Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Influenza virus haemagglutinin

Proprietary Product Name: Fluzone High-Dose

Sponsor: Sanofi-Aventis Australia

First round report: 7 June 2017
Second round report: 25 October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
AESI	Adverse event of special interest
CDC	United States Centres for Disease Control and Prevention
GMT	Geometric mean titre
HA	Haemagglutinin component of the influenza virus capsule
HAI	Haemagglutinin inhibition test for the presence of antibodies against HA
IIV	Inactivated influenza vaccine
NIP	National Immunisation Program
SAE	Serious adverse event
SOC	System Organ Class
WHO	World Health Organization

1. Introduction

1.1. Identifying information

Submission number	PM-2017-00690-1
Sponsor	Sanofi-Aventis Australia
Trade name	Fluzone High-dose
Active substance	Influenza virus haemagglutinin

1.2. Submission type

This is a submission to register a biological medicine as a New Clinical Entity.

1.3. Drug class and therapeutic indication

Fluzone High-Dose is a trivalent influenza virus vaccine containing the HA antigen of the virus capsule.

The proposed indication is:

> *Fluzone High-Dose is indicated for active immunisation against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons 65 years of age and older.*

1.4. Clinical rationale

Influenza viruses are a group of highly contagious respiratory pathogens which cause regular community based outbreaks worldwide, most prominently in the winter months of temperate regions. Influenza viruses are also a significant cause of respiratory virus outbreaks in closed settings such as hospitals, aged care homes, prisons and cruise-ships. In immune-competent children and younger-adults influenza infections are usually self-limiting and characterised by cough, fever and myalgia. However older adults, immune-compromised individuals and infants can develop severe complications of influenza infection, which include pneumonia, bronchitis and exacerbations of chronic respiratory or cardiac disease. Influenza is estimated to cause approximately 3500 deaths, 18,000 hospitalisations and 300,000 general practice presentations in Australia each year.[1]

Vaccination against influenza A and B is the main way to protect vulnerable people from the potential complications of influenza infection. In Australia, the National Immunisation Program (NIP) recommends annual influenza vaccination for all people over the age of 65 (as well as other vulnerable groups).

Unfortunately, while vaccination in the elderly is associated with a reduced rate of complications from influenza infection this group has a lower rate of developing protective immunity than younger adults. It has been estimated that the efficacy of influenza vaccine in

[1] Impact of Influenza, reference Influenza Specialist Group website, www.isg.org.au

adults > 65 years of age living in the community is only 43% when high levels of virus are circulating compared to about 60% in younger adults. This has led to interest in improving rates of response of influenza vaccine in this group.

Fluzone High-Dose has been developed to deliver an increased dose of HA antigen of 60 µg per strain in each of the three viral strains included in the vaccine compared to 15 µg in the standard adult vaccine presentation. The sponsor anticipated that this would increase the proportion of recipients who develop protective titres against HA from vaccination and thus the efficacy of the vaccine in the > 65 year old group. As with all influenza vaccines, the HA antigen included in the vaccine must be assessed annually to match the continued genetic drift of viruses circulating in the community. The efficacy of vaccine varies between years where there is a 'good' match and those when antibodies elicited by the vaccine are less protective against circulating virus.

1.5. Formulation

1.5.1. Formulation development

The sponsor conducted a Phase I dose ranging study (Study NIH-01-597) which compared the immune response of vaccine containing HA antigen at doses between 15 µg and 60 µg per strain. From this study the 60 µg dose was selected for the Phase II and III Studies FIM01, FIM05, FIM07, and FIM12 respectively. The virus strain selected for each trial was based on the WHO/CDC recommendation for influenza vaccines during the year the trial was conducted.

The strains used in each study were as follows:

Table 1: Influenza strains included in investigational vaccines used in studies evaluated in this submission

		Influenza Vaccine Strains		
Study	**Season**	**A/H1N1**	**A/H3N2**	**B**
01-597	2001-2002	A/New Caledonia/20/99	A/Panama/2007/99	B/Victoria/504/2000
FIM01	2004-2005	A/New Caledonia/20/99	A/Wyoming/03/2003 (a A/Fujian/411/2002-like strain)	B/Jiangsu/10/2003 (a B/Shanghai/361/2002-like strain)
FIM05	2006-2007	A/New Caledonia/20/99/IVR-116	A/Wisconsin/67/2005/X-161	B/Malaysia/2506/04
FIM07	2009-2010	A/Brisbane/59/07	A/Uruguay/716/2007-X175C	B/Brisbane/60/2008
FIM12	Year 1: 2011-2012	A/California/7/2009	A/Victoria/210/2009	B/Brisbane/60/2008
	Year 2: 2012-2013	A/California/7/2009	A/Victoria/361/2001	B/Texas/6/2001 (a B/Wisconsin/1/2020-like virus)

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The sponsor has provided four study reports in support of this application. These all investigated ambulatory subjects > 65 years of age.

Table 2: Summary description of studies submitted in this dossier

Study	Number of Subjects	Design
FIM05	3,876	Double blind, active controlled, multicentre trial comparing immune reactivity of Fluzone High-Dose and Fluzone
FIM12	31,989	Double blind, active controlled, multicentre trial to determine relative vaccine efficacy of Fluzone High-Dose compared to Fluzone
FIM01	414	Double blind, multi-centre, trial comparing immune reactivity of Fluzone High-Dose a and Fluzone
FIM07	9,172	Double blind, active controlled, multicentre trial to determine the relative vaccine efficacy of Fluzone High-Dose compared to Fluzone

Enrolment in Study FIM07 was prematurely discontinued due to the occurrence of the 2009 influenza pandemic and it was provided to support the safety analysis. Secondary efficacy endpoints for the trial were, however, also presented.

The evaluator has reviewed Study NIH-01-597 in this report, which was provided as a literature reference.[2] This was considered significant as it was a dose-ranging study on which supported the selection of 60 µg HA per strain (180 µg total) in Fluzone High-Dose.

The sponsor provided 35 additional literature references, which the evaluator reviewed but are not further discussed in this report.

3. Paediatric data

The submission did not include paediatric data.

4. Good clinical practice

Trials were conducted according to principles of Good Clinical Practice.

[2] Keitel WA, Campbell JD, Treanor JJ, Walter EB, Patel SM, He F, et al. Safety and immunogenicity of an inactivated influenza A/H5N1 vaccine given with or without aluminum hydroxide to healthy adults: results of a phase I-II randomized clinical trial. J Infect Dis. 2008;198(9):1309–16

5. Pharmacokinetics

No pharmacokinetics data were provided.

6. Pharmacodynamics

No pharmacodynamics data were provided.

7. Dosage selection for the pivotal studies

7.1. Study NIH-01-597

Study NIH-01-597 was a Phase I dose-ranging study which examined the immunological response of 202 ambulatory patients > 65 years of age to four doses of Fluzone. Subjects were randomised into equal groups to receive a single dose of trivalent influenza vaccine containing 0 µg (n = 50), 15 µg (n = 51), 30 µg (n = 51) or 60 µg (n = 50) of HA for each virus strain. The study was conducted in 2002 using the H1N1, H3N2 and Influenza B strains current for that year's influenza vaccine. Oral temperature, infection site and systemic symptoms were observed for one week, with blood for serological analysis taken 1 month after the vaccine dose.

