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761. Randomized Study To Compare Immunogenicity And Safety Of Seqirus* Quadrivalent Inactivated Influenza Vaccine With A US-Registered Influenza Vaccine In Paediatric Subjects Aged 5 To 17 Years

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ABSTRACT

Background: Seqirus has commenced a staged clinical program for a quadrivalent inactivated influenza vaccine. Paediatric clinical studies have been initiated following completion of the adult study.
Methods: Children aged 5 through 17 years were randomized 3:1 to receive Seqirus QIV (n=1709) or US-licensed Fluarix® QIV (n=569) in 2015-16 in the USA. Immunogenicity was based on hemagglutination-inhibition (HI) and assessed prevaccination and 28 days postvaccination. Solicited adverse events were assessed for 7 days postvaccination and unsolicited adverse events assessed for 28 days postvaccination. Adverse events were also assessed by age cohorts 5 through 8 years (n=1151) and 9 through 17 years (n=1101). Serious adverse events were followed up for 180 days postvaccination.
Results: Geometric mean titers and seroconversion rates for all four strains demonstrate that the immunogenicity of Seqirus QIV was noninferior to Fluarix QIV. Solicited and unsolicited adverse events in both treatment arms were similar.
Fever rates in children 5 through 8 years old were 4.5% (95% CI: 3.2, 6.1) and 3.6% (95% CI: 1.8, 6.6), for Seqirus QIV and Fluarix QIV, respectively. Severe (≥39°C) fever rates in this age cohort were 1.2% vs 0.7% for Seqirus QIV and Fluarix QIV, respectively.
Conclusions: In children 5 through 17 years, the immunogenicity of the Seqirus quadrivalent inactivated influenza vaccine was demonstrated to be noninferior to Fluarix QIV. The 7-day and 28-day safety and tolerability profile of Seqirus QIV was clinically acceptable and similar to the comparator vaccine.

BACKGROUND AND OBJECTIVES

Seqirus QIV is a quadrivalent inactivated, egg-derived split-virion influenza virus vaccine with all 4 strains split using 1.5% w/v sodium taurodeoxycholate, a concentration at the upper end of the approved splitting range. Residual virus lipids and associated potential for pyrogenic vaccine responses mediated by cytokines are thereby reduced [Rockman, Becher et al. 2014].

- This was a phase 3 randomized, observer-blinded, comparator controlled study of Seqirus QIV versus Fluarix Quadrivalent;
- Conducted at 32 US sites during the 2015-2016 Northern Hemisphere influenza season in male and female subjects 5 through 17 years of age.
- Primary noninferiority objective; to demonstrate Seqirus QIV immunogenicity is not inferior to that of the comparator QIV in subjects 5 through 17 years of age.
- Secondary objectives: immunogenicity, safety and tolerability assessments overall and in two age strata: 5 through 8, and 9 through 17 years of age.

METHODS

- Eligible subjects stratified by age: 5 through 8, and 9 through 17 years of age.
- Quota ensured at least 50% of subjects were 5 through 8 years of age.
- Subjects randomized 3:1, Seqirus QIV: comparator QIV.
- Subjects scheduled to single vaccination or two vaccinations in accordance with ACIP 2015-2016 recommendations [Grohskopf et al. 2015]
- Immunogenicity assessed 28 days after last vaccination by measuring hemagglutination inhibition (HI) antibody titers to the four viral strains in the vaccines.
- Safety and tolerability assessed by monitoring solicited local reactions and systemic adverse events (AEs) over 7 days postvaccination, unsolicited AEs for 28 days following last study vaccination, and serious AEs for 180 days following last study vaccination (Figures 1 & 2).

Figure 1: Study Design, Single Dose Subjects

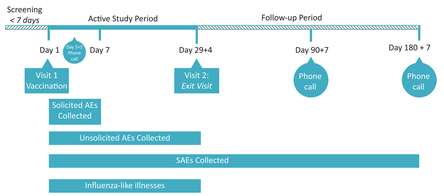


Figure 2: Study Design, Two-dose subjects

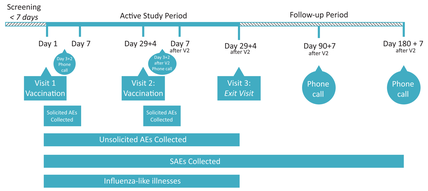
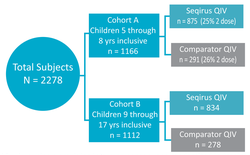


