

FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

FLUAD

**SEASONAL ADJUVANTED TRIVALENT INFLUENZA
VACCINE (aTIV)**

**VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE**

MEETING DATE: SEPTEMBER 15, 2015

<p>ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE</p>

On July 31, 2015 the CSL Group and its Affiliates acquired the influenza vaccines business of Novartis AG in the U.S. The influenza vaccines business previously owned by Novartis is now referred to as NVS Influenza Vaccines. Through the agreements underlying the transaction, individuals previously under the direction and control of Novartis are now under the operational control of the CSL Group and are duly authorized to act with respect to applications, regulatory filings and any other licenses or approvals related to the influenza vaccines business of Novartis which are currently in the name of Novartis and have not yet transferred to the CSL Group.

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List of Abbreviations and Definition of Terms

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AEFI	Adverse Events Following Immunization
AESI	Adverse Events of Special Interest
APC	Antigen-Presenting Cells
aTIV	Adjuvanted Trivalent Influenza Virus Vaccine (Surface Antigen, Inactivated, Adjuvanted With MF59C.1, Egg Derived)
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Proprietary Medicinal Products
DP	drug product
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FD-RCT	First-Dose Randomized, Controlled Trial
GLP	Good Laboratory Practice
GMT	geometric mean titer
HA	hemagglutinin antigen
HI	hemagglutination inhibition
HLT	high-level term
HLGT	high-level group term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILI	influenza-like illness
IM	Intramuscular

List of Abbreviations and Definition of Terms

MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
NA	Neuraminidase
NC	not calculable
NVD	Novartis Vaccines & Diagnostics, Inc.
NOCD	New Onset of Chronic Disease
OR	odds ratio
PCR	polymerase chain reaction
PLT	potentially life-threatening
PPS	per protocol set
PT	preferred term
RCT	randomized controlled trial
RR	relative risk
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SC	Seroconversion
SMQ	standardized MedDRA query
SOC	system organ class
TIV	trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
TLR	toll-like receptor
US	United States
VE	vaccine effectiveness
VRBPAC	Vaccine and Related Biological Products Advisory Committee
WHO	World Health Organization

Trademark Information

<p>The following trademarks are used in this FDA Advisory Committee Briefing Document. In the body of this document, the names of the trademarked products will be written in italics, without the superscript symbol ™ or ®.</p> <p>Trademarks registered in the name of Novartis AG or other related entities:¹</p>	Generic descriptions
Agriflu	Novartis' egg-based trivalent inactivated subunit seasonal influenza vaccine licensed for individuals 18 years of age and older in the US and licensed for individuals 6 months of age and older in Canada. Also referred to in this briefing document as TIV.
Agrippal	Novartis' egg-based trivalent subunit seasonal influenza vaccine licensed for individuals 6 months of age and older in EU and Latin America. Shares the same manufacturing process and antigens as Agriflu. Also referred to in to in this briefing document as TIV.
Celtura	Novartis' cell-based monovalent inactivated subunit A(H1N1) pandemic influenza vaccine containing the adjuvant MF59, licensed for use in individuals 6 months of age and older in countries across the EU and Asia Pacific Regions.
Fluad	Novartis' egg-based trivalent inactivated subunit seasonal influenza vaccine containing the adjuvant MF59 and licensed for use in individuals 65 and older across EU, Canada, Latin America (also licensed for use in 6-24 months of age in Canada). Also referred to in this briefing document as aTIV.
Focetria	Novartis' egg-based monovalent inactivates subunit A(H1N1) pandemic influenza vaccine containing MF59, licensed for use in individuals 6 months of age and older in countries across the EU and Latin America.
MF59	Novartis' propriety oil-in-water emulsion adjuvant utilized in Fluad since 1997

Trademarks of other companies	Generic descriptions
Fluzone High-Dose	Sanofi Pasteur's seasonal influenza vaccine, currently approved in the US specifically for individuals age 65 years and older
Fluzone	Sanofi Pasteur's seasonal influenza vaccine

¹ Legal ownership of the above-referenced marks (other than MF59) was acquired by Seqirus UK Limited as of July 31, 2015.. Recordal of these assignments globally is pending.

1 EXECUTIVE SUMMARY

MF59-adjuvanted TIV (aTIV) is an adjuvanted trivalent influenza vaccine consisting of inactivated viral antigens from three influenza strains and the *MF59* oil-in-water emulsion adjuvant developed by Novartis Vaccines and Diagnostics, Inc. (NVD). The addition of *MF59* to a trivalent influenza vaccine has been shown to enhance the immune response to vaccination (O'Hagan 2012). The safety of the adjuvant, which is based on biodegradable squalene oil, a natural metabolite of cholesterol, has been evaluated in several influenza vaccines licensed for use outside of the United States (US) (O'Hagan 2007).

The proposed aTIV indication in the US is for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus type A subtypes and type B corresponding to the antigens contained in the vaccine. The initial approval of aTIV, if granted, will be based on meeting the requirements for accelerated approval with immunogenicity data (21 CFR 601.41) as outlined in the May 2007 Center for Biologics Evaluation and Research (CBER) Guidance Document regarding US licensure requirements for seasonal influenza vaccines (CBER 2007). In accordance with the accelerated approval process, NVD has committed to conducting a confirmatory clinical trial to assess the clinical benefit of aTIV.

The clinical experience with aTIV in an older adult population is summarized in this briefing document. The evidence provided includes clinical trial data, observational trial data, and post-marketing experience based on the commercial use of aTIV outside of the US.

Burden of Disease, Unmet Need, and Adjuvants

Influenza is one of the most significant infectious viral disease threats in the US, infecting 5% to 20% of the population each year (Sullivan 1993). Influenza affects people of all ages, but it causes the greatest burden in older adults (age 65 and older). Older adults account for more than half of all influenza-related hospitalizations (Thompson 2004) and approximately 90% of influenza-associated deaths in the US (CDC 2010). In addition, during seasons in which influenza A/H3N2 was a prominent strain, mortality rates averaged 2.7 times higher than during other seasons (CDC 2010).

Influenza vaccine effectiveness in the older population is suboptimal, in part due to the age-related decline of immune function known as immunosenescence. Suboptimal effectiveness is compounded in years with a vaccine mismatch to circulating strains (McElhaney 2012). One approach to overcoming the age-related decline of immune function is to increase the immune response following vaccination by adding an adjuvant. An adjuvant may, in some instances, also promote increased antibody responses against influenza strains not included in the vaccine composition. These increases in immune responses in an older population may be relevant to reduction in risk of influenza infection.

aTIV Product Development and Mechanism of Action

aTIV is based on the FDA-approved non-adjuvanted seasonal subunit vaccine *Agriflu*, to which the adjuvant *MF59* is added. Subunit vaccines contain mainly hemagglutinin (HA) and neuraminidase (NA) with low levels of internal influenza proteins (Ahmed 2015). *MF59* is a stable oil-in-water emulsion adjuvant composed of squalene oil, a natural metabolite of cholesterol, which has been studied extensively for nearly 20 years (O'Hagan 2013). The emulsion provides the immuno-stimulatory effect; no individual component of the emulsion raises a similar response on its own (Calabro 2013).

MF59 development was in part spurred because aluminum-based adjuvants do not work well for influenza HA (Davenport 1968). *MF59*'s mechanism of action is an active area of research, and there is increasing understanding of how *MF59* functions as an adjuvant. The current understanding supports the role of *MF59* in generating a transient immuno-stimulatory environment in the muscle. Specifically, *MF59* recruits immune cells into the muscle and promotes their differentiation into antigen presenting cells (O'Hagan 2012). Increasing immune cell recruitment, in turn increases antigen uptake and trafficking to local draining lymph nodes, leading to greater T cell help and B cell expansion (Mosca 2008; Seubert 2008; Calabro 2011). As presented data will show, relative to non-adjuvanted influenza vaccines, *MF59* adjuvanted influenza vaccines demonstrate increased magnitude of antibody and T cell responses, increased antibody responses to non-vaccine influenza strains, and increases in antibody responses that are sustained for 6 to 12 months, depending on the influenza strain.

Clinical Trial Experience

The aTIV clinical development program includes 39 immunogenicity studies enrolling a total of 27,116 subjects, ages 65 years and older. Among these 39 studies, 16 are randomized controlled trials including primary vaccination with aTIV versus non-adjuvanted TIV (FD-RCTs), 7 are controlled revaccination studies that represent continued vaccination of a subset of individuals in the FD-RCTs, and 16 are open-label studies that were primarily conducted for the annual seasonal strain update required in Europe. The 16 FD-RCT trials (including the pivotal immunogenicity study) (Frey 2014), as well as the 7 revaccination studies are the focus of this briefing document.

Immunogenicity responses in the NVD clinical development program were evaluated using validated HI antibody assays at baseline (prior to vaccination), and approximately 3 to 4 weeks after vaccination. The HI assay is an accepted surrogate marker of activity reasonably likely to predict clinical benefit in accordance with the CBER Guidance for licensure of seasonal influenza vaccines.

The pivotal study was designed to demonstrate immunogenicity based on criteria established in CBER's May 2007 Guidance and other criteria agreed upon with CBER as part of scientific

advice. The other 15 FD-RCTs and 7 revaccination studies were originally designed based on European guidance including CHMP criteria (CPMP/BWP/214/96). The pivotal study is considered primary for the assessment of both immunogenicity and safety. After review of the pivotal trial results in September 2013, CBER agreed that the demonstration of non-inferiority of aTIV relative to TIV based on immunogenicity could support an application for licensure under the accelerated approval pathway.

Pivotal Study

The pivotal immunogenicity trial was a phase 3 randomized, controlled, observer-blinded trial to evaluate the safety and immunogenicity of aTIV in comparison to the US-licensed inactivated influenza vaccine (TIV) (Frey 2014). The pivotal trial enrolled 7109 subjects 65 years of age and older (with and without comorbidities) in the US, Philippines, Colombia, and Panama during the 2010 to 2011 Northern Hemisphere influenza season.

The pivotal study's co-primary immunogenicity objectives, evaluated in a stepwise fashion, included:

- Immunologic equivalence of three consecutive production lots (i.e., lot-to-lot consistency) of aTIV
- Non-inferiority of aTIV to TIV against homologous strains
- Superiority of aTIV to TIV against homologous strains

The immune responses were evaluated using HI antibody responses, geometric mean titers (GMTs) and seroconversion rates. Seroconversion was defined as a prevaccination HI titer of <10 and a postvaccination titer of ≥ 40 or at least a 4 fold increase in HI titer from a prevaccination HI titer of ≥ 10 .

Demonstrating non-inferiority required the lower bound of the 95% confidence interval (CI) for the difference in seroconversion rates (aTIV – TIV) to be greater than -10%, and for the lower bound of the 95% CI for GMT ratios (aTIV:TIV) to be greater than 0.67 for all 3 homologous strains (i.e., influenza strains reflected in the vaccine formulation). If non-inferiority was achieved, then superiority of aTIV to TIV was evaluated. Demonstrating superiority required seroconversion rate differences to be significantly greater than 10% and the GMT ratios to be significantly greater than 1.50 for at least 2 of the 3 homologous strains.

Secondary objectives included evaluating non-inferiority and superiority of aTIV to TIV against homologous and heterologous strains (i.e., drifted influenza strains not represented in the vaccine composition) including evaluation in a subgroup of subjects with pre-existing comorbidity (congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency, and neurological/neuromuscular or metabolic disorders, including diabetes mellitus). Antibody responses through 1 year following vaccination were also assessed. Clinical effectiveness of aTIV was compared to TIV for clinically diagnosed influenza like illness (ILI), exacerbation of preexisting chronic disease, health care utilization (emergency room visits,

unscheduled physician visits, hospitalizations for specific conditions), and all-cause mortality using Poisson regression.

Immunogenicity Results, Pivotal Study

The immunologic equivalence of three consecutive lots of aTIV was demonstrated. For remaining immunogenicity analyses, the data from subjects exposed to each of the 3 lots of aTIV were combined for additional analyses.

aTIV was demonstrated to be non-inferior to TIV. As shown in Table 1, the lower bounds of the 95% CI for the difference in percentage of subjects who seroconverted were above -10% for all 3 homologous strains. The lower bounds of the 95% CI for GMT ratios against the 3 homologous strains all exceeded 0.67 (Table 2). These results confirm aTIV is non-inferior to a US licensed inactivated seasonal influenza vaccine, as required by the CBER 2007 guidance for licensure of influenza vaccines.

Table 1. Seroconversion Against Homologous Strains, Non-Inferiority Objective, Pivotal Study

Homologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Non-Inferiority - PPS				<i>Non-Inferiority Bound</i>		
A/H1N1 (California)	69%	58%	9.8% (7.5-12.1)		●	3225 3257
A/H3N2 (Perth)	73%	58%	13.9% (11.7-16.1)		●	3225 3256
B-strain (Brisbane)	33%	29%	3.2% (1.1-5.3)		●	3227 3259

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 2. Geometric Mean (HI) Titers and GMT Ratios, Homologous Strains, Non-Inferiority Objective, Pivotal Study

Homologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Non-Inferiority - PPS						
A/H1N1 (California)	99	70	1.4 (1.32-1.49)			3225 3257
A/H3N2 (Perth)	272	169	1.61 (1.52-1.7)			3225 3256
B-strain (Brisbane)	28	24	1.15 (1.08-1.21)			3227 3259

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

Superiority of aTIV to TIV was not demonstrated. The pre-specified endpoints for difference in seroconversion rates (Table 12) and GMT ratios (Table 13) were not met for 2 of the 3 homologous strains tested. Although the overall objective was not met, aTIV did achieve the superiority threshold for the A/H3N2 strain based on seroconversion (multiplicity-adjusted $P=0.002$).

In addition, in a post-hoc analysis, aTIV elicited consistently higher seroconversion rate differences (lower bound of the 95% CI greater than 0) and GMT ratios (lower bound of the 95% CI greater than 1.0) for all 3 homologous strains as compared to the non-adjuvanted TIV.

The results of the secondary immunogenicity objectives were consistent with the findings from the primary objectives:

- aTIV was demonstrated to be non-inferior to TIV among subjects with pre-existing comorbidities considered at higher risk for influenza complications. The superiority of aTIV to TIV was not demonstrated. However, results favored aTIV over TIV based on seroconversion differences and GMT ratios.
- aTIV was demonstrated to be non-inferior to TIV against heterologous strains among all subjects in the analysis set and in a subgroup of subjects with pre-existing comorbidity. The superiority of aTIV to TIV for heterologous strains was not demonstrated.
- Excepting A/H1N1 antibody responses at day 366, aTIV demonstrated higher antibody titers than TIV against the three homologous influenza strains at day 181 and day 366.
- Significant differences were not demonstrated between vaccines for the clinical effectiveness endpoints

First-Dose Randomized Controlled Trials (FD-RCTs)

In addition to the pivotal study, 15 FD-RCTs were conducted between 1992 and 2009. All 15 studies were (1) conducted in older adults ≥ 65 years of age; (2) were randomized, and conducted in an observer-blind fashion; (3) included the use of a non-adjuvanted TIV control vaccine; (4) included measurements of pre- and post-vaccination hemagglutination-inhibiting antibody (HI) responses.

These 15 FD-RCTs were included in a meta-analysis with the pivotal study and analyzed according to CBER immunogenicity criteria. Relevant immunogenicity findings are based on a dataset from a total of 11,086 subjects. For details about demographics and baseline characteristics, see Section 8.1.

The meta-analysis results demonstrated the non-inferiority of aTIV to TIV with the lower bounds of the 95% CI greater than -10% for seroconversion rate differences and greater than 0.67 for GMT ratios. The results of the meta-analysis of the randomized controlled immunogenicity data support the findings of the pivotal study. See Section 8.2 for details.

Revaccination Trials

A cohort of subjects in the FD-RCTs were followed to evaluate the immunogenicity of aTIV and TIV over the course of two (aTIV n=476, TIV n=315) or three (aTIV n=150, TIV n=84) annual vaccinations for a total of 7 revaccination trials. Study subjects remained in the same vaccine group as randomized for their respective parent trials. The results from the 7 revaccination studies over the course of 2 or 3 cumulative annual injections indicate that the relative immunogenicity benefits of aTIV to TIV did not diminish over time. For details of the revaccination trial results see Section 9.

Observational Trial Data

The effectiveness of aTIV has been assessed in two observational studies to determine vaccine effectiveness (VE) of aTIV relative to TIV.

The first study was a prospective cohort study in Italy conducted in over 107,000 individuals. This study found that vaccination with aTIV was associated with a 25% reduction in risk for influenza- or pneumonia-related hospitalizations compared to vaccination with TIV during the peak of influenza season (relative risk: 0.75; 95% CI: 0.57-0.98) ([Mannino 2012](#)).

The second study was a case-control study in British Columbia, Canada. This study found that the odds ratio of laboratory-confirmed influenza for aTIV relative to TIV was 0.37 (95% CI: 0.14-0.96); or 63% relative VE favoring aTIV ([Van Buynder 2013](#)).

Safety

The safety profile of aTIV was evaluated using five datasets:

- (1) The pivotal study, which is considered primary in the assessment of safety since it is the largest RCT in which subjects received the current formulation of aTIV planned for commercial manufacture.
- (2) The FD-RCTs pooling. This pooling includes the pivotal study, but differs from the list of studies analyzed in the immunogenicity meta-analysis in that it excludes the phase IV study V7P35 due to methodologic differences in how safety was assessed. This pooling consists of 10,952 subjects (aTIV n=5754, TIV n=5198) and is considered supportive for infrequent or rare events such as adverse events of special interest (AESIs), adverse events following immunization (AEFIs), and deaths.
- (3) Seven revaccination trials, including 1 year revaccination data (aTIV n=492, TIV n=330) and 2 year revaccination data (aTIV n=150, TIV n=87), which was used to describe the safety of repeated annual doses of aTIV.
- (4) One large observational study (aTIV n=88,449, TIV n=82,539), which was used to evaluate a subset of AESIs.
- (5) The post-marketing database based on spontaneous safety reports from 1997 to 2014, which was used for further assessment of AESIs and AEFIs.

The primary measures in the pivotal study for assessing safety and tolerability were solicited local and systemic adverse events (AEs) (assessed for 7 days following vaccination), unsolicited AEs (assessed for 21 days following vaccination), and all serious adverse events (SAEs), new onset of chronic diseases (NOCDs), and AEs leading to study withdrawal (assessed for 365 days following vaccination).

The overall summary of AEs (Table 3) in the pivotal study shows that the percentages of subjects reporting unsolicited AEs, SAEs, AEs leading to withdrawal, NOCDs, and AEs leading to death were similar between the aTIV and TIV vaccine groups. Subjects in the aTIV group reported a higher frequency of solicited local AEs (32% vs. 17%, aTIV vs TIV, respectively) and solicited systemic AEs (32% vs 26%). The imbalance in solicited AEs was due primarily to a higher percentage of subjects reporting injection site pain (25% vs 12%) and tenderness (21% vs. 11%), and myalgia (15% vs. 10%).

The majority of the solicited AEs among subjects in the pivotal trial who received aTIV were mild or moderate in severity. The percentage of subjects in both vaccine groups reporting “severe” solicited AEs was <1% per event in each vaccine group. The percentage of subjects reporting ongoing solicited AEs 7 days after vaccination was <1% per event in each vaccine group. Analgesics/antipyretics use was reported by 5% aTIV vs. 4% TIV subjects, and stayed home due to local or systemic reactions was reported by 3% aTIV vs. 2% TIV subjects.

Table 3. Overall Summary of Adverse Events, Pivotal Study Safety Set

Adverse Event Type	aTIV	TIV
Solicited	(N=3505)	(N=3495)
Any solicited AE, 6 hours-7 days	1619 (46%)	1164 (33%)
Any solicited local AE	1137 (32%)	593 (17%)
Any solicited systemic AE	1120 (32%)	902 (26%)
Unsolicited	(N=3545)	(N=3537)
Any unsolicited AE, Days 1-21	551 (16%)	570 (16%)
Any SAE, Days 1-366	264 (7%)	243 (7%)
Any AE leading to withdrawal, Days 1-366	52 (1%)	49 (1%)
New onset of chronic disease, Days 1-366	227 (6%)	223 (6%)
Any AE leading to death, Days 1-366 ^a	51 (1%)	46 (1%)

^a The death of one additional subject in the aTIV group was recorded on a case report form but not as an outcome from AE. For a complete summary of deaths in the pivotal study see Section 11.10.

Unsolicited AEs were reported by 16% of subjects in both the aTIV and TIV vaccine groups in the pivotal study in the 3 weeks following vaccination. The most common unsolicited AEs were nasopharyngitis (aTIV, 2% [n=69] vs. TIV, 2% [n=60]), headache (1% [n=40] vs. 2% [n=55]) and cough (1% [n=34] vs. 1% [n=49]). No clinically relevant imbalance was noted for individual unsolicited AEs.

In the year of follow-up after vaccination, most SAEs in the pivotal study were due to respiratory or cardiac disorders, consistent with the underlying morbidity of the older population enrolled. The rate of SAEs overall was 7% in both vaccine groups. The most commonly reported SAEs were pneumonia (aTIV, 1% [n=32] vs. TIV, 1% [n=35]), acute myocardial infarction (<1% [n=11] vs. <1% [n=7]), and chronic obstructive pulmonary disease (<1% [n=10] vs. <1% [n=14]). Of note, a separate preferred term of myocardial infarction was reported by 0.3% of subjects in both vaccine groups. There were no clinically relevant differences between groups in any of the specific SAEs reported.

NOCDs were described in 6% of subjects in the aTIV group, as well as 6% of subjects in the TIV group.

Few subjects in either vaccine group discontinued due to AEs (aTIV, 1% [n=52] vs. TIV, 1% [n=49]). The most common reasons (based on MedDRA System Organ Class [SOC] definitions) for premature study withdrawal due to AEs were cardiac disorders (aTIV, 1% [n=21] vs. TIV, 1% [n=19]), infections and infestations (aTIV, <1% [n=14] vs. TIV, <1% [n=10]), and nervous system disorders (aTIV, <1% [n=9] vs. TIV, <1% [n=11]).

The mortality rate was comparable between groups in the pivotal study (aTIV, 1% [n=52] vs. TIV, 1% [n=46]) and the FD-RCT pool (1.4% [n=78] vs. 1.6% [n=81]). The most common causes of death in the pivotal trial were cardiac disease, respiratory infections, cerebrovascular

accidents, and neoplasia. The most common causes of death in the FD-RCT were acute myocardial infarction, pneumonia, myocardial infarction, congestive cardiac failure, cerebrovascular accident, and cardiac failure.

AESIs are defined as having a potential immune-related etiology. A list of AESIs based on MedDRA terms was provided by CBER and was used to search the pooled datasets retrospectively. Specific parameters included neuroinflammatory disorders (including narcolepsy), rheumatological disorders, inflammatory bowel disease, thyroid disorders, inflammatory skin disorders, autoimmune hematologic disorders, and vasculitis, among others (see Appendix 14.2.2). In the FD-RCT pool, AESIs were reported by 0.9% of subjects in both groups.

An additional retrospective analysis was conducted to assess infrequent but potentially clinically important AEs occurring following vaccination. These events are referred to as adverse events following immunization (AEFI), and examples include events such as severe hypersensitivity, angioedema, and/or seizures. For a complete list see Appendix 14.2.3. The analysis of AEFIs was performed using the FD-RCT pooling. The incidence of AEFIs was 0.3% in the aTIV group and 0.2% in the TIV group.

The data from revaccination studies including healthy and institutionalized older adult subjects were analyzed as pooled. The data demonstrate increases in percentages of subjects reporting solicited and unsolicited AEs between years 1 and 2 with a subsequent decline in year 3. For further discussion on these findings, see Section 11.14.

A large prospective cohort observational study conducted in Italy, which studied 170,900 doses of vaccine (88,449 aTIV, 82,539 TIV) in 107,661 participants examined for AESI incidence among participants vaccinated with aTIV and TIV. No imbalance in these events was found between the vaccine groups ([Villa 2013](#)).

Since aTIV was first approved in Italy in 1997, data are available from post-marketing surveillance collected over the course of 17 years following the distribution of approximately 76 million doses of aTIV. Analyses of the post-marketing safety database showed no concern relating to the incidence of AESIs and AEFIs nor evidence of disproportionality of these events relative to another licensed influenza vaccine.

The reporting rates were very low for all events (<0.1 event per 100,000 doses). The AESIs/AEFIs with the highest rates per 100,000 doses were arthritis (0.08), angioedema (0.07), Guillain-Barré syndrome (0.04), and demyelination (0.04).

In addition to descriptive analyses of the post-marketing safety database, NVD used the Empirica Signal System with the proportional reporting ratio method to assess for differences in the incidence of AESIs and AEFIs between aTIV and those of *Agrrippal* (also known as *Agriflu*), a TIV licensed in Europe, Canada, and Latin America. The quantitative comparison revealed no

significant imbalance in reporting rates with aTIV and the TIV comparator in the post-marketing setting.

Benefit/Risk Assessment

In a pivotal clinical trial in individuals 65 years of age and older, aTIV was demonstrated to be non-inferior to a US licensed seasonal influenza vaccine, a key criterion for licensure in the US. In addition, aTIV elicited higher immune responses than TIV based on seroconversion and GMTs against homologous and heterologous influenza strains, although superiority criteria were not met. The results of the pivotal study are supported by a meta-analysis including 15 other FD-RCTs for a combined total 11,086 subjects. This meta-analysis also demonstrated the non-inferiority of aTIV to TIV, with aTIV eliciting consistently greater immune responses than non-adjuvanted comparator vaccines.

The safety of aTIV has been well-characterized in the clinical studies, and the vaccination was well-tolerated. The AEs which occurred more frequently among aTIV participants were mild to moderate solicited AEs following vaccination. These events were associated with low incidence of fever, low analgesic/antipyretic use, and low percentages of subjects reporting these reactions as continuing 7 days after vaccination. There was no evidence in the pivotal study or in the larger pooling of FD-RCTs of any additional risks for more serious or severe events beyond those that would be expected with a typical non-adjuvanted influenza vaccination. Data from seven revaccination studies demonstrated no new safety concerns, however, there are limitations in the interpretation of these data based on potential selection bias for subjects who continue in these revaccination studies. . Data from a large observational study, including revaccinated individuals, did not demonstrate increased risk of AESIs. Post-marketing surveillance since initial licensure for use in an older population in 1997 has identified no additional safety concerns.

Taken together, aTIV has a positive overall benefit-risk profile and offers a new, generally safe, vaccine option with data that support increased antibody responses against matched and unmatched influenza strains. This includes increased antibody responses detectable at 6 and 12 months after vaccination in some influenza strains. Data from non-randomized observational studies, which demonstrated relative reduction by aTIV in influenza- and pneumonia-related hospitalizations as well as RT-PCR confirmed influenza, may be supportive of additional benefit. NVD has committed to conducting a confirmatory study to evaluate clinical efficacy with an endpoint of laboratory-confirmed influenza intended to confirm the benefit of aTIV.

2 EPIDEMIOLOGY AND UNMET MEDICAL NEED AMONG OLDER ADULTS

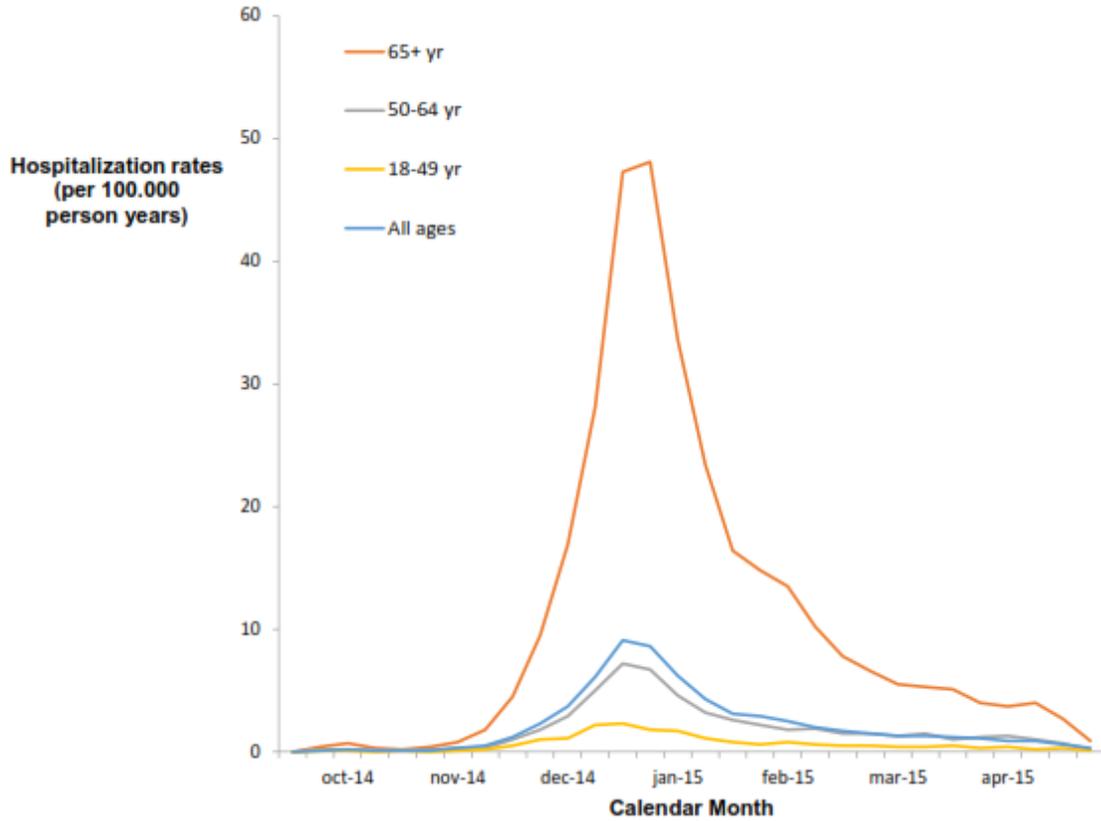
Summary

- Influenza is a major source of morbidity and mortality in the United States, resulting in approximately 226,000 associated hospitalizations and between 3,300 to more than 48,000 deaths every year across all age groups.
- Individuals age 65 and older account for the preponderance of influenza-related hospitalizations and deaths. Approximately 63% of all influenza hospitalizations and 90% of all influenza related deaths occur in older adults.
- The effectiveness of influenza vaccines is diminished in older adults, primarily attributed to the age-related decline of immune function, resulting in a reduced immune response to vaccination. This is compounded in seasons with vaccine mismatch to circulating strains.

2.1 Burden of Disease

Influenza is a communicable acute respiratory disease that is considered to be one of the major infectious disease threats to the human population. An estimated 5% to 20% of the United States (US) population acquires influenza each year ([Sullivan 1993](#)). The resulting burden is significant. Between 3,300 to 48,600 people die from influenza-related causes each year with approximately 90% of these deaths occurring in people 65 years of age and older ([CDC 2010](#)). In addition, approximately 226,000 individuals are hospitalized each year due to influenza of whom 63% are older adults ([Thompson 2004](#)). The rates of influenza-related hospitalization by age category are shown in Figure 1 for the most recent influenza season.