Serum HAI and NA were examined. The primary endpoints of the study were the GMT for serum HAI and NA against each of the vaccine strains one month after immunisation.

Table 3: Comparative GMT of HAI antibodies and Neutralising Antibody in doses of Fluzone between 45µg and 180 µg

Table 1. Geometric Mean Serum HAI and Neutralizing Antibody Responses Before and 1 Month After Immunization*

		Antibody Titer, Geometric Mean (95% CI)											
		Influenza A/H1N1				Influenza A/H3N2				Influenza B			
		HAI		Neutralizing		HAI		Neutralizing		HAI		Neutralizing	
Dose, µg	Participants, No.	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
0	50	20 (16-25)	23 (18-29)	15 (11-21)	12 (9-16)	33 (25-45)	43 (32-57)	45 (30-68)	49 (33-73)	11 (8-14)	10 (8-13)	62 (45-87)	59 (41-85)
15	51	20 (16-25)	37 (30-45)	14 (11-19)	28 (21-37)	45 (31-65)	86 (63-118)	52 (34-80)	101 (70-146)	8 (6-10)	14 (11-18)	57 (44-73)	129 (95-175)
30	51	20 (16-27)	50 (38-66)	15 (11-20)	35 (26-47)	39 (29-53)	91 (69-120)	45 (31-65)	106 (76-148)	8 (6-11)	18 (14-23)	60 (41-88)	152 (111-208)
60	50	22 (18-27)	61 (48-78)	19 (13-28)	50 (36-68)	53 (37-75)	125 (97-160)	58 (39-86)	160 (114-225)	9 (7-12)	24 (18-32)	64 (44-93)	199 (141-282)

Abbreviations: CI, confidence interval; HAI, hemagglutination inhibition.
*We tested for differences among the doses in the geometric mean titers before immunization using analysis of variance. None of these differences were statistically significant. Differences among doses after immunization were analyzed using linear regression models (Table 3).

The difference in GMT for HAI and NA between all dose levels was significant ($p < 0.01$). There was no significant difference between the dose groups in the frequency of systemic reactions reported. There was, however, a dose-related increase in the incidence of injection site discomfort ($p < 0.01$) and redness/swelling ($p = 0.05$).

The 60 µg dose was chosen for further development in Phase II and III studies on the basis of demonstrating superior reactogenicity to the lower two doses with an acceptable safety profile. This was on the basis that increased reactogenicity was likely to be associated with high rates of protection from influenza among recipients of the 60 µg/strain vaccine.

8. Clinical efficacy

8.1. Pivotal efficacy studies

8.1.1. Study FIM05

8.1.1.1. *Study design, objectives, locations and dates*

Study FIM05 was a Phase III multicentre, double blind, active-controlled study in subjects > 65 years of age which compared the immune response of subjects receiving Fluzone High-Dose (n = 2588) to those receiving Fluzone (n = 1288). The study had two main objectives. The first of these was to demonstrate the superiority of immune response in subjects receiving Fluzone High-Dose compared to those receiving Fluzone. The second main objective was to assess the lot consistency of immune response between subjects receiving Fluzone High-Dose from 3 different lots. Immune response was measured 28 days after subjects received a single dose of vaccine.

The study enrolled patients from 31 centres in the USA between 9 October 2006 and 22 January 2007, with follow-up completed on 9 July 2007. This time was chosen to allow vaccination immediately prior to the peak of the Northern respiratory virus season.

8.1.1.2. *Inclusion and exclusion criteria*

- 65 years of age or older
- Ambulatory; defined as not institutionalised, bedridden or homebound.
- Medically stable; chronic illnesses such as diabetes, hypothyroidism or heard disease assessed as controlled with medical therapy.
- Afebrile; patients with a fever were deferred from enrolment until 3 days after resolution of their illness.

Significant exclusion criteria included:

- known allergy to eggs or components of the vaccine
- a history of Guillain-Barre syndrome
- immunosuppressive from underlying illness or treatment
- Use of oral steroids or high doses of inhaled steroids within 1 month prior to vaccination
- Active neoplastic disease or history of haematological malignancy within 5 years of the study.

8.1.1.3. *Study treatments*

Subjects received either Fluzone (15 µg HA per strain, 45 µg in total) or Fluzone High-Dose (60 µg per strain, 180 µg in total) as a single intramuscular injection of 0.5 mL.

Both vaccines contained HA derived from virus strains appropriate to the season in which the study was conducted:

- A/New Caledonia/20/99/IVR-116 (H1N1)
- A/Wisconsin/67/2005/X-161 (H3N2)
- B/Malaysia/2506/04

8.1.1.4. *Efficacy variables and outcomes*

The primary endpoint in Study FIM05 was the anti-HA GMT for each of the three viral strains in the vaccine measured 28 days post vaccination. This was used to assess the equivalence in

anti-HA GMT between the three lots of vaccine used, where equivalence was defined as a ratio of GMT between two lots of vaccine between 0.67 and 1.50.

The secondary endpoint was the percentage of seroconversion among subjects measured one month post-vaccination. Seroconversion was defined as either:

1. Pre-vaccination HAI titre < 1:10 and a post-vaccination titre > 1:40; or
2. Pre-vaccination HAI titre ≥ 1:10 and a minimum four-fold increase in titre post vaccination.

The validated Flu HAI was performed by [information redacted], after assay transfer from sponsor laboratories.

8.1.1.5. *Randomisation and blinding methods*

Subjects were individually randomised to treatment through a central system for allocating an 8-digit trial identification number at enrolment. Treatments were physically indistinguishable 0.5 mL syringes dispatched to study sites, the contents of which were not known to local investigators.

8.1.1.6. *Analysis populations*

Analyses were performed on Full Analysis Set (FAS) and Per-Protocol (PP) populations.

The FAS population included all subjects who received vaccine and provided at least one post-vaccination assessment.

The PP population included all subjects who satisfied the inclusion and exclusion criteria, received vaccine correctly according to randomisation, provided pre- and post- vaccination blood samples and completed Visit 2 within the specified time.

Safety analysis was performed on the FAS population according to the vaccine actually received.

8.1.1.7. *Sample size*

2,588 subjects received Fluzone High-Dose (n = 859, 866 and 863) for Batch 1, 2 and 3 respectively. 1288 subjects received Fluzone.

The sample size calculations were based on the primary endpoint. This indicated that 822 subjects would be required to receive each batch of vaccine to achieve a > 99% power to detect consistency where each comparison between lots was tested at a 95% confidence level.

8.1.1.8. *Statistical methods*

For the primary endpoint of lot consistency 95% confidence intervals were calculated for the ratios of GMT between the Lots 1 to 3; GMT1/GMT2, GMT1/GMT3, GMT2/GMT3. Consistency was demonstrated if the 95% confidence interval for each of these three tests was between 0.67 and 1.5.

For the secondary endpoint of seroconversion the 95% confidence interval of the difference in the proportion of subjects achieving seroconversion on each treatment was calculated. Superiority was concluded if the 95% confidence interval of the difference was entirely outside ≥ 10%, for example, a delta of 10% was specified.

8.1.1.9. *Participant flow*

Participant flow in Study FIM05 is shown in Table 4 below.