Figure 3: Age Stratification, Full Analysis Set (FAS):

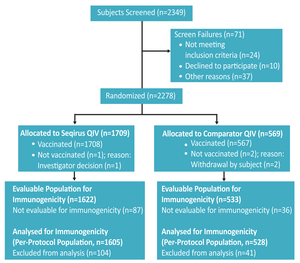


* FAS = All subjects providing informed consent and randomised to treatment

Table 1: Demographics and Baseline Characteristics (Full Analysis Set)

	Seqirus QIV	Comparator QIV
N	1709	569
5-8 yrs stratum	51.2%	51.1%
9-17 years stratum	48.8%	48.9%
Age mean, years	9.5	9.5
Sex, female	48.3%	46.9%
Hispanic or Latino	24.1%	22.8%
White	72.5%	75.6%
Black	21%	19.9%
Asian	0.9%	0.4%

Figure 4: Participant Flow



IMMUNOGENICITY RESULTS

- Seqirus QIV noninferior to Comparator QIV (as measured by postvaccination GMTs, GMT ratios and seroconversion rates) in subjects 5-17 years of age;
- Similar responses seen in both age subgroups and in both vaccine groups (as measured by seroprotection rates and geometric mean fold increases, GMFIs)
- Seqirus QIV HI postvaccination GMTs higher for A strains than for B strains;
- Seqirus QIV GMFIs were: A/H1N1 7.5, A/H3N2 10.7, B/Yam 5.8, and B/Vic 8.3;
- Seqirus QIV seroconversion rates were: A/H1N1 66.3%, A/H3N2 82.9%, B/Yam 58.4%, and B/Vic 72.1%;
- Seqirus QIV seroprotection rates were: A/H1N1 99.7%, A/H3N2 99.4%, B/Yam 75.0%, and B/Vic 90.3%.

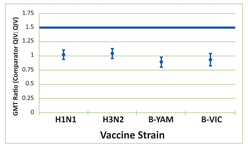
(Analyses performed on the per-protocol set (all vaccinated subjects who had valid pre- and postvaccination HI results, had not received any prohibited medication, and had no protocol deviation medically assessed as potentially impacting immunogenicity results).

Table 2 : Summary of Results for GMT Ratios and Difference in Seroconversion Rates

Strains	GMT Ratio GMT Comp QIV/ GMT Seqirus QIV N=528/1605	GMT Ratio Endpoint Met	Difference in seroconversion rates N=528/1605	SCR% Difference Endpoint Met
A/California/7/2009 (H1N1)	1.01 [0.93, 1.09]	YES	-3.1% [-8.0, 1.8]	YES
A/Switzerland/9715293/ 2013 (H3N2)	1.05 [0.96, 1.15]	YES	0.4% [-4.5, 5.3]	YES
B/Phuket/3073/2013 (B/Yam)	0.89 [0.81, 0.98]	YES	-3.4% [-8.3, 1.5]	YES
B/Brisbane/60/2008 (B/Vic)	0.92 [0.83, 1.02]	YES	-2.0% [-6.9, 2.9]	YES

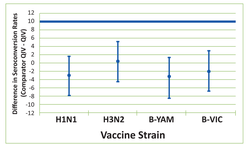
Noninferiority Criteria:
Geometric mean titer (GMT) -Upper bound of 95% CI of GMT ratios should not exceed 1.5
Seroconversion rate (SCR) -Upper bound of 95% CI of SCR rate difference should be ≤ 10%

Figure 5: Ratio of HI Geometric Mean Titers, Subjects 5 through 17 years (Noninferiority Analysis - Per-Protocol Population)



The bold line represents the margin of noninferiority.

Figure 6: Difference in Seroconversion Rates, Subjects 5 through 17 years (Noninferiority Analysis - Per-Protocol Population)



The bold line represents the margin of noninferiority.

