Application Type	BLA Supplement
STN	125254/692
CBER Received Date	November 1, 2017
PDUFA Goal Date	September 1, 2018
Division / Office	DVRPA /OVRR
Committee Chair	Josephine Resnick
Clinical Reviewer(s)	Cynthia Nolletti
Project Manager	Helen Gemignani Timothy Fritz
Priority Review	No
Reviewer Name(s)	Rong Fu
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin Acting Branch Chief, VEB/DB/OBE
Applicant	Seqirus Pty Ltd.
Established Name	Influenza Vaccine
(Proposed) Trade Name	Afluria Quadrivalent, Influenza Vaccine
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Each 0.5 mL dose contains 15µg hemagglutinin from each of the recommended influenza types and subtypes: A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.
Dosage Form(s) and Route(s) of Administration	Sterile suspension for intramuscular injection.
Dosing Regimen	One 0.5 mL dose (persons ≥9 years); one or two 0.5 mL doses (based on prior vaccination history) at least 1 month apart (persons 36 months through 8 years); one or two 0.25 mL doses (based on prior vaccination history) at least 1 month apart (persons 6 through 35 months).
Indication(s) and Intended Population(s)	Active immunization against influenza disease caused by influenza virus present in vaccine for use in persons 6 months of age and older.

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GLOSSARY

AE	Adverse Event
GMT	Geometric Mean Titer
HI	Hemagglutination Inhibition
QIV	Quadrivalent Influenza Vaccine
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate

1. EXECUTIVE SUMMARY

Seqirus submitted BLA supplement 125254/692 to seek an indication for Afluria Quadrivalent Influenza Vaccine (QIV) in children 6 months through 59 months of age. On July 18, 2018, CBER's Biomedical Monitoring review identified an issue with Site #8400445, which raised questions about the quality and integrity of data from this site. Therefore, the applicant was requested to provide explanations for why this site was not excluded from the final analyses and to submit reanalysis results on key immunogenicity and safety data excluding Site #8400445. This review serves as an addendum to my original statistical review dated June 19, 2018, covering the review of Seqirus's responses to this information request. The applicant's explanations for including Site #8400445 in the final analyses are considered acceptable. The reanalysis results excluding Site #8400445 were very similar to the original results including Site #8400445, and there appears to be no impact on the overall interpretation of the study data and conclusions. Overall, I don't have concerns with including data from Site #8400445 in the final analyses following the Statistical Analysis Plan (SAP).

2. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

Amendments STN 125254/692.13 and STN 125254/692.14, which contained the applicant's responses regarding Site #8400445 and reanalysis results excluding this site, were reviewed in this addendum.

3. SUMMARY OF THE APPLICANT'S RESPONSE TO CBER'S INFORMATION REQUEST

3.1 Explanations for Including Site #8400445 in the Final Analyses

In the response, the applicant stated that the subject data from Site #8400445 included in the final study analyses were collected in accordance with the study protocol and analyzed in accordance with the SAP. All subjects identified at the inspection with protocol deviations were identified prior to database lock and excluded accordingly from the immunogenicity analyses. Solicited and unsolicited outcomes were entered by parents/legal guardians into electronic diaries and directly integrated into the clinical database in real-time independent of investigator site personnel. Site compliance was monitored routinely every two weeks during enrollment, and immediate actions were implemented to address the deficiencies at this site that were identified.

3.2 Reanalyses of Primary Immunogenicity Endpoints

Study Site #8400445 represented 2.1% (41 of 1940) of the per protocol population. The reanalysis results on the primary objective of demonstrating noninferiority of Seqirus QIV compared to the Comparator QIV in terms of Hemagglutination Inhibition (HI) geometric mean titer (GMT) and seroconversion rate (SCR) excluding Site #8400445 are presented in Table 1 and Table 2. The differences in GMT ratios, SCR differences, and their confidence limits comparing the analyses including and excluding Site #8400445 were minimal (≤0.01 or 1%). The overall conclusion remained unchanged that all 8 co-primary endpoints meet the noninferiority criteria.

Table 1: Post-vaccination HI Antibody GMTs and Analyses of Noninferiority of Seqirus QIV Relative to Comparator QIV for Each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 months of Age (Per-Protocol Population Excluding Site #8400445)

Strain	Adjusted GMT Seqirus QIV (N=1425[a])	Adjusted GMT Comparator QIV (N = 474[b])	GMT ratio[c] (Comparator QIV / Seqirus QIV) (95% CI)
A/H1N1	353.3	278.8	0.79 (0.71, 0.87)
A/H3N2	391.7	497.4	1.27 (1.14, 1.41)
B/Yamagata	23.5	26.6	1.13 (1.02, 1.26)
B/Victoria	53.9	52.9	0.98 (0.87, 1.11)

[a] Subject (b) (6) was excluded from the adjusted GMT analysis for all strains as the subject did not have information on pre-vaccination history. For A/H3N2, N=1423: subject (b) (6) had missing A/H3N2 post-vaccination titer.

[b] For B/Victoria, N=473: subject (b) (6) had missing B/Victoria pre-vaccination titer.

[c] Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata + Sex + Prior Year Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was maintained only in the model for B/Victoria as the interaction result was significant ($p<0.05$).

Source: Table 14.2.1.1.1 of Attachment 1 submitted to STN 125254/692.14

Table 2: Post-vaccination HI Antibody SCRs and Analyses of Noninferiority of Seqirus QIV Relative to Comparator QIV for Each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 months of Age (Per-Protocol Population Excluding Site #8400445)

Strain	SCR (95% CI) Seqirus QIV (N=1425[a])	SCR (95% CI) Comparator QIV (N = 474[b])	SCR Difference (Comparator QIV - Seqirus QIV) (95% CI)
A/H1N1	78.9 (76.7, 81.0)	68.4 (64.0, 72.5)	-10.5 (-15.7, -5.3)
A/H3N2	82.3 (80.2, 84.3)	84.8 (81.3, 87.9)	2.5 (-2.7, 7.7)
B/Yamagata	38.5 (35.9, 41.0)	42.4 (37.9, 47.0)	3.9 (-1.3, 9.1)
B/Victoria	60.1 (57.5, 62.6)	61.1 (56.5, 65.5)	1.0 (-4.2, 6.2)

[a] For A/H3N2, N=1424: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[b] For B/Victoria, N=473: subject (b) (6) had missing B/Victoria pre-vaccination titer.
Source: Table 14.2.2.1.1 of Attachment 1 submitted to STN 125254/692.14

3.3 Reanalyses of Safety Endpoints

Study Site #8400445 represented 3.1% (69 of 2232) of the overall safety population and 2.9% (62 of 2163) of solicited safety population. After excluding subjects from Site #8400445, the changes in percentages of subjects reporting any or each of the solicited local and systemic adverse events (AEs) within 7 days after any vaccination and in percentages of subjects reporting any unsolicited AEs, Grade 3 unsolicited AEs, related unsolicited AEs, and Grade 3 related unsolicited AEs from Day 1 through Day 28 following any vaccination were minimal (<1%). These changes did not impact the overall conclusions on safety data.

4. CONCLUSIONS

The applicant's explanations for including Site #8400445 in the final analyses are considered acceptable. The reanalysis results excluding Site #8400445 were very similar to the original results including Site #8400445, and there appears to be no impact on the overall interpretation of the study data and conclusions. Overall, I don't have concerns with including data from Site #8400445 in the final analyses following the SAP.