Table 4: Participant flow

	Fluzone Lot 1 n (%)	Fluzone Lot 2 n (%)	Fluzone Lot 3 n (%)	Pooled Fluzone HD n (%)	Standard Fluzone n (%)
Subjects randomized, by randomization group	859	866	863	2588	1288
Randomized but received wrong vaccine [1]	1 (0.1)	13 (1.5)	1 (0.1)	15 (0.6)	1 (0.1)
Randomized but did not receive vaccine [1]	3 (0.3)	2 (0.2)	2 (0.2)	7 (0.3)	7 (0.5)
Vaccinated but vaccine received could not be verified [1]	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.1)	22 (1.7)
Subjects vaccinated, by vaccine actually received	857	848	870	2575	1262
Subjects completed study up to Day 28 [2]	848 (98.9)	847 (99.9)	868 (99.8)	2563 (99.5)	1252 (99.2)
Subjects discontinued up to Day 28 [2]	9 (1.1)	1 (0.1)	2 (0.2)	12 (0.5)	10 (0.8)
Reason for discontinuation up to Day 28 [2]					
Serious adverse event	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.1)	4 (0.3)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Lost to follow-up	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	5 (0.4)
Voluntary withdrawal not due to an adverse event	5 (0.6)	1 (0.1)	1 (0.1)	7 (0.3)	1 (0.1)

	Fluzone Lot 1 n (%)	Fluzone Lot 2 n (%)	Fluzone Lot 3 n (%)	Pooled Fluzone HD n (%)	Standard Fluzone n (%)
Subjects completed study up to Day 180 [2]	843 (98.4)	840 (99.1)	858 (98.6)	2541 (98.7)	1240 (98.3)
Subjects discontinued up to Day 180 [2]	14 (1.6)	8 (0.9)	12 (1.4)	34 (1.3)	22 (1.7)
Reason for discontinuation up to Day 180 [2]					
Serious adverse event	5 (0.6)	5 (0.6)	6 (0.7)	16 (0.6)	11 (0.9)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	3 (0.4)	0 (0.0)	4 (0.5)	7 (0.3)	2 (0.2)
Lost to follow-up	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	7 (0.6)
Voluntary withdrawal not due to an adverse event	5 (0.6)	3 (0.4)	2 (0.2)	10 (0.4)	2 (0.2)

Source Data: Section 9, Table 9.2

[1] Percentages based on subjects randomized.

[2] Percentages based on subjects vaccinated.

There were low rates of discontinuation or loss-to-follow-up in Study FIM05 with > 98% of participants in each treatment arm and batch cohort completing the trial.

8.1.1.10. *Major protocol violations/deviations*

Sixteen subjects across ten sites were incorrectly randomised and did not receive their assigned treatment. In these cases the vaccine the subject actually received was recorded and they were included in the FAS analysis.

For 25 subjects the vaccine the subject received was not recorded. These subjects were excluded from the FAS analysis for efficacy.

8.1.1.11. *Baseline data*

Subjects were well matched between treatment arms and Fluzone High-Dose lots for age, sex and race. The average age of subjects in Study FIM05 was 72.9 years for both Fluzone High-Dose and Fluzone treatment arms. The majority of subjects had received vaccination in the previous year (2005); 82.3% in the Fluzone High-Dose and 82.1% in the Fluzone treatment groups.

8.1.1.12. *Results for the primary efficacy outcome*

Lot consistency is shown in Table 5 below.

Table 5: GMT ratios for comparisons between Lots 1, 2 and 3 of Fluzone High-Dose in Study FIM05

							GMT Ratios					
	Lot 1 (N = 854)		Lot 2 (N = 861)		Lot 3 (N = 861)		Lot 1/Lot 2		Lot 1/Lot 3		Lot 2/Lot 3	
Flu Strain	M	GMT	M	GMT	M	GMT	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI
A/H1N1:New-Caledonia	842	112.77	844	114.63	857	120.02	0.98	(0.90; 1.08)	0.94	(0.86; 1.03)	0.96	(0.87; 1.05)
A/H3N2: Wisconsin	842	595.03	844	628.54	858	603.59	0.95	(0.85; 1.05)	0.99	(0.89; 1.09)	1.04	(0.94; 1.16)
B: Malaysia	842	68.98	844	69.26	856	68.93	1.00	(0.91; 1.09)	1.00	(0.92; 1.09)	1.00	(0.92; 1.10)

Source Data: Section 9, Table 9.57

N is the number of subjects in the Immunogenicity Analysis Set.

M is the number of subjects with a valid serology result for the particular Flu strain, including results reported as <LLOQ.

To demonstrate the lot consistency for Fluzone HD, the limits of the two-sided 95% CIs for GMT ratios for each of the three virus strains should be between 0.67 and 1.50.

The 95% confidence interval of the difference in GMT for HAI antibodies between the three lots of Fluzone High-Dose used in FIM05 was between 0.67 and 1.5 for all comparisons. This met the predefined criteria for equivalence between the lots. The ratios for GMT values between lots observed were between 0.94 comparing lot1/lot2 for H1N1 antibodies, and 1.04 for comparing lot2/lot3 for H3N2 antibodies.

8.1.1.13. *Results for other efficacy outcomes*

Seroconversion rates in Fluzone High-Dose and Fluzone treated subjects are summarised below.

Table 6: Comparison of seroconversion rates in Fluzone High-Dose and Fluzone treated subjects

	Pooled Fluzone HD (N = 2576)			Standard Fluzone (N = 1275)			Difference: HD - Standard	
Flu Strain	n/M	(%)	95% CI	n/M	(%)	95% CI	%	95% CI
A/H1N1: New-Caledonia	1229/2531	(48.56)	(46.59; 50.53)	289/1249	(23.14)	(20.83; 25.58)	25.42	(22.38; 28.46)
A/H3N2: Wisconsin	1749/2531	(69.10)	(67.26; 70.90)	633/1248	(50.72)	(47.91; 53.53)	18.38	(15.08; 21.69)
B: Malaysia	1056/2529	(41.76)	(39.82; 43.71)	374/1249	(29.94)	(27.41; 32.57)	11.81	(8.63; 15.00)

Source Data: Section 9, Table 9.60

The denominator (M) of the percentage is the number of subjects with both pre- and post-vaccination serology results for the strain, including results reported as <LLOQ.

Seroconversion (SC): For subjects with a Day 0 pre-vaccination titer <10 (1/dil): Titer ≥40 (1/dil) on Day 28

For subjects with a Day 0 pre-vaccination titer ≥10 (1/dil): ≥4-fold increase of titer on Day 28

Superiority for a virus strain: The lower limit of the 95% CI of the difference of the seroconversion rates is >10%.

Superiority of Fluzone HD: At least 2 of the 3 virus strains must demonstrate superiority. If one strain fails, then it must demonstrate non-inferiority with the lower limit of the 95% CI ≥ -10%.

Subjects who received Fluzone High-Dose achieved a significantly higher rate of seroconversion than those receiving Fluzone, the margin of superiority being 25.42%, 18.38% and 11.18% for the H1N1, H3N2 and B components of the vaccine respectively.

GMT ratios in Fluzone High-Dose and Fluzone treated subjects are detailed in Table 7 below.

