IMMUNOGENICITY, LOT-TO-LOT CONSISTENCY, AND SAFETY OF AN MF59-ADJUVANTED CELL CULTURE-DERIVED H5N1 (aH5N1c) INFLUENZA VACCINE IN HEALTHY ADULTS

JAMES PETERSON[1], ESTHER VAN TWUIJVER[2], EVE VERSAGE[3], MATTHEW HOHENBOKEN[3]

[1]J Lewis Research, Salt Lake City, UT, USA; [2]Seqirus, Clinical Development, Amsterdam, NL; [3]Seqirus, Clinical Development, Cambridge, MA, USA

INTRODUCTION

Vaccines are the main prophylactic measure against pandemic influenza and have an import role in pandemic preparedness plans worldwide. The ability to rapidly develop and produce a specific monovalent vaccine targeted to a new circulating pandemic strain is paramount. The pathogenicity and direct transmission of avian viruses to humans suggest that H5N1 has important pandemic potential with a high case fatality.

Influenza vaccine manufacturing has relied on embryonated chicken eggs to produce antigen for over 50 years. During a highly pathogenic avian influenza outbreak/pandemic both egg quantity and quality may be compromised. Rapid production of a vaccine specific against an emerging pandemic influenza strain is critical to controlling its spread.

Allocated US Department of Health and Human Services funds have assisted Seqirus' development of an MF59-adjuvanted cell culture-derived monovalent pandemic influenza vaccine.[1] The MF59-adjuvanted cell culture-derived H5N1 (aH5N1c) vaccine is not subject to the potential limitations of egg-based production (e.g. requires large quantities of fertilized eggs; potential for egg-adaption of seed virus and antigenic mismatch), and helps address the medical need for a safe and effective pandemic vaccine.[2,3]

STUDY AIM

To evaluate immunogenicity and lot-to-lot consistency of 3 consecutively produced lots of aH5N1c pandemic vaccine by H5N1 hemagglutination inhibition (HI) antibody responses in healthy subjects ≥18 years of age, and to assess safety.

METHODS

- 3196 subjects were randomized to 4 groups of equal size to receive one of 3 consecutively produced aH5N1c vaccine lots or saline placebo, as 2 observer-blinded doses (**Table 1**).
- 2 doses of vaccine (7.5 µg HA of H5N1 + 0.25 mL MF59 adjuvant, each dose) were administered 3 weeks apart, on Day 1 and Day 22. The co-primary immunogenicity analysis was based on HI antibody titers collected 3 weeks after the second vaccine administration, on Day 43.
- Geometric mean titers (GMTs) and geometric mean ratio (GMR) were analysed.
- Subjects were stratified into 2 age groups, 18 to <65 and ≥65 years of age.
- Solicited local and systemic safety events were monitored for 7 days after each dose. Key unsolicited safety events, such as SAEs, Medically Attended Adverse Events, New Onset of Chronic Diseases (NOCD) and Adverse Events of Special Interest (AESI) were measured through Day 387.

TABLE 1. STUDY DESIGN.

Treatment Arm	Schedule of Vaccine Administration	Exposed by Age Group	
		Age 18 to <65 years	Age ≥65 years
Group A: aH5N1c Lot #1	Day 1, Day 22	403	402
Group B: aH5N1c Lot #2	Day 1, Day 22	398	399
Group C: aH5N1c Lot #3	Day 1, Day 22	397	396
Group D: Placebo	Day 1, Day 22	398	398

RESULTS

The age-appropriate Center for Biologics Evaluation and Research (CBER) immunogenicity criteria at Day 43 were met, as the lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 exceeded the predefined limits of 70% (for subjects 18 to <65 years of age) and 60% (for subjects ≥65 years of age) for the active treatment groups (**Table 2**). Seroconversion rates were similarly met after aH5N1c at Day 43 for age-appropriate CBER criteria for both age groups (data not shown).

The baseline HI GMTs were similar among the active treatment and placebo groups, for both age groups – but appeared slightly higher in the ≥65 years of age group. The HI GMTs increased from baseline in the active treatment groups at Day 22, 3 weeks after the first vaccination. HI GMTs increased further at Day 43, 3 weeks after the second vaccination, in both age groups. The increases (as assessed by GMRs) were greater in the 18 to <65 years of age group than in the ≥65 years of age group (**Table 3**).

Lot-to-lot consistency across 3 consecutively produced lots of aH5N1c vaccine was demonstrated, as assessed by the ratio of GMTs of HI antibody responses to the H5N1 vaccine strain, 3 weeks after the second vaccine administration. The 2-sided 95% CIs of the pairwise comparisons of GMTs between all 3 lots fell between the predefined equivalence ranges of 0.667 and 1.5: Lot #1 vs. #2 - GMT ratio 1.01 (0.9, 1.13); Lot #2 vs. #3 - GMT ratio 0.96 (0.86, 1.08); and, Lot #1 vs. #3 - GMT ratio 0.97 (0.87, 1.09).

TABLE 2: PERCENTAGE OF SUBJECTS (95% CI) WITH HI ≥1:40 AT DAY 1 AND DAY 43 BY CBER AGE.

