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A Postmarketing Safety Study of Q/LAIV in Subjects 2 Through 49 Years of Age

Observational Study NIS

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NIS REPORT SYNOPSIS

A Postmarketing Safety Study of Q/LAIV in Subjects 2 Through 49 Years of Age

Name of Sponsor/Company: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca

Study Period: 03Sep2013-23Jan2014

Phase of Development: Not applicable

Rationale and Background: Influenza is a highly contagious, acute febrile illness of global importance and is the most common vaccine preventable disease in the developed world. In humans, influenza illness is caused by 2 types of viruses: influenza A, with multiple subtypes categorized by hemagglutinin and neuraminidase surface antigens, and influenza B, which circulates as 2 major antigenic lineages. Subtypes A/H3N2 and A/H1N1 are the 2 influenza A subtypes that have circulated and caused human disease since 1977 (Kilbourne, 2006). Influenza epidemics of variable severity occur annually worldwide in all age groups, typically during the winter months in temperate climates. These annual epidemics are thought to result in 3 million to 5 million cases of severe illness and approximately 250,000 to 500,000 deaths every year around the world (WHO, 2005).

Vaccination is the primary method for preventing illness and severe complications related to influenza. Prevention of the spread of influenza by vaccination of children is an important part of influenza control. In 2008, the Advisory Committee on Immunization Practices (ACIP) included all children up to the age of 18 years in its recommendation for annual vaccination (CDC, 2008). Beginning with the 2010-2011 influenza season, ACIP revised the recommendations of annual influenza vaccination to include all eligible individuals 6 months of age or older (CDC, 2010).

FluMist® Quadrivalent, an intranasal, quadrivalent live attenuated influenza vaccine (Q/LAIV), was approved by the United States Food and Drug Administration (US FDA) on 29Feb2012 in individuals 2 to 49 years of age for the prevention of influenza caused by the 2 type A (A/H1N1 and A/H3N2) and 2 type B influenza viruses contained in the vaccine. The approval was predicated on conducting an observational postmarketing safety surveillance study in children 2 years through 8 years of age. The current study implemented this postmarketing commitment between MedImmune and the US FDA. In addition, MedImmune expanded the study to document the safety profile of Q/LAIV in vaccine recipients between 9 years and 49 years of age. The study was conducted in a single season with vaccination of

62,040 individuals with Q/LAIV, including approximately 10,000 to 30,000 individuals in each of the following 4 age groups: 2 to 4, 5 to 8, 9 to 17, and 18 to 49 years.

Objective: The primary objective of this study was to assess the safety of a quadrivalent live attenuated influenza vaccine (Q/LAIV; FluMist® Quadrivalent) within 180 days after vaccination in children and adults 2 through 49 years of age.

Study Design: In this postmarketing, nonrandomized, observational, cohort study, children and adults 2 to 49 years of age were immunized with Q/LAIV as part of routine clinical practice in a large, multi-site health care organization. Using existing data on health care utilization, rates of medically attended events (MAEs) of interest were evaluated in eligible Q/LAIV recipients vaccinated in the health care organization during the 2013-2014 influenza season. Total enrollment was required to include a minimum of 10,000 children 2 through 8 years of age.

As in previous postmarketing safety studies conducted with FluMist (Baxter et al, 2012a, 2012b) (Toback et al, 2013), this study was conducted using data collected by the healthcare organization vaccine study center.

Incidence rates of MAEs and hospitalizations during periods at risk after Q/LAIV vaccination were compared with incidence rates during reference periods later in the follow-up (within-cohort analysis) and with rates in 2 nonrandomized control groups: matched concurrent trivalent inactivated influenza vaccine (TIV) recipient controls and matched unvaccinated controls, both identified from the healthcare organization database.

Subject Population: Individuals vaccinated with Q/LAIV and controls were identified for inclusion in this study via the healthcare organization tracking system database. Immunizations of healthcare organization members were recorded in this database as part of routine care. Because each recipient had a unique medical record number assigned once enrolled in the healthcare organization database and because administration records of all vaccinees were entered into the database, the study population could be assembled from the tracking system on an ongoing basis.

