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Comparison of the safety and immunogenicity of an MF59®-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects

Sharon E. Frey[a], Mari Rose Aplasca-De Los Reyes[b], Humberto Reynales[c], Nancy Nazaire Bermal[d], Uwe Nicolay[d], Vas Narasimhan[d], Eduardo Forleo-Neto[d], Ashwani Kumar Arora[d,*]

[a] Division of Infectious Diseases, Allergy and Immunology, Saint Louis University School of Medicine, Saint Louis, MO, USA
[b] Research Institute for Tropical Medicine, Alabang, Muntinlupa City, Philippines
[c] Centro de Atención e Investigación Médica (CAIMED), Bogotá, Colombia
[d] Novartis Vaccines and Diagnostics Inc., Cambridge, MA, USA

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ABSTRACT

Aim: Adjuvanted influenza vaccines can overcome the poor antibody response of conventional non-adjuvanted vaccines in the elderly. We evaluated the immunogenicity, safety and clinical effectiveness of an MF59®-adjuvanted trivalent influenza vaccine (aTIV) compared with a non-adjuvanted vaccine (TIV) in subjects ≥65 years old, with or without co-morbidities.
Methods: In 2010–2011, subjects (N = 7082) were randomized to receive one dose of aTIV or TIV. Co-primary objectives were to assess lot-to-lot consistency of aTIV, non-inferiority, superiority and immunogenicity 22 days after vaccination. Clinical effectiveness, reactogenicity and serious adverse events were monitored up to Day 366.
Results: The immunological equivalence of three lots of aTIV was demonstrated. aTIV was not only non-inferior to TIV but also elicited significantly higher antibody responses at Day 22 than TIV against all homologous and heterologous strains, even in subjects with co-morbidities. Superiority was not established. Reactogenicity was higher in the aTIV group, but reactions were mild to moderate and transient.
Conclusions: aTIV elicited a significantly higher antibody response than TIV, especially against A/H3N2 strains, although superiority by pre-defined criteria was not formally met. The study demonstrates potential immunological benefits of MF59-adjuvanted influenza vaccines for the elderly.
This trial was registered with www.clinicaltrials.gov (NCT01162122).

1. Introduction

The largest impact of seasonal influenza is seen in the elderly (≥65 years), with the highest rates of mortality and hospitalizations reported in this age group [1]. Vaccination, recommended by the World Health Organization for all people aged six months and older, is the most effective prophylaxis against influenza and is especially important for high-risk groups such as the elderly, chronically ill individuals, health care workers, pregnant women and young children.

Non-adjuvanted trivalent influenza vaccines (TIV) have a lower efficacy in the elderly than in younger adults, which is attributed to age-related immunosenescence [2,3]. One very successful strategy to enhance the immunogenicity of influenza vaccines in the elderly is the addition of adjuvants, such as MF59® (Novartis Vaccines & Diagnostics), a squalene-based oil-in-water emulsion that was first approved for use in seasonal influenza vaccines for the elderly in 1997 [4,5].

MF59 acts by both recruiting antigen-presenting cells to the administration site and by increasing the binding strength of the antibody to the influenza virus, resulting in a more efficient antigen uptake, processing and transportation to the lymph nodes [4,6,7].

Abbreviations: AE, adverse event; aTIV, adjuvanted trivalent influenza vaccine; CBER, Center for Biologics Evaluation and Research; CHMP, European Committee for Medicinal Products for Human Use; FAS, full analysis set; GMT, geometric mean titer; HA, hemagglutinin; HI, hemagglutinin inhibition; ILI, influenza-like illness; PPS, per-protocol set; RR, relative risk; SAE, serious adverse event; TIV, trivalent influenza vaccine.

* Corresponding author at: Novartis Vaccines and Diagnostics S.r.l. Via Fiorentina, 1 I-53100 Siena, Italy. Tel.: +39 0577 539059; fax: +39 0577 278600.
E-mail address: ashwani_kumar.arora@novartis.com (A.K. Arora).

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Several studies in the elderly have demonstrated that adjuvanted TIVs (aTIV) elicit a higher antibody response than non-adjuvanted influenza vaccines against both homologous and heterologous influenza strains [8–15]. aTIV also induces a stronger antibody response than conventional subunit vaccines in other age groups that are at high-risk of influenza-related complications [8,16]. Recently, aTIV was shown to have an overall efficacy of 75% compared with 2% from a non-adjuvanted TIV in 6 to ≤24 month old children [17].

This study aimed to evaluate the lot-to-lot consistency, immunogenicity, clinical effectiveness, reactogenicity, and safety of a MF59-adjuvanted seasonal influenza vaccine in subjects aged ≥65 years, including those who are at higher risk of adverse events owing to underlying chronic conditions.