Age Group	18 to <65 Years		≥65 Years	
Treatment Group	Active Treatment Groups	Placebo	Active Treatment Groups	Placebo
Day 1	**N=1,116**	**N=372**	**N=1,133**	**N=367**
Percentage of subjects with HI Titer ≥1:40	13.0	15.0	27.8	24.5
95% CI	(10.7, 15.6)	(11.5, 19.4)	(24.9, 30.9)	(20.1, 29.6)
Day 43	**N=1,076**	**N=349**	**N=1,080**	**N=351**
Percentage of subjects with HI Titer ≥1:40	95.0	8.5	85.7	20.8
95% CI	(**93.4**, 96.2)	(5.9, 12.1)	(**83.3**, 87.9)	(16.6, 25.8)

Bold indicates CBER criterion met.

CBER criterion for subjects aged 18 to <65 years: The lower bound of the adjusted 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%.

CBER criterion for subjects aged ≥65 years: The lower bound of the adjusted 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 60%.

TABLE 3. IMMUNE RESPONSES (GMT AND GMR) AT DAY 1, DAY 22 AND DAY 43 BY CBER AGE.

Age Group	18 to <65 Years		≥65 Years	
Treatment Group	Active Treatment Groups	Placebo	Active Treatment Groups	Placebo
Day 1	**N=1,116**	**N=372**	**N=1,133**	**N=367**
GMT	13.5	13.7	20.5	20.6
95% CI	(12.8, 14.2)	(12.5, 15.0)	(19.4, 21.8)	(18.6, 22.7)
Day 22	**N=1,115**	**N=370**	**N=1,130**	**N=366**
GMT	50.6	11.6	42.4	14.5
95% CI	(47.6, 53.8)	(10.4, 12.9)	(40.0, 45.0)	(13.1, 16.0)
Day 22/Day 1	**N=1,115**	**N=370**	**N=1,130**	**N=366**
GMR	3.81	0.87	2.14	0.73
95% CI	(3.58, 4.05)	(0.79, 0.97)	(2.02, 2.27)	(0.66, 0.81)
Day 43	**N=1,076**	**N=349**	**N=1,080**	**N=351**
GMT	170.7	11.0	97.9	16.7
95% CI	(160.5, 181.6)	(9.9, 12.2)	(92.1, 104.1)	(15.0, 18.5)
Day 43/Day 1	**N=1,076**	**N=349**	**N=1,080**	**N=351**
GMR	12.70	0.82	4.90	0.83
95% CI	(11.94, 13.51)	(0.73, 0.91)	(4.61, 5.20)	(0.75, 0.92)

SAFETY RESULTS

The frequency of any solicited adverse event (AE), local and systemic, was higher in the active treatment groups than in the placebo group after each vaccination. The frequency of solicited AEs was comparable among the active treatment group lots. The proportion of subjects for whom any solicited AE was reported was lower after the second vaccination than after the first vaccination in both the active treatment and the placebo groups. The most commonly reported solicited local AE was pain (49.9% of aH5N1c treated subjects compared with 14.7% of placebo treated subjects), and was responsible for the majority of the treatment difference. The most commonly reported solicited systemic AE was fatigue. Overall, the solicited AEs in both groups were predominantly either mild or moderate in severity. The frequency of severe solicited AEs in the active treatment groups was 1.9% compared with 2.8% in the placebo group (**Figure 1**).

The proportion of subjects for whom unsolicited AEs were reported was similar for the treatment groups from Day 1 through study termination (53.1% vs. 52.3%). The same pattern was also observed for all categories of unsolicited AEs. The majority of the reported unsolicited AEs were of mild or moderate intensity (**Figure 2**).

FIGURE 1. SUBJECTS (%) WITH AT LEAST ONE SOLICITED EVENT AFTER ANY VACCINATION, AND BY VACCINATION – DAY 1 THROUGH DAY 7.

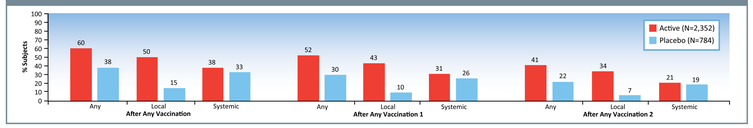
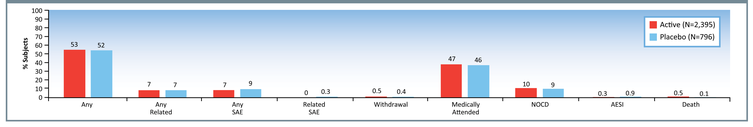


FIGURE 2. SUBJECTS (%) WITH UNSOLICITED ADVERSE EVENTS – DAY 1 THROUGH STUDY TERMINATION.



CONCLUSION

The MF59-adjuvanted, cell culture-derived H5N1 influenza vaccine aH5N1c elicited high levels of antibodies and met CBER immunogenicity criteria at Day 43 for both adult and elderly subjects. The safety profile was clinically acceptable and consistent with prior reported trials of MF59-adjuvanted influenza vaccines. Lot-to-lot manufacturing consistency was demonstrated by equivalence of HI GMTs.

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