Subjects were required to meet all of the following inclusion criteria:

- Age 2 through 49 years (prior to 50th birthday) at the time of vaccination (alternatively, index date for unvaccinated controls)
- Membership in the healthcare organization plan for at least 12 months prior to vaccination/index date (alternatively, index date for unvaccinated controls)

- Continuous enrollment in the healthcare organization plan through 180 days following vaccination/index date.

There were no exclusion criteria.

TIV recipients and unvaccinated controls were matched by subject age (year) and medical center, using frequency matching. Controls were selected on age and sex such that the frequency of these variables in the control populations approximated those in the Q/LAIV population. Children 2 to 4 years old were frequency matched to be within one calendar quarter of the Q/LAIV population birth dates whereas those in the older groups were selected to be within a year.

Study Variables and Statistical Analyses: Table 1 summarizes the planned analyses, including the safety events of interest, the periods at risk for events post vaccination, and reference periods.

Table 1 Summary of Planned Analyses

Event of Interest	Period at Risk Post Vaccination	Reference Period
Hypersensitivity MAEs Seizure/convulsions MAEs	0-3 days	7-9 days
Lower respiratory MAEs Wheezing MAEs Guillain-Barre syndrome MAEs Bell's palsy MAEs Encephalitis MAEs Neuritis MAEs Vasculitis MAEs Any hospitalization Respiratory hospitalization	1-42 days (1-14 days [a])	43-84 days (15-29 days [a])
Narcolepsy/cataplexy MAEs	1-180 days	NA

MAE = medically attended event; NA = not applicable

[a] Secondary analysis

Incidence rates were reported as the number of subjects with an event per 1,000 person-months. If a subject had more than one event in the analysis window, the subject was counted only once. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were estimated for each event for safety comparisons with the control groups, as follows:

- Crude RR and exact 95% CI were calculated without adjustment of any covariate.
- Adjusted RR and corresponding 95% CI were obtained using the Cox proportional hazards model adjusted for calendar time, sex, and health care utilization level. Utilization level was calculated based on the number of clinic visits during the 180 days

prior to the date of vaccination (utilization is dichotomized into 'low' for 0 or 1 visit and 'high' for 2 or more visits).

The analysis was also stratified by age group.

A period effect defined as a time-varying covariate was added to the model for within-cohort analyses.

Results

Study Enrollment and Disposition

A total of 62,040 eligible adults and children 2 to 49 years of age who were administered Q/LAIV during season 2013-2014 were identified.

As specified by the protocol, all study subjects were followed for at least 180 days after vaccination (for Q/LAIV and TIV vaccinees) or index date (for unvaccinated comparators). Of note, one eligible Q/LAIV recipient died within these 6 months of follow-up; a narrative for this event was described in an attachment to the final study report.

A summary of population demographics, including subject age, health care utilization level, and gender, among Q/LAIV recipients, matched TIV recipient controls, and matched unvaccinated controls is presented in Table 2.

Table 2 Description of the Study Population

Demographic	Q/LAIV Recipients N = 62,040 % (n)	TIV Recipients N = 57,185 % (n)	Unvaccinated Controls N = 61,803 % (n)
Age (years)			
2-4	19 (11,636)	18 (10,173)	19 (11,605)
5-8	29 (18,356)	28 (16,314)	30 (18,302)
9-17	40 (24,655)	41 (23,493)	40 (24,574)
18-49	12 (7,393)	13 (7,205)	12 (7,322)
Health care utilization level [a]			
Low	69 (42,518)	63 (35,819)	73 (45,038)
High	31 (19,522)	37 (21,366)	27 (16,765)
Gender			
Female	53 (33,140)	50 (28,610)	48 (29,938)
Male	47 (28,900)	50 (28,575)	52 (31,865)

Table 2 Description of the Study Population

Demographic	Q/LAIV Recipients N = 62,040 % (n)	TIV Recipients N = 57,185 % (n)	Unvaccinated Controls N = 61,803 % (n)

Q/LAIV = quadrivalent live attenuated influenza vaccine; TIV = trivalent live attenuated vaccine

[a] High health care utilization was defined as ≥ 2 visits within the 6 months prior to the date of vaccination or index date; low health care utilization was defined as ≤ 1 visit.