2. Materials and methods

2.1. Study design and objectives

This phase III, randomized, observer-blinded study was conducted across multiple sites in Colombia (four sites), Panama (two sites), The Philippines (11 sites) and the United States of America (21 sites) between August 2010 and November 2011. The study was conducted in accordance with the Declaration of Helsinki, the US Department of Health and Human Services guidelines and the principles of Good Clinical Practice, and was approved by the Ethics Review Committees/Institutional Review Boards for each site. Written informed consent was obtained from all participants before enrollment. The study had three co-primary objectives: to establish the immunological equivalence of three consecutive lots of aTIV for all three homologous strains; to demonstrate the non-inferiority (against all three strains) and superiority (in at least two out of three strains) of post-vaccination geometric mean titers (GMT) and seroconversion rates of aTIV compared with TIV based on the Center for Biologics Evaluation and Research (CBER) criteria; and to evaluate the immunogenicity of aTIV according to the European Committee for Medicinal Products for Human Use (CHMP) criteria against the three strains. Secondary objectives included: non-inferiority and superiority of aTIV over TIV in subjects with pre-defined co-morbidities (high-risk group); superiority of aTIV against heterologous strains in both the entire study population and the high-risk group; assessment of antibody persistence up to one year following vaccination; clinical effectiveness of aTIV compared with TIV; evaluation of the immunogenicity of TIV according to CHMP criteria; and safety assessment during the primary study period and 12 month follow-up period. The study was registered with Clinicaltrials.gov (NCT01162122).

2.2. Subjects

Eligible male and female subjects ≥65 years of age were enrolled. Subjects were excluded if they had any of the following: impaired/altered immune function, behavioral or cognitive impairment, a psychiatric condition, any other condition associated with prolonged bleeding, hypersensitivity to any vaccine components or egg proteins, receipt of vaccines within two weeks (inactivated), four weeks (live attenuated) or six months (seasonal influenza) prior to enrollment, planned vaccination in the three weeks following the study vaccination, receipt of an investigational agent one month prior to enrollment, oral temperature ≥38 °C within three days of vaccination, and planned surgery or hospitalization to occur during the study.

2.3. Study procedure

Subjects were randomly assigned using a web-based system at a ratio of 1:1:1:3 to receive either one of three lots of aTIV, or TIV. At randomization, subjects were stratified into two age cohorts, 65 to ≤75 years and >75 years. All subjects received a single 0.5 mL dose of vaccine on Day 1 of the study. Blood samples (10 mL) were collected prior to vaccination (Day 1) and three weeks after vaccination (Day 22) for immunogenicity analysis. Additional blood samples were obtained from 380 subjects at Day 181 and Day 366 for antibody persistence testing. Response to heterologous strains was analyzed in 25% of subjects from each vaccine group.

2.4. Vaccines

A single 0.5 mL dose of the trivalent MF59-adjuvanted seasonal egg-derived subunit vaccine, aTIV, (Fluad®, Novartis Vaccines and Diagnostics) or the trivalent seasonal egg-derived subunit vaccine, TIV (Agriflu®, Novartis Vaccines and Diagnostics) contained 15 μg of A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 hemagglutinin (HA) antigens, as recommended by the World Health Organization for the 2010–2011 influenza season in the Northern Hemisphere. Lot numbers of the vaccines were: A52P14H1, A52P15H1, A52P16H1 (all aTIV) and 107001A (TIV). A 0.5 mL dose of aTIV contained MF59 formulated with 9.75 mg squalene, 1.18 mg polysorbate 80, 1.18 mg sorbitan trioleate, 0.66 mg sodium citrate dihydrate, and 0.04 mg citric acid monohydrate. Vaccines were administered intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

2.5. Immunogenicity

Antibody responses were evaluated by hemagglutination inhibition (HI) assay [18]. Heterologous (cross-reactive) antibody responses were tested against the following strains, which had a sufficient pool of virus material available for testing: A/Brisbane/10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Since there was an insufficient supply of heterologous A/H1N1 strains at the time of the analysis, a second A/H3N2 strain was selected. All three heterologous strains were found to be antigenically distinct (>4–8 fold difference) from the vaccine strains, when analyzed using antibody responses to ferret antisera: 16-fold and >32 fold differences in HI for the two H3N2 strains, respectively, and a 16-fold difference in the B strains. HI antibody responses at Days 1, 22, 181 and 366 were expressed as GMTs, percentage of subjects achieving seroconversion (negative pre-vaccination antibody titer of <10 to a positive post-vaccination titer of ≥40) or significant increase (≥4-fold increase in post-vaccination HI titer from baseline), and percentage of subjects with HI titers ≥40. Geometric mean ratios (GMRs) were also calculated at Days 22, 181 and 366.

