DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA

BLA Number:	125297
Product Name:	Influenza Virus Trivalent Subunit (A/A/B hemagglutinin and neuraminidase; embryonated hen's eggs) Vaccine, Inactivated (Agrippal®)
Applicant:	Novartis Vaccines and Diagnostics, Inc.
Date Submitted:	July 10, 2008
Review Priority:	Standard
Statistical Branch:	Vaccine Evaluation Branch
Statistical Reviewer:	Tsai-Lien Lin
Through:	Sang Ahnn Acting Team Leader, VBT A. Dale Horne Branch Chief, VEB
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1. EXECUTIVE SUMMARY

To support the license application of Agrippal®, Novartis submitted two pivotal studies (both phase 3) conducted under US IND and 3 supportive studies (two phase 3 studies and one phase 2 study) conducted to satisfy European requirements but reanalyzed according to US age stratum definition. The immunogenicity objectives for these clinical studies are based on the CBER threshold criteria for the two co-primary endpoints, seroprotection rate and seroconversion rate. The comparator Fluvirin in the two pivotal studies was included for safety comparison only, not for immunogenicity comparison.

Based on the results from this submission, the success criteria for immunogenicity objectives are met. Though the immune responses for IVV meet the success criteria for approval, it is noted that IVV may not be as immunogenic as Fluvirin for A strains.

2. BACKGROUND

Novartis' inactivated influenza virus trivalent vaccine (IVV) was initially licensed in Italy in 1986 and has been licensed in over 50 countries worldwide. US development of this vaccine was conducted under BB-IND -b(4)--. In this BLA, Novartis is seeking an indication for active immunization of persons ≥18 years of age against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

Only trials conducted after the removal of thimerosal as a preservative are considered suitable to support immunogenicity claims in this application. Immunogenicity results from 5 studies are presented. Two of these studies, both phase 3 (V71P5 and V71P6), are conducted under US IND and are regarded "pivotal". The US-licensed vaccine, Fluvirin, was used in both studies primarily to provide a comparative assessment of safety and a general assurance of immune response to IVV.

Three additional studies (one phase 2, V58P2, and two phase 3, V58P4 and V58P9) were designed according to European requirements for influenza vaccines and are considered as "supportive". The two supportive phase 3 studies were reanalyzed according to the age strata recommended by CBER. In all three supportive studies, IVV was used as the comparator vaccine for the study vaccine, cell culture-derived influenze (CCI) vaccine. A placebo-controlled efficacy study, V58P13 (conducted under US IND -b(4)--) will become available after this BLA submission.

3. STATISTICAL EVALUATION

Table 1 gives an overview of the study populations in 2 pivotal studies and 3 supportive studies. The % of subjects excluded from the primary immunogenicity analysis

population, PP population, appears to be comparable between the IVV and comparator vaccines in all studies.

Table 1 Overview of the Study Populations

Age		Pivotal Studies				Supportive Studies					
		V71P5 phase 3 2 centers Argentina		**V71P6** phase 3 single center Dominican Rep		**V58P2** phase 2 single center New Zealand		**V58P4** phase 3 5 centers Poland		**V58P9** phase 3 2 centers Lithuania	
		IVV	**Fluvirin**	**IVV**	**Fluvirin**	**IVV**	**CCI**	**IVV**	**CCI**	**IVV**	**CCI**
Adults 18-64 years	**Total Enrolled**	460	232	1290	217	65	72	841	821	171	1029
	MITT population	460 (100%)	232 (100%)	1277 (100%)	216 (100%)	65 (100%)	72 (100%)	837 (100%)	820 (100%)	171 (100%)	1024 (100%)
	PP population	424 (92%)	219 (94%)	1182 (92%)	194 (89%)	65 (100%)	72 (100%)	837 (100%)	818 (100%)	168 (98%)	1017 (99%)
Adults ≥65 years	**Total Enrolled**					48	38	483	509		
	MITT population					48 (100%)	38 (100%)	481 (100%)	507 (100%)		
	PP population					48 (100%)	38 (100%)	481 (100%)	504 (99%)		

The demographic and baseline characteristics (including age, gender, race, weight, height, % prior influenza vaccination, etc) are also mostly balanced between the IVV and comparator groups.

IMMUNOGENICITY RESULTS:

Table 2 summarizes the immunogenicity results of the pivotal and supportive clinical studies.

For all strains and for both endpoints of seroprotection rate (SPR) and seroconversion rate (SCR), IVV met the CBER criteria (i.e., SPR≥70% and SCR≥40% for adults aged 18-64, and SPR≥60% and SCR≥30% for elderly aged ≥65) in all studies, except study V58P2 which is a small phase 2 study. The poor SCR results observed in study V58P2 are probably due to the high rates of previous influenza vaccination (74% and 98% in the IVV group for two age strata) and the high baseline antibody titers against the A strains. This study also failed to meet the SPR criterion for B strain in both age groups. The applicant explained that it may be due to the low sensitivity of the HI assay against the B strain, since the comparator also failed to meet the criterion.