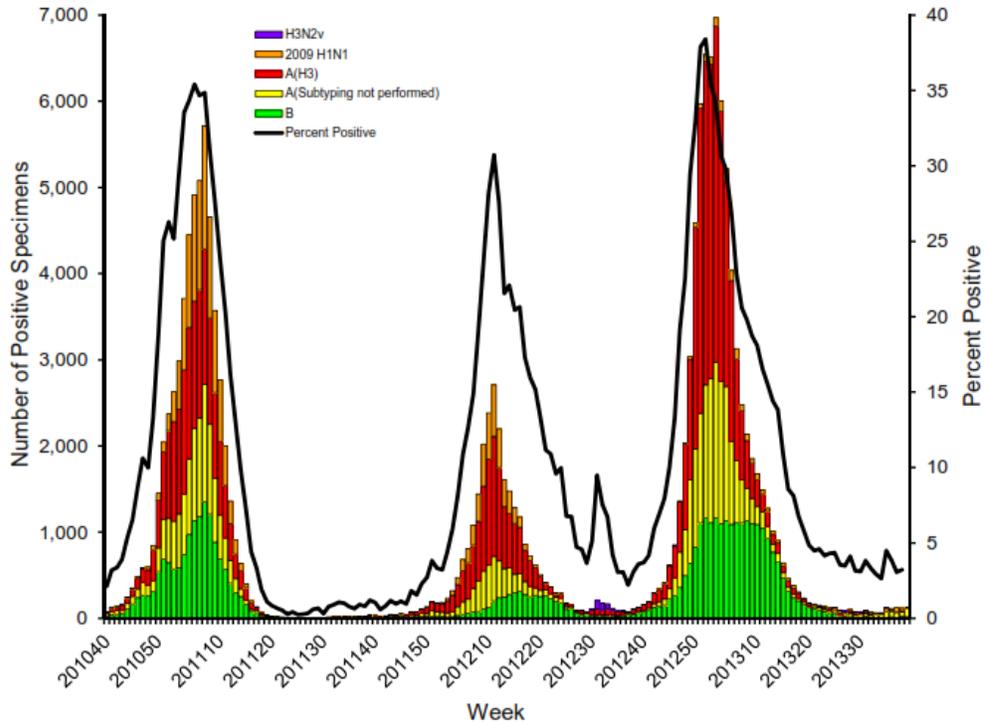
Figure 1. Incidence Rates of Laboratory-Confirmed Influenza-Related Hospitalization by Age During the 2014-2015 Influenza Season



Note: Incidence rates are derived from the weekly increase in cumulative incidence per 100,000, assuming a constant population at risk over the 1- year period. Source: CDC Fluview 2014-15.

During influenza seasons, viral strains from subtype A/H1N1, subtype A/H3N2, and type B commonly circulate. However, not all three strains pose the same infectious threat and disease burden. Influenza type A subtypes tend to predominate over type B in most seasons, with influenza A(H3N2) as the dominant circulating subtype over other influenza A subtypes (Figure 2).

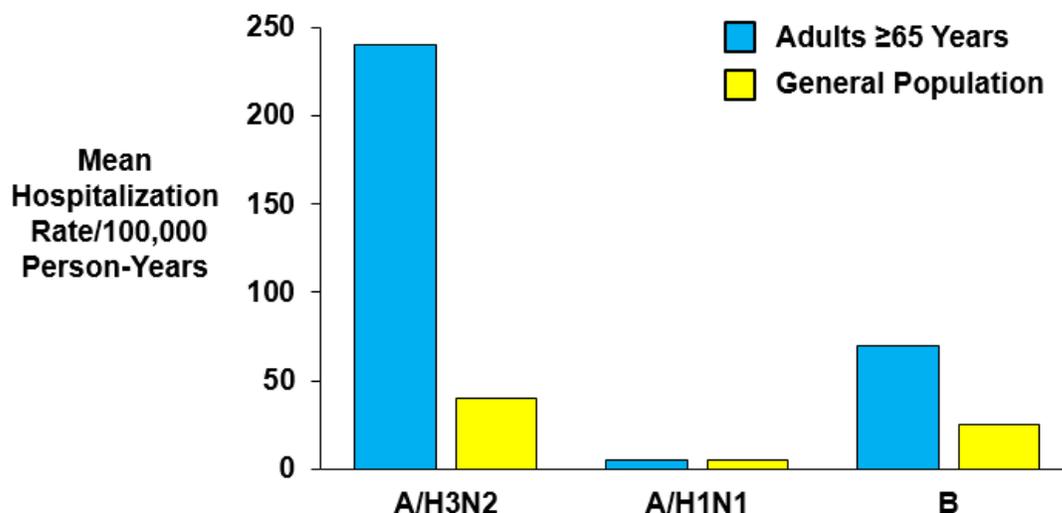
Figure 2. CDC Influenza Positive Tests, 2010-2013



Source: Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2010-2013. Available at: <http://www.cdc.gov/flu/weekly/pdf/12-13%20Season%20Summary.pdf>

In addition, the hospitalization rate among older adults due to A/H3N2 viruses is considerably higher than the rate due to either B viruses or A/H1N1 viruses. The A/H3N2 strain hospitalization rates are nearly five times as high in older adults when compared to the general population (Zhou 2012) (Figure 3).

Figure 3. Hospitalization Rate Among Older Adults and the General Population by Influenza Strain



Source: Zhou H, et al. *Clin Infect Dis.* 2012; 54:1427–1436.

The high rate of influenza-related hospitalization is particularly concerning for this population, as hospitalization in general has been linked to further morbidity. In older adults, functional decline has been shown to occur by the second day of hospitalization, including physical and psychosocial problems such as deconditioning, increased risk for fracture, malnutrition, delirium, and depression. This hospital-related morbidity can lead to a downward spiral involving dependency on a home care-giver or nursing home and deterioration of self-care skills (i.e. activities of daily living), resulting in reduced mobility and quality of life (Hirsch 1990; Creditor 1993; de Vos 2012).

2.2 Vaccination

Annual vaccination against influenza offers the best option to prevent infection (CDC 2013a). Currently, 13 seasonal influenza vaccines are available in the US. Of these 13, only one vaccine, *Fluzone High-Dose* (Sanofi Pasteur), is currently approved in the US specifically for individuals age 65 years and older. This vaccine contains four times as much antigen as standard dose, and was approved in 2009 based on studies demonstrating increased immunogenicity compared to standard dose *Fluzone* (CDC 2014a). Inactivated influenza vaccines elicit hemagglutination inhibition (HI) antibody responses to the influenza strains contained in the vaccine (i.e., homologous immune response) and to closely related isolates. Due to the drift of the circulating influenza virus, influenza vaccines must be updated annually to match the viruses that will most likely circulate in the upcoming season. Antibody responses recognizing more divergent strains within a subtype and to other subtypes (i.e., heterologous immune response) are diminished (Ekiert 2009; CDC 2013b). In any influenza season a (partial) mismatch between the strains included in the vaccine composition and the circulating strains thus is likely to result in reduced VE.

The most recent example of decreased VE against divergent strains occurred during the 2014-2015 influenza season, during which the influenza associated hospitalization rate amongst patients 65 years and older was the highest since the Centers for Disease Control and Prevention began tracking this data in 2005 (CDC 2015a). The predominant circulating viruses were similar to influenza A/Switzerland/9715293/2013, which was an A/H3N2 strain antigenically different from the A/Texas/50/2012-like A/H3N2 strain present in the seasonal vaccine (CDC 2015b). Through routine surveillance conducted by CDC, influenza vaccination this past season offered reduced protection against the predominant circulating viruses, drifted influenza A/H3N2, compared with previous seasons when circulating and vaccine strain viruses were better matched. The majority of influenza associated hospitalizations were associated with influenza A/H3N2. VE was estimated to be 19% (95% CI, 7-29%) across all ages with 18% (95% CI, 6%-29%) and 45% (95% CI, 14%-65%) VE for influenza A/H3N2 and influenza B Yamagata lineage), respectively (CDC 2015c). The reduced estimates of vaccine efficacy have been attributed to the predominance of drifted H3N2 strains during the 2014-2015 season. However, even in seasons with a good antigenic match between circulating strain and vaccine, the effectiveness of most commercially available influenza vaccines is substantially reduced in older adults and other individuals with impaired immune responsiveness (Osterholm 2012).

2.3 Age-Related Decline of Immune Function

The age-related decline of immune function in older adults, also known as immunosenescence, involves the decline in both humoral and cell-mediated immunity, including impaired function of antigen presenting cells (APCs), decreased availability of T cell pool to respond to new antigens, lower antibody responses, decreased high-affinity antibodies, and diminished metabolic activity within memory CD4+ cells (Grozny 2013; Gruver 2007; Uyemura 2002). Immunosenescence is thought to affect the ability of the older population to respond well to vaccination and to resist influenza infection (McElhaney 2012). Post-vaccination haemagglutination inhibition (HI) antibody responses (seroconversion and HI titer ≥ 40) in adults 58 years of age and older were shown to be 10 to 23% lower than in younger individuals evaluated in a review by authors Goodwin et al. (2006). In this same review, the authors observed that clinical vaccine efficacy estimates are considerably lower in the older age cohort: 70-90% clinical vaccine efficacy in young adults versus 17-53% in the older adults, depending on the circulating influenza strain.

In view of the limitations of conventional influenza vaccines in older individuals, there continues to be an unmet need for new generation influenza vaccines that provide more consistent and broader coverage against all seasonal virus subtypes and variants (Wong 2013; Reber 2012).

3 VACCINE COMPOSITION

Summary

- aTIV is based on the FDA-approved non-adjuvanted seasonal subunit vaccine *Agriflu*, to which the adjuvant *MF59* is added.
- Subunit vaccines contain mainly HA and NA with low levels of internal influenza proteins.
- *MF59* is a stable oil-in-water emulsion adjuvant composed of squalene oil, a natural cholesterol metabolite.
- *MF59* has been studied extensively for nearly 20 years.
- The emulsion provides the immuno-stimulatory effect; no individual component of the emulsion raises a similar response on its own.

3.1 Vaccine Design

aTIV consists of two admixed components: inactivated influenza antigens based on the *Agriflu* platform approved in the US on 27 NOV 09 under STN 125297, and *MF59* adjuvant.

3.1.1 Antigens

The trivalent influenza vaccine (TIV) contains influenza virus surface antigens that are antigenically like those of the A/H1N1, A/H3N2, and B influenza virus strains recommended by the WHO, VRBPAC, and EMA for inclusion in an annual seasonal influenza vaccine. The manufacturing processes used to derive the primary surface antigens, hemagglutinin (HA) and neuraminidase (NA), included in aTIV are essentially the same as those used for TIV. aTIV is a subunit vaccine and thus key steps of the manufacturing process include: virus growth (in embryonated hens' eggs), virus purification, virus inactivation, and surface antigen purification. The process results in high HA and NA levels with low levels of internal proteins (e.g. nucleoprotein, etc.) ([Ahmed 2015](#)).

3.1.2 *MF59* Adjuvant

The *MF59* component of aTIV is an oil-in-water emulsion composed of squalene stabilized by both a water-soluble surfactant (polysorbate 80, also known as Tween 80) and an oil-soluble surfactant (sorbitan trioleate, also known as Span 85), in a low ionic strength buffer. The emulsion itself is stable for several years ([Ott 2001](#)). Squalene oil is a natural metabolite of cholesterol and an endogenous cell membrane component ([O'Hagan 2007](#)). No individual component of *MF59* is independently immuno-stimulatory but rather, when assembled into an emulsion of squalene droplets stabilized by surfactant, the assembled components exert the

adjuvant effect (Calabro 2013). *MF59* does not directly activate toll-like receptors (TLRs) like TLR agonists (Miller 2013; Toubi 2004). *MF59* does not activate inflammasomes (Vono 2013).

MF59 is included in influenza vaccines licensed outside of the US such as seasonal vaccine *Fluad* and pandemic (A/H1N1 2009) vaccines *Celtura* and *Focetria*. *MF59* has been combined with other antigens besides influenza (e.g., human immunodeficiency virus, cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, and others). A discussion of these programs is beyond the scope of this briefing document, but no safety concerns have arisen from the evaluation of *MF59* adjuvanted vaccines in these programs.

3.1.3 Dose Selection

The vaccine dose, schedule, and formulation are based on licensed adjuvanted and non-adjuvanted seasonal influenza vaccines and pertinent data from the clinical studies V7P38 and V104P3. These two studies evaluated the effect of dose levels on immune response using a validated hemagglutination inhibition (HI) antibody assay at baseline and subsequently at 3-4 weeks. Hemagglutinin antigen doses of 7.5 (all strains), 15 (all strains) to 30 μg (A/H3N2) per influenza strain, and adjuvant doses ranging from 25 to 100% (equally roughly 2.4 to 9.75 mg squalene per dose) were evaluated. Findings from both V7P38 and V104P3 confirmed that the present formulation of aTIV (including 15 μg HA per influenza strain and 100% dose *MF59*) demonstrated the best antibody response and an acceptable safety profile.

3.1.4 Drug Product Formulation

In 1997, *MF59*-adjuvanted TIV was approved in Italy as a combined drug product under the trade name *Fluad* (O'Hagan 2013). Since the time of its initial approval, aTIV has undergone minor formulation changes, including the removal of thimerosal and the substitution of a 10 mM citrate buffer for water in the *MF59* composition. Both clinical and nonclinical studies have been unable to detect any notable differences regarding immunogenicity and safety between these different formulations. Therefore, safety and immunogenicity data from the different formulations are viewed as relevant.

The aTIV formulation intended for marketing in the US is presented as a thimerosal-free, sterile emulsion for injection, in prefilled syringes. This formulation, which includes squalene, citrate, and surfactants, represents a balance that optimized for immunogenicity, safety, and stability. Squalene and citrate are natural components of the human body. They are rapidly eliminated from the injection site within hours through normal metabolic pathways. In addition, the surfactants are commonly used in other approved parenteral products. The small and controlled droplet size keeps viscosity low for sterile filtration during manufacturing and for ease of injection (O'Hagan 2013).

4 MECHANISM OF ACTION AND RATIONALE FOR PRODUCT DEVELOPMENT

Summary

- *MF59* development was in part spurred because aluminum based adjuvants do not work well with influenza antigens.
- Current research supports the role of *MF59* in generating a transient immunostimulatory environment in the muscle.
- After recruiting immune cells into the muscle, *MF59* promotes their differentiation into antigen presenting cells.
- By increasing immune cell recruitment, there appears to be greater antigen uptake and increased antigen trafficking to local draining lymph nodes, leading to greater T cell help and B cell expansion.
- *MF59* adjuvanted vaccines elicit increased titers against vaccine matched and unmatched influenza strains of the same subtype. Increased titers persist to, time points remote from vaccination. These attributes may be important to address within season antigenic drift or for influenza seasons that end later than usual.

4.1 Mechanism of Action

Adjuvants have been used in combination with vaccines since 1926, when aluminum hydroxide was first used in combination with diphtheria toxoid vaccine. Aluminum based adjuvants have an excellent safety profile in humans but do not work as an adjuvant for influenza antigens (Davenport 1968). Therefore, alternative adjuvants for influenza were needed.

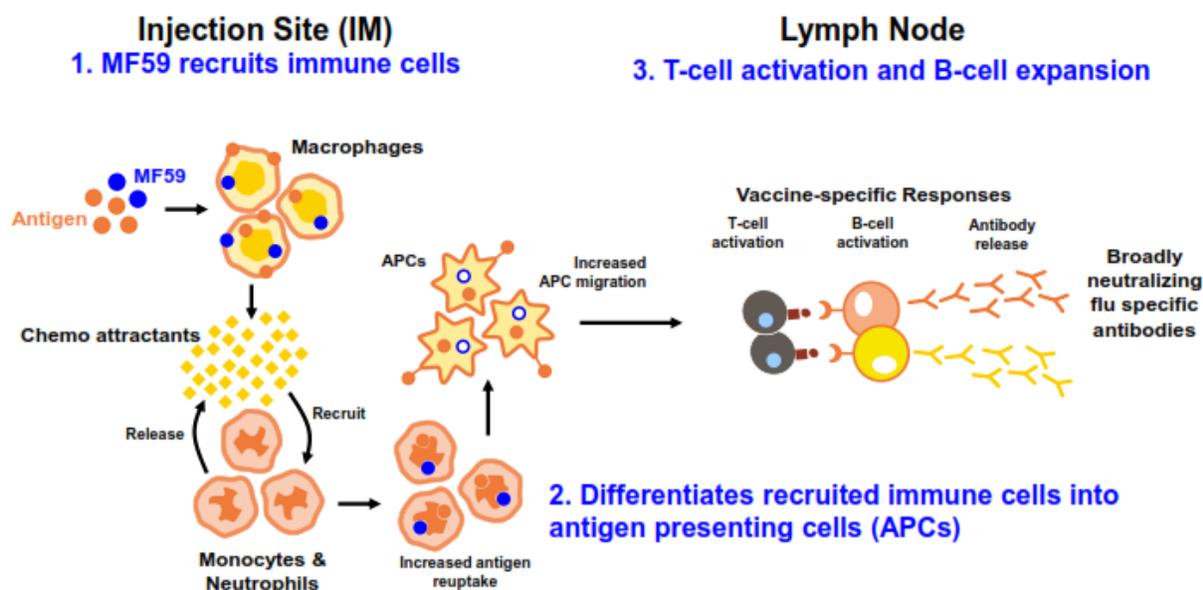
The aTIV adjuvant, *MF59*, is an oil-in-water nanoemulsion. Emulsion-based adjuvants originated nearly 80 years ago, and aside from aluminum salts, oil-based materials were some of the earliest vaccine adjuvant formulations evaluated in humans (Edelman 1980). The squalene-based oil-in-water emulsion adjuvant *MF59* was developed in the 1980s. Since the initiation of its development, there has been a growing body of research elucidating how *MF59* functions as an adjuvant (O'Hagan 2013).

Muscle is the site of injection for most influenza vaccines, and it has few antigen presenting cells. Data from animal studies support the hypothesis that *MF59* recruits immune cells into the muscle and promotes their differentiation into antigen presenting cells (O'Hagan 2012). In animal models, *MF59* injection into muscle alone shows the induction of a transient, immunostimulatory environment at the injection site, which likely is responsible for promoting an enhanced immune response (Calabro 2011). Plausibly, this improved response can address immunosenescence by increasing the level of humoral and cellular responses (O'Hagan 2012).

In contrast to alum adjuvants, which act in part as antigen “depots,” preclinical studies have demonstrated that *MF59* does not act as an antigen depot (Ott 1995). Direct physical interaction between *MF59* and the antigen is not necessary for its immune enhancing effects (O’Hagan 2012). Animal studies indicate that ~90% of the *MF59* squalene component is eliminated from the injection site within 6 hours (Ott 1995). This differs from alum, which can be retained at the injection site for 28 days or longer.

Cell types recruited into muscle by *MF59* injection include monocytes, macrophages, granulocytes, and dendritic cells (O’Hagan 2012). *MF59* has a range of effects on these cells, including increased antigen uptake, release of chemo-attractants, and cell differentiation induction (Mosca 2008; Seubert 2008; Caproni 2012). The higher number of recruited and activated immune cells leads to more efficient antigen transport to the local draining lymph nodes, which in turn results in T cell activation and broader B cell expansion (Figure 4).

Figure 4. *MF59* Mode of Action



Sources: Seubert 2008; Schultze 2008; Khurana 2010; Calabro 2011; Vono 2013

Studies in humans using pandemic influenza antigens and seasonal influenza antigens demonstrate that *MF59* adjuvanted vaccine increases the humoral response to a diverse set of influenza strains (Ansaldi 2008; Galli 2009). It appears that *MF59* may allow for broader recognition of influenza epitopes reflected by higher titers against influenza strains in the vaccine as well as those from antigenically drifted strains.

Although the reasons for these effects are not fully elucidated, a working hypothesis has been generated. By increasing immune cell recruitment to the injection site and thereby to the draining lymph node, *MF59* may reduce the competition between B cells for T cell help in germinal centers. Decreased competition for help could allow the clonal expansion and maturation of B

cells bearing antigen receptors that, before affinity maturation, have lower affinity for their targets. This interpretation is consistent with an analysis of antibody response in subjects immunized with *MF59* adjuvanted pandemic influenza vaccine. Khurana and colleagues showed that there was both an increased epitope breadth recognized and an increase in the affinity of antibodies for their epitopes (Khurana 2010; Khurana 2011).

4.2 Further Rationale for Adjuvant

Annual influenza vaccination in individuals above the age of 6 months is acknowledged as the most successful means for reducing the impact of seasonal influenza outbreaks and is the accepted practice in the US. In order to provide enough doses to supply a large population, considerable investment has been made to ensure that there are adequate doses available. Even with seven influenza vaccine manufacturers providing vaccine to the US population, the total number of doses to be supplied in the 2014/5 influenza season was up to 156 million doses (CDC 2014b). Delays or shortages from one or more manufacturers in the delivery of influenza vaccines to the market risk significant impact to the health of older adults, who are more likely to suffer severe complications due to influenza (Rodewald 2001). The use of adjuvants has been associated with higher immunogenicity at standard (15µg) antigen doses. Therefore adjuvanted vaccines may be a viable means of providing improved vaccines to older adults without constraining vaccine antigen supply.

A further rationale for adjuvant use is the potential for recognizing a broader repertoire of influenza strains. Considering the challenges of identifying and producing well-matched influenza antigens for use in vaccines against circulating strains, an adjuvant which allows for greater breadth in antigenic recognition may be desirable in the event of antigenic drift. In a clinical study of pandemic influenza vaccine candidates, adults who had been vaccinated with an A/H5N3 influenza strain formulated with *MF59* demonstrated higher antibody responses upon exposure to A/H5N1 influenza vaccine years later as compared to individuals who were primed with non-adjuvanted A/H5N3 vaccine (Stephenson 2005). The observations with this pandemic strain are further reflected by increased antibody responses to heterologous seasonal influenza strains in sera from older adult subjects vaccinated with aTIV. These results are described later in this briefing document.

Adjuvant use has also been associated with higher antibody responses for some influenza strains at time points remote from vaccination (e.g., 6 months and 12 months), for details see Section 7.4.4. Although it remains to be confirmed by efficacy studies, this suggests the possibility of longer protection in influenza seasons that end later than usual. The data in clinical trials with older adults are shared later in this briefing document. Of note, in an ongoing NVD sponsored clinical program, significantly higher and more persistent antibody responses and increased vaccine efficacy have been demonstrated following vaccination with aTIV in randomized controlled trials enrolling children ages 6 months to < 6 years of age (Vesikari 2011; Nolan 2014).

5 OVERVIEW OF aTIV REGULATORY STRATEGY

Summary

- aTIV is an inactivated influenza virus vaccine indicated for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.
- NVD is seeking approval for aTIV through the accelerated approval pathway pursuant to 21 CFR 601.41 Subpart E and as outlined in the May 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.
- The efficacy of aTIV is based on an immunogenicity trial of aTIV as compared to a US licensed TIV.
- The immune responses were evaluated using HI antibody responses (geometric mean titers (GMTs) and seroconversion rates), which are regarded as surrogate markers reasonably likely to predict benefit.
- The data obtained from the pivotal immunogenicity study along with the planned initiation of the confirmatory study meet the proposed criteria for accelerated approval of aTIV.

5.1 Indication

aTIV is an inactivated influenza virus vaccine indicated for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

5.2 Rationale for Licensure of aTIV Under Accelerated Approval

There are two regulatory pathways to licensure of a seasonal influenza vaccine: traditional and accelerated. Traditional approval is based on data which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency. Potency is interpreted by the FDA to include effectiveness (21CFR 600.3(s)). The accelerated approval pathway is an approval on the basis of adequate and well-controlled trials establishing that the product has an effect on a surrogate endpoint reasonably likely to predict clinical benefit. Approval under the accelerated approval regulations is subject to the requirement that the applicant study the product further to verify and describe its clinical benefit in a post-marketing setting.

NVD is seeking approval for aTIV through the accelerated approval pathway pursuant to 21 CFR 601.41 Subpart E and as outlined in the May 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. The guidance

states that, “*A non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed seasonal inactivated influenza vaccine (except for those granted accelerated approval whose clinical benefit awaits confirmation) may support an accelerated approval. The study should be adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine (e.g., a total of six co-primary endpoints for a trivalent vaccine): 1) GMT, and 2) seroconversion rates.*”

Accelerated approval is primarily based on data from the pivotal trial, which was a phase III randomized, controlled, observer-blind study to evaluate the safety and immunogenicity of aTIV in comparison to an active US licensed TIV comparator, *Agriflu* that had the same antigen content as the test vaccine. An additional objective of the study was to demonstrate consistency in immunogenic response across multiple aTIV lots. The pivotal study was designed to establish the safety and immunogenicity of aTIV based on pre-specified criteria agreed upon with CBER during a Type-B meeting in March 2010.

The immune responses were evaluated using the HI antibody responses (GMT and seroconversion rates), which are regarded as surrogate markers reasonably likely to predict clinical benefit. NVD has committed to conducting the clinical endpoint confirmatory study to verify and describe the clinical benefit. This study is planned to start in October 2015. The data obtained from the pivotal immunogenicity study along with the planned initiation of the confirmatory study meet the criteria for accelerated approval of aTIV.

5.3 US Regulatory Timeline

The initial IND application for aTIV was filed in May 2010, following a pre-IND meeting in March 2010 to discuss the clinical development plan and the possible pathway for licensure. The regulatory pathway for licensure was also discussed in a pre-BLA meeting in December 2011 taking into consideration the clinical data available from the pivotal study. Based on further discussions with CBER in a Type-C meeting written response in September 2013 and review of additional clinical data, NVD is seeking licensure for aTIV under FDA’s accelerated approval provision program. The proposed confirmatory study is scheduled to begin in October 2015.

6 CLINICAL DEVELOPMENT PROGRAM

Summary

- The aTIV clinical development program includes 39 immunogenicity studies. Of these, 23 were RCTs (16 first-dose trials, 7 revaccination trials) comparing the immunogenicity and safety of aTIV to TIV among adults age 65 and older.
- The focus of this briefing document is the pivotal study, which randomized 7104 subjects. This trial is considered primary in the assessment of immunogenicity and safety.
- In addition to the pivotal study, 15 first-dose randomized controlled trials (FD-RCTs) and 7 revaccination trials were conducted among older individuals.
- The pivotal study randomized subjects in a 1:1:1:3 ratio to one of three lots of aTIV or the TIV comparator group and were followed for 1 year for persistence of effect.
- As defined in the protocol and statistical analysis plan (SAP), the co-primary objectives of the pivotal study were to establish:
 - aTIV lot-to-lot consistency
 - Non-inferiority of aTIV to TIV against 3 homologous strains at Day 22 based on HI antibody responses using CBER Guidance criteria. If non-inferiority was met, superiority was also to be tested. Immunogenicity was assessed in two ways:
 - Seroconversion: non-inferiority was defined as a difference in seroconversion rates between aTIV and TIV with the lower bound of the 2-sided 95% CI greater than -10%; superiority was defined as a difference in seroconversion rates significantly greater than 10%.
 - Geometric Mean Titers (GMTs): non-inferiority was defined as a ratio of the aTIV GMT to the TIV GMT with the lower bound of the 2-sided 95% CI greater than 0.67; superiority was defined as a GMT ratio significantly greater than 1.50. Secondary objectives included analyses of immunogenicity in subjects with pre-existing comorbidity and against heterologous influenza strains. Antibody persistence was assessed based on GMTs and seroconversion at 6 month and 1 year time points in a subgroup of subjects. The clinical effectiveness of aTIV and that of TIV were also compared for several endpoints.
- The same co-primary immunogenicity endpoints used in the pivotal study were applied to the other 15 FD-RCTs and the 7 revaccination studies.

6.1 Overview of Clinical Studies

The aTIV clinical development program includes 39 immunogenicity studies enrolling a total of 27,116 subjects age 65 years and older. These 39 studies include 16 FD-RCTs, 7 revaccination studies, and 16 open-label studies primarily conducted for the annual seasonal strain update required in Europe.

This briefing document focuses on the 16 FD-RCTs and revaccination studies in which aTIV was compared with a non-adjuvanted TIV in individuals age 65 and older. US residents accounted for approximately one-third of study subjects in each vaccine group (aTIV n=2031, TIV n=1669).

As shown in Table 4, the 16 first-dose randomized controlled trials (FD-RCT) which include 11,086 individuals enrolled to study safety and immunogenicity. Of the 16 FD-RCTs, there is one pivotal study ([Frey 2014](#)) conducted from 2010 to 2011, which was designed to address CBER criteria. This study is considered primary for analyses of immunogenicity (aTIV n=3479, TIV n=3482) and safety (aTIV n=3545, TIV n=3537) in the BLA.

The other supportive 15 FD-RCTs (aTIV n=2377; TIV n=1748) were conducted between 1992 and 2009 and were based on European advice initially and EMEA guidance after the release of the Note for Guidance on Harmonisation of Requirements for Influenza Vaccines in 1997 ([EMEA 1997](#)). Three of these 15 trials also evaluated immunogenicity endpoints in response to heterologous strains.

In addition to the FD-RCTs, the program includes 7 revaccination studies (Table 5) which consisted of revaccination of subjects from five of the FD-RCTs at year two (aTIV n=476; TIV n=315) or year three (aTIV n=150; TIV n=84).

Table 4. First-Dose Randomized Controlled Trials

Study	Influenza Season	Day of HI Measurement, Post-vaccination	N Subjects in Full Analysis Set	
			aTIV (N=5856)	TIV (N=5230)
Studies Included in FD-RCT Immunogenicity Meta-Analyses				
V70_27 ^{a,b}	2010-11	22, 181, 366	3479	3482
V7P34	1997-98	28	445	111
V7P30	1996-97	28	301	150
V7P5 ^b	1993-94	28, 180	202	100
V7P8	1994-95	28, 180	192	99
M63P1	2002-03	21, 180	175	174
V7P17	1995-96	28, 56	150	154
V7P24	1996-97	28, 180	149	147
V7P25	1995-96	28, 180	137	134
V7P7	1993-94	28, 135	106	99
V7P27	1996-97	28, 180	100	206
V7P26	1995-96	28, 180	71	70
V104P3	2008-09	21	47	44
V7P6	1993-94	28	47	95
V7P3 ^b	1992-93	28	46	46
V7P35 ^b	1997-98	28, 180	209 ^c	119 ^c

^a V70_27 is the Pivotal Study

^b These studies also evaluated immunogenicity endpoints in response to heterologous strains.

^c The number of subjects in Full Analysis Set (FAS) for study V7P35 as listed here represents a subgroup of vaccinated subjects for which primary immunogenicity analyses were conducted (n=9204 aTIV and n=4557 TIV). Note: Study V7P35 was not included in safety pooling at the request of FDA for methodological differences in safety assessment.

Table 5. Revaccination Trials

Study	Influenza Season	Day of HI Measurement, Post-vaccination	N Subjects in Full Analysis Set	
			aTIV (N)	TIV (N)
V7P3X1	1993-94	28, 180	39	35
V7P3X2	1994-95	28, 180	35	31
V7P5X1	1994-95	28, 180	139	70
V7P5X2	1995-96	28, 180	115	53
V7P7X1	1994-95	28, 180	72	62
V7P8X1	1995-96	28, 180	139	63
V7P25X1	1996-97	28, 180	87	85

6.2 Immune Response Surrogates

Based on the long-standing convention for influenza vaccines and per CBER Guidance, immunological responses in the various aTIV studies were assessed using a validated HI antibody assay at baseline (i.e., before vaccination) and approximately 3 to 4 weeks after vaccination, which is approximately when the HA and NA antibodies reach their peak in humans ([Kunzel 1996](#)).

Studies of influenza infection, including human challenge studies following vaccination, have indicated that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects ([Hobson 1972](#); [de Jong 2003](#)). In concert with the May 2007 CBER Guidance Document on seasonal influenza vaccines, an HI antibody titer of 40 or greater is considered to be an acceptable surrogate marker that is reasonably likely to predict clinical benefit ([CBER 2007](#)).

6.3 Design of the Pivotal Study

The pivotal study was a phase 3 randomized, controlled, observer-blind study to evaluate the safety and immunogenicity of aTIV in comparison to an active TIV comparator that had the same antigen content as the test vaccine and is approved for use in the US. An additional objective of the study was to demonstrate consistency in immunogenic response across multiple aTIV lots.

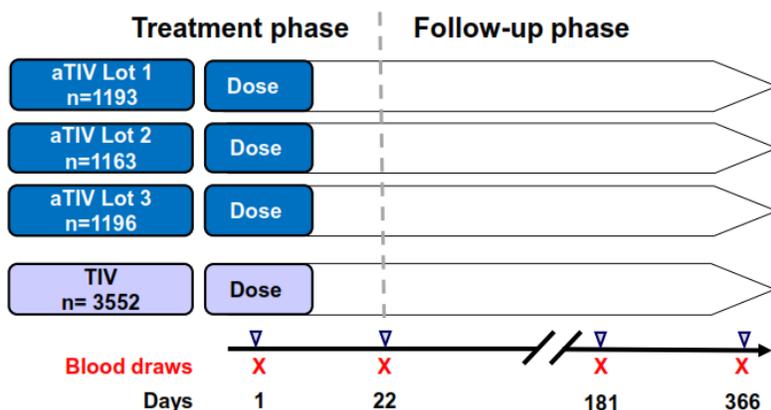
The pivotal study was conducted during the 2010 to 2011 Northern Hemisphere influenza season at 38 clinical sites located in the US, Philippines, Colombia, and Panama. Males and females ≥ 65 years of age were included in the trial. Individuals with known or suspected impairment/alteration of immune function, history of allergy to vaccines, or vaccination against seasonal

influenza in the previous 6 months were excluded. For a full list of inclusion and exclusion criteria see Appendix Section 14.2.1.

