Application Type	Original BLA submission
STN	125614/0
CBER Received Date	October 21, 2016
PDUFA Goal Date	October 20, 2017
Division / Office	DVRPA/OVRR
Committee Chair	Carmen Collazo-Custodio, PhD
Clinical Reviewer(s)	Paula Agger, MD MPH; Rebecca Reindel, MD
Project Manager	Ramachandra Naik, PhD; Michael Smith, PhD
Priority Review	No
Reviewer Name(s)	Rong Fu, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, PhD, Team Leader, Viral and Bioassay Team, VEB/DB/OBE
	Amelia Dale Horne, DrPH Branch Chief, VEB/DB/OBE
	John Scott, PhD Acting Director, DB/OBE
Applicant	GlaxoSmithKline Biologicals
Established Name	Zoster Vaccine Non-Live
(Proposed) Trade Name	Shingrix
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	After reconstitution, each 0.5 mL dose contains 50 μg of gE recombinant protein, 50 mcg of MPL and 50 mcg of QS-21.
Indication(s) and Intended Population(s)	Prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, Shingrix reduces the overall incidence of postherpetic neuralgia.

Table of Contents

GLOSSARY

ANOVA	Analysis of Variance
CI	Confidence Interval
CMV	Cytomegalovirus
Ct	Threshold Cycle
CV	Coefficient of Variation
DLi	Deviation from Linearity
EBV	Epstein Barr Virus
GMT	Geometric Mean Titer
HAI	Haemagglutination Inhibition
HSV	Herpes Simplex Virus
HZ	Herpes Zoster
ICS	Intra-cellular Cytokine Staining
LLOL	Lower Limit of Linearity
LLOP	Lower Limit of Precision
LLOQ	Lower Limit of Quantitation
LOB	Limit of Blank
LOD	Limit of Detection
OD	Optical Density
PBMC	Peripheral Blood Mononuclear Cell
(b) (4)	
qPCR	Quantitative Polymerase Chain Reaction
(b) (4)	
VZV	Varicella Zoster Virus

1. EXECUTIVE SUMMARY

GSK is seeking licensure of the herpes zoster (HZ) vaccine Shingrix (also referred to as HZ/su), indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. This review focuses on multiple assays which were used to generate efficacy and immunogenicity data to support the license application.

Assays used for measurements of primary endpoints in pivotal studies

- Two quantitative Polymerase Chain Reaction (qPCR) assays were used for classification of confirmed herpes zoster cases. Specificity appears to have been demonstrated and cut-off values were established for these two assays; therefore, they are considered suitable for the intended use as qualitative assays in efficacy studies.
- For immunogenicity measurements, the anti-gE ELISA was used to quantify the specific IgG antibodies against the glycoprotein gE of Varicella Zoster virus (VZV) in human sera. The anti-gE ELISA appears to be specific, precise, accurate, and linear over the analytical range. Therefore, it performs adequately to provide the immunogenicity measurements in clinical studies.
- The Haemagglutination Inhibition (HAI) test was used to measure the immune response against different influenza virus strains in the quadrivalent influenza vaccine in a concomitant study when HZ/su was co-administered with a quadrivalent

influenza vaccine. Precision evaluations for the HAI assays for A/Texas/50/2012 and B/Massachusetts/02/2012 strains did not cover the entire analytical range. This may not be a significant concern, as both strains showed a non-increasing trend of variability towards the ends of assay range, and the linearity data -- which included (b)(-- showed perfect agreement in titers for the range not covered in the precision study.

Assays used for measurements of exploratory endpoints in pivotal studies

- (b) (4)
- The Intra-cellular Cytokine Staining (ICS) assay was used to measure the cell mediated immune response expressed as the frequency of antigen-specific CD4+ T cells. This assay is considered to have been validated with acceptable precision and linearity in the lower part of the defined analytical range. Since the observed responses in Zoster studies also lay in the lower part of the analytical range, the assay may provide some useful descriptive information regarding the exploratory objective.
- (b) (4)

Overall, the efficacy and immunogenicity data generated by these assays appear to be adequate, given their respective intended use to support the license application.

2. CLINICAL AND REGULATORY BACKGROUND

Shingrix is a sub-unit vaccine consisting of the recombinant VZV glycoprotein gE as antigen combined with GSK's proprietary Adjuvant System AS01B. The vaccine efficacy was evaluated in two efficacy trials, Zoster-006 and Zoster-022, in adults ≥50 years old, and two qPCR assays (to detect the VZV DNA and β-actin gene DNA) were used to determine the confirmatory herpes zoster cases. The anti-gE ELISA measured the anti-gE immune response, which was used as a primary endpoint in several pivotal studies to evaluate the lot-to-lot consistency (Zoster-007), alternative administration schedules (Zoster-026), and concomitant administration with a quadrivalent influenza vaccine (Zoster-004). The influenza vaccine used in study Zoster-004 contained four virus strains: A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (Yamagata), and B/Brisbane/60/2008 (Victoria). The antigens used in the HAI testing were the same as the vaccine virus strains, except for H1N1, where the test was against A/California/7/2009 (H1N1) because it was considered antigenically equivalent to the vaccine strain. The (b) (4) and gE-specific ICS assays were also used to provide immunogenicity data in two efficacy studies which were assessed as exploratory endpoints. All these assays were performed at GSK Biologicals.