Table 2 Immunogenicity Results: PP Population

Age	Strain	Day 22	Pivotal Studies				Supportive Studies					
			V71P5 phase 3 2 centers Argentina		V71P6 phase 3 single center Dominican Rep		V58P2 phase 2 single center New Zealand		V58P4 phase 3 5 centers Poland		V58P9 phase 3 2 centers Lithuania	
			IVV	Fluvirin	IVV	Fluvirin	IVV	CCI	IVV	CCI	IVV	CCI
Adults 18-64 years	A/H1N1	%SPR (95%CI)	**93%** (90-95)	**99%** (97-100)	**98%** (97-99)	**98%** (95-99)	**82%** (70-90)	79% (68-88)	**90%** (88-92)	**90%** (87-92)	**95%** (91-98)	**94%** (92-95)
		%SCR (95%CI)	**74%** (69-78)	**86%** (81-90)	**94%** (93-95)	**96%** (92-98)	35% (24-48)	22% (13-34)	**65%** (61-68)	**66%** (63-70)	**77%** (70-83)	**81%** (79-84)
	A/H3N2	%SPR (95%CI)	**96%** (94-98)	**100%** (98-100)	**99%** (98-100)	**99%** (97-100)	**97%** (89-100)	**94%** (86-98)	**99%** (98-99)	**99%** (98-99)	**96%** (92-99)	**93%** (91-95)
		%SCR (95%CI)	**72%** (68-76)	**89%** (84-92)	**67%** (65-70)	**84%** (78-88)	29% (19-42)	36% (25-48)	**65%** (61-68)	**64%** (61-68)	**88%** (82-93)	**83%** (80-85)
	B	%SPR (95%CI)	**91%** (87-93)	**86%** (81-91)	**87%** (85-89)	**90%** (85-94)	38% (27-51)	47% (35-59)	**90%** (87-92)	**90%** (88-92)	**88%** (82-92)	**91%** (89-93)
		%SCR (95%CI)	**77%** (72-81)	**74%** (68-80)	**84%** (82-86)	**86%** (80-90)	28% (17-40)	39% (28-51)	**79%** (76-82)	**83%** (81-86)	**70%** (63-77)	**78%** (76-81)
Adults ≥65 years	A/H1N1	%SPR (95%CI)					71% (56-83)	**79%** (63-90)	**85%** (82-88)	**86%** (83-89)		
		%SCR (95%CI)					10% (3-23)	8% (2-21)	**55%** (51-60)	**55%** (50-59)		
	A/H3N2	%SPR (95%CI)					**92%** (80-98)	**95%** (82-99)	**98%** (96-99)	**97%** (95-98)		
		%SCR (95%CI)					10% (3-23)	32% (18-49)	**64%** (60-69)	**68%** (64-72)		
	B	%SPR (95%CI)					38% (24-53)	39% (24-57)	**90%** (87-93)	**90%** (87-93)		
		%SCR (95%CI)					31% (19-46)	34% (20-51)	**74%** (69-77)	**80%** (76-84)		

In the two pivotal studies, though the immune responses of IVV met the CBER threshold criteria, the SCRs are higher in Fluvirin group than in the IVV group against one or both of the A strains, whereas similar results are observed for the two vaccines for the B strain. Novartis thinks that the lower SCRs observed in IVV group does not have clinical relevance since the SCRs for IVV group are consistently above the CBER threshold in all

phase 3 pivotal and supportive studies. Novartis explained that the different technical release specifications and factors influencing the -b(4)- method (eg, different reagents or different assay calculation methods) for IVV and Fluvirin may result in some differences in the antigen content, and therefore produce differences in immunogenicity between the two vaccines.

Lot Consistency was demonstrated in Study V71P6. The 95% CIs for all pairwise GMT ratios among the three lots range from 0.76 to 1.33, and are within the acceptable range of 0.67 to 1.5.

Immunogenicity Results in Subpopulations: Stratified analyses for all five studies and a meta-analysis of immunogenicity for the two pivotal studies demonstrated that previous influenza vaccination and high baseline titers were associated with lower SCRs and postvaccination antibody titers for all 3 viral strains. Age was inversely correlated with immune responses to the vaccines. No differences were found between different genders and between different ethnic groups.

REVIEWER'S COMMENTS:

1. As planned in the protocols, the primary efficacy analyses were descriptive in nature. The lower bounds of the 95%CIs for SPR and SCR were used to determine whether the CBER threshold criteria were met. No immunogenicity comparisons between IVV and the comparator vaccine were performed.
2. The reviewer was able to verify the numerical accuracy of the applicant's immunogenicity results for the two pivotal studies.
3. Although Fluvirin was included in the two pivotal studies not for immunogenicity comparison, it is apparent that IVV is **not non-inferior** to Fluvirin with respect to SCR for both A strains in study V71P5 and for strain A/H3N2 in study V71P6. The differences in SCR between the two vaccines are 17% for strain A/H3N2 with the upper bound of the 95% CI as high as 23% for study V71P5 and 22% for study V71P6. While IVV demonstrated immune responses well above the CBER threshold criteria, the differences in SCR between IVV and Fluvirin are quite large. The differences in SCR between the two vaccines for strain A/H1N1, however, is not consistent across the two pivotal studies (12% for study V71P5 and 2% for study V71P6).

   It is this reviewer's opinion that differences in assay calculation method (provided that the assay methods are valid) may explain IVV's lower immunogenicity to some extent, but cannot fully explain for the magnitude of the differences observed and the inconsistency across studies. Whether this has any clinical or product quality relevance will be up to the clinical and product reviewers' judgment.

SAFETY RESULTS: Please see clinical reviewer's evaluation.

4. CONCLUSIONS

Based on the results from two pivotal phase 3 studies and two supportive phase 3 studies, the threshold criteria for immunogenicity as recommended in the CBER guidance were met. IVV, however, may not be as immunogenic as Fluvirin for strains A.