A total of 7104 subjects, age 65 years and older, were randomized in a 1:1:1:3 ratio, either to one of 3 lots of aTIV or to one lot of TIV, stratified by center and age cohort (65 to 75 years or >75 years). The study period was divided into a treatment phase, which lasted from day 1 through day 22, and a follow-up phase through one year post-immunization (Figure 5). Subjects received a single 0.5-ml dose of assigned study vaccine (aTIV or TIV) intramuscularly on day 1 after randomization. This dose contained 15 µg of HA from each of the A strains (H1N1, H3N2), and B strain, for a total of 45 µg of HA. The study vaccines were administered by unblinded designated healthcare personnel who had no subsequent contact with the subjects.

Blood samples for immunogenicity testing were collected pre-vaccination on day 1 and on day 22 for all subjects. At selected sites in the US, subjects from both vaccine groups (aTIV n=189, TIV n=191) had additional sampling for antibody persistence testing, requiring additional blood collection on day 181 and day 366. Clinical effectiveness endpoints were assessed starting at day 23 through day 366.

Figure 5. Pivotal Study Design Diagram



6.4 Design of First-Dose Randomized Controlled Trials

A comparison of the relative immunogenicity of aTIV and TIV was also performed by combining the supportive 15 FD-RCTs (aTIV n=2377, TIV n=1748) with the pivotal trial in a meta-analysis. All 15 studies were randomized, TIV-controlled, and observer-blinded. Relevant findings are based on a retrospectively created FAS dataset from 5856 aTIV subjects and 5230 TIV subjects.

6.5 Design of Revaccination Trials

Revaccination studies following a cohort of subjects from 5 of the 15 FD-RCTs (n=791), were designed to evaluate repeated annual vaccination for 2 or 3 consecutive years based on the same

immunogenicity endpoints analyzed in the FD-RCTs. Study subjects remained in the same vaccine group as randomized in their respective parent trials.

6.6 Analysis Populations

6.6.1 Pivotal Study

In the pivotal study, multiple analysis sets were defined to assess different study objectives. In addition to the analysis sets defined below, a subgroup of subjects with pre-existing comorbid conditions (congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency, and neurological/neuromuscular, or metabolic disorders including diabetes mellitus) was evaluated for key secondary immunogenicity endpoints to confirm results in a more vulnerable older subject population (see Table 62 Appendix, for additional details).

The analysis populations are defined as follows:

- Full Analysis Set (FAS) Immunogenicity, homologous strains: All randomized subjects who received study vaccination and provided evaluable serum samples on both day 1 and day 22.
 - aTIV n=3479; TIV n=3482
- Per Protocol Set (PPS) Immunogenicity, homologous strains: All subjects in the FAS and had no major protocol violations.
 - aTIV n=3227; TIV n=3259
- FAS, Immunogenicity, heterologous strains: A subgroup of subjects (25% across vaccine groups) were selected for inclusion in the day 22 immunogenicity analysis using heterologous strains.
 - aTIV n=887; TIV n=881
- PPS Immunogenicity, heterologous strains: All subjects in the FAS for heterologous strains who had no major protocol violations.
 - aTIV n=834; TIV n=815
- FAS, Antibody Persistence Testing: A subgroup of subjects from US sites (the first 50 subjects from 8 US study sites) who (1) received a study vaccination and (2) provided evaluable blood samples at day 1, day 22, day 181, and day 366. In the event the subject received non-study influenza vaccine prior to day 366, the subject was to be removed from the analysis.
 - aTIV n=189; TIV n=191
- FAS, Effectiveness: All subjects in the randomized population who received a study vaccination.
 - aTIV n=3541; TIV n=3541
- Modified Full Analysis Set (mFAS), Effectiveness: FAS dataset with exclusions for effectiveness endpoints that occurred after receipt of non-study influenza vaccine.

- aTIV n=3497; TIV n=3499
- Safety Set: All randomized subjects who received a study vaccination and provided post-vaccination safety data.
 - aTIV n=3545; TIV n=3537

6.6.2 First-Dose Randomized Controlled Trials

Due to frequent vaccine strain changes along with the inherent influenza strain-dependent variations in HI antibody responses, traditional methods of combining immunogenicity data across all or subgroups of studies were not considered to be appropriate. Moreover, although immunogenicity results in individual studies were most often based on the per-protocol set (PPS), the definition of the PPS in each individual study was not consistent. As a consequence of this inconsistency, a full analysis set (FAS) was created and globally applied to all RCTs for these analyses.

- Full Analysis Set (FAS), FD-RCT: All randomized subjects who received study vaccination and provided evaluable serum samples before and at any time point after vaccination.
 - aTIV n=5856; TIV n=5230
 - Pivotal trial: aTIV n=3479; TIV n=3482
 - Supportive trials: aTIV n=2377; TIV n=1748

6.6.3 Revaccination Trials

- Full Analysis Set (FAS), Revaccination Studies: Subgroup of the FD-RCT FAS which enrolled in the revaccination studies
 - Vaccination 1 aTIV n=485; TIV n=326
 - Vaccination 2 aTIV n=476; TIV n=315
 - Vaccination 3 aTIV n=150; TIV n=84

6.7 Pivotal Study Objectives

6.7.1 Primary Objectives

As defined by the protocol and statistical analysis plan (SAP), the pivotal study had co-primary immunogenicity objectives evaluated in a stepwise fashion.

6.7.1.1 Lot-to-Lot Consistency Objective

The first co-primary objective was to demonstrate immunologic equivalence of three consecutive production lots of aTIV, as measured by day 22 GMTs for each virus strain in the PPS. Lot-to-lot consistency of aTIV lots could be claimed if the 2-sided 95% CIs of the day 22 GMT ratios for

all 3 strains in all 3 lots were entirely within 0.67 and 1.5. Lot-to-lot consistency needed to be demonstrated to test for the subsequent co-primary immunogenicity objectives.

6.7.1.2 Co-Primary Immunogenicity Objectives

The other co-primary objectives were to: (1) demonstrate non-inferiority of aTIV compared to TIV, as measured by day 22 seroconversion rate differences and GMT ratios, and (2), if non-inferiority was met, evaluate the same endpoints for superiority. Non-inferiority of aTIV to TIV was evaluated in the PPS, and required that all 3 homologous strains demonstrate non-inferiority for percentage of subjects who seroconverted and GMTs ratios. Superiority of aTIV to TIV was evaluated in the FAS, and required that at least 2 of 3 homologous strains demonstrate superiority for both seroconversion rate differences and GMT ratios. The more conservative approach of using the PPS for non-inferiority and FAS for superiority is based on the ICH Guidance on Statistical Principles for Clinical Trials (ICH 1998).

Table 6 shows the pre-specified criteria for non-inferiority and superiority for co-primary immunogenicity objectives that compared aTIV to TIV. Non-inferiority margins were defined by CBER May 2007 guidance. The criteria for superiority, as agreed to by CBER and NVD in March 2010, required the seroconversion rate difference (aTIV-TIV) to be significantly greater than 10 percentage points. Seroconversion was defined as a prevaccination HI titer of < 10 and a postvaccination titer of ≥ 40 or at least a 4 fold increase in HI titer from a prevaccination HI titer of ≥ 10 . For GMTs, a superiority claim required the GMT ratio (aTIV:TIV) to be significantly greater than 1.5.

Table 6. Pre-Specified Criteria for Immunogenicity Endpoints of Inactivated Influenza Vaccine Trials

Endpoint	Definition	Pre-specified Criteria	
		Non-Inferiority	Superiority
Seroconversion (SC) rate difference	SC rate in the aTIV group minus the SC rate in the TIV group	Lower bound of 2-sided 95% CI $\geq -10\%$ for all 3 homologous strains	Significantly greater than 10% for 2/3 homologous strains
Post-vaccination Geometric Mean Titer Ratio	GMT in the aTIV group divided by the GMT in the TIV group	Lower bound of 2-sided 95% CI ≥ 0.67 for all 3 homologous strains	Significantly greater than 1.5 for 2/3 homologous strains

Note: For superiority, criteria for the same 2 of 3 homologous strains must be met for the SC rate difference and post-vaccination GMT ratio. Sources: Non-inferiority criteria: FDA. *Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*. 2007; Superiority criteria: communication with CBER (March 2010).

In addition to the pre-specified objectives, post-hoc analyses were performed on the FAS using the same endpoints (difference in seroconversion and GMT ratios) to assess the comparative

immunogenicity of aTIV to TIV. Seroconversion differences greater than 0 favor aTIV and GMT ratios greater than 1.0 favor aTIV.

6.7.2 Secondary Objectives

6.7.2.1 Secondary Immunogenicity Objectives

Three secondary immunogenicity objectives evaluated non-inferiority and superiority of aTIV to TIV in the same fashion as the co-primary objectives (Seroconversion rate differences and GMT ratios at day 22) for the following populations and strain types:

- In subjects with pre-existing comorbidity² antibody responses were evaluated against homologous strains
- In the subgroup of subjects, referred to as the heterologous analysis set, antibody responses were evaluated against heterologous strains (i.e., influenza variants of the same type/subtype that were not included in the vaccine composition)
- In subjects with pre-existing comorbidity antibody responses were evaluated against heterologous strains

In addition, a secondary immunogenicity objective was to compare in subgroups of all subjects aTIV and TIV HI antibody responses to homologous and heterologous influenza strains at days 181 and 366 post-vaccination. Non-inferiority and superiority were not pre-specified criteria for these analyses.

6.7.2.2 Secondary Clinical Effectiveness Objectives

Several secondary clinical effectiveness objectives evaluated the effectiveness of aTIV compared to TIV by comparing the percentages of subjects with the following parameters:

- Influenza like illness (ILI)
- Exacerbation of preexisting chronic disease
- Health care utilization (emergency room visits, unscheduled physician visits, hospitalizations for specific conditions)
- All-cause mortality

Subjects were followed for safety and clinical effectiveness endpoints via periodic telephone contacts and quarterly clinic visits or scheduled telephone contacts throughout the study. A memory aid was used by subjects to record ILI episodes and safety events starting on day 22 through day 366.

6.7.3 Statistical Methods

For the seroconversion rate component of the co-primary immunogenicity objective, log-linear models were used to compare the difference in effect between the two vaccine groups, adjusting for country and age cohort. For the GMT ratio component of the co-primary immunogenicity

² Comorbid conditions included: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency, and neurological/neuromuscular, or metabolic disorders including diabetes mellitus. For additional details see Appendix, Table 62.

objective, analysis of covariance (ANCOVA) was used to assess the relative effect of the two vaccine groups, adjusting for country, prevaccination titer, and age cohort (65-75 years or >75 years). P-values from tests for superiority were adjusted for multiplicity (i.e., additional statistical tests to assess superiority after establishing non-inferiority) using the methods described by [Dmitrienko et al. 2010](#). All 95% confidence intervals (CI) in the document are presented unadjusted since simultaneous CIs for step-wise procedures with both binary- and normally distributed endpoints were not available.

The first of the secondary immunogenicity objectives (i.e., assessment against homologous strains in subjects with pre-existing comorbidity) was also adjusted for multiplicity to control the type-I error rate using the same statistical models as the co-primary immunogenicity objectives.

The other secondary immunogenicity objectives compared immunogenicity between vaccine groups for heterologous strains. These objectives were evaluated using the same models as the co-primary objective, but were not formally statistically powered or adjusted for multiplicity.

The sample size of 3500 subjects per group (7000 total) was determined to provide adequate statistical power (>90%) to achieve the co-primary and first secondary immunogenicity objectives.

For assessment of the clinical effectiveness endpoints, differences in percentage of subjects between the vaccine groups were compared using Poisson regression models. The study was not powered to assess differences between vaccine groups in the clinical effectiveness endpoints.

6.7.4 Endpoints for Analysis of First-Dose Randomized Controlled Trials and Revaccination Studies

Of the 16 FD-RCTs only the pivotal study was specifically designed to address CBER guidance. The other studies were conducted according to European advice and/or guidance as discussed in Section 6.1. However, the same primary immunogenicity endpoints used in the pivotal study were retrospectively applied to the other 15 FD-RCTs and 7 revaccination studies, respectively, to correspond to CBER guidance.

Although the criteria listed in the CBER May 2007 Guidance are explicitly applicable only to HI antibody responses to homologous influenza strains, HI antibody responses to heterologous strains were measured in the pivotal study and 3 of the other 15 FD-RCTs.

For all FD-RCTs, a meta-analysis for the difference in percentages of subjects who seroconverted was calculated from a linear model with vaccine group and study as fixed effects; 95% CIs were calculated using the bootstrap method. Meta-analysis of the GMT ratios was calculated from a mixed model with baseline titer, vaccine group, and study as fixed effects, and the interaction between study and vaccine group as a random effect.

For each revaccination study, composite results based on the FAS were generated using the same approach as described for the FD-RCTs.

7 IMMUNOGENICITY FINDINGS IN PIVOTAL STUDY

Summary

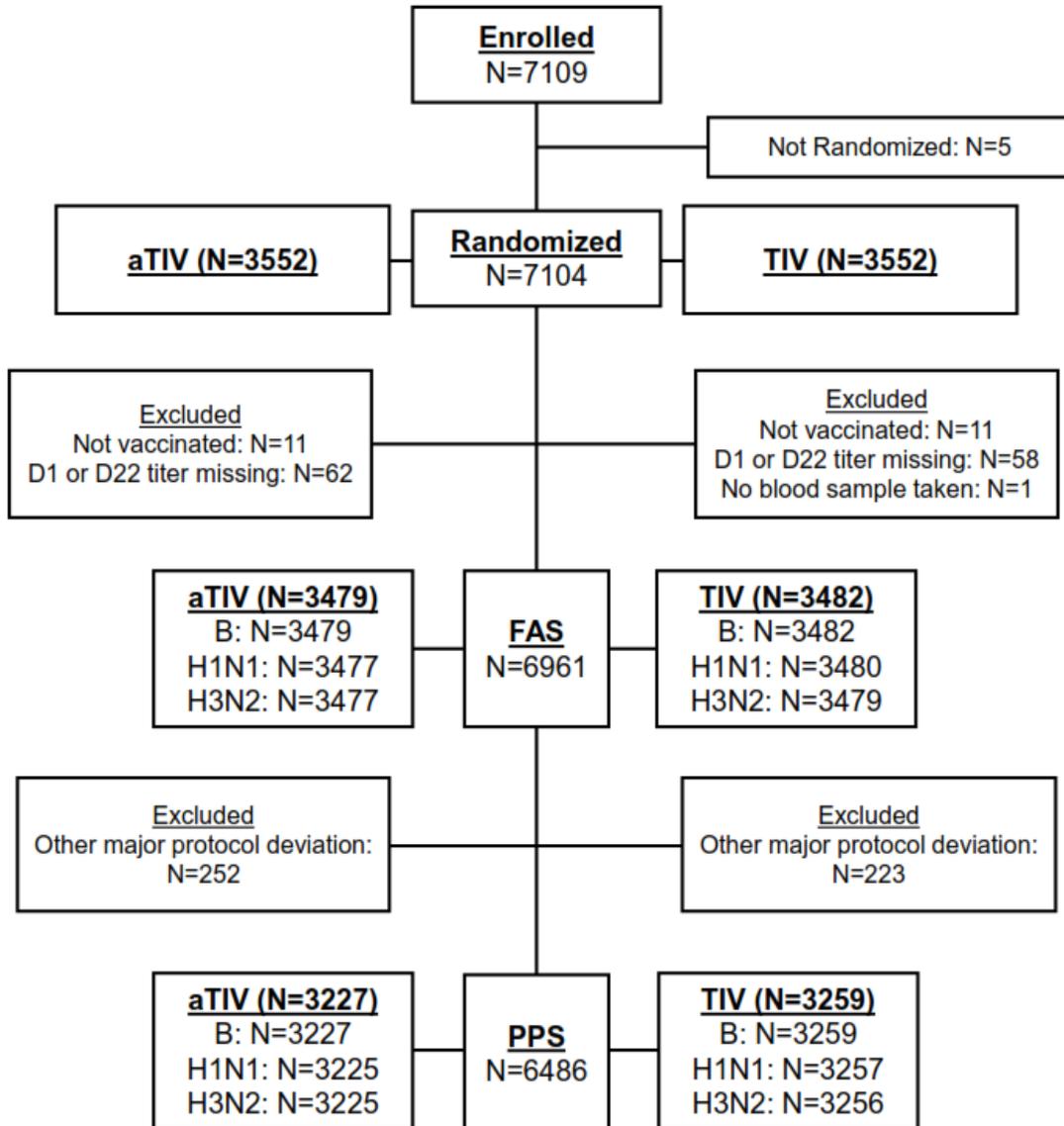
- There were three co-primary primary objectives to evaluate: lot-to-lot consistency, non-inferiority of aTIV as compared to TIV, and superiority of aTIV as compared to TIV. All were assessed based on the day 22 data.
 - Lot-to-lot consistency of aTIV was demonstrated
 - aTIV was non-inferior to TIV for all endpoints based on differences in seroconversion rates and vaccine group GMT ratios against the 3 homologous influenza strains.
 - The overall pre-specified superiority objective for the trial was not met; however, the superiority threshold was achieved for difference in seroconversion rates against one strain, the A/H3N2 strain.
 - In a post-hoc analysis, aTIV elicited higher percentages of subjects with seroconversion and higher vaccine group GMTs as compared to TIV across all three homologous influenza strains.
- Non-inferiority was demonstrated for all secondary immunogenicity objectives. In addition:
 - A higher percentage of subjects with pre-existing comorbidity who received aTIV seroconverted against both homologous influenza A strains than those who received TIV. aTIV also elicited higher day 22 GMTs against all three homologous strains as compared to TIV.
 - In response to the heterologous A strains, a higher percentage of subjects who received aTIV seroconverted than those who received TIV. aTIV also elicited higher day 22 GMTs as compared to TIV.
 - Excepting A/H1N1 strain at day 366, homologous HI antibody titers were higher after vaccination with aTIV across all three strains when measured at days 181 and day 366.
 - There were no significant differences between aTIV and TIV for any of the clinical effectiveness endpoints.

7.1 Subject Disposition

The disposition of subjects in the pivotal study is shown in Figure 6. Of the 7109 subjects enrolled, 5 of those subjects were not randomized to vaccine groups due to insufficient randomization numbers allocated to the sites. Of the 7104 subjects, 22 (11 in each vaccine group) did not receive study vaccine and thus 7082 were randomized and vaccinated. Ultimately,

6961 of the randomized subjects (98.0%) were included in the FAS and 6486 (91.6%) were included in the PPS. Major protocol deviations leading to exclusion from the day 22 PPS were recorded for 9% of subjects (n=325) in the aTIV group and 8% of subjects (n=293) in the TIV group. The most commonly reported major protocol deviations were collection of day 22 blood samples outside of the visit window (6% and 5%, aTIV and TIV, respectively) and missing visit 3 entirely (2% in both groups). All other major protocol deviations occurred in <1% of subjects.

Figure 6. Subject Completion Flowchart, Pivotal Study



At 1 year, 6717 subjects completed the study (94%). The reasons for withdrawal between the two arms were comparable for both the aTIV and TIV group (Table 7). The most frequent reason for early study withdrawal was “lost to follow-up” (aTIV, 2% vs TIV, 3%).

Table 7. Summary of Study Completion, Pivotal Study

	aTIV		TIV		Not randomized	Total	
Enrolled population	3552		3552		5	7109	
Exposed/Vaccinated	3541	(100%)	3541	(100%)	0	7082	(100%)
Completed Study	3361	(95%)	3356	(94%)	0	6717	(94%)
Withdrew Early	190	(5%)	196	(6%)	0	391	(6%)
Death ^a	51	(1%)	46	(1%)	0	97	(1%)
AE	3	(<1%)	2	(<1%)	0	5	(<1%)
Withdrew consent	52	(1%)	43	(1%)	0	95	(1%)
Lost to follow-up	73	(2%)	91	(3%)	2 (40%)	166	(2%)
Inappropriate enrollment	5	(<1%)	4	(<1%)	2 (40%)	11	(<1%)
Administrative reason	1	(<1%)	1	(<1%)	0	2	(<1%)
Protocol deviation	2	(<1%)	2	(<1%)	0	4	(<1%)
Unable to classify	3	(<1%)	7	(<1%)	1 (20%)	11	(<1%)
Reason missing	1	(<1%)	0		0	1	(<1%)

^aThe death of one additional subject in the aTIV group was recorded on a case report form but not as an outcome from the AE; however, prior to death the subject withdrew from the study due to an AE. For a complete summary of deaths in the pivotal study see Section 11.10

7.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics were similar between the two vaccine groups (Table 8). The mean age of subjects was 71.9 years in the aTIV group and 71.8 years in the TIV group. The median age of subjects was 71.0 years in both vaccine groups. Overall, 28% (n=1926) of subjects were over 75 years of age. More female subjects than male subjects participated in the pivotal study. This difference was similar between vaccine groups with 64% (n=2227) of female subjects in the aTIV group and 66% (n=2304) in the TIV group. In each vaccine group, 30% of subjects (aTIV n=1036, TIV n=1055) were from the US.

As the study was enrolled in the 2010/2011 Northern Hemisphere influenza season, baseline data relating to A/H1N1 pandemic 2009 exposure were collected as part of baseline demographics. Receipt of pandemic H1N1 vaccination within the 6 months (“Previous H1N1 Pandemic Vaccination”) preceding enrollment was reported by 2% of subjects in each vaccine group, while <1% in each group reported a history of H1N1 infection within 6 months prior to study enrollment.

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Baseline and demographic characteristics in other immunogenicity datasets (i.e., PPS, antibody persistence, and subjects with pre-existing comorbidity subgroups) were similar between the aTIV and TIV groups.

Table 8. Demographic and Other Baseline Characteristics, Pivotal Study

	aTIV (N=3479)		TIV (N=3482)	
Age (years)				
Mean ± SD	71.9 ± 5.3		71.8 ± 5.3	
Median	71.0		71.0	
Gender, n (%)				
Male	1252	(36%)	1178	(34%)
Female	2227	(64%)	2304	(66%)
Country, n (%)				
Colombia	503	(14%)	495	(14%)
Panama	108	(3%)	102	(3%)
Philippines	1832	(53%)	1830	(53%)
United States	1036	(30%)	1055	(30%)
Ethnic Origin, n (%)				
Asian	1837	(53%)	1840	(53%)
Black	44	(1%)	39	(1%)
Caucasian	969	(28%)	971	(28%)
Hispanic	616	(18%)	613	(18%)
Other	11	(<1%)	16	(<1%)
Native American/Alaskan Pacific/Hawaii	1	(<1%)	3	(<1%)
0	1	(<1%)	0	
Weight (kg), mean ± SD	63.4 ± 19.5		63.4 ± 19.4	
Height (cm), mean ± SD	156.9 ± 11.6		156.7 ± 11.5	
Body Mass Index, mean ± SD	25.4 ± 5.7		25.4 ± 5.6	
Previous Pneumococcal Vaccination, n (%) ^a				
Yes	739	(21%)	717	(21%)
No	2627	(76%)	2664	(77%)
Not done/unknown	113	(3%)	101	(3%)
Previous H1N1 Pandemic Vaccination, n (%) ^b				
Yes	79	(2%)	74	(2%)
No	3389	(97%)	3396	(98%)
Not done/unknown	11	(<1%)	12	(<1%)
H1N1 Disease, n (%) ^c				
Yes	1	(<1%)	2	(<1%)
No	3476	(>99%)	3474	(>99%)
Not done/unknown	2	(<1%)	6	(<1%)

^a History of pneumococcal vaccination within the 5 years preceding enrollment. ^b History of pandemic H1N1 vaccination within the 6 months preceding enrollment. ^c History of pandemic H1N1 disease within the 6 months preceding enrollment.

7.3 Co-Primary Objectives: Lot-to-Lot Consistency, Non-Inferiority and Superiority of Immunogenic Response in Homologous Strains

7.3.1 Lot-to-Lot Consistency

The 95% CIs of GMT ratios for pairwise lot group comparisons fell within the equivalence range of 0.67 to 1.5 for all 3 homologous strains (Table 9). Therefore, the first co-primary objective was met, and results from subjects in each of the aTIV groups could be pooled for comparison with the TIV group.

Table 9. Lot-to-Lot GMT Ratios, Homologous Strains, Pivotal Study

Strain	GMT Ratio (95% CI) ^a		
	Lot 1 : Lot2	Lot 1 : Lot 3	Lot 2 : Lot 3
A/H1N1 (California)	1.12 (1 – 1.24)	1.05 (0.95 – 1.17)	0.94 (0.85 – 1.05)
A/H3N2 (Perth)	1.01 (0.92 – 1.11)	0.99 (0.9 -1.08)	0.98 (0.89 – 1.07)
B-strain (Brisbane)	1 (0.91 – 1.1)	0.96 (0.87 – 1.05)	0.96 (0.87 – 1.05)

^aDay 22 PPS.

7.3.2 Non-Inferiority

aTIV was demonstrated to be non-inferior to TIV. As shown in Table 10 the lower bounds of the 95% CI for the difference in percentage of subjects who seroconverted against the 3 homologous strains were all above -10%. The lower bounds of the 95% CI for GMT ratios against the 3 homologous strains all exceeded 0.67 (Table 11).

Table 10. Seroconversion Against Homologous Strains, Non-Inferiority Objective, Pivotal Study

Homologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Non-Inferiority - PPS				<i>Non-Inferiority Bound</i>		
A/H1N1 (California)	69%	58%	9.8% (7.5-12.1)			3225 3257
A/H3N2 (Perth)	73%	58%	13.9% (11.7-16.1)			3225 3256
B-strain (Brisbane)	33%	29%	3.2% (1.1-5.3)			3227 3259

-20 -15 -10 -5 0 5 10 15 20
 Favors TIV Favors aTIV
 Percent Difference (95% CI)

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 11. Geometric Mean (HI) Titers and GMT Ratios. Homologous Strains, Non-Inferiority Objective, Pivotal Study

Homologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Non-Inferiority - PPS				<i>Non-Inferiority Bound</i>		
A/H1N1 (California)	99	70	1.4 (1.32-1.49)			3225 3257
A/H3N2 (Perth)	272	169	1.61 (1.52-1.7)			3225 3256
B-strain (Brisbane)	28	24	1.15 (1.08-1.21)			3227 3259

0.5 0.67 1.0 1.5 2.0
 Favors TIV Favors aTIV
 GMT Ratio (95% CI)

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

7.3.3 Superiority

Superiority of aTIV to TIV was not demonstrated. The pre-specified endpoints for percentage difference in seroconversion (significantly greater than 10%; Table 12) and GMT ratios (significantly greater than 1.5; Table 13) were not met for 2 of the 3 homologous strains tested.

Although the overall objective was not met, the percentage of subjects in the aTIV group who seroconverted was 13.8% higher than the TIV group against the A/H3N2 strain (multiplicity-adjusted $P=0.002$). While aTIV also exceeded the superiority threshold for GMT ratios against the A/H3N2 strain (GMT ratio: 1.6, 95% CI: 1.51-1.68), after adjusting for multiple comparisons, this result was no longer statistically significant at the 0.05 level ($P=0.055$).

In a post-hoc analysis, aTIV elicited consistently higher rates of seroconversion (all lower bounds of 95% CI exceeded 0) and GMT levels (all lower bounds of 95% CI exceeded 1) than TIV against all 3 homologous strains.

Table 12. Seroconversion Against Homologous Strains, Superiority Objective, Pivotal Study

Homologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Superiority - FAS						
A/H1N1 (California)	68%	59%	9.6% (7.4-11.8)		3477	3480
A/H3N2 (Perth)	72%	58%	13.8% (11.7-16)		3477	3479
B-strain (Brisbane)	33%	30%	3% (1-5)		3479	3482

-20 -15 -10 -5 0 5 10 15 20
 ← Favours TIV Favours aTIV →
Percent Difference (95% CI)

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 13. Geometric Mean (HI) Titers and GMT Ratios, Homologous Strains, Superiority Objective, Pivotal Study

Homologous Strain	Geometric Mean HI Titers		aTIV:TIV	GMT Ratio (95% CI)	N	
	aTIV	TIV			aTIV	TIV
Superiority - FAS						
A/H1N1 (California)	98	71	1.37 (1.29-1.46)		3477	3480
A/H3N2 (Perth)	267	167	1.6 (1.51-1.68)		3477	3479
B-strain (Brisbane)	27	24	1.14 (1.08-1.2)		3479	3482

0.5 0.67 1.0 1.5 2.0
 ← Favours TIV Favours aTIV →
GMT Ratio (95% CI)

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

7.3.4 Subgroup Analyses

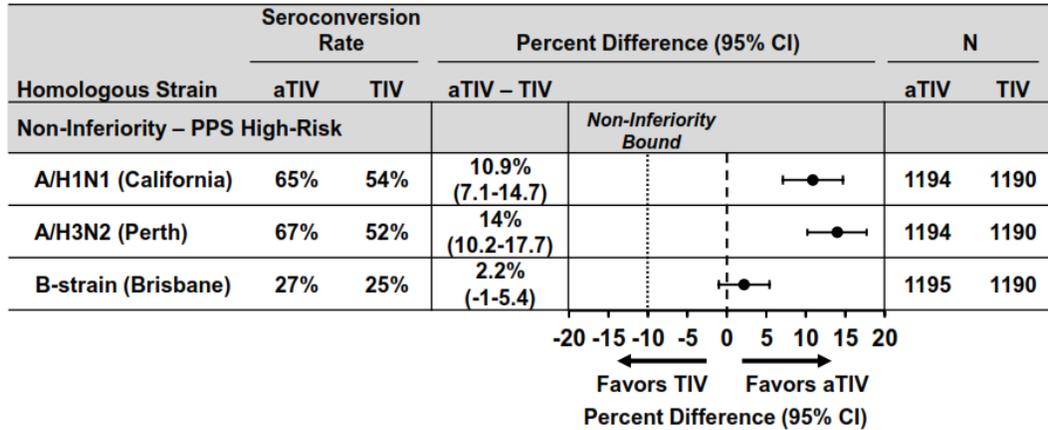
The immunogenic response was evaluated in subpopulations including gender, race, age group, country, and antibody responses prior to vaccination (i.e., seropositivity rates). Greater immunogenicity of aTIV relative to TIV was generally shown across the analyzed subpopulations similar to the comparison between vaccine groups overall, indicating consistency in immunogenic response. These results are shown by homologous strain for differences in seroconversion and vaccine group GMT ratios in detail in the Appendix, Table 56 - Table 61.

7.4 Secondary Objectives

7.4.1 Immunogenicity Against Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Non-Inferiority Objective

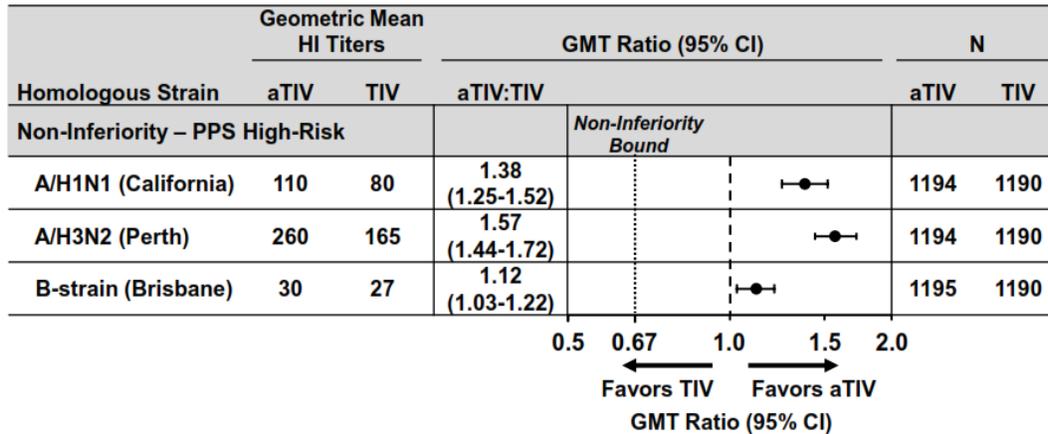
aTIV was demonstrated to be non-inferior to TIV among subjects with pre-existing comorbidity, defined as having one or more of the following: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency, and neurological/neuromuscular, or metabolic disorders including diabetes mellitus. Against the 3 homologous strains, the lower bounds of the 95% CI for seroconversion rate differences were all greater than -10% (Table 14). Similarly, the lower bounds of the 95% CI for GMT ratios were all greater than 0.67 (Table 15).