Although the (b) (4) immune response was planned as an exploratory endpoint, no real data were generated because of the high correlation between the (b) (4) antibodies and the anti-gE (b) (4) antibodies.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

This review summarizes the validation or qualification approaches and results for assays used in five pivotal studies. The qualification of a different anti-gE ELISA (performed at (b) (4)) used for early phase trials was also submitted but is not reviewed here.

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

The following documents submitted to STN 125614/0 m5.3.1.4 were reviewed:

- Method validation report: Determination of varicella-zoster viral status in clinical samples by PCR assay (Version 2.0; June 21, 2012)
- Method validation report: Detection of β-actin DNA in clinical samples originating from VZV-like dermal skin lesions by quantitative PCR (Version 2.0; February 21, 2012)
- Method validation report for quantitative (b) (4) anti-gE VZV (Version 4.0, February 18, 2014)
- Revalidation report for Haemagglutination Inhibition assay with the H1N1v strain (Version 01; October 29, 2009)
- Method validation report for Haemagglutination Inhibition test with the H3N2 influenza strain A/Texas/50/2012 wild type (Version 2.0; March 10, 2015)
- Method validation report for Haemagglutination Inhibition test with the influenza strain B/Massachusetts/02/2012 wild type (Version 1.0; July 26, 2013)
- Validation report for Haemagglutination Inhibition test with the influenza B strain B/Brisbane/60/2008 (Version 01; March 1, 2011)
- Method validation report: Performance characteristics and validation: (b) (4) Version 6; May, 2016)
- Method validation report for Zoster ICS (Version 3; July, 2016)
- Performance characteristics and qualification (b) (4)

In addition, the reviewer reviewed the following information submitted in amendments to the original BLA submission:

- Amendment 11: m1.11.3: Response to CBER information request (dated February 21, 2017) regarding clarification on tables for the clinical assays and information on the HAI assay validation reports and SOPs, included in m5.3.1.4.
- Amendment 12: m1.4.1: Letters authorizing cross-reference to BLAs for the HAI test.

4. DISCUSSION OF INDIVIDUAL ASSAYS

4.1 VZV qPCR

The VZV qPCR assay is used to detect and quantify VZV DNA (the (b) (4) portion) in dermal clinical samples. Although the assay is quantitative, the final outcome is qualitative (presence or absence of VZV DNA). (b) (4)

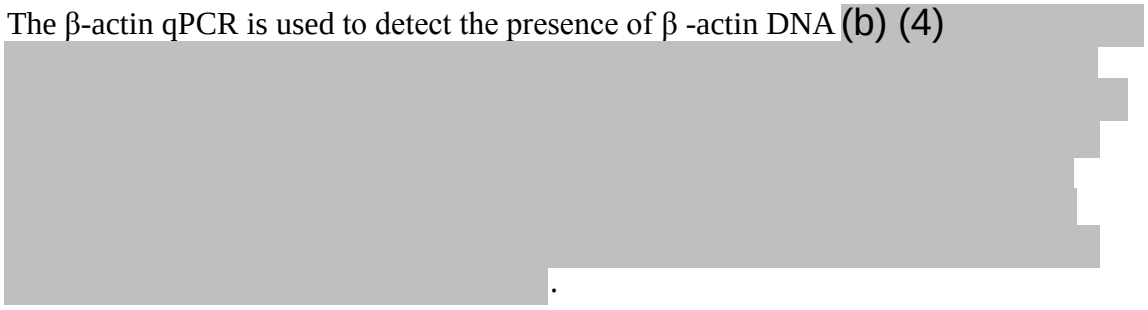
The validation is summarized below.

(b) (4)

(b) (4)

4.2 β-actin qPCR

The β-actin qPCR is used to detect the presence of β -actin DNA (b) (4)



.

(b) (4)

4.3 Anti gE-ELISA

The anti-gE ELISA is used to quantify the specific IgG antibodies against the glycoprotein gE of VZV in human sera. The initial and complementary validation reports of this assay were previously submitted to IND 13857/108 and IND 13857/190 and have been reviewed by statistical reviewers. A summary of the assay validation is provided below.