2.6. Clinical effectiveness

The clinical effectiveness was evaluated from Days 23 to 366 by rates of: influenza-like illness (ILI); exacerbation of pre-existing chronic disease; health care utilization for community-acquired influenza or pneumonia, cardiopulmonary disease, cardiac disease, respiratory or pulmonary disease; and mortality. ILI was defined as temperature of ≥37.2 °C or feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat.

2.7. Safety

Subjects were observed for 30 min after vaccination for immediate reactions and were provided with diary cards to record solicited

local or systemic adverse reactions that occurred up to seven days after vaccination. Solicited local adverse reactions included injection site pain, erythema, induration, swelling and tenderness. Solicited systemic adverse reactions included fever (≥38 °C), chills, myalgia, arthralgia, headache, nausea, fatigue, vomiting and diarrhea. Reactions and adverse events (AEs) were defined as mild, moderate or severe by the investigator. Unsolicited AEs were collected from Day 1 to Day 22 after vaccination. All serious AEs (SAEs), new onset of chronic disease (NOCD), and AEs leading to study withdrawal were collected throughout the study. The investigator categorized all SAEs and AEs as probably related, possibly related or not related to vaccine.

2.8. Statistical analyses

2.8.1. Sample size

Assuming a 10% dropout rate, the sample size per lot of aTIV was sufficient to demonstrate equivalence of the lots with 99.1% power. A sample size of $N = 3500$ each in the aTIV (pooled) and TIV groups was considered adequate to obtain an overall power of 94.6% to demonstrate the co-primary objectives of non-inferiority and superiority of aTIV compared with TIV. Lot-to-lot consistency, non-inferiority, and superiority were evaluated sequentially. For all objectives, GMTs were adjusted for country, age group and baseline titer.

2.8.2. Lot-to-lot consistency

Equivalence was demonstrated for three lots of aTIV if, for each strain, the two-sided 95% CI of the ratios of GMTs on Day 22 between pairs of vaccine lots was within the range of 0.67–1.5.

2.8.3. Non-inferiority and superiority

aTIV was considered non-inferior to TIV if, for all three homologous strains, the lower bound of the 2-sided 95% CI of the ratio of GMTs was >0.67 and if the lower bound of the 95% CI of the differences in the seroconversion rates was >−10%. aTIV was considered superior to TIV if, for at least two of the three strains, the ratio of GMTs was >1.5 and the difference in seroconversion rates was greater than >10%. These margins were calculated using CBER criteria. Significance testing was done with multiplicity-adjusted one-sided p-values and a significance level of 0.025.

2.8.4. Immunogenicity

For subjects >60 years of age, the following CHMP criteria apply: GMR of >2.0; the percentage of subjects achieving seroconversion or significantly increased antibody titers is >30%; and the percentage of subjects achieving an HI titer ≥40 is >60% (seroprotection).

2.8.5. Clinical effectiveness

This endpoint was exploratory therefore the study was not designed for its assessment. Relative vaccine effectiveness was calculated in terms of relative risk (RR) of aTIV compared with TIV. RR was calculated using a Poisson regression model, with country as a covariate. Mortality risk was estimated by a hazard ratio.

2.8.6. Sample groups

For the analysis of lot-to-lot consistency and non-inferiority, the per-protocol set (PPS) was used i.e. all subjects providing evaluable serum samples on both Days 1 and 22 who had no major protocol deviations. The full analysis set (FAS), i.e. all subjects providing evaluable serum samples on both Days 1 and 22, was used for all other measures, except persistency, which was based on a subset of subjects from US sites only who provided evaluable sera at all four time points.

Table 1
Study population demographics for enrolled subjects.

	aTIV	TIV
	$N = 3479$	$N = 3482$
Mean age (years ± SD)	71.9 ± 5.3	71.8 ± 5.3
65 to ≤75 years (%)	72	73
>75 years (%)	28	27
Male (%)	36	34
Asian (%)	53	53
Black (%)	1	1
Caucasian (%)	28	28
Hispanic (%)	18	18
Native American/Hawaii (%)	<1	<1
Other (%)	<1	<1
Weight (kg ± SD)	63.4 ± 19.5	63.4 ± 19.4
Height (cm ± SD)	156.9 ± 11.6	156.7 ± 11.5
Body mass index	25.4 ± 5.7	25.4 ± 5.6
Previous Pneumococcal Vaccination (%)	21	21
Previous H1N1 Vaccination (%)	2	2
A/H1N1 confirmed infection (%)	<1	0
Current smoker (%)	<1	<1

Table 2
Ratios between geometric mean titers (95% CI) for three lots of aTIV at Day 22 tested against homologous strains. Data are shown for the per-protocol set.