Table 14. Seroconversion Against Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Non-Inferiority Objective, Pivotal Study



Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 15. Geometric Mean (HI) Titers and GMT Ratios, Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Non-Inferiority Objective, Pivotal Study



Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

7.4.2 Immunogenicity Against Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Superiority Objective

Superiority of aTIV to TIV was not demonstrated among subjects with pre-existing comorbidity. Differences in seroconversion (Table 16) and GMT ratios (Table 17) were not significantly greater than 10% and 1.5, respectively, for 2 of 3 strains.

However, in a post-hoc analysis the percentage of subjects who seroconverted in the aTIV group was higher than the TIV group for both homologous A strains based on a lower 95% CI exceeding 0. aTIV also elicited higher GMTs than TIV for all 3 homologous strains in subjects with pre-existing comorbidity based on a lower 95% CI exceeding 1.

Table 16. Seroconversion Against Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Superiority Objective, Pivotal Study

Homologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Superiority – FAS High-Risk						
A/H1N1 (California)	64%	54%	10.2% (6.5-13.9)		1299	1273
A/H3N2 (Perth)	66%	53%	13.3% (9.7-16.9)		1299	1273
B-strain (Brisbane)	27%	25%	1.7% (-1.4-4.8)		1300	1273

-20 -15 -10 -5 0 5 10 15 20
 Favors TIV Favors aTIV
 Percent Difference (95% CI)

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 17. Geometric Mean (HI) Titers and GMT Ratios, Homologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Superiority Objective, Pivotal Study

Homologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Superiority – FAS High-Risk						
A/H1N1 (California)	106	80	1.32 (1.2-1.45)		1299	1273
A/H3N2 (Perth)	249	162	1.54 (1.42-1.68)		1299	1273
B-strain (Brisbane)	30	27	1.11 (1.03-1.21)		1300	1273

0.5 0.67 1.0 1.5 2.0
 Favors TIV Favors aTIV
 GMT Ratio (95% CI)

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

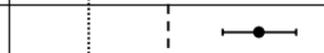
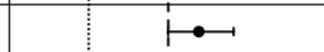
7.4.3 Immunogenicity Against Heterologous Strains, Non-Inferiority and Superiority Objectives

Heterologous antibody responses were tested against strains considered antigenically dissimilar from the vaccine including A/Brisbane/10/2007-like (H3N2), A/Wisconsin/67/2005-like (H3N2), and B/Malaysia/2506/2004-like (CDC 2014c). For reference, the vaccine strains included in the aTIV and TIV vaccines were A/California/7/2009-like (H1N1), A/Perth/16/2009-like (H3N2), and B/Brisbane/60/2008-like.

For all subjects with heterologous testing as well as the subgroup of subjects with pre-existing comorbidity, aTIV was demonstrated to be non-inferior to TIV. Superiority was not demonstrated.

In a post-hoc analysis, the seroconversion rate and GMTs in the aTIV group were both higher than in the TIV group for all comparisons against the heterologous A strains. These results are shown in detail in the following tables.

Table 18. Seroconversion Against Heterologous Strains, Non-Inferiority Objective, Pivotal Study

Heterologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Non-Inferiority – PPS				<i>Non-Inferiority Bound</i>		
A/H3N2 (Brisbane)	57%	46%	11.9% (7.3-16.5)		834	814
A/H3N2 (Wisconsin)	56%	45%	11.5% (6.9-16.2)		834	815
B-strain (Malaysia)	40%	37%	3.9% (0-8.3)		834	814

-20 -15 -10 -5 0 5 10 15 20
 ← Favours TIV Favours aTIV →
 Percent Difference (95% CI)

Note: Differences in percentages of subjects with seroconversion rates are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 19. Geometric Mean (HI) Titers and GMT Ratios, Heterologous Strains, Non-Inferiority Objective, Pivotal Study

Heterologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Non-Inferiority – PPS						
				<i>Non-Inferiority Bound</i>		
A/H3N2 (Brisbane)	185	128	1.45 (1.29-1.63)	-----●-----	834	814
A/H3N2 (Wisconsin)	518	382	1.36 (1.23-1.5)	-----●-----	834	815
B-strain (Malaysia)	44	41	1.09 (0.98-1.21)	-----●-----	834	814

0.5 0.67 1.0 1.5 2.0
 ← Favours TIV Favours aTIV
 GMT Ratio (95% CI)

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

Table 20. Seroconversion Against Heterologous Strains, Superiority Objective, Pivotal Study

Heterologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Superiority – FAS						
				<i>Superiority Bound</i>		
A/H3N2 (Brisbane)	58%	46%	12.8% (8.4-17.2)	-----●-----	887	880
A/H3N2 (Wisconsin)	56%	45%	12.5% (8.1-17)	-----●-----	887	881
B-strain (Malaysia)	41%	38%	4.2% (0-8.4)	-----●-----	887	880

-20 -15 -10 -5 0 5 10 15 20
 ← Favours TIV Favours aTIV
 Percent Difference (95% CI)

Note: Differences in percentages of subjects with seroconversion rates are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 21. Geometric Mean (HI) Titers and GMT Ratios, Heterologous Strains, Superiority Objective, Pivotal Study

Heterologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Superiority – FAS						
A/H3N2 (Brisbane)	181	122	1.49 (1.33-1.67)		887	880
A/H3N2 (Wisconsin)	508	369	1.38 (1.25-1.52)		887	881
B-strain (Malaysia)	44	40	1.09 (0.99-1.21)		887	880

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

Table 22. Seroconversion Against Heterologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Non-Inferiority Objective, Pivotal Study

Heterologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Non-Inferiority – PPS High-Risk						
A/H3N2 (Brisbane)	52%	39%	12.6% (5.1-20)		302	307
A/H3N2 (Wisconsin)	51%	38%	12.1% (4.6-19.7)		302	307
B-strain (Malaysia)	35%	33%	3.7% (-3-10.5)		302	307

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 23. Geometric Mean (HI) Titers and GMT Ratios, Heterologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Non-Inferiority Objective, Pivotal Study

Heterologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Non-Inferiority – PPS High-Risk						
A/H3N2 (Brisbane)	188	140	1.35 (1.13-1.61)		302	307
A/H3N2 (Wisconsin)	483	375	1.29 (1.1-1.5)		302	307
B-strain (Malaysia)	58	53	1.11 (0.95-1.3)		302	307

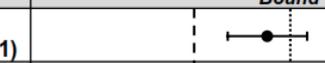
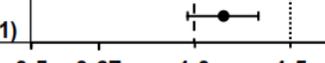
Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

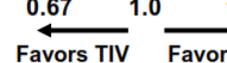
Table 24. Seroconversion Against Heterologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Superiority Objective, Pivotal Study

Heterologous Strain	Seroconversion Rate		Percent Difference (95% CI)		N	
	aTIV	TIV	aTIV – TIV		aTIV	TIV
Superiority – FAS High-Risk						
A/H3N2 (Brisbane)	52%	39%	12.4% (5.2-19.5)		330	333
A/H3N2 (Wisconsin)	51%	38%	12.6% (5.4-19.8)		330	333
B-strain (Malaysia)	36%	33%	3.4% (-3.1-10)		330	333

Note: Differences in percentages of subjects with seroconversion are adjusted for country and age cohort. 95% CIs are not adjusted for multiplicity.

Table 25. Geometric Mean (HI) Titers and GMT Ratios, Heterologous Strains in Subgroup of Subjects with Pre-Existing Comorbidity, Superiority Objective, Pivotal Study

Heterologous Strain	Geometric Mean HI Titers		GMT Ratio (95% CI)		N	
	aTIV	TIV	aTIV:TIV		aTIV	TIV
Superiority – FAS High-Risk						
A/H3N2 (Brisbane)	182	134	1.36 (1.15-1.61)		330	333
A/H3N2 (Wisconsin)	463	362	1.28 (1.1-1.48)		330	333
B-strain (Malaysia)	56	50	1.13 (0.97-1.31)		330	333

0.5 0.67 1.0 1.5 2.0

 Favors TIV Favors aTIV
 GMT Ratio (95% CI)

Note: GMT ratios are adjusted for country, age cohort, and prevaccination HI titer. 95% CIs are not adjusted for multiplicity.

7.4.4 Antibody Responses Remote from Vaccination

In order to evaluate if antibody responses in each vaccine group were sustained over time, GMTs were assessed in serum samples at 6 months and 1 year post-vaccination. The GMT ratio (aTIV/TIV) at each time point was evaluated, and if the lower limit of the 95% CI was greater than 1, this was regarded as a nominally significant difference. No formal statistical comparison was performed and no adjustments were made for baseline, country, or age in this subgroup due to the small size of this subgroup. At day 181, the point estimates for the GMT ratios were greater than one for all three homologous influenza strains, but only A/H3N2 demonstrated a nominally significant difference in GMT ratio (Table 26). At day 366, the point estimates for influenza B and A/H3N2 were greater than one, but only A/H3N2 demonstrated a nominally significant difference in GMT ratio. The point estimate for A/H1N1 was less than 1 at this time point, and this was not nominally significant.

For heterologous strains tested, GMT ratios at day 181 were as follows: A/Brisbane (H3N2) strain 1.24 (95% CI: 0.97-1.58), A/Wisconsin (H3N2) 1.18 (95% CI: 0.91-1.53), and B/Malaysia 1.03 (95% CI: 0.83-1.26). GMT ratios for heterologous strains tested at day 366 were as follows: A/Brisbane (H3N2) strain 1.04 (95% CI: 0.81-1.35), A/Wisconsin (H3N2) 1.04 (95% CI: 0.79-1.37), and B/Malaysia 0.96 (95% CI: 0.79-1.17). These results demonstrate point estimates that exceed 1 for the A/H3N2 heterologous strains at both later timepoints and only at day 181 for the heterologous B strain.

Table 26. Geometric Mean (HI) Titers, Homologous Strains Following Vaccination Including Remote Timepoints, Pivotal Study

Strain	Time	GMTs		GMT Ratio (95% CI)
		aTIV N=189	TIV N=191	
A/H1N1 (California)	Day 1	17	19	0.9 (0.69-1.18)
	Day 22	85	72	1.17 (0.9-1.51)
	Day 181	35	34	1.05 (0.82-1.33)
	Day 366	25	26	0.94 (0.73-1.22)
A/H3N2 (Perth)	Day 1	22	22	1 (0.77-1.29)
	Day 22	131	92	1.42 (1.11-1.82)
	Day 181	62	46	1.35 (1.06-1.71)
	Day 366	35	27	1.3 (1.01-1.67)
B-strain (Brisbane)	Day 1	12	12	0.97 (0.78-1.2)
	Day 22	25	21	1.21 (0.98-1.49)
	Day 181	12	11	1.12 (0.9-1.39)
	Day 366	10	10	1.03 (0.83-1.27)

Note: Bolded rate differences reflect nominally significant results. No adjustments were made for baseline, country, or age in the persistence subgroup due to its small sample size.

7.4.5 Clinical Effectiveness Endpoints

Parameters of clinical effectiveness were evaluated as secondary objectives of the study. The endpoints included: influenza like illness (ILI), exacerbation of preexisting chronic disease, health care utilization (emergency room visits, unscheduled physician visits, hospitalizations for specific conditions), and all-cause mortality.

7.4.5.1 Influenza-Like Illness

Influenza-like illness was defined as fever of $\geq 37.2^{\circ}\text{C}$ or feverishness in a study subject and at least 2 of the following symptoms: headache, myalgia, cough, or sore throat. (Feverishness is defined as the subject's subjective report of fever or a chill). Laboratory confirmation of influenza was not included in the evaluation of ILI, reducing the specificity of ILI case definition.

As shown in Table 27, no significant difference in ILI incidence was noted between vaccine groups. Additionally, total numbers of ILIs reported for each vaccine group were compared in order to account for multiple ILIs in some subjects; similarly, no significant difference was observed.

Table 27. Relative Risk of Influenza-Like Illness Across Vaccine Groups, Day 22 Through Day 366, Pivotal Study

Analysis Type	Risk Ratio (95% CI)
Subjects with ≥1 ILI	1.02 (0.87-1.19)
Total reported ILIs	1.02 (0.88-1.17)

Note: Risk ratios reflect aTIV:TIV and are adjusted for country.

7.4.5.2 Exacerbation of Pre-existing Chronic Disease

Exacerbation of preexisting chronic disease was defined as an emergency room visit, unscheduled physician visit, or hospitalization for any of the following: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal insufficiency, neurological/neuromuscular, or metabolic disorders including diabetes mellitus. As shown in Table 28, no significant differences were observed in the percentage of subjects reporting exacerbation of preexisting chronic conditions (95% CI of all Risk Ratios include 1).

Table 28. Percentages of Subjects and Relative Risk Ratios for Exacerbation of Pre-existing Chronic Disease in Subjects with Pre-existing Comorbidity, Day 1 Through Day 366, Pivotal Study

Pre-Existing Condition	aTIV	TIV	Risk Ratio (95% CI)
Any	55 (4%) N=1307	48 (4%) N=1281	1.35 (0.80-2.26)
Asthma	12 (7%) N=162	7 (4%) N=157	1.65 (0.65-4.19)
Neurological/Neuromuscular & Metabolic Disorders	22 (2%) N=1082	15 (1%) N=1050	1.42 (0.74-2.75)
Chronic Obstructive Pulmonary Disease	18 (11%) N=171	19 (11%) N=174	0.96 (0.50-1.83)
Congestive Heart Failure	3 (4%) N=76	10 (13%) N=79	0.31 (0.08-1.11)
Hepatic Disease	1 (8%) N=13	0 N=13	N/A
Renal Insufficiency	1 (2%) N=49	0 N=57	N/A

Note: Risk ratios reflect aTIV:TIV and are adjusted for country.

7.4.5.3 Healthcare Utilization

Healthcare utilization was assessed as the percentage of subjects with an emergency room visit, unscheduled physician visit, or hospitalization due to community-acquired influenza or pneumonia, cardiopulmonary disease, cardiac disease, respiratory or pulmonary disease. In the

overall study population, there were no significant differences between vaccine groups (Table 29).

Table 29. Comparison of Subjects Reporting Healthcare Utilization, Day 1 Through Day 366, Pivotal Study

Type of Visit	aTIV N=3499	TIV N=3502	Risk Ratio (95% CI)
Any	275 (8%)	289 (8%)	0.95 (0.81-1.12)
Emergency room visit	65 (2%)	56 (2%)	1.16 (0.81-1.66)
Hospitalization	70 (2%)	67 (2%)	1.04 (0.75-1.46)
Unscheduled physician visit	217 (6%)	229 (7%)	0.95 (0.79-1.14)

Note: Risk ratios reflect aTIV:TIV and are adjusted for country.

7.4.5.4 Mortality

All-cause mortality was comparable in the overall study population. In the aTIV group, 1% (52/3540) of subjects died compared to 1% (46/3541) of TIV subjects (Hazard Ratio: 1.13; 95% CI: 0.76-1.68).

8 IMMUNOGENICITY FINDINGS IN FIRST-DOSE RANDOMIZED CONTROLLED TRIALS

Summary

- All 16 FD-RCTs were included in a meta-analysis to evaluate the cumulative immunogenic experience comparing aTIV and TIV.
- aTIV was demonstrated to be non-inferior to TIV for all homologous strains based on the meta-analytic results of seroconversion differences and GMT ratios.
- For heterologous influenza strains, the pivotal trial and 3 additional trials of the FD-RCTs evaluated the immunogenicity of aTIV to TIV. In all comparisons, aTIV was demonstrated to be non-inferior to TIV based on seroconversion rate differences and GMT ratios.

8.1 Demographics and Baseline Characteristics

In the FAS of 16 FD-RCTs, 5856 aTIV subjects and 5230 TIV subjects were analyzed. The age, sex, race, country of residence, prior vaccination history, and percentage of subjects seronegative at baseline (HI antibody titer < 10) were generally similar between aTIV and TIV recipients (Table 30). Approximately two-thirds of subjects were 65 to 74 years old, approximately 60% were female, and one-third were from the US.

Table 30. Demographics and Baseline Characteristics in 16 FD-RCTs for Meta-Analysis

Attribute/Variable	aTIV N=5869	TIV N=5236
Age Group, n (%)		
65 to 74 years	3876 (66.0%)	3475 (66.4%)
75 years and older	1986 (33.8%)	1759 (33.6%)
Sex, n (% of total)		
Male	2332 (39.7%)	1982 (37.9%)
Female	3537 (60.3%)	3254 (62.1%)
Race		
Caucasian	3545 (64.6%)	3014 (61.0%)
Black	75 (1.4%)	56 (1.1%)
Asian	1847 (33.7%)	1851 (37.5%)
Other	17 (0.3%)	30 (0.4%)
Unknown	385	295
Residence		
United States	2031 (34.6%)	1669 (31.9%)
Rest of World	3838 (65.4%)	3567 (68.1%)
Were vaccinated against influenza in previous 12 months, n (%)		
No	3962 (73.1%)	3902 (79.9%)
Yes	1461 (26.9%)	983 (20.1%)
Unknown	446	380
Baseline HI antibody, A/H1N1, n (%)		
HI titer ≥ 10	4102 (70.1%)	3439 (65.8%)
HI titer < 10	1752 (29.9%)	1789 (34.2%)
Baseline HI antibody, A/H3N2, n (%)		
HI titer ≥ 10	5117 (88.4%)	4558 (87.2%)
HI titer < 10	677 (11.6%)	669 (12.8%)
Baseline HI antibody, Type B, n (%)		
HI titer ≥ 10	3932 (67.1%)	3327 (63.6%)
HI titer < 10	1924 (32.9%)	1903 (36.4%)

Note: Denominators may differ slightly from analysis to analysis because of missing HI antibody levels for a particular strain at particular time points and/or other missing information.

8.2 Immunogenicity Against Homologous Strains in FD-RCT Meta-Analysis

The results from the meta-analysis of the 16 FD-RCTs, as well as study-specific differences for percentages of subjects with seroconversion between aTIV and TIV are shown in Table 31. The

estimated pooled seroconversion rate differences across the 16 trials were 9.5% (95% CI: 5.2-13.9) for A/H1N1, 10.5% (95% CI: 6.6-14.5) for A/H3N2, and 12.7% (95% CI: 8.6-16.8) for the B-strain, demonstrating non-inferiority.

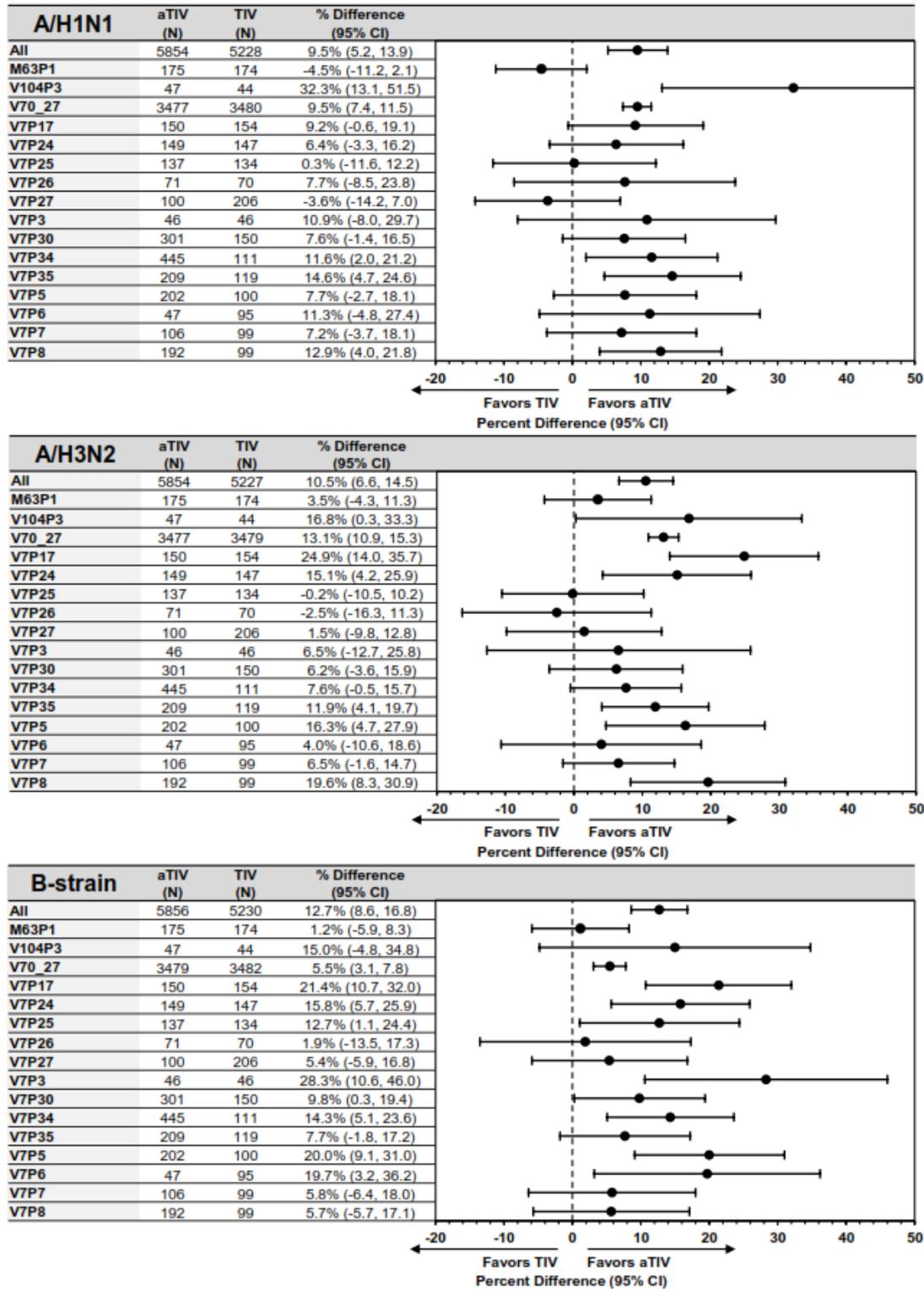
In 40 of the 48 study comparisons, aTIV was non-inferior to TIV (lower bound of 95% CI greater than -10%). Nearly all instances in which the non-inferior threshold was not met occurred in studies with group sample sizes of 100 or less and instances in which seroconversion rates varied from 25% to 75%, a range in which a binomial proportion is most statistically variable.

Overall, aTIV tended to have higher percentages of subjects with seroconversion than TIV across the studies (lower bound of 95% CI greater than 0).

The meta-analyzed result for the 16 FD-RCTs, as well as study-specific differences for GMT ratios are shown in Table 32. The estimated pooled GMT ratios across the 16 trials were 1.15 (95% CI: 1.01-1.31) for A/H1N1, 1.30 (95% CI: 1.18-1.44) for A/H3N2, and 1.23 (95% CI: 1.15-1.31) for the B-strain, demonstrating non-inferiority of aTIV to TIV.

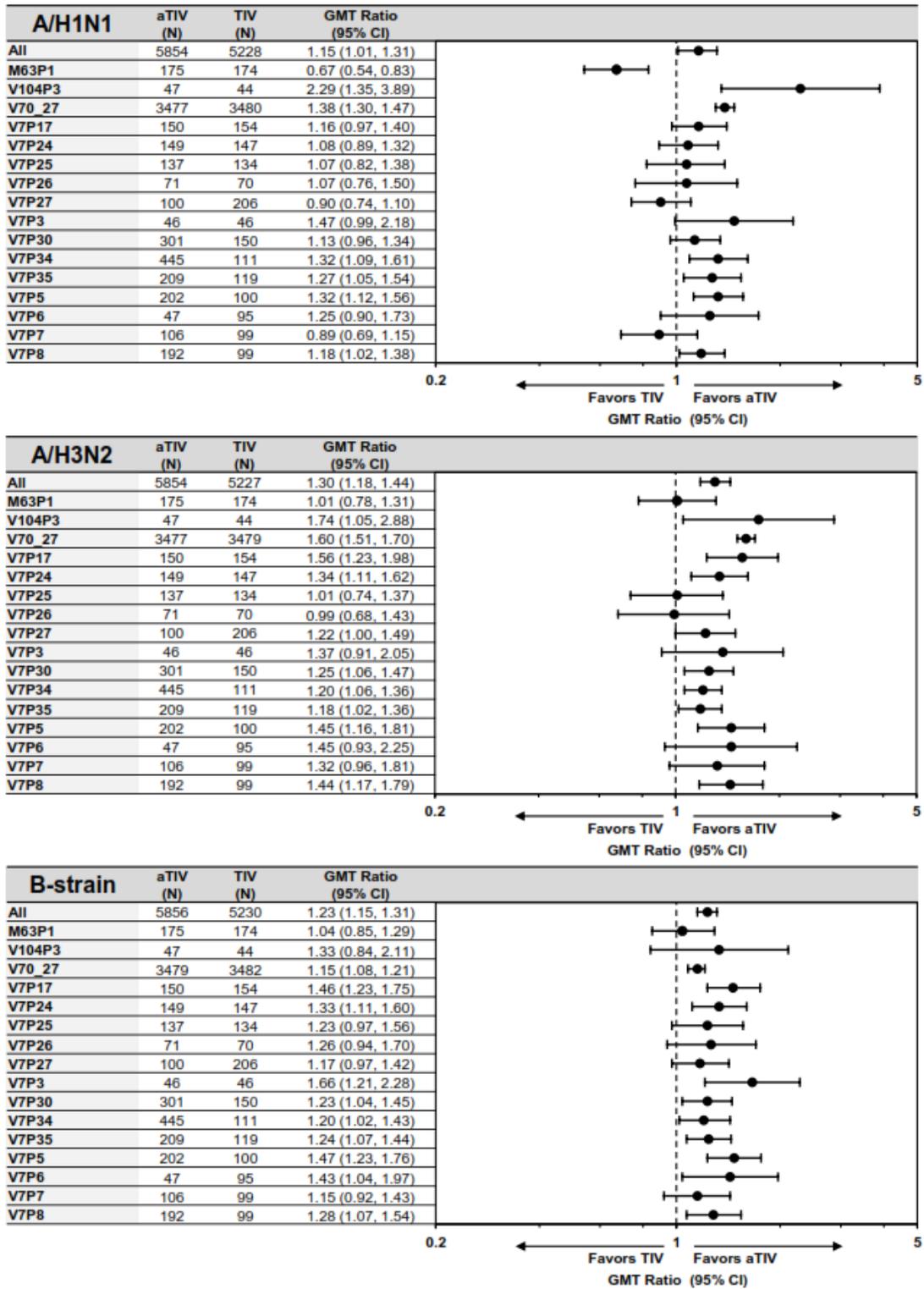
In 47 of 48 study comparisons, aTIV was non-inferior to TIV based on GMT ratios (lower bound of 95% CI greater than 0.67). Overall, aTIV tended to elicit higher GMTs than TIV (lower bound of 95% CI greater than 1.0).

Table 31. Differences in Seroconversion for Homologous Strains, FD-RCTs



Note: V70_27 is the Pivotal Study.

Table 32. GMT Ratios for Homologous Strains, FD-RCTs



Note: V70_27 is the Pivotal Study.

8.3 Immunogenicity Against Heterologous Strains in FD-RCTs

In addition to the pivotal trial, 3 other randomized controlled trials in the FD-RCT evaluated the HI antibody response of aTIV versus TIV to heterologous influenza strains. The criteria listed in the CBER May 2007 Guidance are explicitly applicable only to HI antibody responses to homologous influenza strains. However, the same criteria were applied to the heterologous strains as a stringent means of assessing post-vaccination antibody responses.

In all comparisons, aTIV was non-inferior to TIV as shown in Table 33 for seroconversion differences (lower bound of the 95% CI greater than -10%) and in Table 34 for GMT ratios (lower bound of the 95% CI greater than 0.67). Moreover, in 9 of 10 possible outcomes for the seroconversion differences, the lower bound of the 95% CI exceeded 0. In 7 of 10 possible outcomes for GMT ratios, the lower bound of the 95% CI exceeded 1.

Table 33. Differences in Seroconversion for Heterologous Strains, FD-RCTs

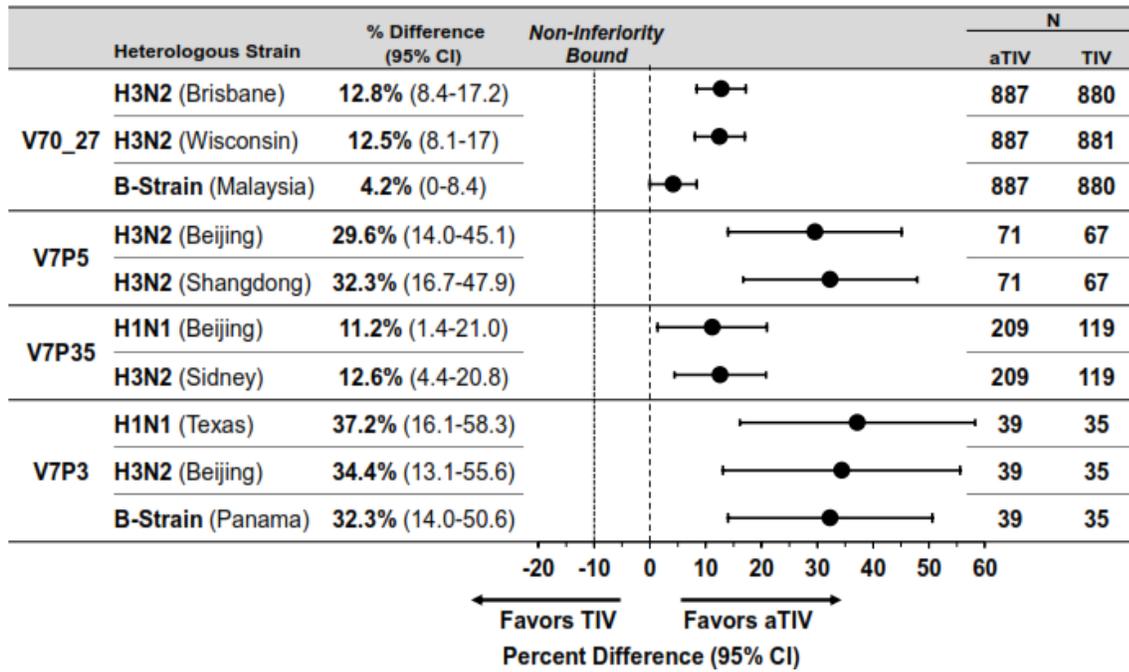
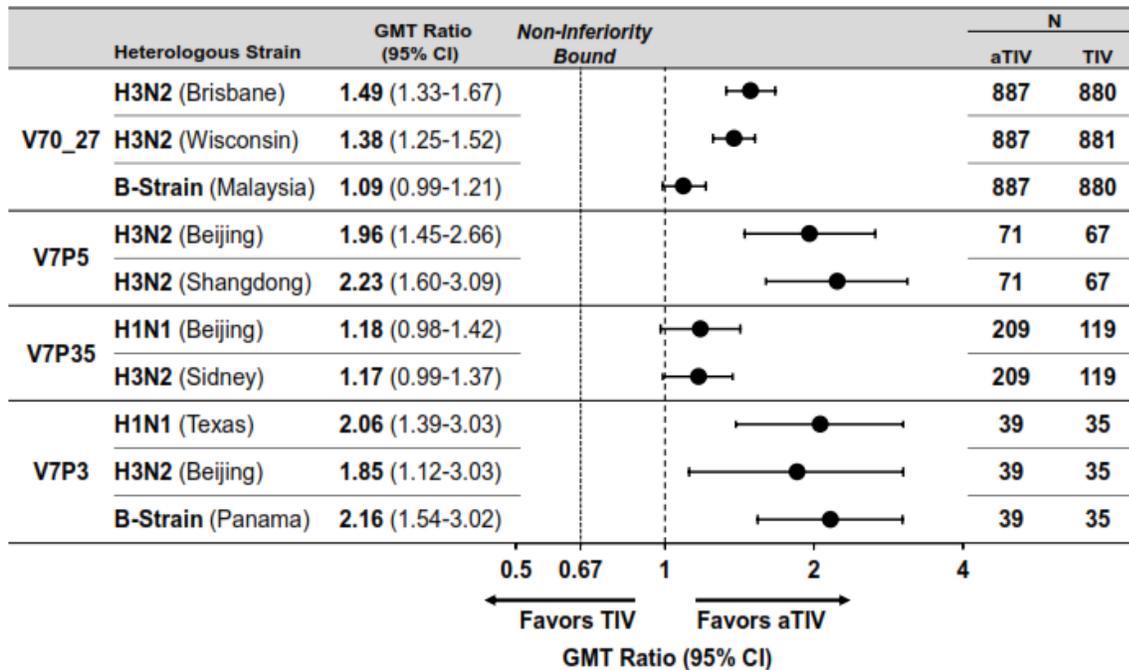


Table 34. GMT Ratios for Heterologous Strains, FD-RCTs



Note: V70_27 is the Pivotal Study.

