STATISTICAL REVIEW AND EVALUATION

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FDA #: STN 125127

SPONSOR: GlaxoSmithKline Biologicals

NAME of PRODUCT: Fluarix, Influenza Vaccine (split virion, inactivated)

DOCUMENT SUBMITTED: Original BLA application for Fluarix, Influenza Vaccine (split virion, inactivated) dated May 25, 2005.

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BACKGROUND

The sponsor's purpose of this application is "to pursue development of the Fluarix vaccine for US licensure under the Accelerated Approval Regulations." The clinical program to support licensure of Fluarix™ consists of one US, randomized, placebo-controlled study (N=~1,000), and three German studies (two non-randomized). Immunogenicity (seroconversion rate, and percentage of subjects with serum HI titer ≥1:40) and safety data from the above four trials were provided in this BLA submission. Formal clinical efficacy data were *not* provided.

US – 001

This was a multi-center (4 sites), double-blind, randomized study to compare the safety and immunogenicity of Fluarix vs. placebo. A total of 956 subjects, 18 to 64 years of age, were randomized (4:1 ratio) to either Fluarix or placebo.

Immunogenicity

Seroconversion rate and percentage of subjects with a serum HI titer ≥1:40 were the two co-primary immunogenicity endpoints. Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold increase in post-vaccination titer.

Tables 1 and 2 show the primary immunogenicity results (based on per-protocol analyses). All the numbers in the tables were confirmed by the reviewer, using the sponsor-provided dataset SERO_COD.XPT.

Table 1. Seroconversion rate at post-vaccination Day 21

Antibody	Group	N	Seroconversion Rate	95% CI
H1N1	Fluarix	745	59.6%	(**56.0**%, 63.1%)
	Placebo	190	0.0%	(0.0%, 1.9%)
H3N2	Fluarix	745	61.9%	(**58.3**%, 65.4%)
	Placebo	190	1.1%	(0.1%, 3.8%)
B	Fluarix	745	77.6%	(**74.4**%, 80.5%)
	Placebo	190	1.1%	(0.1%, 3.8%)

Table 2. Percentage of subjects with serum HI titer ≥1:40 at post-vaccination Day 21

Antibody	Group	N	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	Fluarix	745	96.6%	(**95.1**%, 97.8%)
	Placebo	190	51.1%	(43.7%, 58.4%)
H3N2	Fluarix	745	99.1%	(**98.1**%, 99.6%)
	Placebo	190	65.3%	(58.0%, 72.0%)
B	Fluarix	745	98.8%	(**97.7**%, 99.4%)
	Placebo	190	51.1%	(43.7%, 58.4%)

Safety

There was one death reported in the Fluarix group. The death was attributed to atherosclerotic cardiovascular disease, occurring 17 days after vaccination. There was no other serious adverse event.

FLU – 051

This was a multi-center (8 sites), open-label, non-controlled study to determine the reactogenicity and immunogenicity of Influsplit SSW/Fluarix. A total of 114 *volunteers*, 18 years of age or older, were enrolled in this study.

Immunogenicity

Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold increase in post-vaccination titer.

Tables 3, 4, 5, and 6 show the primary immunogenicity results (based on all evaluable subjects). The numbers in these tables were generated by the reviewer, using the sponsor-provided dataset IMMUNO.XPT.

Table 3: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects 18-60 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	58	82.8%	(70.6%, 91.4%)	98.3%	(90.8%, 100%)
H3N2	58	67.2%	(53.7%, 79.0%)	98.3%	(90.8%, 100%)
B	58	84.5%	(72.6%, 92.7%)	98.3%	(90.8%, 100%)

Table 4: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects >60 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	54	57.4%	(43.2%, 70.8%)	94.4%	(84.6%, 98.8%)
H3N2	54	55.6%	(41.4%, 69.1%)	94.4%	(84.6%, 98.8%)
B	54	59.3%	(45.0%, 72.4%)	94.4%	(84.6%, 98.8%)