Strain	Lot 1:Lot 2 ($N = 1072$)	Lot 1:Lot 3 ($N = 1078$)	Lot 2:Lot 3 ($N = 1075$)
A/H1N1	1.12 (1.00–1.24)	1.05 (0.95–1.17)	0.94 (0.85–1.05)
A/H3N2	1.01 (0.92–1.11)	0.99 (0.90–1.08)	0.98 (0.89–1.07)
B strain	1.00 (0.91–1.10)	0.96 (0.87–1.05)	0.96 (0.87–1.05)

2.8.7. Safety

Safety data were evaluated descriptively.

3. Results

As shown in Fig. 1, a total of 7109 elderly subjects were enrolled, of which 7104 were randomly assigned and 7082 were vaccinated ($N = 3541$ in each group). Overall, 98% subjects in each group completed the study at Day 22. A total of 2573 subjects with underlying medical conditions were included in the high-risk subgroup. The FAS and PPS included 98% and 92% of vaccinated subjects, respectively. The two vaccine groups were similar with respect to age, sex and ethnicity (Table 1).

3.1. Lot-to-lot consistency

The immunological equivalence of the Day 22 antibody responses for the three lots of aTIV was demonstrated for all three vaccine strains (Table 2). As lots were shown to be equivalent, data from subjects in all three lots were pooled for all further analysis.

3.2. Non-inferiority and superiority

The immunogenicity of aTIV at Day 22 was significantly higher ($p < 0.001$) than TIV and hence non-inferior for both homologous and heterologous A strains, in both the entire study population and the high-risk group (Table 3). However, aTIV did not meet the predefined superiority criteria at Day 22 neither in the entire study population nor in the high-risk group.

3.3. Immunogenicity: CHMP criteria

The HI antibody responses induced by aTIV and TIV against all tested strains are summarized in Fig. 2. Baseline GMTs were similar against all strains. All three CHMP criteria were met by the aTIV group against both homologous and heterologous strains in both the entire study population and the high-risk group. The TIV group