9 IMMUNOGENICITY FINDINGS IN REVACCINATION TRIALS

Summary

- Seven revaccination studies evaluated the immunogenicity of aTIV compared to TIV over the course of consecutive annual influenza immunizations.
- The H1N1 component of 1 revaccination study did not change over the course of three consecutive influenza seasons, enabling a unique assessment of longitudinal GMTs between aTIV and TIV from year to year.
- Results indicate the immunogenicity of aTIV is not diminished after repeat vaccination.

Immunogenicity results from a retrospective analysis of 7 revaccination studies which involved the annual administration of two (aTIV n=476; TIV n=315) or three (aTIV n=150; TIV n=84) consecutive yearly vaccines are shown by strain in Table 35 for differences in seroconversion and in Table 36 for GMT ratios. Only subjects who were in both the parent and revaccination studies were included in the analysis.

For each study-specific outcome, aTIV was demonstrated to be non-inferior to TIV in 31 of 36 comparisons based on seroconversion rate differences (non-inferiority defined as lower limit of 95% CI > -10%) (Table 35), and in 35 of 36 comparisons based on GMT ratios (non-inferiority defined as lower limit of 95% CI > 0.67) (Table 36).

Table 35. Differences in Seroconversion for Homologous Strains, Revaccination Trials

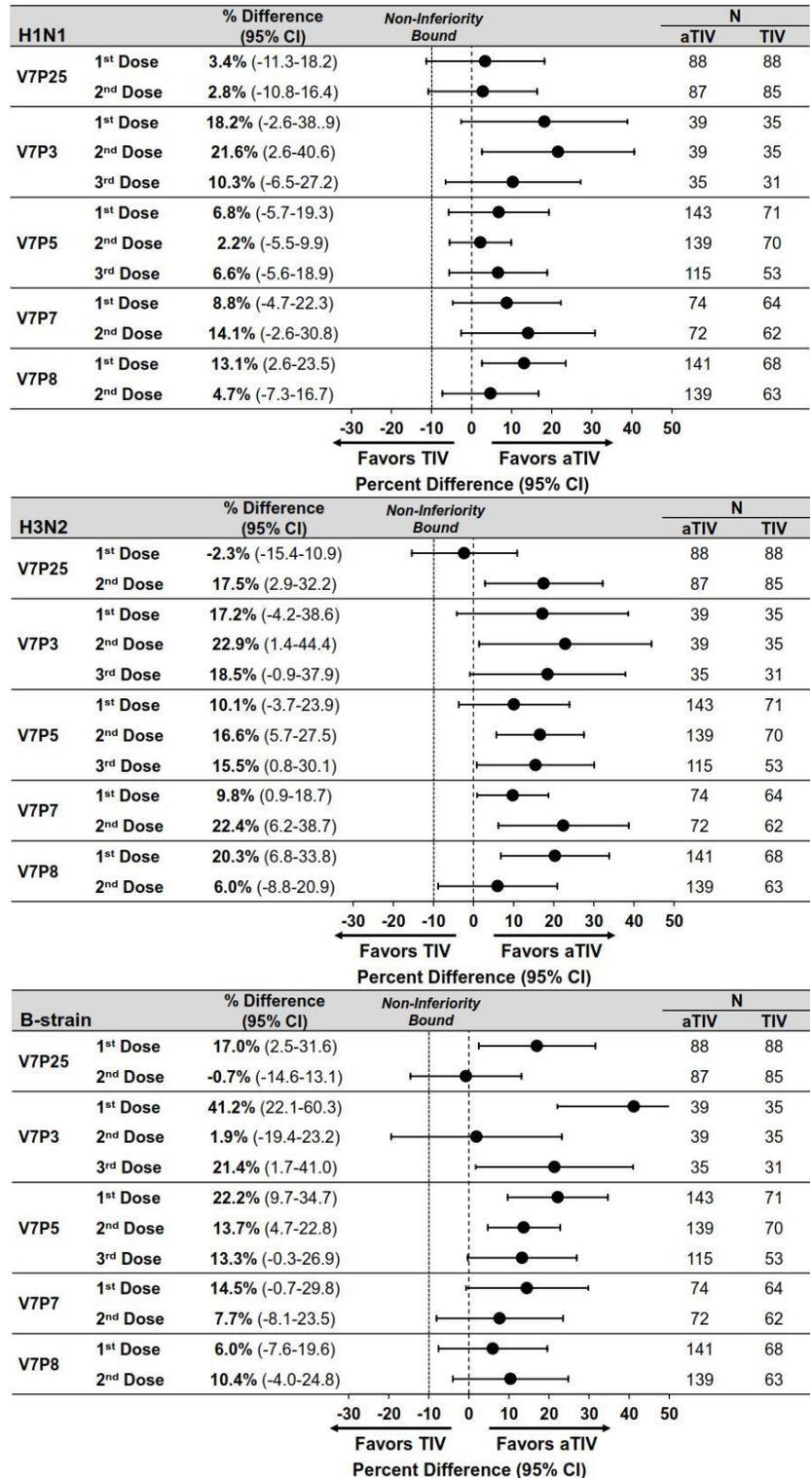
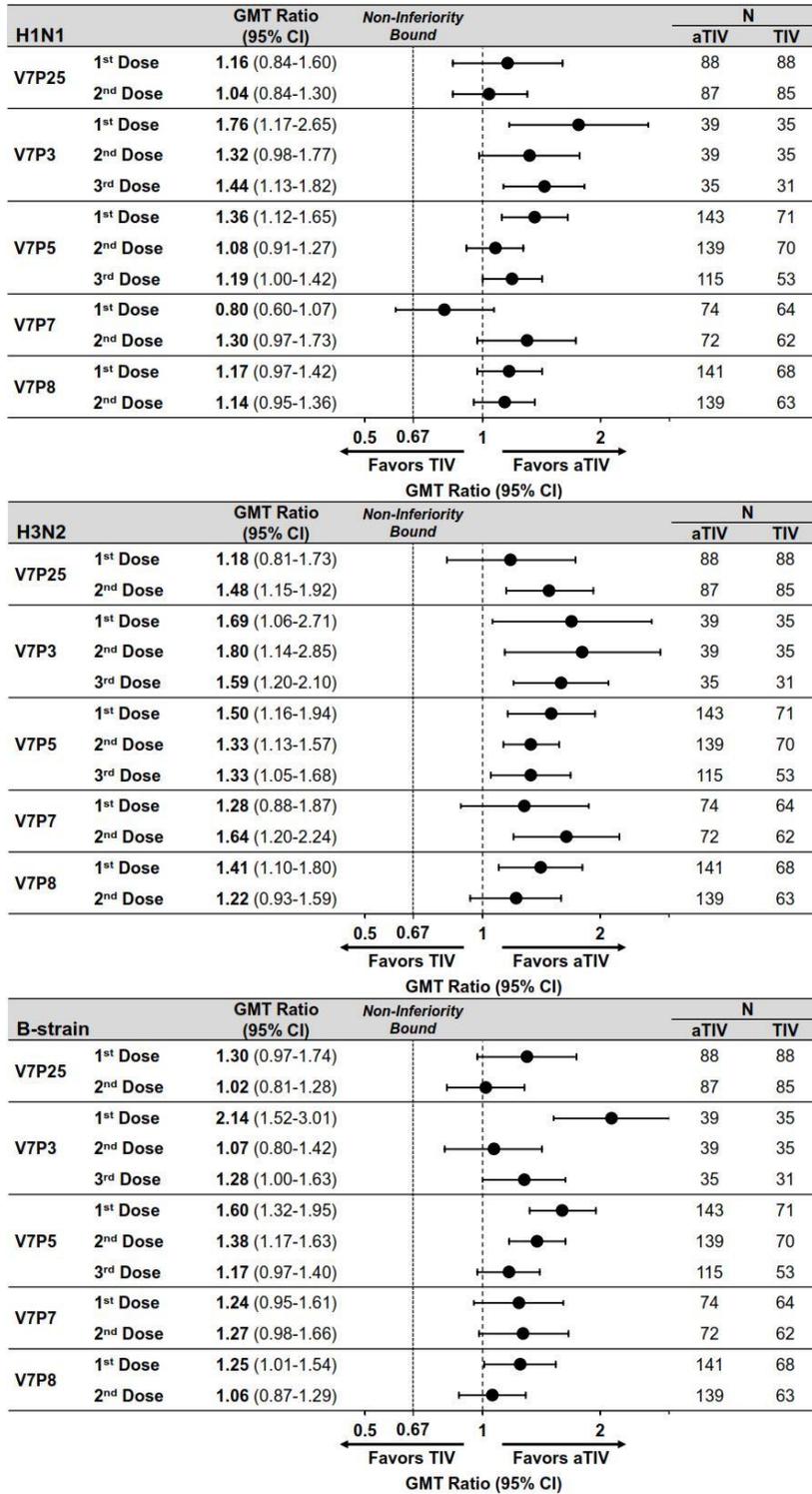
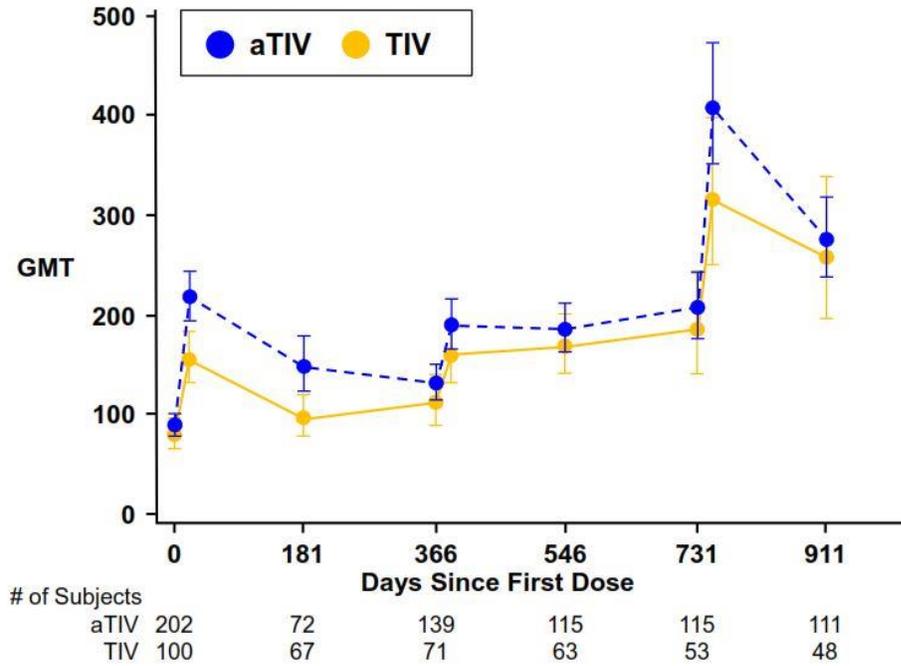


Table 36. GMT Ratios for Homologous Strains, Revaccination Trials



In one of the revaccination studies (V7P5), the H1N1 component of the vaccine did not change over the three consecutive seasons of vaccination, and the immune responses from the subjects provide a unique opportunity to show that the unadjusted GMT point estimates against the strain were higher in the aTIV compared with the TIV group in each successive year (Figure 7).

Figure 7. Longitudinal GMTs for 3 Consecutive Years



The results from the 7 revaccination studies, including the longitudinal H1N1 analysis, demonstrate that the immunogenicity response after repeated (consecutive) annual vaccination with aTIV is not diminished.

10 ADDITIONAL CLINICAL EFFECTIVENESS STUDIES

Summary

- The effectiveness of aTIV has also been assessed in two observational studies conducted in Canada and Italy using both influenza infection and influenza related hospitalization as measures to determine aTIV vaccine effectiveness relative to TIV.
- A case-control study in British Columbia, Canada, using a negative case control design, found a vaccine effectiveness of 63% (95% CI 4% –86%) in preventing lab-confirmed influenza for older adults vaccinated with aTIV compared to persons vaccinated with TIV.
- A prospective cohort study in Italy conducted from 2006 to 2009 in over 107,000 older adults found that vaccination with aTIV was associated with a 25% reduction in risk for influenza or pneumonia-related hospitalizations during the peak of influenza season as compared to vaccination with TIV (relative risk: 0.75; 95% CI: 0.57-0.98).

10.1 British Columbia Effectiveness Study

The British Columbia Effectiveness Study evaluated the comparative effectiveness of aTIV and standard TIV in reducing laboratory confirmed influenza in older adults ([Van Buynder 2013](#)). NVD provided financial support for this study through an unrestricted research grant.

10.1.1 General Methodology

The British Columbia Effectiveness Study was a community-based case-control study conducted in Canada that evaluated the comparative effectiveness of aTIV against non-adjuvanted trivalent influenza vaccine (TIV) and no vaccination in reducing laboratory confirmed influenza in older adults. The study used the commonly applied negative case control design to estimate influenza vaccine effectiveness which is a method also applied by the CDC through the US Flu Vaccine Effectiveness (VE) Network.

The study included older adults of 65 years and over living in three health authority districts of British Columbia. Patients who reported ILI or respiratory disease in hospital and general practitioner settings were swabbed and tested for influenza as part of routine care.

Participants were classified as cases if the polymerase chain reaction (PCR)-test was positive for influenza and if they met a clinical case definition of ILI. Participants were classified as a control if the test was negative.

For both cases and controls, information was then collected regarding demographics, medical history, health care provider, residency, hospitalization and influenza vaccination status. This information was obtained from the subjects themselves and their health care providers.

The effectiveness of aTIV to prevent influenza infection relative to TIV or no vaccination was estimated by comparing the previous vaccination status (aTIV, TIV or no vaccination) between cases and controls using logistic regression analysis. Crude and adjusted analyses were performed to control for potential confounding variables. Vaccine effectiveness for each vaccine type was calculated as 1 minus the corresponding odds ratio of confirmed influenza (vaccinated population/unvaccinated population) ([Greenwood 1915](#)).

10.1.2 Baseline Demographics

Compared to TIV, aTIV vaccine was found to be more frequently used in those over 85 years of age (58.2% for aTIV and 27.4% for TIV) and for residents in long term care facilities (77% for aTIV and 29% for TIV).

10.1.3 Effectiveness Findings

After adjusting for age, sex, long term care residency, chronic conditions, health authority, and week of testing, aTIV was significantly protective against influenza across all populations evaluated (adjusted VE = 58%; 95% CI: 5-82; $P = 0.038$), while TIV appeared to be ineffective (adjusted VE = -2%; 95% CI: -139-57; $P = 0.970$) relative to no vaccination. The adjusted relative vaccine effectiveness of aTIV to TIV was 63% (95% CI: 4-86; $P = 0.040$) (based on an odds ratio of laboratory-confirmed influenza for aTIV relative to TIV = 0.37; 95% CI: 0.14-0.96). The subgroup analysis of subjects who were not long-term care residents produced similar results.

10.2 Effectiveness of Adjuvanted Influenza Vaccination in Older Adult Subjects in Northern Italy

10.2.1 General Methodology

The Lombardia Influenza Vaccine Effectiveness (LIVE) Study was an observational, prospective cohort study performed in the Northern Italian health districts of Cremona, Mantova, Pavia, Lecco, and Bergamo ([Mannino 2012](#)).

The study was performed during the 2006-2007, 2007-2008, and 2008-2009 influenza seasons. For all three seasons, there was partial mismatch for B strains. For the 2007-2008 season, there was a total mismatch for the A/H1N1-like strain and a partial mismatch for the A/H3N2-like strain. The investigators determined that the only mismatches which could have appreciably affected vaccine effectiveness were those of the 2007-2008 season.

Subjects older than 65 years of age were invited to participate in the study, and the choice of which influenza vaccine to give to each study subject (either aTIV or TIV) was left to the individual provider to be determined on the basis of local influenza vaccination policy.

All those who accepted participation were administered a questionnaire to record basic demographic data and information on potential confounders (e.g., smoking history, conditions affecting immune response, functional status, presence of children in the household, and influenza vaccine receipt within the previous year). Additionally, the presence of chronic disease or other relevant routinely collected medical history information was ascertained through linkage with health records.

The outcome of the study was hospitalizations for influenza or pneumonia during the influenza season as identified from administrative databases. No laboratory confirmation of influenza virus was available for the study. Accordingly, to increase the specificity of the identification of cases hospitalized for influenza-related conditions in absence of laboratory confirmation, the investigators defined a priori the primary analysis to be based upon the peak risk window of the influenza season to provide the greatest specificity of the outcome.

Stratified and regression analyses were performed, including the use of the propensity score to adjust for confounding in the absence of randomization of vaccination.

10.2.2 Baseline Demographics

Over the 3 influenza seasons, 170,988 vaccinations (comprising 88,449 and 82,539 doses of aTIV and TIV, respectively) were administered by the subjects' health care providers. Overall, approximately 107,661 subjects participated in the study, 43,667 of whom participated for multiple years. Due to the nature of this observational study, in which providers selected the vaccine for their patients, selection bias resulted in more chronically ill patients being recruited into the aTIV group. The greatest imbalance between the two groups was observed in the percentages of subjects with functional impairment, history of pneumonia, influenza or emphysema, and those suffering from chronic obstructive pulmonary and heart diseases. Additionally, the mean age of the aTIV recipients was higher (76.5 years) than the mean age observed among subjects who received TIV (74.9 years).

10.2.3 Effectiveness Findings

After adjustment for cofounders, aTIV was shown to reduce hospitalization rates for influenza and pneumonia during the peak of the influenza seasons. The risk ratio for aTIV relative to TIV was 0.75 (95% CI 0.57-0.98), which indicates an approximate 25% relative reduction in influenza/pneumonia-related hospitalizations. As might be expected, the observed effectiveness of aTIV was attenuated when the peak risk window of the outcome was extended to include the less influenza-specific hospitalizations outside of the peak of influenza season.

11 PRECLINICAL AND CLINICAL SAFETY

Summary

- A comprehensive preclinical program evaluating aTIV safety was performed and no safety signals were detected.
- The clinical safety program evaluating aTIV safety is based on five sources of data: post-marketing safety data (1997 to 2014), an observational study, the pivotal study (V70_27), a pooled analysis of 15 FD-RCTs, and 7 revaccination trials.
- The pivotal trial is regarded as a large (V70_27, n= 7,082 subjects), randomized, controlled study with a long follow-up period (1 year) and is the primary trial considered for safety.
- Data from other randomized, controlled trials with similar safety data collection practices were pooled with the pivotal trial (FD-RCT, n= 10,952 subjects) to evaluate for trends in less frequently occurring events such as adverse events of special interest (AESIs) and adverse events following immunization (AEFIs).
- In the pivotal study, the safety data demonstrated:
 - A higher percentage of subjects in the aTIV group than the TIV group reported solicited local AEs (32% vs. 17%) and solicited systemic AEs (32% vs. 26%).
 - The solicited AEs with greater reporting in the aTIV group as compared to TIV included all local injection site AEs (pain, tenderness, erythema, induration, swelling) as well as myalgia, fatigue, headache, and chills.
 - The majority of solicited AEs in both vaccine groups were mild in severity and few subjects reported ongoing AEs at the end of the 7 day observation period (<1% in each group).
 - There was no imbalance in the percentages of subjects with unsolicited AEs in the first 3 weeks after vaccination (16% of subjects in each group).
 - Similar percentages of subjects in each vaccine group experienced SAEs (7% per group), AEs leading to study withdrawal (1% per group), new onset chronic diseases (NOCDs; 6% per group) and death (1% per group) during the year of follow-up after vaccination.
- In the pooled FD-RCT analysis, the safety data demonstrated:
 - Similar percentages of subjects experienced death (1.4%, aTIV vs. 1.6%, TIV), AESIs (0.9% in both groups), and AEFIs (0.3%, aTIV and 0.2%, TIV).

- Results from a 107,000-patient prospective cohort study found no differences in the rate of AESIs in patients who were vaccinated with aTIV or TIV.
- Analysis of post-marketing data shows a cumulative reporting rate of 1.12 cases per 100,000 doses that was comparable to the TIV comparator (*Agrippal*).

11.1 Overview of Safety Data Sources

The sections that follow summarize the preclinical and clinical aTIV safety experience. In addition to the preclinical studies that follow, the clinical safety experience comes from six key sources of data collected from older individuals exposed to the vaccine. These sources include: an analysis of post-marketing safety data from a reporting period of 1997 through 2014, a published safety report from a large observational study with over 100,000 individuals analyzed, the pivotal study (V70_27), a pooled analysis of 15 FD-RCTs, and 7 revaccination trials. All clinical data analyzed support that aTIV has a safety profile that is similar to non-adjuvanted influenza vaccine, except an increase in mild reactogenicity.

11.2 Overview of Preclinical Safety Experience

The preclinical support for aTIV is based on pharmacology and toxicology studies in several species. These studies demonstrated that aTIV is immunogenic and did not cause local or systemic toxicity. In addition, *MF59* (alone and with antigen) has been evaluated extensively in preclinical studies. *MF59* is not associated with any potential for systemic toxicity and it has a low order of local reactogenicity.

Primary pharmacology studies were performed in mice to evaluate aTIV. Mice are appropriate for the study of influenza because they respond immunologically to vaccination, and can be infected with the influenza virus (Brett 2009). These studies, performed via the subcutaneous or intramuscular routes, demonstrated that immunization of both young and old mice with TIV or aTIV, elicits a dose-related antigen-specific antibody response, even in seropositive mice. Other effects associated with immunization included proliferation of spleen-derived lymphocytes, reduction in lung viral load following subsequent challenge with influenza virus, and protection against challenge with lethal doses of influenza virus up to 200 days post-vaccination. In all cases, the presence of *MF59* increased the immune response in both young and old mice (Higgins 1996).

aTIV was tested in GLP toxicology studies. Rabbits were selected because influenza antigens elicit an immunologic response, the full clinical dose and volume of vaccine can be administered using the clinical route of administration, and sufficient blood can be taken to assess clinical chemistry and hematology parameters. In a GLP repeat-dose toxicity study (Study No. 488182), 3 intramuscular doses of aTIV were administered 14 days apart to male and female rabbits. Parameters assessed included mortality, clinical signs, injection site evaluations, body weights, food and water consumption, ophthalmic examinations, heart rate, respiratory rate and body temperature, hematology, and clinical chemistry. Necropsies were performed 2 days and 14 days

after the last vaccination, and included terminal organ weights and full macroscopic post-mortem examinations. Microscopic evaluation of selected tissues/organs was performed. The findings in this study were consistent with evaluation of other *MF59*-adjuvanted vaccines, and included a transient increase in fibrinogen, a slight decrease in prothrombin time, and a slight decrease in activated partial thromboplastin time in some females, with a return to baseline values within the 2 week recovery period. These changes are consistent with the acute phase response, which is expected following administration of an immunologically active substance. Histopathologically, mild inflammation at the injection sites and reactive changes in the draining lymph node were observed, with a decrease in both incidence and severity during the 2 week recovery period. There were no systemic adverse effects, and the vaccine elicited strain-specific antibodies and was well tolerated locally.

In a GLP reproductive and developmental toxicity study (Study No. AB09779), aTIV was administered to female rabbits by intramuscular injection at the clinical dose and volume twice before mating and twice during gestation. aTIV did not cause maternal or embryofetal toxicity, was not teratogenic, and had no effects on post-natal development. aTIV was immunogenic in maternal rabbits, developing fetuses had comparable titers, and antibodies persisted through the first 4 weeks of life (lactation period) in offspring born to treated female rabbits.

A GLP Guinea pig study was conducted to assess potential for delayed contact hypersensitivity. A standard study design, the Magnusson-Kligman Maximization Test, was used. aTIV did not cause hypersensitivity.

Findings in studies with *MF59* combined with antigens or *MF59* alone were attributable to the adjuvant, with no notable adverse effects seen with the antigen-adjuvant combination. In general, although immunogenicity is enhanced, toxicological findings with *MF59*-adjuvanted vaccines are comparable to findings with *MF59* alone. *MF59* did not affect cardiovascular and neurological parameters after repeated administrations in dogs. *MF59* is not genotoxic (Ames test) or clastogenic (mouse micronucleus), is not a dermal sensitizer (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

The completed program of studies with aTIV complies with current guidelines for the preclinical development of vaccines, and these studies support the clinical use of aTIV.

11.3 Methodology of Safety Data Collection in Clinical Trials

Preclinical studies did not determine any novel vaccine-related safety concerns, so the prospective collection of safety data included an evaluation of solicited AEs and unsolicited AEs. Further subcategories of unsolicited AEs were also evaluated: AEs leading to withdrawal, serious adverse events (SAEs), deaths, and new onset of chronic disease (or NOCD, collected in the pivotal trial only). For the BLA, additional analyses were performed to evaluate for adverse events of special interest (AESI, see Appendix Section 14.2.2) and adverse events following immunization (AEFI, see Appendix Section 14.2.3), which represent a class of adverse event

with potential association to immune mediated phenomena. The latter events were analyzed retrospectively and according to pre-specified definitions.

In the clinical trials included in this briefing document, local and systemic AEs following vaccination were actively solicited during either a 4-day or 7-day period following study vaccine administration. These AEs were collected either using a diary card completed by the subject or via telephone contact.

Solicited local AEs included injection site erythema, swelling, induration, ecchymosis, pain and tenderness. However, swelling and tenderness were not collected in all studies. For the solicited local AEs of erythema, swelling, induration, and ecchymosis, the largest single diameter was summarized in the integrated safety analyses as per the CBER guidance (CBER 2007): ‘none’ (0 mm), ‘grade 0’ (1-24 mm), ‘grade 1’ (25-50 mm), ‘grade 2’ (51-100 mm) or ‘grade 3’ (>100 mm). The severity of tenderness and pain occurring up to 7 days after each vaccination was to be categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), severe (unable to perform normal daily activity) or potentially life threatening (PLT) (caused a specific severe reaction, required emergency room visit or required hospitalization). The latter category was collected in only two studies: V70_27 and V104P3.

Solicited systemic AEs included chills, myalgia, arthralgia, headache, fatigue, malaise, fever, rash, diarrhea, nausea, vomiting and sweating and were categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), severe (unable to perform normal daily activity) or PLT. As above, some events (fatigue, rash, diarrhea, malaise, vomiting, and sweating) were collected in a subset of studies and the severity category of PLT was collected in only two studies: V70_27 and V104P3.

Finally, a third type of safety data were solicited for 7 days following vaccination in most studies: “Use of analgesic/antipyretic medication” and “Did the subject stay home due to a local or systemic AE.”

For the analyses of solicited events in the FD-RCT pooling, PLT events were combined with severe events into a single category and percentages of subjects with solicited AEs are calculated using only those studies where the specific event was collected.

Unsolicited AEs were collected for up to 366 days after vaccination, depending on the study design. Most studies collected all unsolicited AEs for a 1- to 4-week period after study vaccination, followed by an observation period wherein only specific subcategories of unsolicited AEs were collected prospectively. The subcategories of unsolicited AEs included:

- Serious adverse events (SAE), defined as AEs that either:
 - Result in death
 - Are life-threatening

- Require or prolong subject's hospitalization
- Result in persistent or significant disability/incapacity
- Result in a congenital anomaly/birth defect
- Or are important and significant medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above
- AEs leading to withdrawal: defined as AEs with an action taken of 'withdrawn from study due to AE', 'AE withdrawal' or 'no further study vaccination due to AE' on the termination case report form
- New Onset of Chronic Disease (NOCD): defined as AEs that, in the judgment of the investigator, represented the new emergency of a chronic illness in the time following vaccination. NOCD were assessed prospectively in the pivotal study only.
- Deaths: defined as AEs with an outcome of "death" or "fatal"

In several studies, hospitalization and death were captured both as outcomes of adverse events and on a separate CRF page, in the preparation of the pooled analysis, an imputation was done to ensure that all hospitalizations were captured as SAE and the maximum number of deaths were captured.

Further unsolicited AEs were defined and retrospectively analyzed to support the BLA. The events analyzed were gathered from the entire period of observation following subject vaccination. These events include:

- Adverse Events of Special Interest (AESI): defined as potential immune-mediated AEs
- Adverse Events Following Immunization (AEFI): defined as AEs that were of potential allergic or anaphylactic etiology, rather than autoimmune etiology

11.4 Sources of Clinical Trial Safety Data and Extent of Exposure

Clinical trial safety data are provided in this briefing document from a large pivotal study, a pooled analysis of 15 randomized, controlled trials (including the pivotal study), and 7 revaccination trials. Within the BLA, data from a total of 58 clinical trials were reviewed, including the trials described above as well as: data from non-older adults subjects, uncontrolled trials, a Phase IV trial, trials with adjuvanted comparator vaccines, and trials wherein aTIV was administered according to a different schedule than its intended use. The conclusions from the broader studies remain supportive of the conclusions described in the sections that follow.

The primary analysis of safety data comes from the pivotal trial. The pivotal study was a large, randomized, controlled study comparing aTIV with a non-adjuvanted, US licensed comparator vaccine and included a 12 month follow-up period after vaccination. Within this study safety data are available from 7,019 subjects exposed.

Supportive data are available from a pooling of 15 FD-RCTs including the pivotal study but excluding the phase IV study V7P35 due to methodologic differences in how safety was

assessed. This pooling is based on randomized, controlled trials including a non-adjuvanted influenza vaccine as a comparator, for additional details on demographics and baseline characteristics see Appendix, Table 63. As shown in Table 37, safety data are available for 10,952 subjects exposed in these trials. This pooling was performed to assess for less commonly occurring events, such as AESIs and AEFIs. The duration of follow-up after vaccination varied from 21 days to 365 days in the 15 studies analyzed.

Table 37. Number of Subjects in the FD-RCT Safety Pooling

Study	Duration of Safety Follow-up (Days)	Influenza Season	aTIV (N=5754)	TIV (N=5198)
V70_27	365	2010-11	3545	3537
V7P34	28	1997-98	448	112
V7P30	28	1996-97	301	150
V7P5	181	1993-94	212	105
V7P8	180	1994-95	204	104
M63P1	180	2002-03	175	175
V7P17	56	1995-96	154	156
V7P24	180	1996-97	150	151
V7P25	180	1995-96	142	141
V7P7	135	1993-94	109	105
V7P27	180	1996-97	102	206
V7P26	180	1995-96	72	70
V104P3	21	2008-09	47	44
V7P6	28	1993-94	47	96
V7P3	28	1992-93	46	46

Note: V70_27 is the Pivotal Study.

Subjects from FD-RCT parent studies who participated in 7 revaccination studies were included in a data pooling entitled RCT-EXT. Five of these studies provided a second vaccination in the year that followed the primary vaccination study. These five studies enrolled 822 subjects (aTIV n=492; TIV n=330). Subjects in two of these trials were enrolled into two studies evaluating safety after a third vaccination two years following the primary vaccination study. These two studies enrolled 237 subjects (aTIV n=150, TIV n=87).

