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| Application Type | Efficacy Supplement |
| STN | 125297/118 |
| CBER Received Date | April 2, 2019 |
| PDUFA Goal Date | January 31, 2020 |
| Division / Office | OVRR |
| Committee Chair | Josephine Resnick |
| Clinical Reviewer | Rachel Zhang |
| Project Managers | Katherine Berkhousen, Joseph Kulinski |
| Priority Review | No |
| Reviewer Name | Jennifer Kirk |
| Review Completion Date / Stamped Date | |
| Concurrence | Lei Huang<br>Concurring Reviewer,<br>Viral and Bioassay Team, VEB, DB |
| | Tsai-Lien Lin<br>Branch Chief,<br>Vaccine Evaluation Branch, DB |
| Applicant | Seqirus Inc. |
| Established Name | Influenza Virus Vaccine |
| Trade Name | Agriflu |
| Pharmacologic Class | Vaccine |
| Formulation, including Adjuvants, etc | 45 µg HA/0.5ml |
| Dosage Form and Route(s) of Administration | Suspension for intramuscular injection (PFS, MDV) |
| Indication and Intended Populations | Active immunization for the prevention of disease caused by influenza. Approved in adults 18 years of age and older |

## Table of Contents

## 1. Executive Summary

In this supplemental Biologics Licensing Application (BLA), Sequris Inc. submitted the results from two pediatric (V71_18 and V70_29) and one older adult (V71_22) studies for inclusion in the Agriflu label. Each of these studies was previously submitted and reviewed. Therefore, this review focused on the totality of evidence from these three studies. The two pediatric studies had protocol and Good Clinical Practice non-compliance and failed to meet their primary immunogenicity endpoints of non-inferiority compared to active competitors, and the results of these studies were inconclusive. The older adult study failed to meet the primary immunogenicity endpoint, leading to inconclusive results. Therefore, I defer to the clinical reviewer to determine whether it is appropriate to include the evidence from these studies in the label.

## 2. Clinical and Regulatory Background

Agriflu is a trivalent influenza vaccine that was first approved for use in adults aged 18 years and older under accelerated approval on November 27, 2009 and received full approval on October 29, 2010. The original approval included post-marketing commitments to conduct an immunogenicity and safety study in children 3 to 17 years of age (Study V71_18), an immunogenicity and safety study in children aged 6 months to less than 3 years old (Study V71_20), and a non-inferiority immunogenicity study in adults 50 years of age and older (Study V71_22). In lieu of Study V71_20, Study V70_29, which was designed to support US licensure of Fluad, was submitted to fulfill the requirement to conduct an immunogenicity and safety study in children 6 months to less than 3 years old.

Study V71_18 was submitted in BLA 125297/46, Study V70_29 was submitted in BLA 125297/49, and Study V71_22 was submitted in BLA 125297/63. All three studies were reviewed by a statistical reviewer when submitted to their respective BLA amendments.

In response to an information request, pediatric study V71P5 was submitted to this BLA to supplement the two pediatric studies. V71P5 was previously submitted to BLA 125297/0 and was reviewed as part of the original licensing application.

## 3. Submission Quality and Good Clinical Practices

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

## 5. Sources of Clinical Data and Other Information Considered in the Review

Because the individual studies submitted in this supplement were previously reviewed by statistical reviewers, the focus of this review is a synthesis of the evidence from these studies to support the proposed labeling change. Therefore, no individual discussion of the studies is presented beyond an overview of the studies in Section 6.

This review refers to the files from Modules 5 of BLA 125297/118.0 and BLA 125297/118.3, as well as the clinical statistical review memos from BLA 125297/0, BLA 125297/46, BLA 125297/49, and BLA 125297/63.

# 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

## 6.1 Pediatric Trials

Pediatric studies V71_18 and V70_29 are summarized in Table 1. Both pediatric studies failed to meet their pre-specified non-inferiority criteria for at least one endpoint. V71_18 met the CBER criteria for 2 of 3 strains for seroconversion and for 1 of 3 strains for geometric mean titers. However, sites in Study V71_18 had serious non-compliance with International Council for Harmonization Good Clinical Practice (GCP), and the statistical review of V71_18 noted that while sensitivity analyses excluding subjects from sites with severe GCP non-compliance and subjects that were inadvertently unblinded did not affect the study conclusions, there is still uncertainty about the overall study conduct. For Study V70_29, analyses of both the per-protocol set and the full analysis set failed to meet the pre-specified non-inferiority criteria. Furthermore, non-compliance with the study protocol and GCP was identified during monitoring at one study site.

Study V71P5, which was previously reviewed for the original licensing application, was submitted to this BLA to supplement the two pediatric studies. V71P5 enrolled adults and children aged 3 to 17 years old. Evaluation of the immunogenicity of Agriflu was a secondary objective, and as noted in the statistical review of V71P5 from the original licensing application, the immunogenicity analyses were descriptive. No hypothesis tests comparing Agriflu to the control vaccine were performed. Furthermore, the descriptive results suggest that Agriflu may not have met non-inferiority criteria had hypothesis testing been performed, even after accounting for differences in the immunogenicity assay used across the treatment groups.