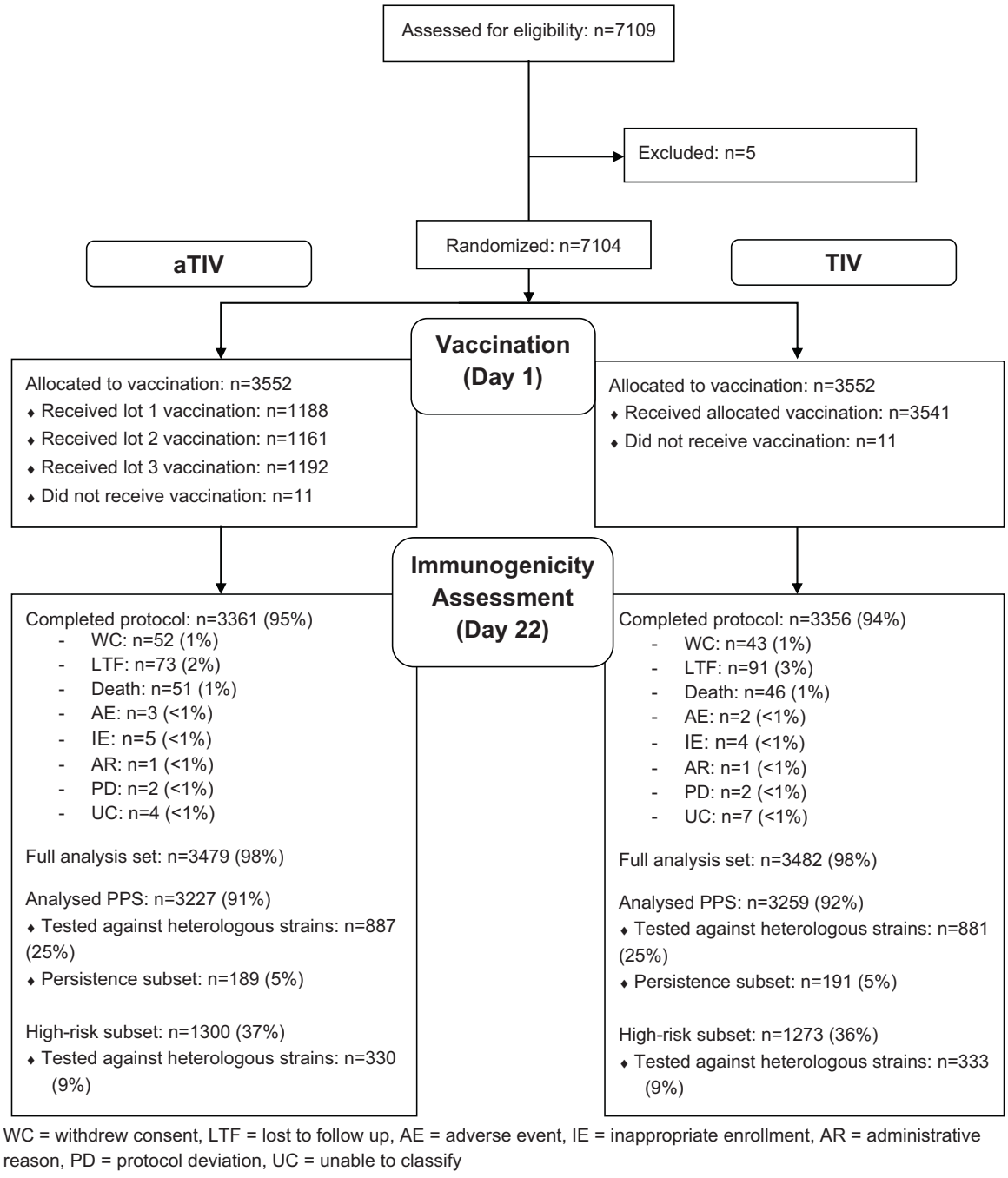

Fig. 1. Study design and subject disposition, indicating numbers of subjects, vaccination allocations, details of immunogenicity subsets and reasons for exclusion from analyses.

also met all three CHMP criteria against all tested strains, except in terms of seroprotection against the homologous B strain for the entire study population, where the seroprotection level was 58.9%.

3.4. Persistence analysis

In general, at six months (Day 181) and one year (Day 366) after vaccination, the subjects in the aTIV group ($N = 189$) had slightly higher GMTs and seroprotection rates than the TIV subjects ($N = 191$) against all strains (Fig. 3). Against the homologous A/H3N2 strain, the aTIV group had significantly higher GMTs (Days 181 and 366) and seroprotection rates (Day 366 only). All other differences between the vaccine groups were not statistically significant.

3.5. Clinical effectiveness

ILI was reported by 322 and 314 subjects in aTIV and TIV groups, respectively. No significant difference was observed in the clinical effectiveness between aTIV and TIV in terms of ILI [RR: 0.91; 95% CI: 0.71–1.16], exacerbation of pre-existing chronic disease [RR: 1.35; 95% CI: 0.8–2.26], healthcare utilization [RR: 0.95; 95% CI: 0.81–1.12] or mortality [hazard ratio: 1.13; 95% CI: 0.76–1.68].

3.6. Safety

Overall, rates of reactogenicity were higher in the aTIV group (46%) compared with the TIV group (33%). Local solicited adverse