11.5 Adverse Events in the Pivotal Study

The percentages of subjects with unsolicited AEs, SAE, and AEs that led to withdrawal, AESIs, and AEFIs were comparable between the aTIV and TIV groups in the pivotal study. A higher percentage of subjects in the aTIV than the TIV group reported solicited AEs (46% vs. 33%) (Table 38).

Table 38. Overall Summary of Adverse Events, Pivotal Study Safety Set

Adverse Event Type	aTIV	TIV
Solicited	(N=3505)	(N=3495)
Any solicited AE, 6 hours-7 days	1619 (46%)	1164 (33%)
Any solicited local AE	1137 (32%)	593 (17%)
Any solicited systemic AE	1120 (32%)	902 (26%)
Unsolicited	(N=3545)	(N=3537)
Any unsolicited AE, Days 1-21	551 (16%)	570 (16%)
Any SAE, Days 1-366	264 (7%)	243 (7%)
Any AE leading to withdrawal, Days 1-366	52 (1%)	49 (1%)
New onset of chronic disease, Days 1-366	227 (6%)	223 (6%)
Any AE leading to death, Days 1-366 ^a	51 (1%)	46 (1%)

^a One additional subject died in the aTIV group; however, prior to death the subject withdrew from the study due to an AE. For a complete summary of deaths in the pivotal study see Section 11.10.

11.6 Solicited Adverse Events in Primary Vaccination Studies

Pivotal Study: Solicited local AEs (aTIV, 32% vs. TIV, 17%; Table 39), and solicited systemic AEs (aTIV, 32% vs. TIV, 26%; Table 40) were reported by higher percentages of subjects from 6 hours to 7 days following vaccination for subjects receiving aTIV then those who received TIV. This increase in solicited AEs was due primarily to a higher incidence of pain (25% vs 12%) and tenderness (21% vs. 11%) at the injection site, as well as myalgia (15% vs. 10%) following vaccination with aTIV. The incidence of fever (4% vs. 3%; fever was defined as an oral temp $\geq 38^{\circ}\text{C}$) was low and similar between vaccine groups (Table 40). The majority of solicited AEs in both vaccine groups were mild or moderate AEs. The percentages of subjects described as experiencing a severe solicited AE were low in both groups (< 1.0% per event). Percentages of subjects describing ongoing solicited AEs 7 days after vaccination were also low among subjects in both vaccine groups (<1% per event) (Table 41).

Furthermore, the use of analgesics/antipyretics (5% vs. 4%), and the incidence of subjects who stayed home due to local or systemic reactions (3% vs. 2%) were low and similar between the aTIV and TIV groups, respectively.

Table 39. Solicited Local Adverse Events 6 Hours to 7 Days Following Vaccination, Pivotal Study Safety Set

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV	
Any Solicited Local AE	Any (N = 3505 vs. 3495)	1137	(32%)	593	(17%)
Erythema	Any (N = 3492 vs. 3485)	43	(1%)	18	(1%)
	Mild (25 to ≤50 mm)	37	(1%)	17	(<1%)
	Moderate (51 to ≤100 mm)	6	(<1%)	1	(<1%)
	Severe (>100 mm)	0		0	
Induration	Any (N = 3494 vs. 3488)	45	(1%)	17	(<1%)
	Mild (25 to ≤50 mm)	35	(1%)	17	(<1%)
	Moderate (51 to ≤100 mm)	10	(<1%)	0	
	Severe (>100 mm)	0		0	
Tenderness	Any (N = 3495 vs. 3483)	739	(21%)	391	(11%)
	Mild	628	(18%)	349	(10%)
	Moderate	106	(3%)	36	(1%)
	Severe	5	(<1%)	6	(<1%)
Swelling	Any (N = 3495 vs. 3488)	43	(1%)	15	(<1%)
	Mild (25 to ≤50 mm)	35	(1%)	14	(<1%)
	Moderate (51 to ≤100 mm)	7	(<1%)	1	(<1%)
	Severe (>100 mm)	1	(<1%)	0	
Pain	Any (N = 3495 vs. 3485)	875	(25%)	425	(12%)
	Mild	726	(21%)	351	(10%)
	Moderate	138	(4%)	66	(2%)
	Severe	11	(<1%)	8	(<1%)

Table 40. Solicited Systemic and Other Adverse Events with Onset 6 Hours to 7 Days Following Vaccination by Severity, Pivotal Study Safety Set

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV	
Any Solicited Systemic AE	Any (N = 3505 vs. 3495)	1120	(32%)	902	(26%)
Chills	Any (N = 3495 vs. 3485)	235	(7%)	163	(5%)
	Mild	169	(5%)	111	(3%)
	Moderate	53	(2%)	43	(1%)
	Severe	12	(<1%)	9	(<1%)
	PLT	1	(<1%)	0	
Myalgia	Any (N = 3496 vs. 3487)	515	(15%)	339	(10%)
	Mild	414	(12%)	251	(7%)
	Moderate	91	(3%)	63	(2%)
	Severe	10	(<1%)	25	(1%)
	PLT	0		0	
Arthralgia	Any (N = 3492 vs. 3486)	296	(8%)	272	(8%)
	Mild	232	(7%)	196	(6%)
	Moderate	57	(2%)	56	(2%)
	Severe	7	(<1%)	20	(1%)
	PLT	0		0	
Headache	Any (N = 3495 vs. 3486)	463	(13%)	391	(11%)
	Mild	343	(10%)	281	(8%)
	Moderate	105	(3%)	89	(3%)
	Severe	15	(<1%)	20	(1%)
	PLT	0		1	(<1%)
Fatigue	Any (N = 3494 vs. 3484)	466	(13%)	361	(10%)
	Mild	344	(10%)	254	(7%)
	Moderate	109	(3%)	85	(2%)
	Severe	13	(<1%)	21	(1%)
	PLT	0		1	(<1%)
Nausea	Any (N = 3492 vs. 3482)	101	(3%)	98	(3%)
	Mild	81	(2%)	72	(2%)
	Moderate	14	(<1%)	21	(1%)
	Severe	5	(<1%)	5	(<1%)
	PLT	1	(<1%)	0	
Vomiting	Any (N = 3494 vs. 3483)	48	(1%)	59	(2%)
	Mild	33	(1%)	38	(1%)
	Moderate	13	(<1%)	17	(<1%)
	Severe	1	(<1%)	4	(<1%)
	PLT	1	(<1%)	0	

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV	
		Count	Percentage	Count	Percentage
Diarrhea	Any (N = 3494 vs. 3485)	168	(5%)	158	(5%)
	Mild	111	(3%)	119	(3%)
	Moderate	44	(1%)	30	(1%)
	Severe	12	(<1%)	8	(<1%)
	PLT	1	(<1%)	1	(<1%)
Fever (≥38°C)	(N=3418 vs. 3420)	122	(4%)	116	(3%)
Analgesic/anti-pyretic used	(N=3467 vs. 3447)	158	(5%)	122	(4%)
Stayed home due to reaction	(N=3481 vs. 3463)	103	(3%)	84	(2%)

Table 41. Solicited Adverse Events Ongoing After 7 Days Following Vaccination, Pivotal Study Safety Set

Adverse Event Type	Ongoing After 7 Days	
	aTIV (n=3516)	TIV (n=3503)
Arthralgia	6 (<1%)	5 (<1%)
Chills	3 (<1%)	2 (<1%)
Diarrhea	4 (<1%)	6 (<1%)
Erythema	5 (<1%)	7 (<1%)
Fatigue	9 (<1%)	11 (<1%)
Headache	12 (<1%)	20 (<1%)
Myalgia	8 (<1%)	6 (<1%)
Nausea	1 (<1%)	4 (<1%)
Pain	5 (<1%)	6 (<1%)
Swelling	1 (<1%)	0
Tenderness	2 (<1%)	1 (<1%)
Vomiting	1 (<1%)	1 (<1%)

FD-RCT Safety Pooling: Results from the FD-RCT safety pooling are generally consistent with the findings from the pivotal study on solicited AEs (see Appendix, Table 64 - Table 67). Solicited AEs were more commonly reported following vaccination with aTIV. The most commonly reported solicited AEs were injection site pain and tenderness as well as myalgia, fatigue, and headache.

11.7 Unsolicited Adverse Events in Primary Vaccination Studies

Pivotal Study (V70 27): There were no notable imbalances in the percentages of subjects reporting unsolicited AEs from days 1 to 21 following vaccination in the pivotal study (Table 42). The most commonly reported AEs by preferred term from days 1 through 21 were nasopharyngitis (aTIV, 2% vs. TIV, 2%), headache (1% vs. 2%), and cough (1% per group).

Table 42. Unsolicited Adverse Events by Preferred Term ($\geq 0.5\%$), Days 1 through 21, Pivotal Study Safety Set

Preferred Term	All Unsolicited AEs			
	aTIV (N=3545)		TIV (N=3537)	
Any unsolicited AE	551	(16%)	570	(16%)
Nasopharyngitis	69	(2%)	60	(2%)
Headache	40	(1%)	55	(2%)
Cough	34	(1%)	49	(1%)
Upper respiratory tract infection	35	(1%)	31	(1%)
Arthralgia	26	(1%)	24	(1%)
Diarrhea	22	(1%)	22	(1%)
Fatigue	17	(<1%)	23	(1%)
Dizziness	23	(1%)	21	(1%)
Pyrexia	21	(1%)	18	(1%)
Myalgia	14	(<1%)	22	(1%)

FD-RCT Safety Pooling: Results from the FD-RCT safety pooling are generally consistent with the findings from the pivotal study on unsolicited AEs (see Appendix, Table 68). Unsolicited AEs were reported by similar percentages of subjects. The most commonly reported unsolicited AEs were: nasopharyngitis, hypertension, and headache.

11.8 Serious Adverse Events in Primary Vaccination Studies

Pivotal Study (V70 27): In the pivotal study, the percentages of subjects reporting SAEs were comparable overall, with a rate of 7% in each vaccine group through 1 year following vaccination. An analysis of SAEs by Preferred Term (PT) reporting in 5 or more subjects in one vaccine group demonstrated that percentages of subjects reporting these SAEs were similar between the two vaccine groups (Table 43). In the first 21 days following vaccination, the percentages of subjects reporting SAEs were also similar between vaccine groups (1% per group; aTIV n=19 vs. TIV n=20).

Table 43. Serious Adverse Events with Onset From Day 1 through Day 366 Reported in ≥ 5 Subjects in Either Vaccine Group, by Preferred Term, Pivotal Study Safety Set

Preferred Term	aTIV (N=3545)		TIV (N=3537)	
Any SAE	264	(7%)	243	(7%)
Pneumonia	32	(1%)	35	(1%)
Acute myocardial infarction	11	(<1%)	7	(<1%)
Chronic obstructive pulmonary disease	10	(<1%)	14	(<1%)
Myocardial infarction	10	(<1%)	9	(<1%)
Cardiac failure congestive	8	(<1%)	16	(<1%)
Cerebrovascular disorder	8	(<1%)	3	(<1%)
Hypertension	8	(<1%)	8	(<1%)
Urinary tract infection	8	(<1%)	6	(<1%)
Coronary artery disease	7	(<1%)	6	(<1%)
Chest pain	7	(<1%)	3	(<1%)
Cholecystitis	7	(<1%)	2	(<1%)
Osteoarthritis	7	(<1%)	12	(<1%)
Bronchitis	5	(<1%)	1	(<1%)
Diabetes mellitus	5	(<1%)	2	(<1%)
Gastroenteritis	5	(<1%)	6	(<1%)
Atrial fibrillation	4	(<1%)	8	(<1%)
Cerebrovascular accident	4	(<1%)	10	(<1%)
Upper gastrointestinal hemorrhage	4	(<1%)	7	(<1%)
Anemia	2	(<1%)	5	(<1%)

Note: Only SAEs reported in ≥ 5 subjects in either vaccine group are included by preferred term. As a result, the sum of the preferred term N's does not equal the 'Any SAE' total for either vaccine group.

FD-RCT Safety Pooling: Analyses of the FD-RCT safety pooling also showed comparable percentages of subjects reporting serious AEs in each vaccine group (see Appendix, Table 69).

11.9 Adverse Events Leading to Withdrawal in Primary Vaccination Studies

Pivotal Study (V70 27): The frequency of adverse events leading to withdrawal (i.e., premature discontinuation) in the pivotal study were low overall and occurred at a similar rate in both vaccine groups (1% per group; Table 44). The most common AEs leading to withdrawal by SOC were cardiac disorders (aTIV n=21 vs. TIV n=19), infections & infestations (n=14 vs. n=10) and nervous system disorders (n=9 vs. n=11). No notable differences between groups were identified for any particular event or SOC.

Table 44. Unsolicited Adverse Events Leading to Withdrawal From day 1 to Day 366 by System Organ Class, Pivotal Study Safety Set

System Organ Class	aTIV (N=3545)	TIV (N=3537)
Any AE leading to Premature Withdrawal	52 (1%)	49 (1%)
Cardiac disorders	21 (1%)	19 (1%)
Infections & infestations	14 (<1%)	10 (<1%)
Nervous system disorders	9 (<1%)	11 (<1%)
Neoplasms, benign and malignant	6 (<1%)	5 (<1%)
Gastrointestinal disorders	3 (<1%)	5 (<1%)
General disorders and administration site conditions	3 (<1%)	1 (<1%)
Renal & urinary disorders	3 (<1%)	2 (<1%)
Respiratory, thoracic & mediastinal disorders	3 (<1%)	4 (<1%)
Metabolism & nutrition disorders	2 (<1%)	0
Vascular disorders	1 (<1%)	1 (<1%)
Blood & lymphatic system disorders	0	1 (<1%)
Injury & poisoning	0	2 (<1%)

FD-RCT Safety Pooling: Similar results were seen in the FD-RCT pooling, which demonstrated comparable percentages of subjects reporting AE leading to withdrawal: 1.3% in the aTIV group and 1.4% in the TIV group (see Appendix Table 70).

11.10 Deaths in Primary Vaccination Studies

Pivotal Study (V70 27): The rate of death was balanced between groups in the pivotal study (aTIV, 1% [n=52] vs. TIV, 1% [n=46]). All-cause mortality by post-vaccination time frame is shown in Table 45. Most frequently reported causes of death in the pivotal study include cardiac disease (0.5% in both vaccine groups), respiratory infections (0.3% aTIV, 0.2% TIV), cerebrovascular accidents and neoplasms (0.2% both vaccine groups).

Table 45. All-Cause Mortality by Time, Pivotal Study Safety Set

Post-vaccination Timeframes	aTIV (n=3545)	TIV (n=3537)
Total	52 (1%)	46 (1%)
Day 1-21	0	0
Day 22-180	17 (<1%)	21 (<1%)
Day 181-366	35 (<1%)	25 (<1%)

FD-RCT Safety Pooling: Similar to the pivotal study, the rate of death was balanced between vaccine groups in the FD-RCT pooling (aTIV, 1.4% vs. TIV, 1.6%). Results for the FD-RCT pooling are shown in Table 46. Consistent with the underlying comorbidities in the older population enrolled in the FD-RCT pooling, the most common reasons for death by SOC were cardiac disorders (aTIV, 0.6% vs. TIV, 0.9%), infections and infestations excluding influenza (0.3% vs. 0.2%), and nervous system disorders (0.2% vs. 0.3%).

Table 46. Summary of Deaths by System Organ Class and Preferred Term for >1 Subjects in Either Vaccine Group, FD-RCT Safety Pooling

SOC or PT Associated with Death	aTIV (N=5754)		TIV (N=5198)		Relative Risk (95% CI)^a
Any death	78	(1.4%)	81	(1.6%)	0.74 (0.54-1.02)
Cardiac disorders	36	(0.6%)	45	(0.9%)	0.61 (0.39-0.94)
Cardiac failure congestive	7	(0.1%)	13	(0.3%)	0.38 (0.15-0.97)
Myocardial infarction	8	(0.1%)	12	(0.2%)	0.49 (0.20-1.21)
Acute myocardial infarction	8	(0.1%)	5	(0.1%)	1.29 (0.42-3.98)
Cardiac failure	2	(<0.1%)	6	(0.1%)	0.23 (0.05-1.13)
Cardiac failure acute	3	(0.1%)	3	(0.1%)	0.74 (0.15-3.69)
Cardio-respiratory arrest	4	(0.1%)	0		NC
Cardiac arrest	0		3	(0.1%)	NC
Myocardial ischemia	3	(0.1%)	0		NC
Atrial fibrillation	2	(<0.1%)	0		NC
Cardiac disorder	2	(<0.1%)	0		NC
Coronary artery disease	0		2	(<0.1%)	NC
Infections and infestations	17	(0.3%)	11	(0.2%)	1.24 (0.58-2.67)
Pneumonia	9	(0.2%)	7	(0.1%)	1.05 (0.39-2.82)
Pulmonary tuberculosis	2	(<0.1%)	2	(<0.1%)	0.80 (0.11-5.72)
Septic shock	3	(0.1%)	1	(<0.1%)	2.60 (0.27-25.2)
Sepsis	2	(<0.1%)	1	(<0.1%)	1.61 (0.14-18.1)
Nervous system disorders	13	(0.2%)	13	(0.3%)	0.77 (0.36-1.68)
Cerebrovascular accident	6	(0.1%)	5	(0.1%)	0.85 (0.26-2.81)
Cerebrovascular disorder	3	(0.1%)	1	(<0.1%)	2.39 (0.25-23.2)
Cerebral hemorrhage	2	(<0.1%)	1	(<0.1%)	1.73 (0.16-19.3)
Hemorrhagic stroke	0		2	(<0.1%)	NC
Neoplasms	9	(0.2%)	8	(0.2%)	0.91 (0.35-2.38)
Gastric cancer	0		2	(<0.1%)	NC
Metastatic neoplasm	2	(<0.1%)	0		NC
Gastrointestinal disorders	4	(0.1%)	7	(0.1%)	0.43 (0.13-1.48)
Upper gastrointestinal hemorrhage	1	(<0.1%)	2	(<0.1%)	0.41 (0.04-4.53)
Respiratory, thoracic and mediastinal disorders	5	(0.1%)	4	(0.1%)	1.00 (0.27-3.75)
Respiratory failure	1	(<0.1%)	3	(0.1%)	0.27 (0.03-2.66)
General disorders and administration site conditions	5	(0.1%)	2	(<0.1%)	1.83 (0.35-9.51)
Multi-organ failure	3	(0.1%)	1	(<0.1%)	2.46 (0.25-23.9)

SOC or PT Associated with Death	aTIV (N=5754)	TIV (N=5198)	Relative Risk (95% CI)^a
Renal and urinary disorders	3 (0.1%)	3 (0.1%)	0.75 (0.15-3.76)
Renal failure chronic	1 (<0.1%)	2 (<0.1%)	0.37 (0.03-4.15)
Vascular disorders	3 (<0.1%)	2 (<0.1%)	1.18 (0.19-7.14)
Hypertension	2 (<0.1%)	1 (<0.1%)	1.60 (0.14-17.9)
Metabolism and nutrition disorders	2 (<0.1%)	2 (<0.1%)	0.61 (0.09-4.38)
Hepatobiliary disorders	2 (<0.1%)	0	NC
Injury, poisoning and procedural complications	0	2 (<0.1%)	NC

^a Relative risks are presented as aTIV/TIV, and are calculated from a Poisson Regression Model including terms for duration of follow-up of adverse events. Note: Each subject is counted only once within each System Organ Class and Preferred Term. NC = Not calculated

11.11 New Onset of Chronic Disease in Primary Vaccination Studies

New onset of chronic disease (NOCD) was prospectively assessed in the pivotal study only. In both vaccine groups, NOCD was reported for 6% of subjects. As shown in Table 47, the most common NOCDs by SOC were ‘vascular disorders’, ‘metabolism and nutrition disorders’, ‘musculoskeletal, connective tissue, and bone disorders’, and ‘cardiac disorders’ (1% in both groups for each of these categories). Within these SOCs, the most commonly reported preferred terms were hypertension (SOC: vascular disorders), Type II diabetes mellitus, hypercholesterolemia, and dyslipidemia (SOC: metabolism and nutrition disorders), osteoarthritis, rheumatoid arthritis, and arthritis (SOC: musculoskeletal, connective tissue, and bone disorders), and cardiac failure congestive, atrial fibrillation, and coronary artery disease (SOC: cardiac disorders). With the exception of hypertension, which was reported in 1% of subjects in both vaccine groups, all other events were reported by less than 1% of subjects in both vaccine groups.

Table 47. New Onset of Chronic Disease, Days 1 to 366, Pivotal Study Safety Set

SOC Preferred Term	aTIV (N=3545)	TIV (N=3537)
Any NOCD	227 (6%)	223 (6%)
Vascular disorders	50 (1%)	51 (1%)
Hypertension	47 (1%)	43 (1%)
Metabolism and nutrition disorders	44 (1%)	33 (1%)
Type II diabetes mellitus	11 (<1%)	9 (<1%)
Hypercholesterolemia	10 (<1%)	10 (<1%)
Dyslipidemia	9 (<1%)	3 (<1%)
Musculoskeletal / connective tissue / bone disorders	38 (1%)	27 (1%)
Osteoarthritis	11 (<1%)	11 (<1%)
Rheumatoid arthritis	5 (<1%)	2 (<1%)
Arthritis	5 (<1%)	1 (<1%)
Cardiac disorders	25 (1%)	31 (1%)
Cardiac failure congestive	6 (<1%)	9 (<1%)
Atrial fibrillation	2 (<1%)	7 (<1%)
Coronary artery disease	6 (<1%)	6 (<1%)

11.12 Adverse Events of Special Interest in Primary Vaccination Studies

Adverse events of special interest (AESI) after immunization with an adjuvanted vaccine include events of an immune-related etiology. AESIs were not prospectively defined or collected in any of the aTIV studies. Rather, AESIs were retrospectively identified using a list of MedDRA Preferred Terms (PTs) and one High Level Term (HLT). Specific terms selected include neuroinflammatory disorders (including narcolepsy), rheumatological disorders, inflammatory bowel disease, thyroid disorders, inflammatory skin disorders, autoimmune hematologic disorders, vasculitis, among others (see Appendix Section 14.2.2).

Due to the low incidence of AESIs, these results are presented for the FD-RCT pooling of 15 trials, including the pivotal study. The percentage of subjects with any AESI was 0.9% in both aTIV and TIV groups (Table 48). The relative risk of AESIs did not reach a level of nominally significant difference (i.e., the upper and lower bounds of the RR above or below 1) between the vaccine groups for any single event. However, for the preferred term of “rheumatoid arthritis”, the relative risk ratio was 2.25. Further details relating to the analysis of arthritic events are provided in Section 11.12.2.

AESIs were also analyzed in the FD-RCT pooling by time of onset relative to vaccination. The percentages of subjects reporting AESIs within 30 days of vaccination were similar, but somewhat higher in the aTIV group, with a rate of 0.4% (n=23) in the aTIV group and 0.2% (n=10) in the TIV group. For the periods 31 to 180 days and >180 days post-vaccination, the

percentage of subjects reporting AESIs were similar between groups, with percentages of subjects of 0.4% and 0.5% for the period within 31 and 180 days after vaccination, and 0.2% and 0.3% for the period >180 days after vaccination, respectively.

Table 48. Adverse Events of Special Interest (AESI), FD-RCT Safety Pooling

SOC Preferred Term	aTIV (N=5754)		TIV (N=5198)		Relative Risk (95% CI)^a
Any AESI	52	(0.9%)	45	(0.9%)	1.04 (0.70-1.55)
Musculoskeletal & connective tissue disorders	26	(0.5%)	16	(0.3%)	1.47 (0.79-2.75)
Arthritis	15	(0.3%)	13	(0.3%)	1.02 (0.49-2.16)
Rheumatoid arthritis	7	(0.1%)	3	(0.1%)	2.25 (0.58-8.73)
Myositis	3	(0.1%)	0		NC
Polyarthritits	1	(<0.1%)	0		NC
Nervous system disorders	10	(0.2%)	13	(0.3%)	0.63 (0.28-1.45)
Radiculitis	3	(0.1%)	6	(0.1%)	0.39 (0.10-1.59)
Polyneuropathy	2	(<0.1%)	2	(<0.1%)	0.80 (0.11-5.72)
Radiculopathy	1	(<0.1%)	2	(<0.1%)	0.43 (0.04-4.78)
VII nerve paralysis	2	(<0.1%)	0		NC
Encephalomyelitis	1	(<0.1%)	0		NC
Somnolence	1	(<0.1%)	0		NC
Guillain-Barré syndrome	0		1	(<0.1%)	NC
Neuritis	0		1	(<0.1%)	NC
Radiculitis lumbosacral	0		1	(<0.1%)	NC
Endocrine disorders	4	(0.1%)	9	(0.2%)	0.44 (0.13-1.42)
Hypothyroidism	4	(0.1%)	9	(0.2%)	0.44 (0.13-1.42)
Respiratory, thoracic & mediastinal disorders	2	(<0.1%)	5	(0.1%)	0.40 (0.08-2.05)
Sleep apnea syndrome	2	(<0.1%)	5	(0.1%)	0.40 (0.08-2.05)
Gastrointestinal disorders	2	(<0.1%)	2	(<0.1%)	0.85 (0.12-6.09)
Colitis	1	(<0.1%)	2	(<0.1%)	0.43 (0.04-4.84)
Crohn's disease	1	(<0.1%)	0		NC
Vascular disorders	2	(<0.1%)	2	(<0.1%)	0.80 (0.11-5.72)
Arteritis	1	(<0.1%)	1	(<0.1%)	0.79 (0.05-12.9)
Temporal arteritis	0		1	(<0.1%)	NC
Thromboangiitis obliterans	1	(<0.1%)	0		NC
Psychiatric disorders	3	(0.1%)	0		NC
Sleep disorder	3	(0.1%)	0		NC
Skin & subcutaneous tissue disorders	2	(<0.1%)	0		NC
Psoriasis	2	(<0.1%)	0		NC
Blood & lymphatic system disorders	1	(<0.1%)	0		NC
Idiopathic thrombocytopenic purpura	1	(<0.1%)	0		NC

^a Relative risks are presented as aTIV/TIV, and are calculated from a Poisson Regression Model including terms for duration of follow-up of adverse events. Note: Each subjects is counted only once within each System Organ Class and Preferred Term. NC = Not calculated

11.12.1 Narcolepsy as an Adverse Event of Special Interest

Narcolepsy was included as an AESI in the aTIV retrospective analysis since this disorder was reported in children receiving an AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in several European countries ([Partinen 2012](#); [Miller 2013](#)). Potential narcolepsy events were searched for across all aTIV clinical studies using both narrow and broad definitions with corresponding PTs (see Appendix, Section 14.2.2 for details). No events in the database were identified using the narrow definition of narcolepsy, and the only events identified based on the broad definition of narcolepsy were sleep disorder (n=3 aTIV and n=0 TIV), sleep apnea syndrome (n=2 and n=5), lethargy (n=1 and n=0), and somnolence (n=1 and n=0) in the older adult subjects. The number of broad definition narcolepsy events was therefore similar in both vaccine groups.

11.12.2 Arthritis Disorders as Adverse Events of Special Interest

As described in Section 11.11, arthritis disease events, primarily the PTs of arthritis and rheumatoid arthritis, were the most frequently reported AESIs in both the aTIV and TIV groups. These events were further analyzed in the FD-RCT population.

Within the first 30 days after vaccination, similar numbers of subjects in each vaccine group reported arthritis (0.1% in both groups, n=6 vs. n=5 for aTIV and TIV, respectively) and more subjects in the aTIV group reported rheumatoid arthritis (0.1% aTIV vs. <0.1% TIV, n=5 vs. n=2 for aTIV and TIV, respectively). Within the following 31 to 180 days after vaccination, numbers of subjects in each vaccine group were similar for both events: arthritis (0.1% [n= 7] vs. 0.2% [n=8] and rheumatoid arthritis (<0.1% [n=2] vs. <0.1% [n=1]) for aTIV and TIV, respectively. For days 181 to 366 after vaccination, numbers of subjects in each vaccine were again similar for both events: arthritis (<0.1% [n=2] vs. 0 and rheumatoid arthritis (<0.1% [n=1] vs. <0.1% [n=1]) for aTIV and TIV, respectively.

Based on review of available clinical data for each of the events described above and based on the prevalence of arthritis and rheumatoid arthritis in an older adult population, there was insufficient evidence to suggest a causal association with vaccination for arthritis and rheumatoid arthritis.

Limited but additional data are available from the evaluation of other *MF59*-containing influenza vaccines administered to individuals with a history of rheumatoid arthritis. Publications by [Elkayam et al \(2011\)](#) (n=41 subjects with rheumatoid arthritis given *Focetria*, an *MF59* adjuvanted A/H1N1 pandemic 2009 vaccine) and [Milanetti et al \(2014\)](#) (n=30 subjects with rheumatoid arthritis given *Focetria*) demonstrated no evidence of a clinical flare of rheumatoid arthritis nor significant changes of the Anti Nuclear Antibody titer, Rheumatoid Factor, or other inflammatory indices following vaccination.

11.13 Adverse Events Following Immunization in Primary Vaccination Studies

An additional retrospective analysis to assess rare but potentially clinically important AEs associated with vaccination in general was performed using the FD-RCT pooling. These adverse events following immunization (AEFI) were identified using 3 SMQs (“angioedema”, “anaphylactic reaction”, and “Generalized Convulsive Seizures Following Immunization”) and 1 PT (febrile convulsions) to identify hypersensitivity-type events (anaphylactic reactions and angioedema) and seizures (see Appendix Section 14.2.3). Due to the low incidence of events, results from the FD-RCT pooling are presented.

The incidence of AEFIs were 0.3% (n=15) in the aTIV group and 0.2% (n=10) in the TIV group. There were no clinically meaningful differences between vaccine groups in the percentages of subjects of specific AEFIs or types of AEFIs (Table 49). In both vaccine groups, <0.1% of subjects reported AEFIs as SAEs (aTIV n=5 vs. TIV n=2). These events were convulsion (n=4) and angioedema (n=1) in the aTIV group and corneal edema (n=1) and shock (n=1) in the TIV group. No events of febrile convulsions were identified in the FD-RCT pool.

Table 49. Adverse Events Following Immunization (AEFI), FD-RCT Safety Pooling

Adverse Event Type	aTIV (N=5754)		TIV (N=5198)		Relative Risk (95% CI) ^a
Any AEFI	15	(0.3%)	10	(0.2%)	1.35 (0.61-3.02)
Angioedema SMQ	10	(0.2%)	7	(0.1%)	1.27 (0.48-3.35)
Urticaria	6	(0.1%)	5	(0.1%)	1.07 (0.32-3.51)
Angioedema	2	(<0.1%)	0		N/C
Eyelid edema	2	(<0.1%)	0		N/C
Corneal edema	0		1	(<0.1%)	N/C
Eye swelling	0		1	(<0.1%)	N/C
Anaphylactic reaction SMQ	2	(<0.1%)	2	(<0.1%)	0.95 (0.13-6.76)
Dyspnea	1	(<0.1%)	1	(<0.1%)	0.99 (0.06-15.89)
Cough	1	(<0.1%)	0		N/C
Eye pruritus	0		1	(<0.1%)	N/C
Pruritus	1	(<0.1%)	0		N/C
Rash	1	(<0.1%)	0		N/C
Shock	0		1	(<0.1%)	N/C
Generalized Convulsive Seizures Following Immunization SMQ	3	(0.1%)	1	(<0.1%)	2.73 (0.28-26.42)
Convulsion	3	(0.1%)	0		N/C
Epilepsy	0		1	(<0.1%)	N/C

^aRelative risks are presented as aTIV/TIV. NC = Not calculated

11.14 Safety in Revaccination Studies

Subjects from 5 of the 15 FD-RCTs were enrolled in revaccination studies that continued through a second consecutive vaccination. Two of the second revaccination studies continued through a third vaccination, for a total of 7 revaccination studies. The data from these revaccination studies (RCT-EXT) were pooled for the analysis of safety. Data following the first vaccination among the subgroup of subjects (aTIV n=492, TIV n=330) are provided as a baseline for second and third vaccination comparisons (i.e., the same subjects analyzed for the second vaccination are included in the analysis of the first vaccination). Of note, subjects who received vaccination 1 but did not receive a subsequent vaccination in an extension study were excluded from this pooling. As a consequence, the data for this pooling may be influenced by selection (enrollment) bias. Subjects with AEs following vaccination 1 may have been less likely to participate in the extension studies, and therefore less likely to be included in this pooling. Furthermore subjects who died in the primary study were also removed from the analysis. The second revaccination (vaccination 3) dataset in the RCT-EXT pooling only includes data from a subgroup of subjects vaccinated in the parent study who subsequently received a second and a third vaccination (aTIV n=150, TIV n=87).