Source: Attachment 1 to cover letter

Almost half (48%) of the 62,040 Q/LAIV recipients were 2 to 8 years of age; per the study protocol, TIV recipients and unvaccinated controls were age-matched to Q/LAIV recipients. Health care utilization level was higher among Q/LAIV recipients (31%) than among unvaccinated controls (27%), but lower than among matched TIV recipients (37%). The proportion of female subjects was higher among Q/LAIV recipients than among TIV and unvaccinated controls: 53%, 50%, and 48%, respectively.

Event Rate Comparisons Within Cohort

Table 3 presents a summary comparison of within-cohort rates of events within the periods of risk post vaccination compared with the control periods, including all ages and any setting.

Table 3 Summary of Comparisons Within Cohort: All Ages and Any Setting

Safety Event	Period at Risk [a]		Reference Period [a]		Crude Relative Risk (Exact 95% CI)	Adjusted Relative Risk (Exact 95% CI)
	No. of Events	Rate [b]	No. of Events	Rate [b]		
Hypersensitivity	14	1.96	17	2.78	0.71(0.34;1.44)	0.81(0.39;1.66)
Seizures/convulsions	0	0.00	5	0.82	0.00(0.00;0.70)	NE
Lower respiratory infection	157	1.81	246	2.88	0.63(0.52;0.77)	0.77(0.58;1.02)
Wheezing	121	1.40	159	1.86	0.75(0.59;0.95)	0.82(0.59;1.14)
Guillain-Barré syndrome	0	0	0	0	NE	NE
Bell's palsy	0	0.00	2	0.02	0.00(0.00;3.43)	NE
Encephalitis	0	0	0	0	NE	NE
Neuritis	17	0.20	18	0.21	0.93(0.47;1.83)	0.44(0.17;1.17)
Vasculitis	0	0	0	0	NE	NE
Any hospitalization	41	0.47	49	0.57	0.83(0.54;1.25)	0.60(0.31;1.16)
Respiratory hospitalization	3	0.03	0	0.00	NE(0.58;NE)	NE

CI = confidence interval; NE = not estimable

[a] The periods at risk were Days 0-3 for hypersensitivity and seizures/convulsions and Days 1-42 for all other safety events. Control periods were Days 7-9 for hypersensitivity and seizures/convulsions and Days 43-84 for all other safety events.

[b] Rates are reported per 1,000 person-months

Source: MA-VA-MEDI3250-1115 Tables, Table 1, Table 15, Table 38, Table 64, Table 79, Table 93, Table 105, Table 114

None of these crude or adjusted relative risks indicated a significantly higher risk during the period at risk.

For each of the 11 safety events of interest, further comparisons were conducted in 4 specific settings (all visits and admission, clinic visits, emergency department, hospital admissions) and in 5 different age groups (all ages, 2 – 4 years, 5 – 8 years, 9 – 17 years, 18 – 49 years), equaling a total of 209 ([11×4×5]- 11) comparisons or statistical tests.

Of the 209 comparisons, 2 (1.0%) indicated a statistically significant higher risk during the period at risk than during the control period:

The risk of hypersensitivity among Q/LAIV recipients 5 to 8 years of age was higher during Days 0-3 than Days 7-9 among all visits and admissions (5 cases, Days 0-3; 0 cases, Days 7-9, p=0.05).

The same risk was higher when the analysis was restricted to and among clinic visits only (5 cases, Days 0-3; 0 cases, Days 7-9, p=0.05).

None of these children visited an emergency department or was hospitalized. The risk of hypersensitivity among all Q/LAIV recipients 2 to 49 years of age was comparable between Days 0-3 and Days 7-9; a total of 14 subjects presented with hypersensitivity from Days 0-3 compared with 17 subjects during Days 7-9.

Further comparisons between event incident rates during the first 2 weeks after Q/LAIV administration and during Weeks 3 and 4 did not indicate other significantly higher risk following Q/LAIV administration.