Table 7: Comparative GMT for HAI antibodies in Fluzone High-Dose and Fluzone treated subjects

	Pooled Fluzone HD (N = 2576)			Standard Fluzone (N = 1275)			GMT Ratios	
Flu Strain	M	GMT	95% CI	M	GMT	95% CI	HD/Standard	95% CI
A/H1N1:New-Caledonia	2543	115.79	(111.41; 120.34)	1252	67.29	(63.65; 71.13)	1.72	(1.61; 1.84)
A/H3N2: Wisconsin	2544	608.87	(583.54; 635.30)	1252	332.46	(310.44; 356.05)	1.83	(1.70; 1.98)
B: Malaysia	2542	69.06	(66.60; 71.60)	1252	52.34	(49.48; 55.35)	1.32	(1.24; 1.41)

Source Data: Section 9, Table 9.61

N is the number of subjects in the Immunogenicity Analysis Set.

M is the number of subjects with a valid serology result for the particular flu strain, including results reported as <LLOQ.

Superiority for a virus strain: The lower limit of the 95% CI for GMT ratio is >1.5.

Superiority of Fluzone HD: At least 2 of the 3 virus strains must demonstrate superiority. If one strain fails, then it must demonstrate non-inferiority with the lower limit of the 95% CI >0.67.

Subjects who received Fluzone High-Dose had significantly higher GMT titres for HAI antibodies than those who received Fluzone.

Reverse cumulative plots of HAI antibody titre are provided in Figure 1. These indicate that the pre-vaccination titres of HAI antibodies were similar between the Fluzone High-Dose and Fluzone subjects.

Figure 1: Reverse cumulative distribution curves of antibody titres against H1N1, H3N2 and B vaccine strains 28 days post vaccination

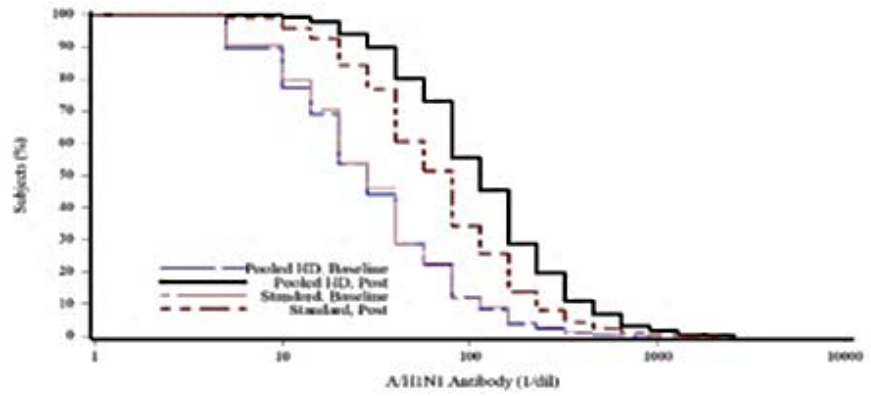


Figure 5.2: Reverse Cumulative Distribution Curves of Antibody Titers Against Strain A/H3N2 at Baseline and 28 Days Post-Vaccination - Immunogenicity Analysis Set

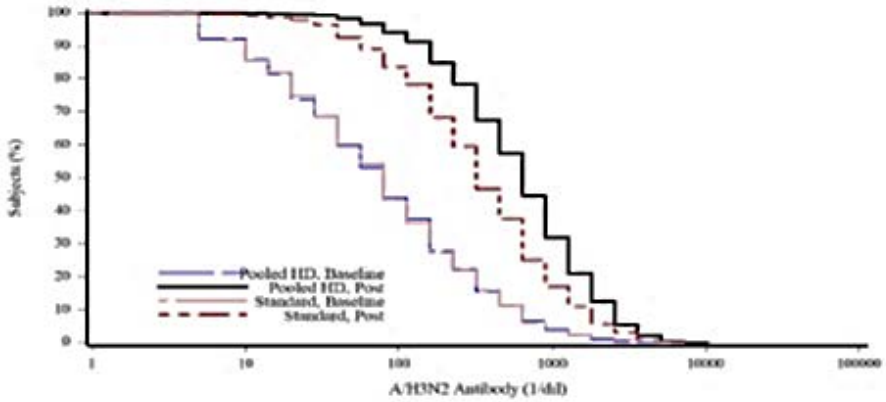
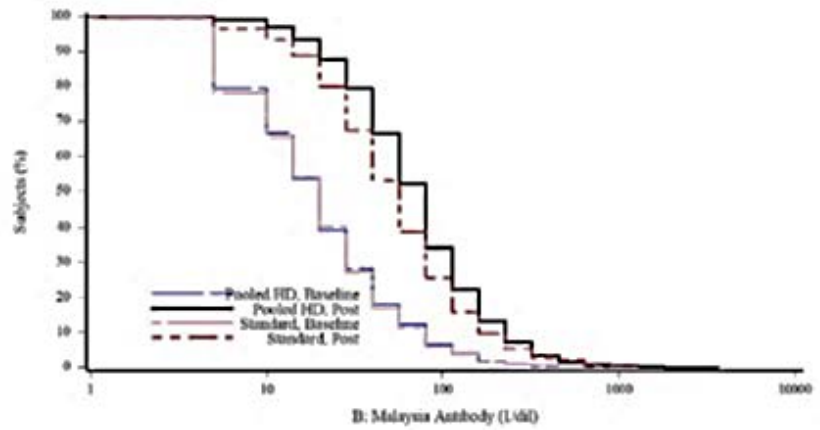


Figure 5.3: Reverse Cumulative Distribution Curves of Antibody Titers Against Strain B at Baseline and 28 Days Post-Vaccination -- Immunogenicity Analysis Set



Post hoc analyses of GMT for HAI antibodies indicated slight differences in the ratio between Fluzone High-Dose and Fluzone subjects when stratified for age (above or below 75 years), gender (male or female) or medical history (presence or absence of cardiac or respiratory disease). However, in these analyses GMT for HAI antibodies remained higher in the Fluzone High-Dose than the Fluzone treated subjects for all strains of influenza virus.

Seroprotection

Seroprotection, defined by a HAI antibody titre of ≥ 1:40 was assessed post vaccination.

Table 8: Comparative rates of seroprotection in subjects treated with Fluzone High-Dose and Fluzone

	Pooled Fluzone HD (N = 2576)			Standard Fluzone (N = 1275)			Difference: HD - Standard	
Flu Strain	n/M	(%)	95% CI	n/M	(%)	95% CI	%	95% CI
A/H1N1:New-Caledonia	2286/2543	(89.9)	(88.66; 91.04)	961/1252	(76.8)	(74.32; 79.07)	13.14	(10.52; 15.75)
A/H3N2: Wisconsin	2526/2544	(99.3)	(98.88; 99.58)	1208/1252	(96.5)	(95.31; 97.44)	2.81	(1.74; 3.88)
B: Malaysia	2015/2542	(79.3)	(77.64; 80.83)	846/1252	(67.6)	(64.90; 70.16)	11.70	(8.66; 14.73)

Source Data: Section 9, Table 9.62

Seroprotection (SP): Titer ≥ 40 (1/dil), measured on D28.

The denominator (M) of the percentage is the number of subjects with a valid serology result for the particular flu strain, including results reported as <LLOQ.

This indicated that seroprotection was achieved in 89.9%, 99.3% and 79.3% of subjects against the H1N1, H3N2 and B components of the vaccine respectively. The difference was statistically significant for all three strains at a 95% confidence level, but small e.g. 2.81% for the H3H2 strain.