Table 5: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects <65 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	74	78.4%	(67.3%, 87.1%)	96.0%	(88.6%, 99.2%)
H3N2	74	67.6%	(55.7%, 78.0%)	97.3%	(90.6%, 99.7%)
B	74	78.4%	(67.3%, 87.1%)	96.0%	(88.6%, 99.2%)

Table 6: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects ≥65 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	38	55.3%	(**38.3**%, 71.4%)	97.4%	(**86.2**%, 99.9%)
H3N2	38	50.0%	(**33.4**%, 66.6%)	94.7%	(**82.3**%, 99.4%)
B	38	60.5%	(**43.4**%, 76.0%)	97.4%	(**86.2**%, 99.9%)

Safety

One serious adverse event was reported (acute abscess of tonsillar tract).

Reviewer's comments

1. The reviewer obtained a different seroconversion rate for H3N2 for the 18-60 year-olds. The sponsor's rate was 69%, and the reviewer obtained 67.2%.
2. The reviewer obtained a different seroconversion rate for H1N1 for the >60 year-olds. The sponsor's rate was 59%, and the reviewer obtained 57.4%.

FLU – 052

This was a multi-center (29 sites), open-label, randomized, phase IV study to evaluate the reactogenicity and immunogenicity of Influsplit SSW/Fluarix, FLUAD, and INFLEXAL V. A total of 827 subjects, over 60 years of age, were randomized and vaccinated.

Immunogenicity

Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold increase in post-vaccination titer.

Tables 7, 8, and 9 show the primary immunogenicity results (based on per-protocol analyses). The numbers in the tables were generated by the reviewer, using the sponsor-provided dataset IMMUNO.XPT.

Table 7. Seroconversion rate

Antibody	Group	N	Seroconversion Rate	95% CI
H1N1	**Influsplit/Fluarix**	273	78.4%	(**73.0**%, 83.1%)
	Fluad	275	70.2%	
	Inflexal V	272	68.0%	
H3N2	**Influsplit/Fluarix**	273	67.0%	(**61.1**%, 72.6%)
	Fluad	275	70.2%	
	Inflexal V	272	63.2%	
B	**Influsplit/Fluarix**	273	77.3%	(**71.9**%, 82.1%)
	Fluad	275	80.7%	
	Inflexal V	272	72.8%	

Table 8. Percentage of subjects with serum HI titer ≥1:40

Antibody	Group	N	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	**Influsplit/Fluarix**	273	93.8%	(**90.2**%, 96.3%)
	Fluad	275	89.5%	
	Inflexal V	272	87.1%	
H3N2	**Influsplit/Fluarix**	273	90.1%	(**85.9**%, 93.4%)
	Fluad	275	88.4%	
	Inflexal V	272	83.1%	
B	**Influsplit/Fluarix**	273	91.2%	(**87.2**%, 94.3%)
	Fluad	275	94.9%	
	Inflexal V	272	89.7%	

Table 9: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 for subjects ≥65 years of age in Influsplit/Fluarix group (N=162 out of 273)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	162	75.3%	(**67.9**%, 81.7%)	92.6%	(**87.4**%, 96.1%)
H3N2	162	66.1%	(**58.2**%, 73.3%)	92.0%	(**86.7**%, 95.7%)
B	162	74.7%	(**67.3**%, 81.2%)	93.2%	(**88.2**%, 96.6%)

Safety

There was one serious adverse event in the Influsplit/Fluarix group (angina pectoris/ tachyarrhythmia). Also there were 3 serious adverse events in Influsplit/Fluarix group after the active phase (acute pancreatitis, cardiac failure, and rectal cancer). Two (acute pancreatitis and cardiac failure) of the three ended in death.