Of note, no case of narcolepsy/cataplexy was observed during 180 days' follow-up (31,020 person-years).

Event Rate Comparisons Between Q/LAIV Recipients and Matched TIV Recipient Controls

Table 4 presents a summary comparison of rates of events between Q/LAIV recipients and matched TIV recipient controls, including all ages and any setting.

Table 4 Summary of Comparisons Between Q/LAIV Recipients and TIV Recipient Controls: All Ages and Any Setting

Safety Event	Q/LAIV Recipients		TIV Recipients		Crude Relative Risk (Exact 95% CI)	Adjusted Relative Risk (Exact 95% CI)
	No. of Events	Rate [a]	No. of Events	Rate [a]		
Hypersensitivity	14	1.96	25	3.80	0.52(0.26;0.99)	0.52(0.27;1.03)
Seizures/convulsions	0	0.00	5	0.76	0.00(0.00;0.76)	NE
Lower respiratory Infection	157	1.81	239	3.00	0.61(0.49;0.74)	(0.61(0.50;0.75)
Wheezing	121	1.40	167	2.09	0.67(0.53;0.84)	0.66(0.52;0.84)
Guillain-Barré syndrome	0	0	0	0	NE	NE
Bell's palsy	0	0	2	0.03	0.00 (0.00, 3.20)	NE
Encephalitis	0	0	0	0	NE	NE
Neuritis	17	0.20	17	0.21	0.92(0.47;1.83)	1.05(0.53;2.06)
Vasculitis	0	0	0	0	NE	NE
Any hospitalization	41	0.47	120	1.50	0.31(0.22;0.45)	0.35(0.24;0.50)
Respiratory hospitalization	3	0.03	11	0.14	0.25(0.06;0.85)	0.28(0.08;1.01)

CI = confidence interval; NE = not estimable; Q/LAIV = quadrivalent live attenuated influenza vaccine; TIV = trivalent inactivated vaccine

Note: The periods at risk were Days 0-3 for hypersensitivity and seizures/convulsions and Days 1-42 for all other safety events.

[a] Rates are reported per 1,000 person- months

Source: MA-VA-MEDI3250-1115 Tables, Table 240, Table 255, Table 280, Table 306, Table 319, Table 333, Table 350, Table 365

No risk was found to be significantly higher among Q/LAIV recipients than TIV recipient controls. Conversely, the incidence rates of lower respiratory infections, wheezing, and any hospitalization were found to be significantly lower for the Q/LAIV recipient cohort than for the TIV recipients control group ($p < .01$).

Additional analyses by setting and age group did not identify any other risk that was significantly higher among Q/LAIV recipients.

Of note, the risk of wheezing during the first 42 days after vaccine administration was also lower among Q/LAIV recipients than among the TIV recipient controls 2 to 4 years of age (66 cases, Q/LAIV recipients; 90 cases, TIV recipient controls; adjusted relative risk = 0.67 [0.48;0.92]). The risk of wheezing during the first 14 days after vaccine administration was also lower among Q/LAIV recipients than among TIV recipient controls 2 to 49 years of age (30 cases, Q/LAIV recipients; 52 cases, TIV recipient controls; adjusted relative risk = 0.51 [0.32;0.81]). The rate difference between the two cohorts was driven by a large difference among children 2 to 4 years of age (14 cases, Q/LAIV recipients; 29 cases, TIV recipient controls; adjusted relative risk = 0.46 [0.24;0.88]).

Event Rate Comparisons Between Q/LAIV Recipients and Matched Unvaccinated Controls

Table 5 presents a summary comparison of rates of events between Q/LAIV recipients and matched unvaccinated controls, including all ages and any setting.