8.1.2. Study FIM 12

8.1.2.1. *Study design, objectives, locations and dates*

Study FIM12 was a Phase III study which compared the clinical efficacy of Fluzone High-Dose and Fluzone in preventing influenza in patients > 65 years of age over two consecutive seasons. 14,500 and 17,500 subjects were randomised 1:1 to receive either Fluzone High-Dose or Fluzone in the first and second study years respectively. Vaccination of subjects was completed prior to 15 November in each study year to precede the onset of the peak of the northern respiratory virus season.

Following vaccination subjects were followed through active and passive surveillance to 30 April the following year. Passive surveillance was implemented by subjects being instructed to contact the study site if they experienced defined symptoms of influenza. Active surveillance consisted of all subjects being contacted by a call centre once or twice per week until 30 April to ask if they had experienced any symptoms of respiratory illness. Twice weekly calls were scheduled during the peak of the influenza season; January to March (Year 1) and January to February (Year 2).

Nasopharyngeal swabs were taken from subjects who reported illness for PCR confirmation of influenza. The study site also collected history regarding concomitant illness such as pneumonia, and systemic symptoms if illness. Subjects were followed for 30 days after reporting illness.

Subjects who enrolled in Year 1 could re-enrol in Year 2 of the study. If the 17,489 subject enrolled in Year 2 of Study FIM12 7,645 had previously enrolled in Year 1. The vaccine formulation changed between the two years of the study. Thus the reported number of subjects analysed in the study actually represent 'subject-years' of vaccination.

Study FIM12 was conducted between 6 September 2011 and 31 May 2013 at 126 centres in the USA and Canada.

8.1.2.2. *Inclusion and exclusion criteria*

There were no screening criteria for participation in Study FIM12.

Enrolled subjects were > 65 years of age and able to attend scheduled visits.

Subjects could enrol in both years of the trial.

Significant exclusion criteria included:

- known allergy to eggs or components of the vaccine
- a history of Guillain-Barré syndrome
- vaccination against influenza in the 6 months preceding the study vaccination

8.1.2.3. *Study treatments*

Subjects received one 0.5 mL dose of either Fluzone High-Dose or Fluzone containing 60 µg or 15 µg of HA respectively for each of the three influenza strains in the vaccine. The strains in the vaccine were:

- Year 1:
  - A/California/7/2009 (H1N1)
  - A/Victoria/210/2009 (H3N2)
  - B/Brisbane/60/2008
- Year 2:
  - A/California/7/2009 (H1N1)
  - A/Victoria/361/2011 (H3N2)
  - B/Texas/6/2011

8.1.2.4. *Efficacy variables and outcomes*

Primary endpoint

The primary endpoint of Study FIM12 was the occurrence of culture or PCR confirmed influenza in subjects > 14 days after vaccination who had a protocol-defined ILI. This was used to calculate the relative vaccine efficacy of Fluzone High-Dose compared to Fluzone.

A protocol defined ILI was determined by at least one of; sore throat, cough, sputum production, wheezing or difficulty breathing *and* at least one of; fever > 37.2°C, shivering, fatigue, headache or myalgia.

An alternate clinical endpoint, the Modified CDC-defined ILI was also measured. A case of Modified-CDC-defined ILI was defined as the occurrence of a fever of > 37.2°C degrees centigrade with cough or sore throat.

Secondary and observational endpoints

Several secondary endpoints examined the occurrence of influenza which was similar to the vaccine strains. 'Antigenic similarity' was concluded when a culture-confirmed isolate was considered similar to the vaccine-components when tested against a standardised panel of ferret HAI antibodies. 'Similarity to the vaccine components' was concluded when a culture-confirmed isolate was considered similar to one of the vaccine strains according to genetic sequence or HAI antigenicity.

The rate of pneumonia, onset or exacerbation of cardio-respiratory conditions and occurrence of health care utilisation was defined as an observational endpoint.

8.1.2.5. *Randomisation and blinding methods*

Randomisation was administered through a central allocation of identification numbers using the same process as Study FIM05.

8.1.2.6. *Analysis populations*

Two analyses sets were used.

The Full Analysis Set (FAS) was defined for each study year as including all subjects who received study vaccine.

The Per-Protocol analysis set was a subset of the FAS which excluded;

- Subjects who did not meet all inclusion or had at least on exclusion criteria for the study
- Subjects who did not receive vaccine
- Subject receive a vaccine which was deemed unacceptable for use
- Subject received incorrect vaccine for their randomisation
- Surveillance contact was not made at least once after 28 days

Missing data was not replaced or imputed in the FAS set.

8.1.2.7. *Sample size*

The study enrolled 31,989 subjects allocated to Fluzone (n = 15,998) and Fluzone High-Dose (n = 15,991).

A sample of at least 30,000 was calculated as necessary to achieve 80% power to detect at least a 9.1% difference in the vaccine efficacy of Fluzone High-Dose and Fluzone.

8.1.2.8. *Statistical methods*

The observed rate of influenza in the two treatment arms was used to calculate the relative vaccine efficacy of the Fluzone High-Dose and Fluzone using the calculation:

The VE of Fluzone High-Dose relative to Fluzone was estimated for the primary endpoint by:

Relative VE = 1 - [(CHD/NHD) / (CFL/NFL)]

where:

- Relative VE is the efficacy of Fluzone High-Dose vaccine relative to that of Fluzone vaccine
- CHD is the number of cases in the Fluzone High-Dose Group
- NHD is the number of subjects in the Fluzone High-Dose Group
- CFL is the number of cases in the Fluzone Group
- NFL is the number of subjects in the Fluzone Group

CIs for relative VE were calculated by an exact method conditional on the total number of cases

in both groups. The efficacy estimate given above may be restated as:

Relative VE = $1 - N_{FL}/N_{HD} \times q/1-q$

where q is the proportion of cases who received Fluzone High-Dose. Thus

$q/1-q$

is equivalent to

C_{HD}/C_{FL}

Given the total number of cases, C_{HD} has a binomial distribution $(q, C_{HD}+C_{FL})$. Thus, a CI for q may be constructed using the exact Clopper-Pearson method for binomial proportions. Since q/1-q is a strictly increasing function of q, a CI for VE may be constructed.

Fluzone High-Dose would be considered superior to Fluzone if the lower bound of the 95% two sided CI for relative VE was > 9.1% for the primary objective. An interim analysis was to be conducted by an IDMC at the end of the first year if the total number of primary endpoint cases at that time was at least 80, with the possibility of stopping the trial if efficacy was demonstrated; however, this number was not realised.

There was no hypothesis testing of secondary endpoints.

8.1.2.9. *Participant flow*

A total of 31,989 subjects were enrolled, of whom 95% completed the study overall. Study completion rates, loss to follow-up and withdrawals due to adverse events occurred at similar rates between the treatment arms (Table 9).