Reviewer's comments

1. The reviewer obtained a different seroconversion rate for B in the Influsplit/Fluarix group. The sponsor's rate was 77.7%, and the reviewer obtained 77.3%.
2. The reviewer obtained a different seroconversion rate for H1N1 in the Fluad group. The sponsor's rate was 70.5%, and the reviewer obtained 70.2%.
3. The reviewer obtained a different seroconversion rate for B in the Inflexal group. The sponsor's rate was 73.2%, and the reviewer obtained 72.8%.

FLU – 058

This was a multi-center (4 sites), open-label, non-controlled study to determine the reactogenicity and immunogenicity of Influsplit SSW/Fluarix. A total of 120 volunteers, 18 years of age or older, were enrolled in this study.

Immunogenicity

Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥1:10 and a minimum four-fold increase in post-vaccination titer.

Tables 10, 11, 12, and 13 show the primary immunogenicity results (based on all evaluable subjects). The numbers in the tables were generated by the reviewer, using the sponsor-provided dataset IMMUNO.XPT.

Table 10: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects 18-60 years of age)

Antibody	**N**	**Seroconversion Rate**	**95% CI**	**% of subjects w/ HI titer ≥1:40**	**95% CI**
H1N1	64	64.1%	(**51.1**%, 75.7%)	95.3%	(**86.9**%, 99.0%)
H3N2	64	71.9%	(**59.2**%, 82.4%)	100%	(**94.4**%, 100%)
B	64	78.1%	(**66.0**%, 87.5%)	96.9%	(**89.2**%, 99.6%)

Table 11: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects >60 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	56	55.4%	(41.5%, 68.7%)	87.5%	(75.9%, 94.8%)
H3N2	56	78.6%	(65.6%, 88.4%)	94.6%	(85.1%, 98.9%)
B	56	76.8%	(63.6%, 87.0%)	94.6%	(85.1%, 98.9%)

Table 12: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects <65 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	74	63.5%	(51.5%, 74.4%)	94.6%	(86.7%, 98.5%)
H3N2	74	70.3%	(58.5%, 80.3%)	100%	(95.1%, 100%)
B	74	77.0%	(65.8%, 86.0%)	96.0%	(88.6%, 99.2%)

Table 13: Seroconversion rate and percentage of subjects with serum HI titer ≥1:40 (subjects ≥65 years of age)

Antibody	N	Seroconversion Rate	95% CI	% of subjects w/ HI titer ≥1:40	95% CI
H1N1	46	54.4%	(39.0%, 69.1%)	87.0%	(73.7%, 95.1%)
H3N2	46	82.6%	(68.6%, 92.2%)	93.5%	(82.1%, 98.6%)
B	46	78.3%	(63.6%, 89.1%)	95.7%	(85.2%, 99.5%)

Safety

No serious adverse event was reported.

Reviewer's comments

1. The reviewer obtained a different seroconversion rate for H3N2 for the 18-60 year-olds. The sponsor's rate was 73.4%, and the reviewer obtained 71.9%.

Reviewer's overall comments

1. For 18-60 year-olds, the success criteria were (a) the lower limit of the 2-sided 95% CI for seroconversion rate to each of the 3 vaccine strains must be ≥40%, and (b) the lower limit of the 2-sided 95% CI for percentage of subjects with serum HI titer ≥1:40 to each of the 3 vaccine strains must be ≥70%. For >60 year-olds, the success criteria were (a) the lower limit of the 2-sided 95% CI for

seroconversion rate to each of the 3 vaccine strains must be ≥30%, and (b) the lower limit of the 2-sided 95% CI for percentage of subjects with serum HI titer ≥1:40 to each of the 3 vaccine strains must be ≥60%. The sponsor-provided 4 studies met the above success criteria.

2. Among ~1,250 who received Fluarix, there were 3 serious adverse events reported (one death due to atherosclerotic disease, one acute abscess of tonsillar tract, and one angina pectoris/tachyarrthmia). The sponsor concluded that all 3 serious adverse events were not related to the vaccine.