Using this analysis approach, after primary vaccination the percentages of subjects were 40.2% aTIV vs 31.8% TIV for solicited AEs and 15.7% and 15.8% for unsolicited AEs (Table 50). With this pooled approach, after the 1st revaccination the percentages of subjects were 48.8% aTIV vs 45.8% TIV for solicited AEs and 32.3% and 41.2% for unsolicited AEs. After 2nd revaccination the percentages of subjects were 35.3% aTIV vs. 25.3% TIV for solicited AEs and 7.3% and 8.0% for unsolicited AEs. Across all three years, more subjects reported solicited local AEs than reported solicited systemic AEs. For both solicited and unsolicited AEs, there was an apparent rise in AE reporting with 1st revaccination that was no longer apparent after 2nd revaccination. However, as shown in Table 51, a pattern across the individual solicited AEs was not detected.

Table 50. Summary of Adverse Events, RCT-EXT Safety Pooling

Adverse Event Type	N subjects with event (% of subjects)					
	Vaccination 1 ^a		Vaccination 2		Vaccination 3	
	aTIV (N=492)	TIV (N=330)	aTIV (N=492)	TIV (N=330)	aTIV (N=150)	TIV (N=87)
Solicited AE	198 (40.2%)	105 (31.8%)	240 (48.8%)	151 (45.8%)	53 (35.3%)	22 (25.3%)
Solicited Local AE	114 (23.2%)	40 (12.1%)	156 (31.7%)	77 (23.3%)	44 (29.3%)	14 (16.1%)
Solicited Systemic AE	68 (13.8%)	41 (12.4%)	85 (17.3%)	47 (14.2%)	18 (12.0%)	7 (8.0%)
Unsolicited AE	77 (15.7%)	52 (15.8%)	159 (32.3%)	136 (41.2%)	11 (7.3%)	7 (8.0%)
Unsolicited AE, Days 1-7	46 (9.3%)	34 (10.3%)	78 (15.9%)	66 (20.0%)	1 (0.7%)	1 (1.1%)
Unsolicited AE, Days 1-30	71 (14.4%)	50 (15.2%)	124 (25.2%)	95 (28.8%)	6 (4.0%)	5 (5.7%)

^aOnly subjects who participated in a vaccination 2 or vaccination 3 extension study were included in summaries of vaccination 1 results.

Table 51. Incidence of Overall and Severe Solicited Adverse Events, Days 1 to 7, RCT-EXT Safety Pooling

Adverse Event Type	% of subjects with event (% of subjects with severe event)					
	Vaccination 1		Vaccination 2		Vaccination 3	
	aTIV (N=492)	TIV (N=330)	aTIV (N=492)	TIV (N=330)	aTIV (N=150)	TIV (N=87)
Any Solicited Local AE	23.2% (1.4%)	12.1% (0.3%)	31.7% (1.4%)	23.3% (0.3%)	29.3% (0.7%)	16.1% (0)
Erythema	3.3% (0.2%)	1.5% (0%)	6.1% (0.6%)	5.2% (0)	6.0% (0)	1.1% (0)
Induration	1.8% (0.2%)	2.7% (0.3%)	2.0% (0.2%)	1.5% (0)	3.3% (0)	0 (0)
Pain at Injection Site	19.5% (1.0%)	7.3% (0)	27.2% (0.6%)	20.9% (0.3%)	28.0% (0.7%)	16.1% (0)
Tenderness	56.4% (2.6%)	25.7% (0)	28.2% (0)	11.4% (0)	NA	NA
Any Solicited Systemic AE	13.8% (1.2%)	12.4% (0.6%)	17.3% (0.4%)	14.2% (0.3%)	12.0% (1.3%)	8.0% (0)
Chills	3.3% (0.4%)	4.1% (0.3%)	3.5% (0)	2.7% (0)	2.7% (0)	0 (0)
Myalgia	3.3% (0.4%)	1.7% (0.3%)	4.0% (0)	1.4% (0)	1.3% (0)	2.3% (0)
Arthralgia	2.4% (0.4%)	1.0% (0.3%)	0.9% (0)	1.7% (0)	0.7% (0)	3.4% (0)
Headache	5.5% (0.2%)	5.1% (0.3%)	8.8% (0)	5.1% (0)	4.0% (0.7%)	3.4% (0)
Malaise	6.0% (0.4%)	6.8% (0.3%)	9.1% (0)	7.5% (0.3%)	6.7% (0)	3.4% (0)
Nausea	2.6% (0)	1.7% (0)	2.6% (0)	2.7% (0.3%)	3.3% (0)	2.3% (0)
Fever	1.5% (0.4%)	0.5% (0)	1.2% (0.4%)	0.9% (0)	0.7% (0.7%)	0 (0)

The pooled analysis described in the previous tables removed subjects who had died. In order to review all safety data and to ensure that AEs leading to hospitalization and deaths were available for review in this briefing document, data for the full analysis set of subjects enrolled in the primary vaccination studies and extension studies for vaccination 1 is displayed in Table 52. The numbers of subjects with an AE leading to hospitalization in year 1 were 40 and 27 for aTIV and TIV, respectively. In years 2 and 3, the numbers of subjects were 36 and 25, and 5 and 4 for aTIV and TIV, respectively. The numbers of subjects who died in year 1 were 16 and 22 for aTIV and TIV, respectively. In year 2, the numbers of subjects who died were 17 and 6. No deaths were reported for either vaccine group in year 3.

Table 52. Adverse Event Leading to Hospitalization and Death, Safety FAS

Adverse Event Type	N subjects with event (% of subjects), Safety FAS					
	Vaccination 1 ^a		Vaccination 2		Vaccination 3	
	aTIV (N=713)	TIV (N=501)	aTIV (N=492)	TIV (N=330)	aTIV (N=150)	TIV (N=87)
AE leading to hospitalization	40 (5.6%)	27 (5.4%)	36 (7.3%)	25 (7.6%)	5 (3.3%)	4 (4.6%)
Deaths	16 (2.2%)	22 (4.4%)	17 (3.5%)	6 (1.8%)	0	0

^a Denominators for season 1 were derived from the full analysis safety set.

11.15 Prospective Cohort Safety Analysis of AESIs

The Lombardia Influenza Vaccine Effectiveness (LIVE) Study was a prospective cohort study of 107,661 subjects 65 years or older conducted in Italy from 2006 to 2009 (Villa 2013). This study was also described in Section 10.

A secondary objective of the LIVE Study was to assess for the occurrence of AESIs. A predefined list of ICD-9 codes associated with hospitalization and specific AESI categories (anaphylaxis, autoimmune hepatitis, Bell's palsy, convulsions, demyelinating disorders, encephalitis, Guillain-Barré syndrome, immune thrombocytopenic purpura, and vasculitis) were used to identify potential cases. The medical charts for potential cases were examined by an independent team of medical experts for immunology and neurological AESIs, blinded with respect to the subjects' identity, condition, and time of vaccination.

Cumulative incidences (number of cases per 100,000) were calculated for each new-onset AESI for two time windows (biologically plausible and 6 months). Biologically plausible time windows, as defined by the WHO, FDA, and European Centre for Disease Control, span up to 60 days following vaccination depending on the AESI. See Appendix, Table 71 for more information.

Table 53 shows the number of AESI cases defined by the investigators as "definite," "probable," and "possible" during biologically plausible time windows. Table 54 shows the number of AESI cases defined by the investigators as "definite," "probable," "possible," and "cannot be ruled out" during a 6 month time window. The number of events increased, as expected, with the expanded inclusion criteria and reporting time. When the inclusion criteria were narrowed to definitive probable cases, the number of vasculitis cases decreased to 2 in the aTIV group. In the analyses conducted, the authors concluded that the safety profile was similar for older adult subjects receiving aTIV and TIV.

Table 53. Adverse Events of Special Interest (AESI) During Biologically Plausible Time Windows, LIVE Study

Outcome	aTIV (N=88,449)			TIV (N=82,539)			Difference	
	No. of Cases ^a	Risk ^b	(95% CI)	No. of Cases ^a	Risk ^b	(95% CI)	Risk ^b	(95% CI)
Anaphylaxis	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Autoimmune hepatitis	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Bell’s Palsy	1	1.13	(0.03-6.30)	0	0.00	(0.00-4.47)	1.13	(-1.09-3.35)
Convulsions	4	4.52	(1.23-11.58)	6	7.27	(2.67-15.82)	-2.75	(-10.06-4.57)
Demyelinating disorders	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Encephalitis	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Guillain-Barré syndrome	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Immune thrombocytopenic purpura	2	2.26	(0.27-8.17)	1	1.21	(0.03-6.75)	1.05	(-2.88-4.98)
Vasculitis	2	2.26	(0.27-8.17)	0	0.00	(0.00-4.47)	2.26	(-0.87-5.39)

^aNo. of Cases included those classified as either “definite,” “probable,” or “possible.” ^bCumulative incidence (number of cases per 100,000 person). Source: Villa 2013

Table 54. Adverse Events of Special Interest (AESI) During 6-Month Time Window, LIVE Study

Outcome	aTIV (N=88,449)			TIV (N=82,539)			Difference	
	No. of Cases ^a	Risk ^b	(95% CI)	No. of Cases ^a	Risk ^b	(95% CI)	Risk ^b	(95% CI)
Anaphylaxis	5	5.65	(1.84-13.19)	7	8.48	(3.14-17.47)	-2.83	(-10.83-5.17)
Autoimmune hepatitis	0	0.00	(0.00-4.17)	1	1.21	(0.03-6.75)	-1.21	(-3.59-1.16)
Bell's Palsy	2	2.26	(0.27-8.17)	2	2.42	(0.29-8.75)	-0.16	(-4.75-4.43)
Convulsions	47	53.14	(39.05-70.66)	51	61.79	(46.01-81.23)	-8.65	(-31.39-14.11)
Demyelinating disorders	0	0.00	(0.00-4.17)	0	0.00	(0.00-4.47)	0.00	N/A
Encephalitis	0	0.00	(0.00-4.17)	1	1.21	(0.03-6.75)	-1.21	(-3.59-1.16)
Guillain-Barré syndrome	2	2.26	(0.27-8.17)	5	6.06	(1.97-14.14)	-3.80	(-9.96-2.37)
Immune thrombocytopenic purpura	6	6.78	(2.49-14.76)	10	12.12	(5.81-22.28)	-5.33	(-14.59-3.93)
Vasculitis	12	13.57	(7.01-23.70)	4	4.85	(1.32-12.41)	8.72	(-0.31-17.74)

^aNo. of Cases included those classified as either "definite," "probable," "possible," and "cannot be ruled out." ^bCumulative incidence (number of cases per 100,000 persons). Source: Villa 2013

11.16 Post-marketing Data

The post-marketing safety experience with aTIV based on its use outside of the US spans over 17 years (May 1997 through April 2014) with nearly 76 million doses distributed. During this time, 852 spontaneous aTIV-confirmed AE reports involving individuals over the age of 65 were received and 3,047 events were reported for a cumulative reporting rate of 1.12 cases per 100,000 doses. The most commonly reported systemic reactions among the older adults were fever (17% of cases), asthenia (6%), chills (5%), malaise (5%), and fatigue (5%), and the most common local reactions were erythema (9%), swelling (7%) and pain (5%).

Thirty nine percent (n= 334) of cases contained at least one SAE. Of these SAEs, the most commonly reported were dyspnea (n=35), fever (n=34), and Guillain-Barré syndrome (n=30). Five percent (n= 43) of spontaneous reports among the older adults were associated with a fatal outcome. The cause of death was unknown in most cases (n=16). In cases where the cause of death was known, the most common causes of death were pulmonary edema (n=6), respiratory tract infection (n=4), and cardiac failure and/or respiratory failure (n=3).

A comprehensive search strategy was used to identify AESIs and AEFIs. The reporting rates were very low for all events (<0.1 event per 100,000 doses). The AESIs/AEFIs with the highest rates per 100,000 doses were arthritis (0.08), angioedema (0.07), Guillain-Barré syndrome (0.04), and demyelination (0.04). Reports of arthritis are expected based on the background incidence of this disease in an older patient population. Reports of angioedema (associated with anaphylaxis) and Guillain-Barré syndrome are continuously monitored as a potential risk in the aTIV and TIV Risk Management Plans (RMPs).

Using the Empirica Signal System and proportional reporting ratio method ([Banks 2005](#)), the incidence of AESIs and AEFIs associated with aTIV were compared to TIV (*Agrippal*).

A signal of disproportionate reporting is considered detected if all the following conditions are met: a) Proportional reporting ratio (PRR) > 2; b) Chi-square, applying Yates correction > 4; c) the number of individual case safety reports (ICSRs) in each group > 2. The results of this analysis are presented in Table 55 and revealed no disproportionality of AESIs/AEFIs in subjects vaccinated with aTIV compared to those vaccinated with the TIV comparator.

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Table 55. Disproportionality for AESI / AEFI in Older Adults ≥ 65 Years for aTIV vs. TIV, Post-marketing Safety

AESI / select clinically important AEFI	<i>Fluad</i> (aTIV) (N=852) n (%)	<i>Agrippal</i> (TIV) (N=318) n (%)	Proportional reporting ratio (<i>Fluad</i> vs. <i>Agrippal</i>)	Continuity corrected Chi Square^a	Signal according to screened proportional ratio method
Anaphylactic reaction (SMQ) [broad]	26 (3.05%)	8 (2.52%)	1.213	0.084	No
Angioedema (SMQ) [narrow]	50 (5.87%)	24 (7.55%)	0.778	0.836	No
Arthritis (SMQ) [broad]	61 (7.16%)	25 (7.86%)	0.911	0.08	No
Blood autoimmune disorders (HLT) (Custom Term)	5 (0.59%)	1 (0.31%)	1.866	0.014	No
Cardiomyopathies (HLT) (Custom Term)	2 (0.23%)	0	1.87	0.005	No
Connective tissue disorders (excl LE) (HLT) (Custom Term)	2 (0.23%)	0	1.87	0.005	No
Cranial nerve disorders (excluding neoplasms) (Custom Term)	14 (1.64%)	3 (0.94%)	1.742	0.379	No
Demyelination (SMQ) [narrow]	32 (3.76%)	18 (5.66%)	0.664	1.614	No
Enteritis PT	1 (0.12%)	1 (0.31%)	0.373	0.005	No
Febrile convulsion PT	2 (0.23%)	0	1.87	0.005	No
Generalised convulsive seizures following immunisation (SMQ) [narrow]	8 (0.94%)	2 (0.63%)	1.493	0.024	No
Glomerulonephritis and nephrotic syndrome (HLT) (Custom Term)	2 (0.23%)	0	1.87	0.005	No
Guillain-Barre syndrome (SMQ) [narrow]	30 (3.52%)	15 (4.72%)	0.746	0.601	No
Hyperthyroidism (SMQ) [broad]	3 (0.35%)	0	2.618	0.168	No
Hypothyroidism (SMQ) [broad]	3 (0.35%)	0	2.618	0.168	No
Ischaemic colitis (SMQ) [broad]	1 (0.12%)	3 (0.94%)	0.124	2.53	No
Muscular autoimmune disorders	3	0	2.618	0.168	No

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AESI / select clinically important AEFI	<i>Fluad</i> (<i>aTIV</i>) (N=852) n (%)	<i>Agrippal</i> (<i>TIV</i>) (N=318) n (%)	Proportional reporting ratio (<i>Fluad</i> vs. <i>Agrippal</i>)	Continuity corrected Chi Square^a	Signal according to screened proportional ratio method
(HLT) (Custom Term)	(0.35%)				
Myelitis PT	3 (0.35%)	0	2.618	0.168	No
Myositis PT	1 (0.12%)	2 (0.63%)	0.187	0.791	No
Narcolepsy (Custom Term) ^b	13 (1.53%)	2 (0.63%)	2.426	0.848	No
Noninfectious encephalitis (SMQ) [narrow]	5 (0.59%)	8 (2.52%)	0.233	6.184	No
Peripheral neuropathies NEC (HLT) (Custom Term)	7 (0.82%)	5 (1.57%)	0.523	0.652	No
Polyneuropathy PT	4 (0.47%)	8 (2.52%)	0.187	7.642	No
Radiculitis PT	3 (0.35%)	2 (0.63%)	0.56	0.02	No
Radiculitis brachial PT	2 (0.23%)	0	1.87	0.005	No
Raynaud's phenomenon PT	1 (0.12%)	0	1.122	0.263	No
Severe cutaneous adverse reactions (SMQ) [narrow]	6 (0.7%)	2 (0.63%)	1.12	0.067	No
Skin autoimmune disorders NEC (HLT) (Custom Term)	1 (0.12%)	1 (0.31%)	0.373	0.005	No
Systemic lupus erythematosus (SMQ) [narrow]	2 (0.23%)	1 (0.31%)	0.746	0.168	No
Thrombocytopenias (HLT) (Custom Term)	10 (1.17%)	7 (2.2%)	0.533	1.065	No
Vasculitis (SMQ) [narrow]	10 (1.17%)	3 (0.94%)	1.244	0	No

^a A continuity corrected chi square value of 3.84 corresponds to a p-value of 0.05. Note: Based on sales data from 01 May 1997 through 30 Apr 2014.

^b See Appendix, Section 14.2.2 for a list of PTs searched under this category. Of note, no report of the PT: Narcolepsy seen

12 BENEFIT/RISK ASSESSMENT

Older adults face the greatest burden of influenza. The CDC estimates that over half of all influenza-related hospitalizations and approximately 90% of deaths associated with influenza in the US occur in individuals 65 years or older (CDC 2010). Annual vaccination against influenza offers the best protection to prevent infection and reduce disease severity from seasonal influenza (CDC 2013a). However, older individuals are affected by age-related decline of the immune system, known as immunosenescence, and vaccine effectiveness is substantially decreased in this population (McElhaney 2012; Osterholm 2012). Furthermore, during the 2014-5 season, a drifted strain of A/H3N2 contributed to significant morbidity amongst older adults (CDC 2015b). Currently, only one vaccine (*Fluzone High-Dose*, Sanofi Pasteur) is licensed in the US specifically for individuals 65 years of age and older. *Fluzone High-Dose* contains four times the amount of antigen (180 µg) as the standard dose of inactivated influenza vaccine as well as aTIV (CDC 2014a).

For the susceptible population of persons 65 years of age and older, aTIV specifically targets age-related immunosenescence by stimulating humoral and cell-mediated immune responses (O'Hagan 2012). aTIV offers immunogenic benefits without increasing the standard antigen dose. The evidence base for the benefits of aTIV is large, and includes a 7000-subject pivotal study, 15 additional randomized controlled trials, 7 revaccination studies with re-immunization, a case-control study, and a large prospective cohort study.

In the pivotal study, aTIV was demonstrated to be non-inferior to TIV against both homologous and heterologous strains, as well as in a subgroup of subjects with chronic medical conditions that place them at high risk for complications from influenza. aTIV demonstrated the greatest benefits over TIV, including superiority in seroconversion, against A/H3N2. Moreover, in post-hoc analyses, aTIV consistently elicited higher immune responses than TIV.

In addition to immune responses assessed at day 22 post-vaccination, aTIV demonstrated higher antibody levels than TIV through 1 year for most homologous influenza strains, suggesting the potential for persistence of aTIV's immunogenic effect in an older population. Higher antibody responses against heterologous influenza strains following vaccination with aTIV suggests a possibility of greater immune recognition of mismatched influenza strains. The clinical benefit of both findings should be evaluated further in efficacy or effectiveness trials.

Additional studies support the results of the pivotal trial. A meta-analysis of the 16 FD-RCTs spanning 20 years found that aTIV was non-inferior to TIV. Overall, aTIV elicited higher GMTs and seroconversion rates than TIV across the FD-RCTs. Seven revaccination studies of the randomized controlled trials support that these immunologic benefits are not diminished with re-immunization for 2 and 3 consecutive, annual vaccinations. Data from seven revaccination studies demonstrated no new safety concerns, however, there are limitations in the interpretation of these data based on potential selection bias for subjects who continue in these revaccination studies.

Two non-randomized observational studies provide supportive evidence of aTIV's impact on influenza disease. In a case-control study in Canada, the relative effectiveness of aTIV was 63% higher than TIV against lab-confirmed influenza ([Van Buynder 2013](#)). In a large prospective cohort study in over 107,000 older individuals in Italy, vaccination with aTIV led to 25% fewer influenza or pneumonia-related hospitalizations than vaccination with TIV ([Mannino 2012](#)).

The risk profile of aTIV has been evaluated by a large body of evidence. In addition to the RCTs, revaccination studies, and observational studies, the safety database is augmented by nearly 17 years of post-marketing surveillance outside the US on more than 76 million distributed aTIV doses. The pivotal trial showed that, except for an increase in mild reactogenicity, the safety profile of aTIV was generally similar to TIV.

Safety data analyses from the pooling of 15 FD-RCTs and 7 revaccination studies support the pivotal trial findings. A large observational study demonstrated no increased risk of AESI. Ongoing post-marketing surveillance has not detected a disproportionate risk of AESIs or AEFIs as compared to another licensed non-adjuvanted influenza vaccine, nor has the surveillance detected any safety issue novel to influenza vaccines.

Overall, aTIV demonstrates a positive benefit/risk profile for vaccination against influenza among individuals 65 years of age and older. The benefits are based on confirmation of non-inferiority versus another US licensed influenza vaccine as demonstrated by a surrogate endpoint (evaluation of HI antibody responses against A and B influenza strains). Additional benefit of aTIV is supported by its clinical effectiveness shown in observational studies, but the limitations of non-randomized observational studies are acknowledged. Extensive safety studies indicate that aTIV is well-tolerated and has an acceptable safety profile, which is similar to other licensed vaccines, without signs of increased risk of autoimmune disease, including narcolepsy. These data are supportive of continued aTIV use in the prevention of influenza in individuals 65 years of age and older.

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14 APPENDICES

14.1 Supplementary Data Tables

Table 56. Subgroup Analyses for Seroconversion Against Homologous Strain H1N1, Pivotal Study

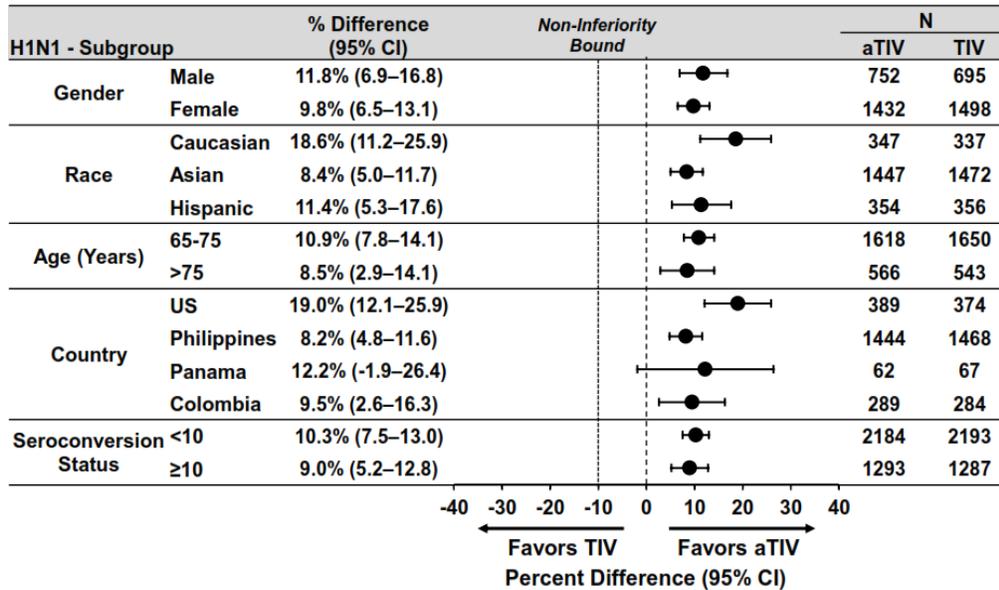


Table 57. Subgroup Analyses for Seroconversion Against Homologous Strain H3N2, Pivotal Study

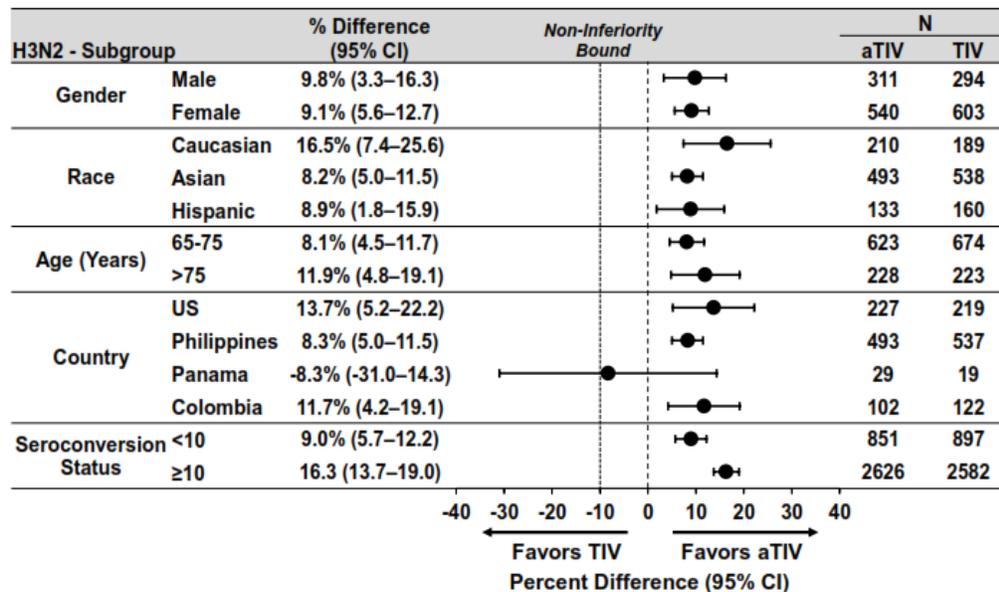


Table 58. Subgroup Analyses for Seroconversion Against Homologous B Strain, Pivotal Study

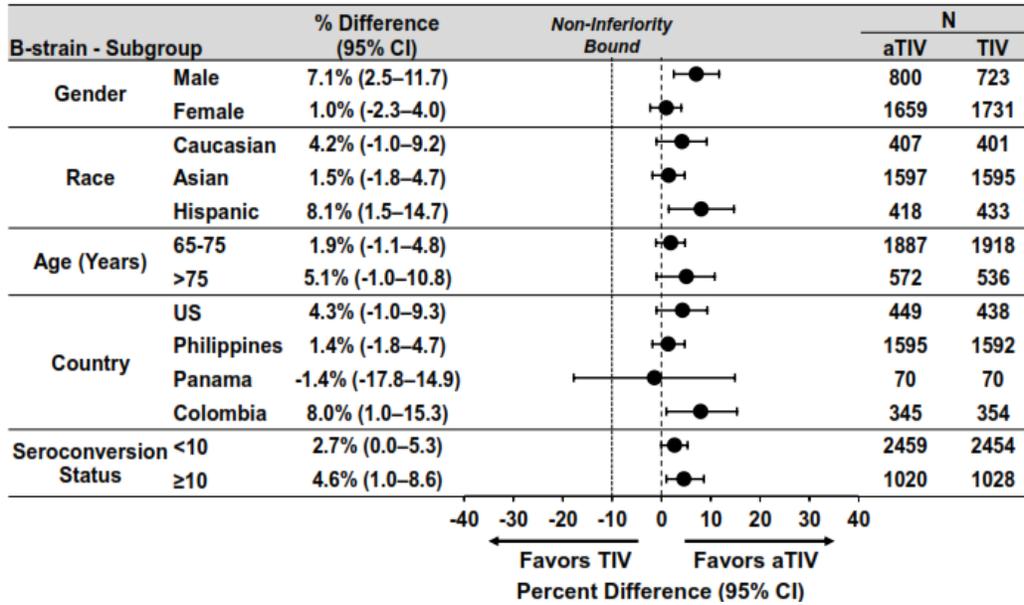


Table 59. Subgroup Analyses for GMT Ratios, Homologous Strain H1N1, Pivotal Study

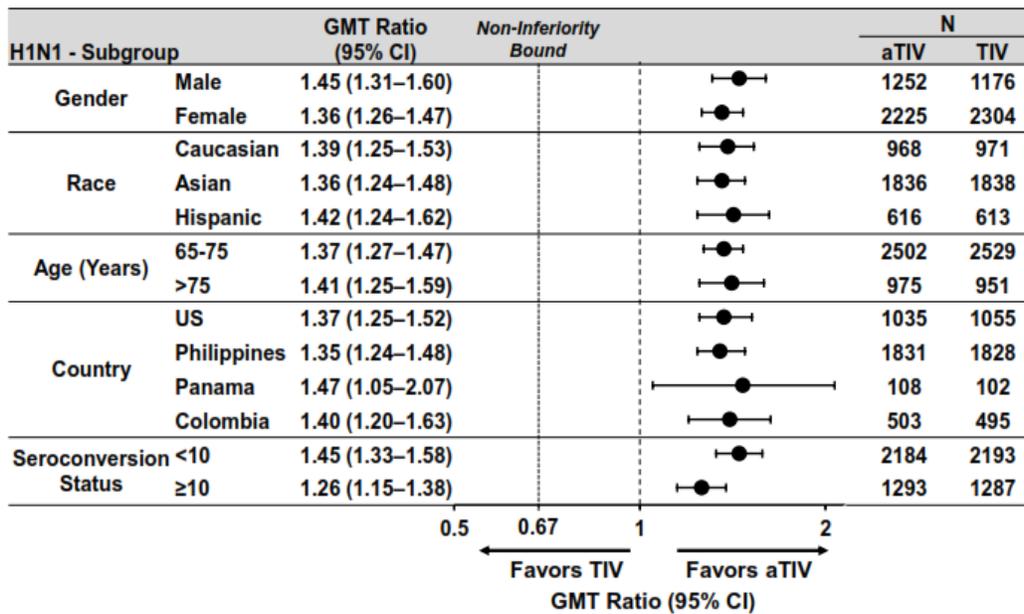


Table 60. Subgroup Analyses for GMT Ratios, Homologous Strain H3N2, Pivotal Study

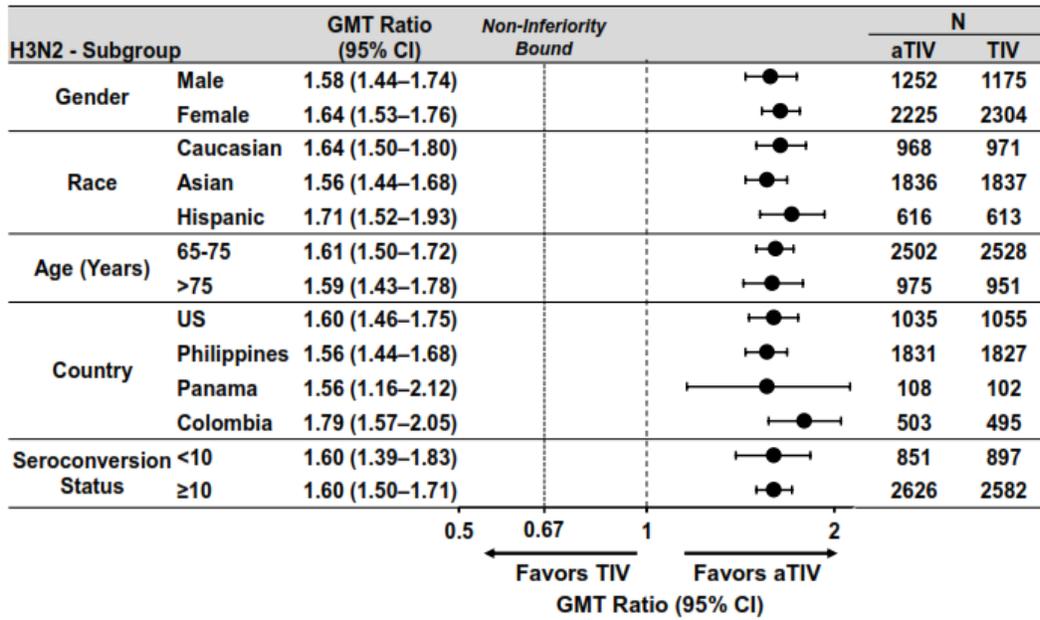


Table 61. Subgroup Analyses for GMT Ratios, Homologous B Strain, Pivotal Study

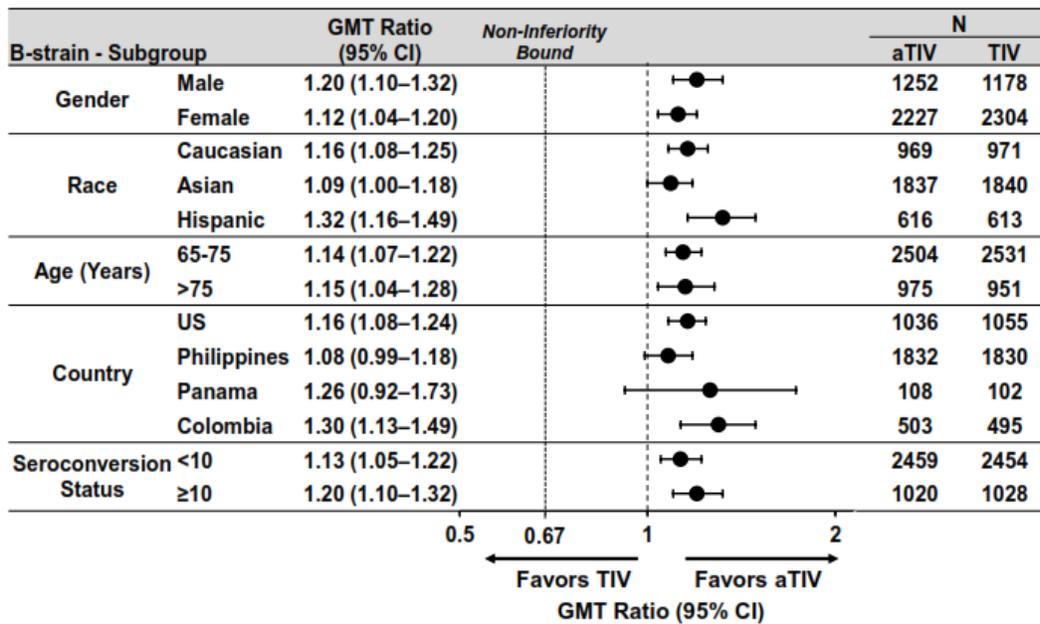


Table 62. Subjects with Pre-Existing Comorbidity, Day 22 FAS

Comorbidity	aTIV (N=1300)		TIV (N=1273)	
Any comorbidities	1300	(100%)	1273	(100%)
Congestive heart failure	77	(6%)	79	(6%)
Chronic obstructive pulmonary disease	171	(13%)	174	(14%)
Asthma	162	(12%)	155	(12%)
Hepatic disease	13	(1%)	13	(1%)
Renal insufficiency	49	(4%)	57	(4%)
Neurological/neuromuscular, or metabolic disorders including diabetes mellitus	1076	(83%)	1045	(82%)

Individual subjects may have multiple comorbidities. Pre-existing comorbidities in the day 22 PPS were similar to the day 22 FAS for both aTIV and TIV.