Table 5 Summary of Comparisons Between Q/LAIV Recipients and Matched Unvaccinated Controls: All Ages and Any Setting

Safety Event	Q/LAIV Recipients		Unvaccinated Controls		Crude Relative Risk (Exact 95% CI)	Adjusted Relative Risk (Exact 95 % CI)
	No. of Events	Rate [a]	No. of Events	Rate [a]		
Hypersensitivity	14	1.96	10	1.41	1.39(0.62;3.25)	1.32(0.58;2.97)
Seizures/convulsions	0	0.00	4	0.56	0.00(0.00;1.11)	NE
Lower respiratory Infection	157	1.81	153	1.78	1.02(0.82;1.28)	1.00(0.80;1.25)
Wheezing	121	1.40	99	1.15	1.22(0.93;1.59)	1.20(0.92;1.57)
Guillain-Barré syndrome	0	0	0	0	NE	NE
Bell's palsy	0	0	2	0.02	0.00(0.00;3.46)	NE
Encephalitis	0	0	0	0	NE	NE
Neuritis	17	0.20	11	0.13	1.54(0.72;3.40)	1.29(0.60;2.79)
Vasculitis	0	0	0	0	NE	NE

Table 5 Summary of Comparisons Between Q/LAIV Recipients and Matched Unvaccinated Controls: All Ages and Any Setting

Safety Event	Q/LAIV Recipients		Unvaccinated Controls		Crude Relative Risk (Exact 95% CI)	Adjusted Relative Risk (Exact 95 % CI)
	No. of Events	Rate [a]	No. of Events	Rate [a]		
Any hospitalization	41	0.47	50	0.58	0.82(0.54;1.24)	0.76(0.50;1.15)
Respiratory hospitalization	3	0.03	3	0.03	1.00(0.17;5.80)	0.85(0.17;4.23)

CI = confidence interval; NE = not estimable; Q/LAIV = quadrivalent live attenuated influenza vaccine

Note: The periods at risk were Days 0-3 for hypersensitivity and seizures/convulsions and Days 1-42 for all other safety events.

[a] Rates are reported per 1,000 person-months.

Source: MA-VA-MEDI3250-1115 Tables, Table 119, Table 134, Table 157, Table 183, Table 198, Table 206, Table 220, Table 235

None of these crude or adjusted relative risks indicated a significantly higher incidence rate among Q/LAIV recipients than among matched unvaccinated controls.

Out of the 209 additional comparisons by settings and age groups, 3 (1.4%) indicated a statistically significant higher risk during the period at risk among Q/LAIV recipients than among unvaccinated controls:

The risk of any lower respiratory infection/pneumonia among children 2 to 4 years of age who visited the clinic was higher within 42 days after Q/LAIV administration than in unvaccinated controls (77 cases, Q/LAIV; 51 cases, unvaccinated controls; adjusted relative risk = 1.50 [1.05;2.14]). However, the risk of any lower respiratory infection/pneumonia was not higher among children 2 to 4 years of age who visited an emergency department (6 cases, Q/LAIV recipients; 9 cases, unvaccinated controls; adjusted relative risk = 0.65 [0.23;1.82]) and no Q/LAIV recipient 2 to 4 years of age was hospitalized for lower respiratory infection/pneumonia.

The risk of wheezing among all children 2 to 4 years of age was higher for Q/LAIV recipients than unvaccinated controls (66 cases, Q/LAIV recipients; 44 cases, unvaccinated controls; adjusted relative risk = 1.50 [1.03;2.20]).

A similar difference for wheezing among children 2 to 4 years of age was observed when the analysis was restricted to clinic visits (62 cases, Q/LAIV recipients; 39 cases, unvaccinated controls; adjusted relative risk = 1.59 [1.06;2.37]). However, no difference was observed among children 2 to 4 years of age who visited the emergency department (4 cases, Q/LAIV

recipients; 5 cases, unvaccinated controls; adjusted relative risk = 0.83 [0.22;3.09]). No child 2 to 4 years of age was hospitalized for wheezing.

Of note, the risks of any hospitalization among children 5 to 8 years of age and subjects 18 to 49 years of age were significantly lower among Q/LAIV recipients than among matched unvaccinated controls (children 5 to 8 years: 2 cases, Q/LAIV recipients; 13 cases, unvaccinated controls; adjusted relative risk = 0.14 [0.03;0.63]; subjects 18-49 years: 6 cases, Q/LAIV recipients, 14 cases, unvaccinated controls; adjusted relative risk = 0.33 [0.13;0.87]).

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