**Table 1.** Summary of Pediatric Trials Submitted to BLA 125297/118

| Study Characteristic | Study V71_18* | Study V70_29* |
|---|---|---|
| Population | healthy children 3–17 years of age | healthy children 6–<72 mo. of age |
| Sites per Country | Columbia: 1; Mexico: 1; Panama: 4; The Philippines: 7 | Australia: 8; Argentina: 5; Chile: 2; The Philippines: 12; South Africa: 5 |
| Randomization | 3–8 years: stratified by age group (3-4, 5-6, 7-8 years)<br><br>9–17 years: simple | Block stratified by center and age group (6–<24, 24–<36, ≥36mo) |
| Allocation Ratio | 2:1 Agriflu to control (Fluvirin for children 4 to 17 years old or Fluzone for 3 to 4 years old) | 6–<24mo: 3:2:2 Fluad, Fluzone, Agriflu<br><br>24–<36mo: 3:2:2 Fluad, Fluzone, Agriflu<br><br>≥36mo: 4:1:1 Fluad, Fluzone, Agriflu |
| Sample Size | 2,804 enrolled<br>1,386 in immunogenicity cohort | 6,100 enrolled and randomized<br>2,655 immunogenicity cohort |
| Primary Immunogenicity Endpoint | HAI titers and seroconversion at 21 days post-vaccination | HAI titers and seroconversion at 50 days post-vaccination |
| Non-Inferiority Success Criteria (CBER criteria) | Upper-bound of two-sided 95% CI for the GMTR† ≤1.5<br><br>Upper bound of the two-sided 95% CI for the difference in SCR† ≤10% | Lower bound of two-sided 97.4% CI for the GMTR‡ > 0.677<br><br>Lower bound of two-sided 97.4% CI for the difference in SCR‡ > -10% |
| Primary Immunogenicity Per-Protocol Set Results by Influenza Strain | *GMTRs*<br>A/H1N1: 1.32 (1.11, 1.56)<br>A/H3N2: 1.48 (1.34, 1.64)<br>B: 0.95 (0.85, 1.07)<br><br>*SCR*<br>A/H1N1: -1% (-4%, 2%)<br>A/H3N2: 10% (6%, 14%)<br>B: -1% (-5%, 3%) | *GMTRs*<br>A/H1N1: 0.76 (0.62, 0.93)<br>A/H3N2: 0.77 (0.68, 0.89)<br>B: 0.95 (0.85, 1.07)<br><br>*SCR*<br>A/H1N1: -1% (-4%, 2%)<br>A/H3N2: 10% (6%, 14%)<br>B: -1% (-5%, 3%) |

*mo: months; HAI: hemagglutinin inhibition; CI: confidence interval; GMTR: geometric mean titer ratio; SCR: seroconversion rate, defined as post-vaccination titers > 40 for subjects with pre-vaccination titers ≤ 10 or at least a 4-fold increase in titers compared to baseline for subjects with pre-vaccination titers > 10; GMT: geometric mean titer

†$GMTR = GMT_{Control}/GMT_{Agriflu}$; difference in $SCR = SCR_{Control} - SCR_{Agriflu}$

‡ $GMTR = GMT_{Agriflu}/GMT_{Fluad}$; difference in $SCR = SCR_{Agriflu} - SCR_{Fluad}$

*Source: The reviewer created this table based on the V71_18 Synopsis and the V70_29 Synopsis.*

## 6.2 Older Adult Trial

Study V71_22 was a multicenter, phase IV, randomized, active-controlled, observer-blind study of the immunogenicity and safety of Agriflu compared to Fluvirin in healthy adults aged 50 years and older. Approximately 2,668 adults were randomized 1:1 to Agriflu or Fluvirin using a stratified randomization by age group (≥50–64 years old, ≥65 years old) and center. The primary immunogenicity endpoint was hemagglutinin inhibition titers at 21 days after vaccination, with non-inferiority defined as:

- 95% confidence interval upper bound for $GMT_{Fluvirin}/GMT_{Agriflu} \leq 1.5$

- 95% confidence interval upper bound for the ($SCR_{Fluvirin}$ - $SCR_{Agriflu}$) ×100% ≤ 10%

where GMT is the geometric mean titer and SCR is the seroconversion rate, defined as post-vaccination titers > 40 for subjects with pre-vaccination titers ≤ 10 or a 4-fold increase in post-vaccination titers for subjects with pre-vaccination titers > 10, in the respective study group.

The primary immunogenicity results in the per-protocol population are shown in Table 2. Agriflu did not meet the primary non-inferiority success criteria for 2 of 3 influenza strains for both endpoints. The statistical review of V71_22 noted that there were no critical statistical issues with the study.

**Table 2.** Study V71_22 Primary Immunogenicity Results in the Per-Protocol Population

| Strain | Geometric Mean Titer Ratios | Differences in Seroconversion Rates |
|---|---|---|
| A/H1N1 | 1.85 (1.66, 2.06) | 9% (5.6%, 11.5%) |
| A/H3N2 | 1.5 (1.38, 1.64) | 13% (10.1%, 16.1%) |
| B | 1 (0.93, 1.08) | -1% (-5%, -2.3%) |

*Source: The reviewer created this table based on the V71_22 Synopsis.*

## 10. CONCLUSIONS

The pediatric studies (V71_18 and V70_29) provide results that are likely uncertain because of trial conduct issues and that did not meet their primary immunogenicity objective to establish non-inferiority of the Agriflu immune response. Overall, the pediatric studies are inconclusive as to whether Agriflu has a non-inferior immune response in children aged 6 months to 17 years old. The adult study (V71_22) does not provide adequate evidence to support the conclusion that Agriflu has non-inferior immunogenicity compared to Fluad in adults aged 50 years and older. Therefore, I defer to the clinical reviewer to determine the significance of the evidence these studies provide.