Table 63. Demographics and Subject Characteristics at Baseline, FD-RCT Safety Pooling

Characteristic	aTIV (N=5754)	TIV (N=5198)
Age (years), mean \pm SD	72.9 \pm 6.2	72.8 \pm 6.2
Age group (years), %		
50 to <65	0.1%	<0.1%
65 to <75	66.0%	66.6%
75 to <85	28.5%	27.8%
\geq 85	5.4%	5.5%
Sex, %		
Male	38.9%	37.1%
Female	61.1%	62.9%
BMI (kg/m ²), mean \pm SD	25.6 \pm 5.2	25.6 \pm 5.3
Race, %		
Asian	33.9%	37.5%
Black	1.3%	1.1%
Caucasian	64.5%	60.9%
Other	0.3%	0.4%
Hispanic/Latino ethnicity, %	11.5%	12.6%
Geographic Location, %		
USA	35.5%	32.3%
Rest of World	64.5%	67.7%

Table 64. Overall Summary of Adverse Events, FD-RCT Safety Pooling

Adverse Event Type	aTIV (N=5754)	TIV (N=5198)
Any Solicited AE	2818 (49.4%)	1837 (35.7%)
Solicited Local AE	1959 (34.5%)	938 (18.4%)
Solicited Systemic AE	1573 (27.5%)	1156 (22.4%)
Any Unsolicited AE	1427 (24.8%)	1388 (26.7%)
Any SAE	358 (6.2%)	341 (6.6%)
Any AE leading to withdrawal	77 (1.3%)	75 (1.4%)
Any AE leading to death	73 (1.3%)	71 (1.4%)

Table 65. Solicited Local Adverse Events 1 to 7 Days (including 30 minutes), FD-RCT Safety Pooling

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV		Relative Risk ^a (95% CI)
Any Solicited Local AE	Any (N = 5754 vs. 5198)	1972	(34.5%)	949	(18.4%)	1.85 (1.73-1.98)
	Mild (25 to ≤50 mm)	1601	(28.0%)	793	(15.6%)	
	Moderate (51 to ≤100 mm)	339	(5.9%)	128	(2.5%)	
	Severe (>100 mm)	32	(0.6%)	17	(0.3%)	
Erythema	Any (N = 5754 vs. 5198)	172	(3.0%)	86	(1.7%)	1.86 (1.43-2.41)
	Mild (25 to ≤50 mm)	127	(2.2%)	73	(1.4%)	
	Moderate (51 to ≤100 mm)	40	(0.7%)	13	(0.3%)	
	Severe (>100 mm)	5	(0.1%)	0		
Induration	Any (N = 5754 vs. 5198)	145	(2.5%)	60	(1.2%)	2.20 (1.62-3.00)
	Mild (25 to ≤50 mm)	105	(1.8%)	43	(0.8%)	
	Moderate (51 to ≤100 mm)	37	(0.6%)	13	(0.3%)	
	Severe (>100 mm)	3	(0.1%)	4	(0.1%)	
Tenderness	Any (N=3591 vs. 3583)	791	(22.2%)	434	(12.2%)	1.82 (1.63-2.02)
	Mild	670	(18.8%)	390	(11.0%)	
	Moderate	115	(3.2%)	38	(1.1%)	
	Severe	6	(0.2%)	6	(0.2%)	
Swelling	Any (N = 3767 vs. 3756)	58	(1.6%)	22	(0.6%)	2.61 (1.60-4.26)
	Mild (25 to ≤50 mm)	43	(1.2%)	19	(0.5%)	
	Moderate (51 to ≤100 mm)	13	(0.3%)	3	(0.1%)	
	Severe (>100 mm)	2	(0.1%)	0		
Pain	Any (N = 5754 vs. 5198)	1621	(28.3%)	704	(13.7%)	2.00 (1.84-2.17)
	Mild	1352	(23.6%)	597	(11.6%)	
	Moderate	245	(4.3%)	95	(1.8%)	
	Severe	24	(0.4%)	12	(0.2%)	
Ecchymosis	Any (N = 47 vs. 44)	2	(4.3%)	0		NC
	Mild	2	(4.3%)	0		
	Moderate	0		0		
	Severe	0		0		

^a Relative risks are presented as aTIV/TIV for events of any severity, and were calculated from a Cochran Mantel Haenszel estimator adjusted by study. NC = Not calculated.

Table 66. Solicited Systemic Adverse Events 1 to 7 Days (including 30 minutes), FD-RCT Safety Pooling

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV		Relative Risk ^a (95% CI)
Any Solicited Systemic AE	Any (N = 5754 vs. 5198)	1573	(27.5%)	1156	(22.4%)	1.23 (1.15-1.32)
	Mild	1071	(18.7%)	766	(14.8%)	
	Moderate	394	(6.9%)	293	(5.7%)	
	Severe	106	(1.9%)	95	(1.8%)	
Chills	Any (N = 5708 vs. 5152)	329	(5.8%)	206	(4.0%)	1.48 (1.25-1.75)
	Mild	241	(4.2%)	145	(2.8%)	
	Moderate	70	(1.2%)	47	(0.9%)	
	Severe	18	(0.3%)	14	(0.3%)	
Myalgia	Any (N = 5708 vs. 5152)	720	(12.7%)	405	(7.9%)	1.55 (1.38-1.74)
	Mild	576	(10.2%)	304	(5.9%)	
	Moderate	120	(2.1%)	70	(1.4%)	
	Severe	24	(0.4%)	31	(0.6%)	
Arthralgia	Any (N = 5708 vs. 5152)	382	(6.7%)	315	(6.2%)	1.11 (0.96-1.29)
	Mild	296	(5.2%)	227	(4.4%)	
	Moderate	69	(1.2%)	65	(1.3%)	
	Severe	17	(0.3%)	23	(0.4%)	
Headache	Any (N = 5708 vs. 5152)	641	(11.3%)	499	(9.8%)	1.16 (1.04-1.30)
	Mild	483	(8.5%)	355	(6.9%)	
	Moderate	138	(2.4%)	114	(2.2%)	
	Severe	20	(0.4%)	30	(0.6%)	
Fatigue	Any (N = 3767 vs. 3756)	500	(13.4%)	391	(10.5%)	1.27 (1.13-1.44)
	Mild	373	(10.0%)	279	(7.5%)	
	Moderate	113	(3.0%)	87	(2.3%)	
	Severe	14	(0.4%)	25	(0.7%)	
Malaise	Any (N = 2163 vs. 1615)	166	(7.7%)	94	(5.8%)	1.24 (0.95-1.61)
	Mild	122	(5.6%)	77	(4.8%)	
	Moderate	32	(1.5%)	12	(0.7%)	
	Severe	12	(0.6%)	5	(0.3%)	
Nausea	Any (N = 5708 vs. 5152)	156	(2.8%)	136	(2.7%)	1.01 (0.80-1.28)
	Mild	120	(2.1%)	99	(1.9%)	
	Moderate	27	(0.5%)	30	(0.6%)	
	Severe	9	(0.2%)	7	(0.1%)	
Vomiting	Any (N = 3592 vs. 3581)	51	(1.4%)	62	(1.7%)	0.82 (0.57-1.18)
	Mild	36	(1.0%)	39	(1.1%)	

Adverse Event Type	Severity (N = aTIV vs. TIV)	aTIV		TIV		Relative Risk ^a (95% CI)
	Moderate	13	(0.4%)	19	(0.5%)	
	Severe	2	(0.1%)	4	(0.1%)	
Diarrhea	Any (N = 3592 vs. 3581)	172	(4.8%)	158	(4.5%)	1.09 (0.88-1.34)
	Mild	114	(3.2%)	119	(3.4%)	
	Moderate	44	(1.2%)	30	(0.8%)	
	Severe	14	(0.4%)	9	(0.3%)	
Rash	Any (N = 1857 vs. 1370)	9	(0.5%)	6	(0.4%)	0.61 (0.19-1.98)
Fever ($\geq 38^{\circ}\text{C}$)	(N=5754 vs. 5198)	139	(2.6%)	125	(2.5%)	1.09 (0.86-1.39)

^a Relative risks are presented as aTIV/TIV for events of any severity, and were calculated from a Cochran Mantel Haenszel estimator adjusted by study.

Table 67. Other Solicited Adverse Events with Onset 6 Hours to 7 Days Following Vaccination by Severity, FD-RCT Safety Pooling

Adverse Event Type	N Evaluated (aTIV vs. TIV)	aTIV		TIV		Relative Risk ^a (95% CI)
Stayed home due to reaction	(5533 vs. 4977)	132	(2.4%)	103	(2.1%)	1.19 (0.92-1.54)
Analgesic/antipyretic used	(5708 vs. 5152)	618	(10.9%)	411	(8.1%)	1.12 (1.00-1.25)

^a Relative risks are presented as aTIV/TIV, and were calculated from a Cochran Mantel Haenszel estimator adjusted by study.

Table 68. Unsolicited Adverse Events Reported in $\geq 0.5\%$ of Subjects by Preferred Term, FD-RCT Safety Pooling

Adverse Event Type	aTIV (N=5754)		TIV (N=5198)		Relative Risk ^a (95% CI)
Any unsolicited AE	1427	(24.8%)	1388	(26.7%)	0.94 (0.87-1.01)
Nasopharyngitis	86	(1.5%)	72	(1.4%)	1.14 (0.84-1.56)
Hypertension	81	(1.4%)	93	(1.8%)	0.81 (0.60-1.10)
Headache	61	(1.1%)	77	(1.5%)	0.73 (0.52-1.03)
Pneumonia	51	(0.9%)	54	(1.0%)	0.85 (0.58-1.24)
Upper respiratory tract infection	49	(0.9%)	47	(0.9%)	1.00 (0.67-1.49)
Cough	48	(0.8%)	54	(1.0%)	0.86 (0.58-1.27)
Arthralgia	43	(0.7%)	43	(0.8%)	0.91 (0.60-1.39)
Bronchitis	43	(0.7%)	57	(1.1%)	0.63 (0.42-0.93)
Osteoarthritis	39	(0.7%)	38	(0.7%)	0.95 (0.60-1.48)
Diarrhoea	34	(0.6%)	39	(0.8%)	0.80 (0.51-1.27)
Dizziness	30	(0.5%)	24	(0.5%)	1.20 (0.70-2.06)
Injection site erythema	30	(0.5%)	23	(0.4%)	1.07 (0.62-1.84)
Pyrexia	30	(0.5%)	21	(0.4%)	1.37 (0.79-2.40)
Myalgia	29	(0.5%)	26	(0.5%)	1.03 (0.61-1.75)
Cardiac failure congestive	27	(0.5%)	36	(0.7%)	0.65 (0.39-1.07)
Cerebral ischaemia	27	(0.5%)	22	(0.4%)	0.98 (0.56-1.73)
Insomnia	27	(0.5%)	21	(0.4%)	1.06 (0.60-1.88)

^a Relative risks are presented as aTIV/TIV, and are calculated from a Poisson regression model including terms for duration of follow-up for AEs.

Table 69. Serious Adverse Events Reported in $\geq 0.2\%$ of Subjects in Either Vaccine Group, by Preferred Term, FD-RCT Safety Pooling

Preferred Term	aTIV (N=5754)		TIV (N=5198)		Relative Risk ^a (95% CI)
Any SAE	384	(6.7%)	366	(7.0%)	0.95 (0.82-1.09)
Pneumonia	41	(0.7%)	42	(0.8%)	0.90 (0.58-1.38)
Cardiac failure congestive	16	(0.3%)	26	(0.5%)	0.52 (0.28-0.97)
Myocardial infarction	13	(0.2%)	15	(0.3%)	0.70 (0.33-1.47)
Acute myocardial infarction	12	(0.2%)	9	(0.2%)	1.18 (0.50-2.82)
Cerebrovascular accident	10	(0.2%)	14	(0.3%)	0.59 (0.26-1.34)
Chronic obstructive pulmonary disease	10	(0.2%)	14	(0.3%)	0.70 (0.31-1.57)
Hypertension	9	(0.2%)	8	(0.2%)	1.09 (0.42-2.82)
Osteoarthritis	9	(0.2%)	15	(0.3%)	0.58 (0.25-1.32)
Atrial fibrillation	7	(0.1%)	12	(0.2%)	0.54 (0.21-1.37)

^a Relative risks are presented as aTIV/TIV, and are calculated from a Poisson regression model including terms for duration of follow-up for AEs.

Table 70. Adverse Events Leading to Withdrawal in At Least 3 Subjects in Either Vaccine Group, by Preferred Term, FD-RCT Safety Pooling

Preferred Term	aTIV (N=5754)		TIV (N=5198)		Relative Risk ^a (95% CI)
Any AE leading to withdrawal	77	(1.3%)	75	(1.4%)	0.80 (0.58-1.10)
Pneumonia	9	(0.2%)	8	(0.2%)	0.92 (0.35-2.40)
Acute myocardial infarction	8	(0.1%)	5	(0.1%)	1.29 (0.42-3.98)
Myocardial infarction	8	(0.1%)	12	(0.2%)	0.49 (0.20-1.21)
Cerebrovascular accident	6	(0.1%)	4	(0.1%)	1.07 (0.30-3.83)
Cardiac failure congestive	4	(0.1%)	9	(0.2%)	0.33 (0.10-1.07)
Cardiac failure acute	3	(0.1%)	3	(0.1%)	0.74 (0.15-3.69)
Cardio-respiratory arrest	3	(0.1%)	0		NC
Cerebrovascular disorder	3	(0.1%)	1	(<0.1%)	2.39 (0.25-23.2)
Multi-organ failure	3	(0.1%)	1	(<0.1%)	2.46 (0.25-23.9)
Myocardial ischaemia	3	(0.1%)	0		NC
Septic shock	3	(0.1%)	1	(<0.1%)	2.60 (0.27-25.2)

^a Relative risks are presented as aTIV/TIV, and are calculated from a Poisson regression model including terms for duration of follow-up for AEs. Note: NC = not calculable.

Table 71. Biologically Plausible Time Windows for Predefined Adverse Events of Special Interest, LIVE Study

Outcome	Biologically Plausible Time Windows, Days
Anaphylaxis	0-2
Autoimmune hepatitis	0-60
Bell's Palsy	0-60
Convulsions	0-14
Demyelinating disease	0-42
Encephalitis and encephalomyelitis	0-42
Guillain-Barré syndrome	0-42
Immune thrombocytopenic purpura	0-42
Vasculitis	0-42

Source: Villa et al 2013

14.2 Supplementary Information

14.2.1 Pivotal Study Inclusion/Exclusion Criteria

Inclusion Criteria

- Males and females of age ≥ 65 years on the day of vaccination.
- Individuals who had given written consent after the nature of the study was explained according to local regulatory requirements.
- Individuals able to attend all scheduled visits and to comply with all study procedures.
- Individuals with access to a working telephone and able to receive periodic telephone calls.

Exclusion Criteria

- Individuals with behavioral or cognitive impairment or a psychiatric condition that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
- Individuals who were not able to comprehend and/or follow all required study procedures for the whole period of the study.
- Individuals with history of any illness that, in the opinion of the investigator, might pose additional risk to the subjects due to participation in the study.
- Known or suspected impairment/alteration of immune function, including:
 - Receipt of immune stimulants within 60 days prior to visit 1.
 - Receipt of corticosteroids, defined as:
 - Continuous use with a dosage equivalent to >15 mg/day of oral prednisone for 90 days preceding vaccination
 - Sporadic use with a dosage equivalent to >40 mg/day of oral prednisone for >14 consecutive days in the 90 days preceding vaccination
 - Use of topical or inhalant corticosteroids is acceptable
 - Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to visit 1 or planned during the duration of the study.
 - Receipt of anti-cancer chemotherapy or radiation therapy within the past 12 months.
 - Acquired immunodeficiency
 - HIV infection or HIV-related disease
 - Heritable immunodeficiency
 - Abnormalities of splenic or thymic function
- Individuals with a known bleeding diathesis, or any other condition that may be associated with prolonged bleeding.

- History of Guillain-Barré syndrome.
- Individuals with history of allergy to vaccine components and/or a history of any anaphylaxis, serious vaccine reactions or hypersensitivity to influenza viral proteins, egg proteins (including ovalbumin), polymyxin, neomycin, betapropiolactone, thimerosal/ sodium ethylmercuriothiosalicylate/ mercury and nonylphenol ethoxylate/ nonoxynol-9 (spermicide).
- Receipt of another investigational agent within 30 days prior to enrollment in the study or before completion of the safety follow-up period in another study, whichever is longer, prior to enrollment and unwilling to refuse participation in another clinical study through the end of the study. NOTE: Concomitant participation in an observational trial (not involving drugs, vaccines, or medical devices) is acceptable.
- Individuals who received any other vaccines within 2 weeks for inactivated vaccines or 4 weeks for live vaccines prior to enrollment in this study or who were planning to receive any vaccine within 3 weeks from the study vaccine.
- Individuals who received vaccination against seasonal influenza in the previous 6 months.
- Research staff directly involved with the clinical study or family/household members of research staff. Research staff is individuals with direct or indirect contact with study subjects, or study site personnel who have access to any study documents containing subject information. This would include receptionists, persons scheduling appointments or making screening calls, regulatory specialists, laboratory technicians, etc.
- Individuals with oral temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) on day of study vaccination. NOTE: Vaccinations were not to be administered to any subject with a clinically significant active infection (as assessed by the investigator) or measured oral (sublingual) temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ within 3 days of the intended date of vaccination. If either of these was observed or reported, vaccination should have been postponed until the subject's temperature remained below $38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ for at least 3 days or until the investigator felt that the subject's acute illness had stabilized, as appropriate.
- Individuals with history of substance or alcohol abuse within the past 2 years.
- Individuals providing consent who do not consent to the retention of their serum samples after study completion.
- Elective surgery or hospitalization planned prior to enrollment to occur during the treatment phase.
- Elective surgery or hospitalization planned prior to enrollment to occur during the follow-up phase that, according to the opinion of the investigator, might pose additional risk to the subject.
- Subjects deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized without his/her consent.
- Subjects from whom blood cannot be drawn at visit 1.

General Category	Specific Category	Specific AESI PT And HLT*
	Demyelinating Disease	Demyelination Acute Disseminated Encephalomyelitis Leukoencephalomyelitis Concentric Sclerosis Neuromyelitis Optica Chronic Inflammatory Demyelinating Polyradiculoneuropathy Demyelinating Polyneuropathy Leukoencephalopathy Lewis-Sumner Syndrome Marchiafava-Bignami Disease Acute Haemorrhagic Leukoencephalitis
	Encephalitis	Encephalitis Encephalomyelitis Encephalitis Allergic Encephalitis Brain Stem Encephalitis Haemorrhagic Encephalitis Toxic Encephalitis Post Immunisation Panencephalitis
	Myelitis	Myelitis
	Guillain-Barre Syndrome	Transverse Myelitis
	Guillain-Barre Syndrome	Guillain-Barre Syndrome
	Miller Fisher Syndrome	Miller Fisher Syndrome
	Myasthenia Gravis	Myasthenia Gravis
	Ocular Myasthenia	Ocular Myasthenia
	Narcolepsy (Narrow) ^a	Narcolepsy
		Cataplexy
		Sleep Attacks
		Sleep Paralysis
		Sudden Onset Of Sleep
		Hypersomnia
	Narcolepsy (Broad) ^a	Sleep Disorder
		Somnolence
		Stupor
		Lethargy
		Sedation
		Sleep Inertia
		Dyssomnia
		Delayed Sleep Phase
		Poor Quality Sleep
		Sleep Study Abnormal
		Abnormal Sleep-Related Event
		Sleep Phase Rhythm Disturbance
		Rapid Eye Movements Sleep Abnormal

General Category	Specific Category	Specific AESI PT And HLT*
		Sleep Disorder Due To General Medical Condition, Insomnia Type Sleep Disorder Due To General Medical Condition, Parasomnia Type Sleep Disorder Due To General Medical, Condition, Hypersomnia Type Sleep Disorder Due To General Medical Condition, Mixed Type Sleep Disorder Due To A General Medical Condition Hypersomnia Related To Another Mental Condition Hypersomnia-Bulimia Syndrome Pickwickian Syndrome Sleep Apnoea Syndrome Hypnagogic Hallucination Hypnopompic Hallucination Advanced Sleep Phase Circadian Rhythm Sleep Disorder Delayed Sleep Phase Irregular Sleep Phase Sleep Phase Rhythm Disturbance
Musculoskeletal Disorders	Systemic Lupus Erythematosus Sjogren's Syndrome Scleroderma Dermatomyositis Polymyositis Myositis Arthritis	Systemic Lupus Erythematosus Cutaneous Lupus Erythematosus Sjogren's Syndrome Scleroderma Systemic Sclerosis Crest Syndrome Morphoea Dermatomyositis Polymyositis Myositis Rheumatoid Arthritis Juvenile Arthritis Polymyalgia Rheumatica Arthritis Reactive Reiter's Syndrome Psoriatic Arthropathy Spondylitis Ankylosing Spondylitis Spondyloarthropathy Still's Disease Adult Onset Seronegative Arthritis SLE Arthritis Arthritis

General Category	Specific Category	Specific AESI PT And HLT*
	Mixed Connective Tissue Disease	Autoimmune Arthritis Polyarthritis Caplan's Syndrome Felty's Syndrome Palindromic Rheumatism Mixed Connective Tissue Disease
Gastrointestinal Disorders	Inflammatory Bowel Disease Coeliac Disease	Crohn's Disease Enteritis Colitis Colitis Ulcerative Proctitis Ulcerative Sigmoiditis Coeliac Disease
Metabolic Diseases	Autoimmune Thyroiditis Insulin Dependent Diabetes Mellitus Addison's Disease	Autoimmune Thyroiditis Basedow's Disease Hypothyroidism Hyperthyroidism Type 1 Diabetes Mellitus Addison's Disease
Skin Disorders	Psoriasis Vitiligo Erythema Nodosum Autoimmune Bullous Skin Disease Stevens-Johnson Syndrome	Psoriasis Vitiligo Erythema Nodosum Pemphigus Pemphigoid Dermatitis Herpetiformis Stevens-Johnson Syndrome Erythema Multiforme Toxic Epidermal Necrolysis Anaemia Haemolytic Autoimmune
Hematologic Disorders	Autoimmune Hemolytic Anemia Thrombocytopenia	Thrombocytopenias (Hlt)*
Other Autoimmune Disorders	Anti-Neutrophil Cytoplasmic Antibody Antiphospholipid Syndrome Vasculitis	Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis Antiphospholipid Syndrome Vasculitis Diffuse Vasculitis Renal Vasculitis Leukocytoclastic Vasculitis Behcet's Syndrome Temporal Arteritis Takayasu's Arteritis Microscopic Polyangiitis

General Category	Specific Category	Specific AESI PT And HLT*
		Polyarteritis Nodosa Allergic Granulomatous Angiitis Henoch-Schonlein Purpura Henoch-Schonlein Purpura Nephritis Kawasaki's Disease Aortitis Arteritis Arteritis Coronary Thromboangiitis Obliterans Capillaritis Cerebral Arteritis Cogan's Syndrome Cutaneous Vasculitis Erythema Induratum Injection Site Vasculitis Lupus Vasculitis Granulomatosis With Polyangiitis Tolosa-Hunt Syndrome Pernicious Anemia Autoimmune Hepatitis Primary Biliary Cirrhosis Primary Sclerosing Cholangitis Autoimmune Glomerulonephritis Autoimmune Uveitis Autoimmune Cardiomyopathy Sarcoidosis Raynaud's Phenomenon
		Pernicious Anaemia Autoimmune Hepatitis Biliary Cirrhosis Primary Cholangitis Sclerosing Glomerulonephritis Uveitis Autoimmune Myocarditis Sarcoidosis Raynaud's Phenomenon

*all terms are PT unless otherwise noted

^a In the absence of a Standard MedDRA Query (SMQ) for narcolepsy, these narcolepsy-related MedDRA preferred terms (PT) were used in searching both databases ([Tsai 2011](#)). Case reports captured under these searches were reviewed and adjudicated using the diagnostic criteria for narcolepsy recommended by the American Academy of Sleep Medicine ([Ahmed 2010](#)). Among those required criteria for a definite diagnosis of narcolepsy, with or without cataplexy, is “excessive daytime sleepiness of at least 3 months duration” ([Tsai 2011](#)).

14.2.3 Definitions of Adverse Events Following Immunization

The following list of MedDRA SMQs and PTs was used to search the safety database for AEFIs.

SMQ	PT
Anaphylactic reaction (SMQ) [broad – algorithmic = Narrow terms or (B and C) or (D and (B or C))]	Anaphylactic reaction (Narrow) Anaphylactic shock (Narrow) Anaphylactic transfusion reaction (Narrow) Anaphylactoid reaction (Narrow) Anaphylactoid shock (Narrow) Circulatory collapse (Narrow) First use syndrome (Narrow) Kounis syndrome (Narrow) Shock (Narrow) Type I hypersensitivity (Narrow) Acute respiratory failure (Broad) - B Asthma (Broad) - B Bronchial oedema (Broad) - B Bronchospasm (Broad) - B Cardio-respiratory distress (Broad) - B Chest discomfort (Broad) - B Choking (Broad) - B Choking sensation (Broad) - B Circumoral oedema (Broad) - B Cough (Broad) - B Cyanosis (Broad) - B Dyspnoea (Broad) - B Hyperventilation (Broad) - B Laryngeal dyspnoea (Broad) - B Laryngeal oedema (Broad) – B Laryngospasm (Broad) - B Laryngotracheal oedema (Broad) - B Nasal obstruction (Broad) - B Oedema mouth (Broad) - B Oropharyngeal spasm (Broad) - B Oropharyngeal swelling (Broad) – B Respiratory arrest (Broad) - B Respiratory distress (Broad) - B Respiratory dyskinesia (Broad) - B Respiratory failure (Broad) - B Reversible airways obstruction (Broad) - B Sensation of foreign body (Broad) - B Sneezing (Broad) – B Stridor (Broad) - B Swollen tongue (Broad) - B Tachypnoea (Broad) - B Throat tightness (Broad) - B Tongue oedema (Broad) - B Tracheal obstruction (Broad) - B

SMQ	PT
	Tracheal oedema (Broad) - B Upper airway obstruction (Broad) - B Wheezing (Broad) - B Allergic oedema (Broad) - C Angioedema (Broad) - C Erythema (Broad) - C Eye oedema (Broad) - C Eye pruritus (Broad) - C Eye swelling (Broad) - C Eyelid oedema (Broad) - C Face oedema (Broad) - C Fixed eruption (Broad) - C Flushing (Broad) - C Generalised erythema (Broad) - C Injection site urticaria (Broad) – C Lip oedema (Broad) - C Lip swelling (Broad) - C Ocular hyperaemia (Broad) - C Oedema (Broad) - C Periorbital oedema (Broad) - C Pruritus (Broad) - C Pruritus allergic (Broad) - C Pruritus generalised (Broad) - C Rash (Broad) - C Rash erythematous (Broad) - C Rash generalised (Broad) - C Rash pruritic (Broad) - C Skin swelling (Broad) - C Swelling (Broad) - C Swelling face (Broad) - C Urticaria (Broad) – C Urticaria papular (Broad) – C Blood pressure decreased (Broad) – D Blood pressure diastolic decreased (Broad) – D Blood pressure systolic decreased (Broad) – D Cardiac arrest (Broad) – D Cardio-respiratory arrest (Broad) – D Cardiovascular insufficiency (Broad) – D Diastolic hypotension (Broad) – D Hypotension (Broad) - D

SMQ	PT
Angioedema (SMQ) [narrow]	Allergic oedema Angioedema Circumoral oedema Conjunctival oedema Corneal oedema Epiglottic oedema Eye oedema Eye swelling Eyelid oedema Face oedema Gingival oedema Gingival swelling Gleich's syndrome Hereditary angioedema Idiopathic angioedema Idiopathic urticarial Laryngeal oedema Laryngotracheal oedema Limbal swelling Lip oedema Lip swelling Oculorespiratory syndrome Oedema mouth Oropharyngeal swelling Palatal oedema Periorbital oedema Pharyngeal oedema Scleral oedema Small bowel angioedema Swelling face Swollen tongue Tongue oedema Tracheal oedema Urticaria Urticaria cholinergic Urticaria chronic Urticaria papular
Febrile convulsion	Febrile convulsion
Generalised Convulsive Seizures Following Immunisation (SMQ) [narrow]	Atonic seizures Automatism epileptic Autonomic seizure Clonic convulsion Convulsion Convulsion in childhood

SMQ	PT
	Convulsion neonatal Convulsion prophylaxis Convulsive threshold lowered Drop attacks Epilepsy Febrile convulsion Grand mal convulsion Myoclonic epilepsy Postictal headache Postictal paralysis Postictal state Psychomotor seizures Status epilepticus Tonic convulsion Uncinate fits