Table 9: Participant flow in Study FIM12

	Year 1			Year 2			Combined		
	Fluzone High-Dose† n (%)‡	Fluzone† n (%)‡	Total n (%)‡	Fluzone High-Dose† n (%)‡	Fluzone† n (%)‡	Total n (%)‡	Fluzone High-Dose† n (%)‡	Fluzone† n (%)‡	Total n (%)‡
Subjects enrolled and randomized	7254	7246	14500	8737	8752	17489	15991	15998	31989
Subjects vaccinated*	7253 (99.99)	7244 (99.97)	14497 (99.98)	8737 (100.00)	8749 (99.97)	17486 (99.98)	15990 (99.99)	15993 (99.97)	31983 (99.98)
Subjects completing trial	6881 (94.86)	6837 (94.36)	13718 (94.61)	8376 (95.87)	8373 (95.67)	16749 (95.77)	15257 (95.41)	15210 (95.07)	30467 (95.24)
Subjects terminating early	373 (5.14)	409 (5.64)	782 (5.39)	361 (4.13)	379 (4.33)	740 (4.23)	734 (4.59)	788 (4.93)	1522 (4.76)
Reason for early termination									
Lost to follow up	130 (1.79)	145 (2.00)	275 (1.90)	122 (1.40)	135 (1.54)	257 (1.47)	252 (1.58)	280 (1.75)	532 (1.66)
Non-compliance with protocol	42 (0.58)	71 (0.98)	113 (0.78)	125 (1.43)	124 (1.42)	249 (1.42)	167 (1.04)	195 (1.22)	362 (1.13)
Other adverse event	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.03)	1 (0.01)	4 (0.02)	3 (0.02)	1 (0.01)	4 (0.01)
Serious adverse event	52 (0.72)	45 (0.62)	97 (0.67)	50 (0.57)	61 (0.70)	111 (0.63)	102 (0.64)	106 (0.66)	208 (0.65)
Voluntary withdrawal not due to adverse event	149 (2.05)	148 (2.04)	297 (2.05)	61 (0.70)	58 (0.66)	119 (0.68)	210 (1.31)	206 (1.29)	416 (1.30)

* Subjects vaccinated classified according to randomized group.

† Randomized treatment.

‡ % = percentage of subjects enrolled and randomized.

8.1.2.10. *Major protocol violations/deviations*

A total of 186 subjects were excluded from the per-protocol analysis for protocol deviations. The most common of these was not being contacted during the surveillance period (n = 93). Rates of protocol deviations were similar between treatment arms (Table 10).

Table 10: Major protocol violations occurring in Fluzone High-Dose and Fluzone treatment arms in Study FIM12

	Year 1			Year 2			Combined		
	Fluzone High-Dose† n (%)	Fluzone† n (%)	Total n (%)	Fluzone High-Dose† n (%)	Fluzone† n (%)	Total n (%)	Fluzone High-Dose† n (%)	Fluzone† n (%)	Total n (%)
Subjects enrolled and randomized, by randomization group	7254	7246	14500	8737	8752	17489	15991	15998	31989
Subjects vaccinated, by vaccine received - Full (as treated) Analysis Set	7254	7243	14497	8738	8748	17486	15992	15991	31983
Full (as randomized) Analysis Set *	7253 (99.99)	7244 (99.97)	14497 (99.98)	8737 (100.00)	8749 (99.97)	17486 (99.98)	15990 (99.99)	15993 (99.97)	31983 (99.98)
Per Protocol Analysis Set*	7209 (99.38)	7207 (99.46)	14416 (99.42)	8683 (99.38)	8704 (99.45)	17387 (99.42)	15892 (99.38)	15911 (99.46)	31803 (99.42)
Reasons for exclusion from the Per Protocol Analysis Set *†									
Did not receive vaccine as randomized	5 (0.07)	7 (0.10)	12 (0.08)	4 (0.05)	8 (0.09)	12 (0.07)	9 (0.06)	15 (0.09)	24 (0.08)
Did not satisfy the inclusion and exclusion criteria	4 (0.06)	2 (0.03)	6 (0.04)	6 (0.07)	5 (0.06)	11 (0.06)	10 (0.06)	7 (0.04)	17 (0.05)
Did not have surveillance contact	27 (0.37)	23 (0.32)	50 (0.34)	30 (0.34)	13 (0.15)	43 (0.25)	57 (0.36)	36 (0.23)	93 (0.29)
Received another seasonal influenza vaccine between vaccination and the end of surveillance	9 (0.12)	6 (0.08)	15 (0.10)	7 (0.08)	14 (0.16)	21 (0.12)	16 (0.10)	20 (0.13)	36 (0.11)
Other protocol deviation likely to impact responses for primary and secondary endpoints	0 (0.00)	1 (0.01)	1 (0.01)	7 (0.08)	8 (0.09)	15 (0.09)	7 (0.04)	9 (0.06)	16 (0.05)

* Percentages based on subjects randomized.

† Each subject is counted only once according to the order shown.

8.1.2.11. *Baseline data*

Of the subjects enrolled, 43.4% were male and 56.6% were female, with the population having a mean age of 73.3 years. The treatment arms were balanced for race, sex and age. The proportion of subjects reporting at least one specified chronic co-morbidity was similar between the Fluzone High-Dose (67.22%) and Fluzone (67.24) treatment arms (Table 11).

Table 11: Summary of pre-existing medical conditions among Fluzone High-Dose and Fluzone treated subjects in Study FIM12

	Year 1		Year 2		Combined	
	Fluzone High-Dose N=7254 n (%)	Fluzone N=7243 n (%)	Fluzone High-Dose N=8738 n (%)	Fluzone N=8748 n (%)	Fluzone High-Dose N=15992 n (%)	Fluzone N=15991 n (%)
Subjects with at least one pre-specified chronic comorbidity	5007 (69.02)	4953 (68.38)	5743 (65.72)	5799 (66.29)	10750 (67.22)	10752 (67.24)
Subjects with at least two pre-specified chronic comorbidities	2594 (35.76)	2574 (35.54)	2790 (31.93)	2830 (32.35)	5384 (33.67)	5404 (33.79)
Blood Disorders						
Sickle Cell Disease	2 (0.03)	4 (0.06)	14 (0.16)	12 (0.14)	16 (0.10)	16 (0.10)
Cardiac Disorders						
Coronary Artery Disease	1347 (18.57)	1299 (17.93)	1389 (15.90)	1432 (16.37)	2736 (17.11)	2731 (17.08)
Atrial Fibrillation	540 (7.44)	520 (7.18)	563 (6.44)	592 (6.77)	1103 (6.90)	1112 (6.95)
Valvular Heart Disease	397 (5.47)	386 (5.33)	347 (3.97)	355 (4.06)	744 (4.65)	741 (4.63)
Congestive Heart Failure	229 (3.16)	215 (2.97)	222 (2.54)	231 (2.64)	451 (2.82)	446 (2.79)
Endocrine And Metabolic Disorders						
Diabetes Mellitus	1704 (23.49)	1709 (23.60)	1885 (21.57)	1927 (22.03)	3589 (22.44)	3636 (22.74)
Hypothyroidism	1456 (20.07)	1441 (19.90)	1758 (20.12)	1784 (20.39)	3214 (20.10)	3225 (20.17)

8.1.2.12. *Results for the primary efficacy outcome*

The calculated relative vaccine efficacy of 24.24% (95% CI 9.71-36.50) demonstrated the superiority of Fluzone High-Dose to Fluzone using the pre-specified margin of superiority of 9.1% and the protocol-defined case definition of influenza (Table 12).