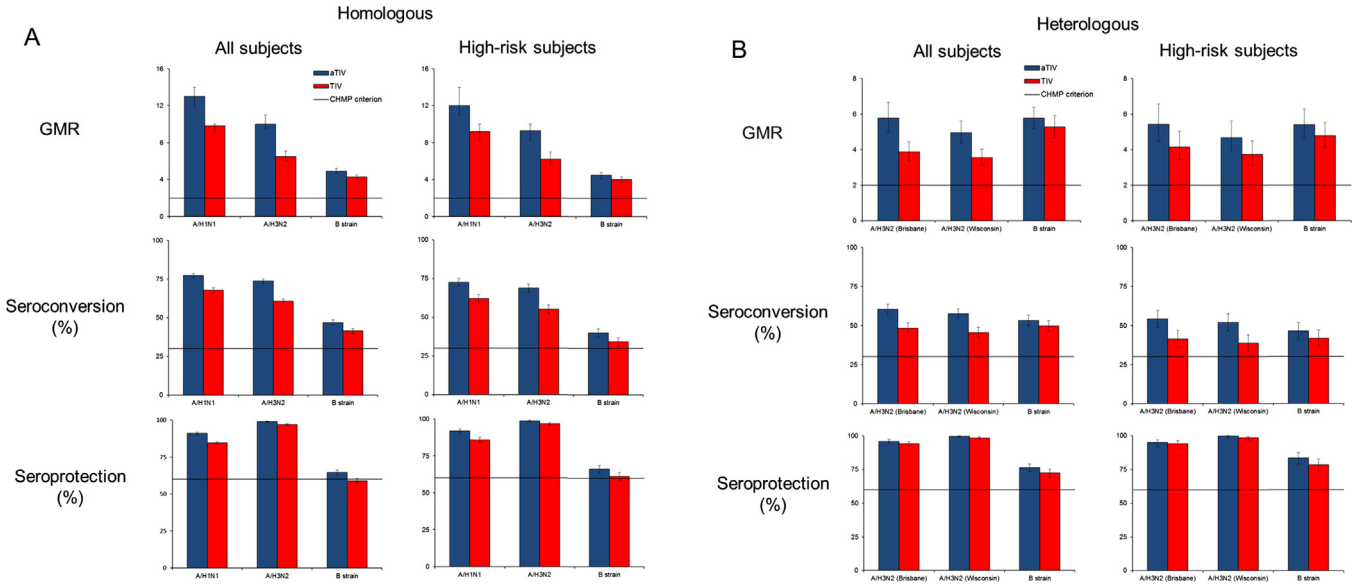

Fig. 2. Geometric mean ratio (GMR), percentage of subjects showing seroconversion and percentage of subjects seroprotected (±95% CI) for all (A) homologous and (B) heterologous strains at Day 22 post-vaccination. Lines represent the relevant CHMP criterion for each measure. Data presented are for the full analysis set.

reactions were reported by 32% of subjects in the aTIV group and by 17% in TIV group, and systemic solicited adverse reactions were reported by 32% of subjects in the aTIV group and 26% in the TIV group. Injection site pain and tenderness were the most commonly reported solicited local adverse reactions (Table 4). Reactions were mostly mild to moderate in intensity and were resolved within four days of vaccination.

Unsolicited AEs were reported by 16% of subjects in both vaccine groups, the most common being nasopharyngitis (2% in each group). SAEs were reported by 7% of subjects in each vaccine group. One SAE in the aTIV group (bronchitis) and three SAEs in the TIV group (asthmatic crisis, chronic obstructive pulmonary disease and Guillain–Barré syndrome) were considered as possibly or probably vaccine-related. NOCD was reported in 6% of subjects in each vaccine group. In total there were 98 deaths during the study, 52 (1.5%) in aTIV group and 46 (1.3%) in TIV group.

One death (230 days after study vaccination) of a TIV vaccine recipient was considered possibly vaccine-related. The subject was a 69 year old Caucasian female with a history of embolization from the right carotid artery and cancer of the left breast. The cause of death was recorded at autopsy as respiratory depression secondary to Guillain–Barré syndrome. Seven deaths were recorded as a consequence of influenza (three in the aTIV and four in the TIV group), although none of these subjects had laboratory-confirmed influenza reported during the study.

4. Discussion

Conventional non-adjuvanted seasonal trivalent influenza vaccines have been shown to perform inadequately in elderly subjects [2,3]. In previous studies, MF59-adjuvanted vaccines (aTIVs) have demonstrated increased immunogenicity, providing increased vaccine effectiveness in older adults [6,8,11,19,20]. In this study we assessed sequentially the lot-to-lot consistency of aTIV, the non-inferiority and superiority of aTIV compared with the non-adjuvanted trivalent influenza vaccine (TIV), and whether aTIV met CHMP criteria for this age group.

The present study met two of its co-primary objectives. Immunological equivalence of the three lots of aTIV was established and aTIV was shown to be non-inferior to TIV. Although superiority was not achieved according to pre-defined criteria, post-vaccination GMTs and seroconversion rates were significantly higher for the aTIV group than those for the TIV group, except against the heterologous B strain. TIV failed to meet the CHMP criterion for seroprotection against the homologous B strain for the total study population whereas aTIV met all the CHMP criteria in terms of GMR, seroconversion and seroprotection against all tested strains.

Overall, the largest difference in antibody responses between the aTIV and TIV groups were observed against the homologous A/H3N2 strain. TIV has been reported to provide a very low protective effect in the elderly against A/H3N2 infection, which

Table 3
Ratios between geometric mean titers (GMT) and differences in seroconversion rates at Day 22 (95% CI) for aTIV compared with TIV for the entire study population and for the high-risk subgroup (per-protocol set).

Strain	Entire study population		High-risk group	
	Ratio of GMT	Difference in seroconversion (%)	Ratio of GMT	Difference in seroconversion (%)
Homologous strains				
A/H1N1	**1.40 (1.32–1.49)**	**9.2 (7.1–11.3)**	**1.38 (1.25–1.52)**	**11.1 (7.5–14.6)**
A/H3N2	**1.61 (1.52–1.70)**	**12.7 (10.5–14.9)**	**1.57 (1.44–1.72)**	**13.5 (9.8–17.2)**
B strain	**1.15 (1.08–1.21)**	**5.2 (3.0–7.4)**	**1.12 (1.03–1.21)**	**5.0 (1.4–8.5)**
Heterologous strains				
A/H3N2 (Wisconsin)	**1.45 (1.29–1.63)**	**11.3 (6.7–15.9)**	**1.35 (1.13–1.61)**	**12.3 (4.8–19.9)**
A/H3N2 (Brisbane)	**1.36 (1.23–1.50)**	**11.9 (7.3–16.6)**	**1.29 (1.10–1.50)**	**12.6 (5.0–20.2)**
B strain	**1.09 (0.98–1.21)**	**4.0 (−0.4–8.4)**	**1.11 (0.95–1.30)**	**4.8 (−2.1–11.8)**