Figure 7 : GMTs

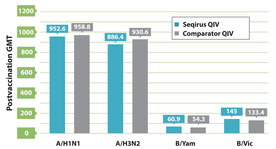
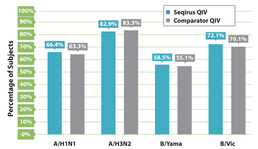


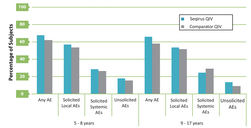
Figure 8 : Seroconversion Rates



SAFETY RESULTS

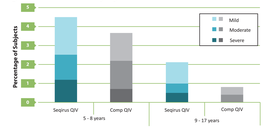
- Seqirus QIV safety profile generally similar to Comparator QIV, both generally well tolerated;
- Similar incidences of solicited local reactions and systemic adverse events;
- Only significant increase in relative risk for systemic AEs: myalgia in the 9-17 years Seqirus QIV group;
- No unsolicited AE reported by > 10% of subjects in any vaccine group or age cohort;
- Most common unsolicited AEs: cough (2.0% overall [Seqirus QIV, 2.1%, Comparator QIV, 2.0%]), pyrexia (1.4% overall), oropharyngeal pain (1.3% overall), and vomiting (1.0% overall);
- No deaths, AEs of special interest, or AEs leading to withdrawal;
- 10 subjects reported 13 SAEs (11 reported by 8 subjects in the Seqirus QIV group (0.5%) and 2 reported by 2 subjects in the Comparator QIV group (0.4%);
- No SAE related to vaccination by the Investigator.

Figure 9: Summary of Adverse Events



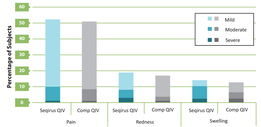
Minor differences exist between Seqirus QIV and comparator QIV; all confidence intervals overlap

Figure 10: Summary of Fever Events



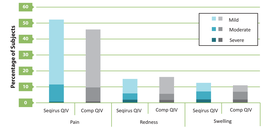
•Seqirus QIV fever rate similar to comparator QIV in both age groups
— 5 - 8 years: 4.5% (95% CI: 3.2, 6.1) vs 3.6% (95% CI: 1.8, 6.6)
— 9 - 17 years: 2.1% (95% CI:1.3, 3.4) vs 0.8% (95% CI: 0.1, 2.7)

Figure 11: Solicited Local Adverse Reactions (5 - 8 years age group)



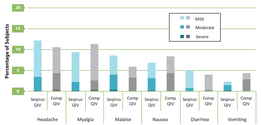
Solicited local adverse reactions similar between treatment groups

Figure 12: Solicited Local Adverse Reactions (9 - 17 years age group)



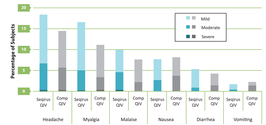
Solicited local adverse reactions similar between treatment groups

Figure 13: Solicited Systemic Adverse Events (5 - 8 years age group)



Solicited systemic adverse events similar between treatment groups; most events mild or moderate in intensity

Figure 14: Solicited Systemic Adverse Events (9 - 17 years age group)



Solicited systemic adverse events similar between treatment groups; most events mild or moderate in intensity

CONCLUSIONS

- The immunogenicity of Seqirus QIV, as measured by postvaccination HI GMTs, GMT ratios and SCRs, fulfilled the criteria for noninferiority in comparison to that elicited by a US-licensed Comparator QIV, in subjects 5 through 17 years of age.
- Similar patterns of robust immune responses (descriptively characterized by seroprotection rates [the percentage of subjects with a HI Titer ≥ 40], SCRs and GMFIs by study vaccine and by age stratum) were seen overall in subjects 5 through 17 years, and also within each of the two age strata of 5 through 8 years and 9 through 17 years, for both study vaccines.
- Seqirus QIV was shown to be clinically acceptable in terms of the safety and tolerability profile, which was similar to that seen for the US-licensed Comparator QIV

References:
Rockman S, Becher D, Dyson A, Koernig S, Morelli AB, Barnden M, Camuglia S, Soupourmas P, Pearse M, Maraskovsky E. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Vaccine. 2014 Jun 24;32(30):3869-76.
Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015–16 Influenza Season. MMWR 2015 (August 7);64 (No 30):818-825.

Other Information
This study is registered at clinicaltrials.gov: Identifier NCT02545543 with the Official Title:
A Phase 3, Randomized, Multicenter, Observer-Blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a bioCSL Quadrivalent Inactivated Influenza Virus Vaccine (bioCSL QIV) with a US-Licensed 2015-2016 Quadrivalent Inactivated Comparator Influenza Vaccine (Comparator QIV) in a Pediatric Population 5 Through 17 Years of Age.
*Note: The sponsor, Seqirus, was previously known as bioCSL. It should therefore be noted that Seqirus QIV was previously referred to as bioCSL QIV.

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