These results did not differ between the per-protocol and FAS analyses. The relative efficacy of Fluzone High-Dose/Fluzone was higher for H3N2 influenza (23.30) and influenza B (25.48) than for H1N1 influenza (11.09). The relative vaccine efficacy for Fluzone High-Dose/Fluzone for H1N1 was -33.53, for example, Fluzone was superior in Year 2 of the study. There were, however, low numbers of H1N1 cases observed over the study, which is reflected in the wide confidence intervals for the estimate of relative vaccine efficacy for this strain.

Table 12: Relative rates of influenza according to protocol-defined and Modified CDC case definitions in Fluzone High-Dose and Fluzone treated subjects in Study FIM12

	Year 1			Year 2			Combined		
	Fluzone High-Dose N=7253 n (%)	Fluzone N=7244 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=8737 n (%)	Fluzone N=8749 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=15990 n (%)	Fluzone N=15993 n (%)	Relative Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	23 (0.32)	42 (0.58)	45.31 (6.95; 68.60)	205 (2.35)	259 (2.96)	20.74 (4.43; 34.33)	228 (1.43)	301 (1.88)	24.24 (9.71; 36.50)
Influenza A	16 (0.22)	34 (0.47)	53.00 (12.49; 75.77)	174 (1.99)	216 (2.47)	19.33 (1.05; 34.32)	190 (1.19)	250 (1.56)	23.99 (7.84; 37.39)
A/H1N1	4 (0.06)	6 (0.08)	33.42 (-180.8; 86.18)	4 (0.05)	3 (0.03)	-33.52 (-811.5; 77.41)	8 (0.05)	9 (0.06)	11.09 (-159.6; 70.15)
A/H3N2	11 (0.15)	25 (0.35)	56.05 (7.41; 80.48)	160 (1.83)	198 (2.26)	19.08 (-0.17; 34.72)	171 (1.07)	223 (1.39)	23.30 (5.97; 37.53)
Influenza B	7 (0.10)	8 (0.11)	12.61 (-175.8; 73.02)	31 (0.35)	43 (0.49)	27.81 (-17.26; 56.02)	38 (0.24)	51 (0.32)	25.48 (-15.68; 52.36)
Victoria lineage	2 (0.03)	4 (0.06)	50.06 (-248.4; 95.48)	7 (0.08)	7 (0.08)	-0.14 (-234.6; 70.03)	9 (0.06)	11 (0.07)	18.17 (-117.2; 70.03)
Yamagata lineage	3 (0.04)	2 (0.03)	-49.81 (-1694; 82.84)	21 (0.24)	34 (0.39)	38.15 (-9.68; 65.89)	24 (0.15)	36 (0.23)	33.32 (-14.89; 61.94)
Associated with modified CDC-defined influenza-like illness	10 (0.14)	11 (0.15)	9.20 (-135.5; 65.43)	86 (0.98)	110 (1.26)	21.71 (-4.76; 41.65)	96 (0.60)	121 (0.76)	20.65 (-4.60; 39.94)
Influenza A	8 (0.11)	10 (0.14)	20.10 (-124.8; 72.60)	78 (0.89)	94 (1.07)	16.91 (-13.39; 39.26)	86 (0.54)	104 (0.65)	17.29 (-11.13; 38.58)
A/H1N1	1 (0.01)	1 (0.01)	0.12 (-7740; 98.73)	2 (0.02)	1 (0.01)	-100.3 (-11716; 89.57)	3 (0.02)	2 (0.01)	-50.03 (-1696; 82.81)
A/H3N2	6 (0.08)	8 (0.11)	25.09 (-146.2; 78.58)	71 (0.81)	87 (0.99)	18.28 (-13.11; 41.13)	77 (0.48)	95 (0.59)	18.93 (-10.66; 40.77)
Influenza B	2 (0.03)	1 (0.01)	-99.75 (-11685; 89.60)	8 (0.09)	16 (0.18)	49.93 (-23.99; 81.45)	10 (0.06)	17 (0.11)	41.17 (-36.05; 75.92)
Victoria lineage	1 (0.01)	1 (0.01)	0.12 (-7740; 98.73)	2 (0.02)	0 (0.00)	NA	3 (0.02)	1 (0.01)	-200.1 (-15652; 75.91)
Yamagata lineage	1 (0.01)	0 (0.00)	NA	5 (0.06)	14 (0.16)	64.24 (-5.07; 89.92)	6 (0.04)	14 (0.09)	57.13 (-18.74; 86.50)

The results were similar using the modified CDC case definition of influenza. The lower numbers of patients achieving this more restrictive definition of illness reduced the accuracy of the estimate of vaccine efficacy, including very low numbers of H1N1 influenza. Using this case definition the relative vaccine efficacy against H1N1 influenza was unfavourable for Fluzone High-Dose; -50.03 (95% CI -1696, 82.80)

8.1.2.13. *Results for other efficacy outcomes*

Relative vaccine efficacy against culture-confirmed influenza caused by viral types antigenically similar to those contained in the vaccine

The relative vaccine efficacy for Fluzone High-Dose/Fluzone for influenza types which were antigenically similar to the vaccine strains was 31.44 indicating superior protection with Fluzone High-Dose to the standard dose vaccine (Table 13).

Table 13: Relative rates of influenza caused by virus antigenically similar to that contained in the vaccine in Fluzone High-Dose and Fluzone treated subjects in Study FIM12 (per protocol analysis)

	Year 1			Year 2			Combined		
	Fluzone High-Dose N=7209 n (%)	Fluzone N=7207 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=8683 n (%)	Fluzone N=8704 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=15892 n (%)	Fluzone N=15911 n (%)	Relative Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	2 (0.03)	7 (0.10)	71.44 (-50.02; 97.10)	61 (0.70)	85 (0.98)	28.06 (-1.14; 49.09)	63 (0.40)	92 (0.58)	31.44 (4.51; 51.05)
Influenza A	2 (0.03)	7 (0.10)	71.44 (-50.02; 97.10)	44 (0.51)	56 (0.64)	21.24 (-19.02; 48.17)	46 (0.29)	63 (0.40)	26.90 (-8.62; 51.13)
A/H1N1	1 (0.01)	3 (0.04)	66.68 (-315.0; 99.37)	2 (0.02)	0 (0.00)	NA	3 (0.02)	3 (0.02)	-0.12 (-647.5; 86.59)
A/H3N2	1 (0.01)	4 (0.06)	75.01 (-152.6; 99.49)	42 (0.48)	56 (0.64)	24.82 (-14.19; 50.84)	43 (0.27)	60 (0.38)	28.25 (-7.93; 52.66)
Influenza B	0 (0.00)	0 (0.00)	NA	17 (0.20)	29 (0.33)	41.24 (-10.58; 69.71)	17 (0.11)	29 (0.18)	41.31 (-10.44; 69.74)
Victoria lineage	0 (0.00)	0 (0.00)	NA	0 (0.00)	0 (0.00)	NA	0 (0.00)	0 (0.00)	NA
Yamagata lineage	0 (0.00)	0 (0.00)	NA	17 (0.20)	29 (0.33)	41.24 (-10.58; 69.71)	17 (0.11)	29 (0.18)	41.31 (-10.44; 69.74)
Associated with modified CDC-defined influenza-like illness	0 (0.00)	3 (0.04)	100.00 (-141.9; 100.00)	22 (0.25)	42 (0.48)	47.49 (10.02; 70.15)	22 (0.14)	45 (0.28)	51.05 (16.77; 72.01)
Influenza A	0 (0.00)	3 (0.04)	100.00 (-141.9; 100.00)	17 (0.20)	28 (0.32)	39.14 (-15.14; 68.75)	17 (0.11)	31 (0.19)	45.10 (-2.32; 71.50)
A/H1N1	0 (0.00)	1 (0.01)	100.00 (-3799; 100.00)	0 (0.00)	0 (0.00)	NA	0 (0.00)	1 (0.01)	100.00 (-3805; 100.00)
A/H3N2	0 (0.00)	2 (0.03)	100.00 (-432.3; 100.00)	17 (0.20)	28 (0.32)	39.14 (-15.14; 68.75)	17 (0.11)	30 (0.19)	43.27 (-6.23; 70.65)
Influenza B	0 (0.00)	0 (0.00)	NA	5 (0.06)	14 (0.16)	64.20 (-5.18; 89.91)	5 (0.03)	14 (0.09)	64.24 (-5.06; 89.92)
Victoria lineage	0 (0.00)	0 (0.00)	NA	0 (0.00)	0 (0.00)	NA	0 (0.00)	0 (0.00)	NA
Yamagata lineage	0 (0.00)	0 (0.00)	NA	5 (0.06)	14 (0.16)	64.20 (-5.18; 89.91)	5 (0.03)	14 (0.09)	64.24 (-5.06; 89.92)