Bold numbers indicate significantly non-inferior values. Confidence intervals were not adjusted for multiplicity. Statistically significant ratios of GMT and differences in seroconversion were tested on the FAS population and multiplicity adjusted *p*-values were <0.001 for all strains except the heterologous B strain

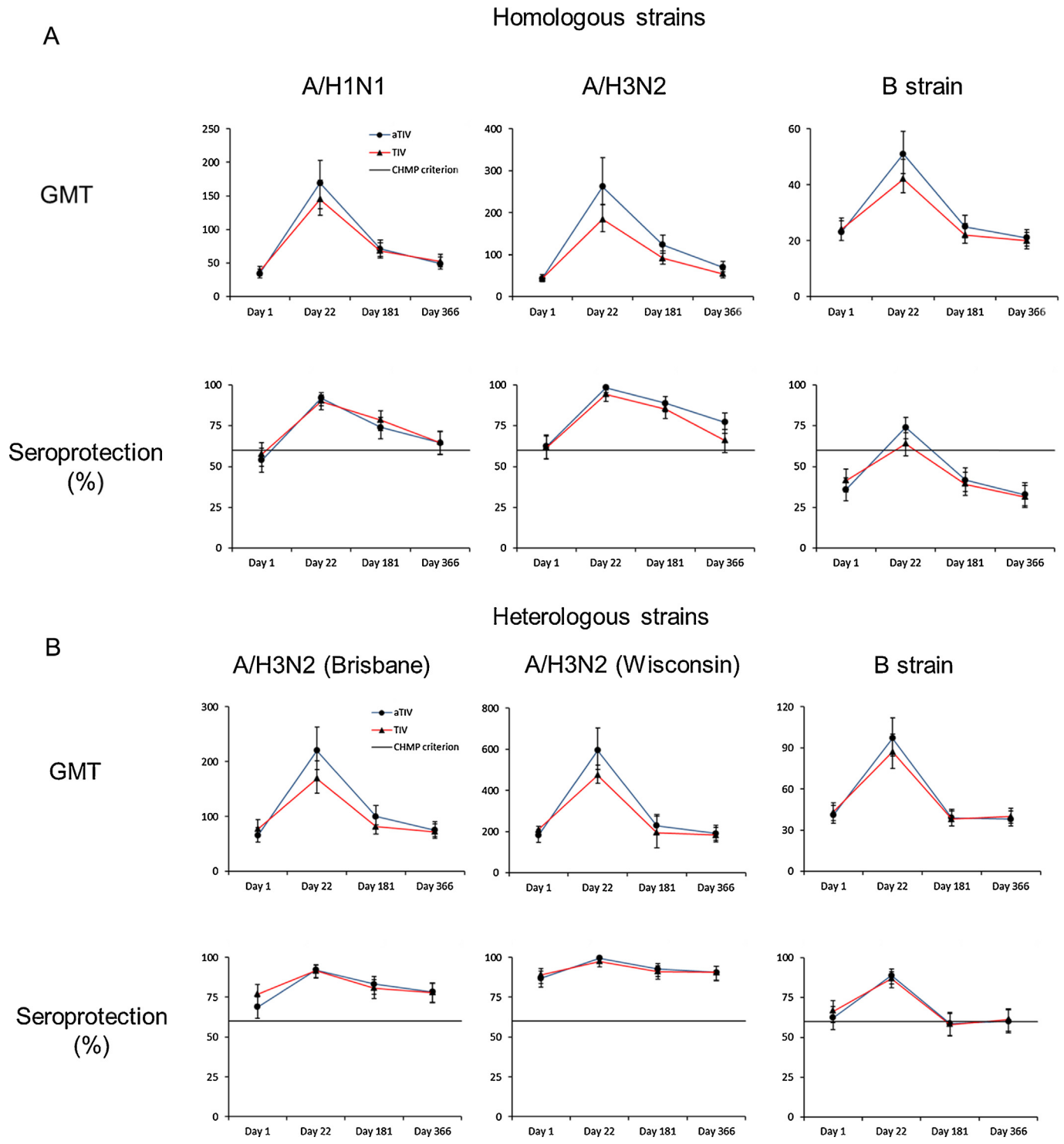

Fig. 3. Persistence of antibody responses at Days 22, 181 and 366 in terms of geometric mean titers (GMT) and percentage of subjects seroprotected (±95% CI) for all (A) homologous and (B) heterologous strains. Lines represent the relevant CHMP criterion for each measure. Data presented are for the persistence analysis subset.

rapidly declines to a minimum within four months of vaccination [21–26]. Furthermore, periodic antigenic drift is faster among A/H3N2 strains than other strains, leading to the frequent emergence of new variants [27]. As influenza outbreaks are often caused by A/H3N2 strains and the burden of infection caused by this subtype is more severe in the elderly [21,28,29], the persistent antibody response induced by aTIV could provide enhanced long-term seroprotection for this age group [10,11,30].