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

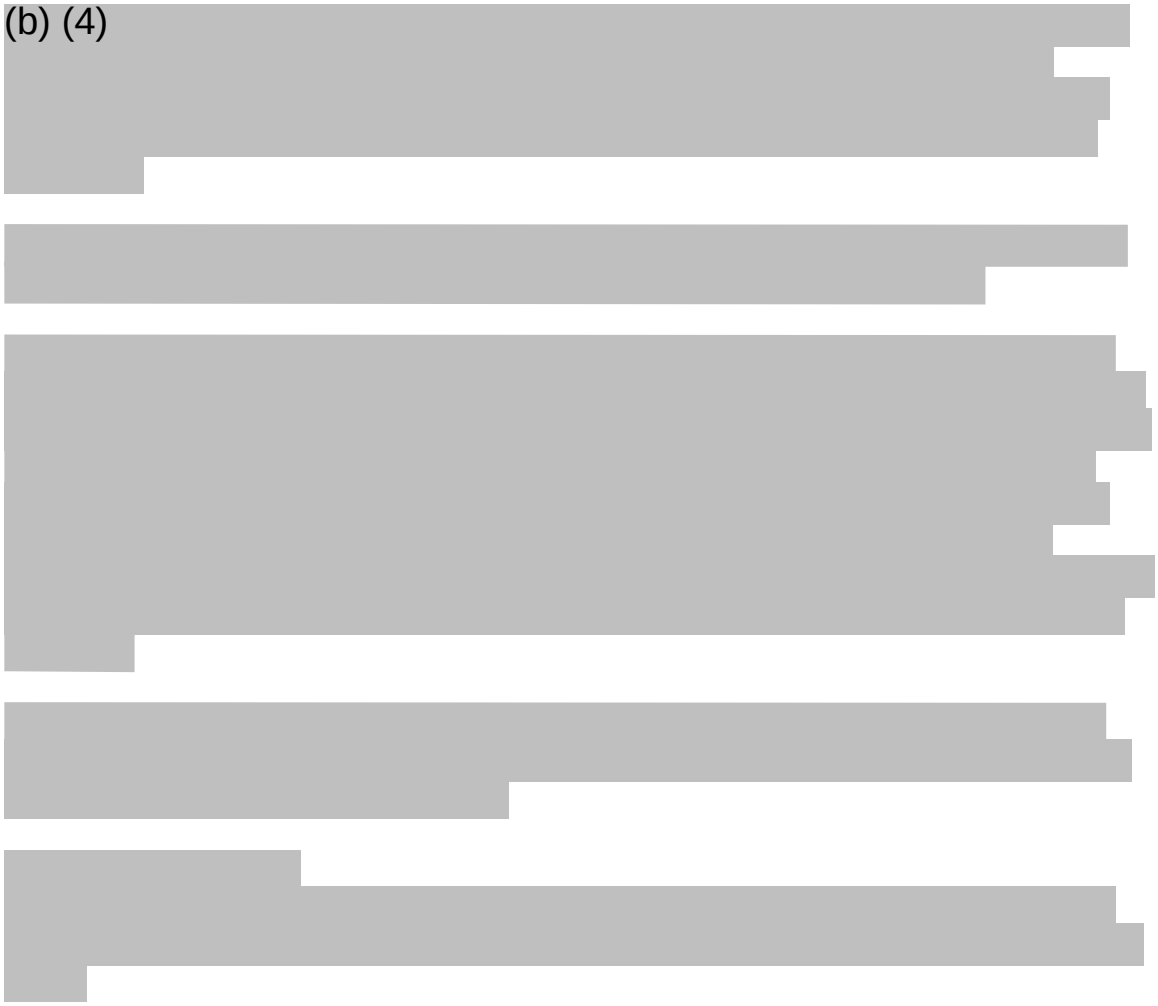
(b) (4)

4.6 ICS assay

The ICS assay is used to measure the cell-mediated immune response using (b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)



5. CONCLUSIONS

The conclusions for individual assays are summarized below:

- For VZV qPCR and β-actin qPCR assays, specificity appears to have been demonstrated and cut-off values were established; therefore, they are considered suitable for the intended use as qualitative assays in clinical studies.
- The anti-gE ELISA (b) (4) appear to be specific, precise, accurate, and linear over the analytical range, and therefore is considered to have adequate performance to support the immunogenicity measurements in clinical studies.
- Precision evaluations for the HAI assays for A/Texas/50/2012 and B/Massachusetts/02/2012 strains did not cover the entire analytical range (i.e., a precision range of (b) (4) versus an analytical range of (b) (4) for A/Texas/50/2012 and a precision range of (b) (4) versus an analytical range of (b) (4) for B/Massachusetts02/2012). This may not be a significant concern, as both strains showed a non-increasing trend of variability towards the ends of assay range, and the linearity data which included (b) (4) showed perfect agreement in (b) (4) for the range not covered in the precision study.
- The ICS assay appears to have been validated to have acceptable precision and linearity for the lower part of the defined analytical range down to the LLOQ. Since

the observed responses in Zoster studies also lay in the lower part of the analytical range, the assay may provide some useful descriptive information regarding the exploratory objective.

- Both the linearity and precision of the (b) (4) assay appear to be not adequately demonstrated in the qualification study over the entire assay range. However, no immunogenicity data were generated from this assay to support this BLA. (b) (4)

Overall, the efficacy and immunogenicity data generated by these assays appear to be adequate, given their respective intended uses to support the license application.