and PHN in the vaccinated and unvaccinated groups, including adjustments for calendar time, age, sex, race/ethnicity, healthcare resource utilization, comorbid conditions, and immunocompromise status. The gender and racial/ethnic distributions of study individuals were overall 53% female, 60% white, 15% Asian or Pacific Islander, 13% Hispanic, and 7% black or African American.

For individuals 50-59 years of age at the time of vaccination, the average VE against HZ over the first 3 years following vaccination was 60% (95% CI: 52, 66), with VE against HZ of 36% (95% CI: -55, 73) in the third year post-vaccination. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against HZ over the first 5 years following vaccination was 49% (95% CI: 47, 52), 46% (95% CI: 43, 48), and 44% (95% CI: 38, 49), respectively, with VE against HZ of 34% (95% CI: 25, 42), 29% (95% CI: 18, 38), and 36% (95% CI: 12, 53), respectively, in the fifth year post-vaccination. Follow-up time for individuals 50-59 years of age was shorter because ZOSTAVAX was approved for use in this age group five years after approval for use in individuals 60 years of age and older.

Insufficient data were available at the time of the interim analysis to assess the outcome of PHN in individuals 50-59 years of age. For individuals 60-69 years of age, 70-79 years of age, and 80 years of age and older at the time of vaccination, the average VE against PHN over the first 5 years following vaccination was 72% (95% CI: 65, 77), 69% (95% CI: 62, 75), and 61% (95% CI: 47, 71), respectively, with VE against PHN of 61% (95% CI: 33, 77), 69% (95% CI: 44, 82), and 34% (95% CI: -49, 71), respectively, in the fifth year post-vaccination. The benefit of ZOSTAVAX in the prevention of PHN can be attributed in part to the effect of the vaccine on the prevention of HZ.

The Advertising and Promotional Labeling Branch (APLB) found the PI to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The clinical data submitted to this BLA supplement continue to support the use of ZOSTAVAX in individuals 50 years of age and older. The submitted analyses are from an interim analysis of an observational study, and these interim data add to the understanding of longer-term effectiveness of ZOSTAVAX. Using observational trial data to present estimates of VE for HZ and PHN in the ZOSTAVAX PI is useful to prescribers. After extensive labeling discussions within OVRR and with the applicant regarding how to present the interim data, the revised draft language in the final draft PI submitted in Amendment 4 on March 28, 2018, was found acceptable by the Review Committee as indicated in the reviews. The Review team and I are in agreement on the approval of this supplement with the revised labeling.

b) Risk/ Benefit Assessment

Risk-Benefit has been considered for this efficacy supplement.

Herpes zoster is a serious disease with potential debilitating morbidity including PHN which remains a significant concern. Shingles can be prevented by vaccine and usually occurs in the older population.

ZOSTAVAX has been licensed by the FDA based on a large double-blind, placebo-controlled efficacy study in 38,000 subjects, with an estimated efficacy of 51% against herpes zoster and the evidence for short-term clinical benefit is well established. The interim analysis of this observational study adds additional data to describe the duration of clinical benefit, which show that effectiveness against herpes zoster appears to decline over time. The data suggest that ZOSTAVAX may confer benefit via prevention of PHN both by prevention of herpes zoster as well as other mechanisms that are not well understood.

The most substantial risks of vaccination with ZOSTAVAX are associated with the inflammation produced at the injection site and erythema, swelling, and pain are also very common. However, most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae. All the evidence indicates that the risks of vaccination with ZOSTAVAX are minor in immunocompetent individuals, and no new safety concerns were raised by this observational study interim analysis. The risk benefit balance for ZOSTAVAX remains favorable.

c) Recommendation for Postmarketing Activities

No additional postmarketing studies are required. Sponsor should complete this current postmarketing study as planned to collect additional data.