Influenza-attributed mortality rates in individuals ≥65 years age have been estimated to 20-times higher in subjects with both chronic heart and lung conditions [31]. For the high-risk group, aTIV elicited significantly higher antibody responses than TIV against all homologous strains and the heterologous A strains which, together with similar results from previous studies, indicate that aTIV might provide more effective protection than conventional TIVs in elderly subjects with co-morbidities [9,16,30].

Table 4
Percentages of subjects experiencing mild to moderate (and severe) solicited local and systemic adverse reactions within one week of vaccination with aTIV or TIV.

	aTIV	TIV
	N = 3505	*N* = 3495
Local adverse reactions		
Any (%)	32 (<1)	17 (<1)
Pain (%)	25 (<1)	12 (<1)
Erythema (%)	1 (0)	1 (0)
Induration (%)	1 (0)	<1 (0)
Swelling (%)	1 (<1)	1 (<1)
Tenderness (%)	21 (<1)	11 (<1)
Systemic adverse reactions		
Any (%)	32 (<1)	26 (<1)
Chills (%)	7 (<1)	5 (0)
Myalgia (%)	15 (<1)	9 (1)
Arthralgia (%)	8 (<1)	7 (1)
Headache (%)	13 (<1)	10 (1)
Fatigue (%)	13 (<1)	9 (1)
Nausea (%)	3 (<1)	3 (<1)
Vomiting (%)	1 (<1)	2 (<1)
Diarrhea (%)	5 (<1)	5 (<1)
Fever (≥38 °C) (%)	4 (<1)	3 (<1)
Analgesic/antipyretic use (%)	5	4

Although the secondary endpoint of effectiveness was not demonstrated, as the study was not suitably powered to statistically assess this exploratory endpoint, previous studies have demonstrated the higher effectiveness of aTIV relative to that of TIV. In a large observational study of 107,661 adults aged ≥65 years, aTIV reduced the risk of hospitalization for influenza or pneumonia by 25% relative to TIV during the peak influenza season [32]. A mathematical model simulating the transmission of influenza in Canada over a ten-year period showed the use of aTIV gave substantial health benefits relative to TIV in adults aged ≥65 years [33]. In addition, a recent study comparing aTIV and a conventional TIV showed an overall vaccine effectiveness of 58% for aTIV in elderly subjects, whereas TIV was ineffective [20]. Therefore despite this study not demonstrating effectiveness, there is mounting evidence for potential higher effectiveness of aTIV compared with TIV. In retrospect, higher clinical effectiveness of aTIV was most probably not demonstrated in this study as ILI was used as a measure of effectiveness. As currently used ILI definitions cover a range of infections with similar symptoms, and not just influenza [34], a considerably larger sample size would be needed to assess the effectiveness specifically on influenza using ILI as a measure. A recent study assessing the efficacy of AS03-adjuvanted TIV with non-adjuvanted TIV in the elderly had a sample size of over 20,000 subjects per group [35], and we estimate that similar sample sizes would have been needed to detect any difference in effectiveness in this study.

In this study, both vaccines demonstrated good tolerability. Rates of reactogenicity were moderately higher in the aTIV group, which is consistent with previous findings [36,37], and most of the solicited adverse reactions were of mild to moderate intensity and transient in nature. The safety profile of MF59-adjuvanted vaccines has been found to be similar to that of non-adjuvanted influenza vaccines across age groups [14,15,37–39], and in this study, the number of subjects reporting adverse events was similar in the aTIV and TIV groups.

In conclusion, in this study, aTIV induced a significantly higher antibody response than TIV three weeks after vaccination, against all three homologous strains and the heterologous A strains, with a similar safety profile, however no increase in effectiveness was observed. The significantly higher immunogenicity of aTIV was also demonstrated for subjects at higher risk of influenza-related complications due to underlying medical conditions.

Conflict of interest statement

UN, NNB, VN, EF, and AKA are permanent employees of Novartis Vaccines and Diagnostics. SF has conducted influenza studies for Novartis and GSK in the past. HR has also conducted influenza studies for Novartis in the past. All other authors declare no potential conflicts of interest.

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Author contributions: All authors participated in the conception, design, and implementation of the trial. All authors were involved in the interpretation of analyzed data and the decision to submit for publication.

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