Relative vaccine efficacy against culture-confirmed influenza caused by viral types similar to those contained in the vaccine

The relative vaccine efficacy for isolated confirmed as similar to the vaccine strains of virus indicates a similar pattern to the overall FAS results (Table 14).

Table 14: Relative rates of influenza caused by virus antigenically similar to that contained in the vaccine in Fluzone High-Dose and Fluzone treated subjects in Study FIM12 (per protocol analysis)

	Year 1			Year 2			Combined		
	Fluzone High-Dose N=7209 n (%)	Fluzone N=7207 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=8683 n (%)	Fluzone N=8704 n (%)	Relative Efficacy % (95% CI)	Fluzone High-Dose N=15892 n (%)	Fluzone N=15911 n (%)	Relative Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	9 (0.12)	25 (0.35)	64.01 (20.29; 85.22)	64 (0.74)	88 (1.01)	27.10 (-1.75; 48.01)	73 (0.46)	113 (0.71)	35.32 (12.42; 52.49)
Influenza A	9 (0.12)	23 (0.32)	60.88 (12.24; 84.07)	47 (0.54)	59 (0.68)	20.15 (-19.16; 46.75)	56 (0.35)	82 (0.52)	31.63 (2.79; 52.21)
A/H1N1	4 (0.06)	6 (0.08)	33.35 (-181.1; 86.17)	3 (0.03)	2 (0.02)	-50.36 (-1700; 82.78)	7 (0.04)	8 (0.05)	12.40 (-176.5; 72.96)
A/H3N2	5 (0.07)	17 (0.24)	70.60 (16.97; 91.52)	44 (0.51)	57 (0.65)	22.62 (-16.71; 49.00)	49 (0.31)	74 (0.47)	33.70 (3.60; 54.76)
Influenza B	0 (0.00)	2 (0.03)	100.00 (-432.3; 100.00)	17 (0.20)	29 (0.33)	41.24 (-10.58; 69.71)	17 (0.11)	31 (0.19)	45.10 (-2.32; 71.50)
Victoria lineage	0 (0.00)	2 (0.03)	100.00 (-432.3; 100.00)	0 (0.00)	0 (0.00)	NA	0 (0.00)	2 (0.01)	100.00 (-433.1; 100.00)
Yamagata lineage	0 (0.00)	0 (0.00)	NA	17 (0.20)	29 (0.33)	41.24 (-10.58; 69.71)	17 (0.11)	29 (0.18)	41.31 (-10.44; 69.74)
Associated with modified CDC-defined influenza-like illness	3 (0.04)	8 (0.11)	62.51 (-56.20; 93.59)	23 (0.26)	43 (0.49)	46.38 (9.03; 69.16)	26 (0.16)	51 (0.32)	48.96 (16.60; 69.45)
Influenza A	3 (0.04)	7 (0.10)	57.15 (-87.68; 92.85)	18 (0.21)	29 (0.33)	37.78 (-15.89; 67.46)	21 (0.13)	36 (0.23)	41.60 (-2.78; 67.60)
A/H1N1	1 (0.01)	1 (0.01)	0.03 (-7748; 98.73)	1 (0.01)	1 (0.01)	-0.24 (-7769; 98.72)	2 (0.01)	2 (0.01)	-0.12 (-1281; 92.74)
A/H3N2	2 (0.03)	6 (0.08)	66.68 (-86.36; 96.71)	17 (0.20)	28 (0.32)	39.14 (-15.14; 68.75)	19 (0.12)	34 (0.21)	44.05 (-0.91; 69.85)
Influenza B	0 (0.00)	1 (0.01)	100.00 (-3799; 100.00)	5 (0.06)	14 (0.16)	64.20 (-5.18; 89.91)	5 (0.03)	15 (0.09)	66.63 (3.40; 90.51)
Victoria lineage	0 (0.00)	1 (0.01)	100.00 (-3799; 100.00)	0 (0.00)	0 (0.00)	NA	0 (0.00)	1 (0.01)	100.00 (-3805; 100.00)
Yamagata lineage	0 (0.00)	0 (0.00)	NA	5 (0.06)	14 (0.16)	64.20 (-5.18; 89.91)	5 (0.03)	14 (0.09)	64.24 (-5.06; 89.92)

Rates of pneumonia, exacerbation of pre-existing health conditions and health care utilisation

Overall the number of cases of pneumonia or onset/exacerbation of pre-existing cardio-respiratory conditions was lower in the Fluzone High-Dose than the Fluzone treated group where the diagnosis of influenza is confirmed (Table 15). The relative risk of these outcomes between the two treatment arms was not significantly different at a 95% level of confidence.

Table 15: Comparative rates of pneumonia, exacerbation of pre-existing health conditions and health-care utilisation in Fluzone High-Dose and Fluzone treated subjects

	Year 1			Year 2			Combined		
	Fluzone High-Dose N=7209 n (rate) *	Fluzone N=7207 n (rate) *	Relative Risk (95% CI)	Fluzone High-Dose N=8683 n (rate) *	Fluzone N=8704 n (rate) *	Relative Risk (95% CI)	Fluzone High-Dose N=15892 n (rate) *	Fluzone N=15911 n (rate) *	Relative Risk (95% CI)
Pneumonia	0 (0.00)	0 (0.00)	NA	3 (0.35)	7 (0.80)	0.43 (0.11; 1.66)	3 (0.19)	7 (0.44)	0.43 (0.11; 1.66)
New onset or exacerbation of pre-existing cardio-respiratory conditions	6 (0.83)	10 (1.39)	0.60 (0.22; 1.65)	40 (4.61)	55 (6.32)	0.73 (0.49; 1.09)	46 (2.89)	65 (4.09)	0.71 (0.49; 1.03)
Health care visits	17 (2.36)	16 (2.22)	1.06 (0.54; 2.10)	130 (14.97)	134 (15.40)	0.97 (0.77; 1.24)	147 (9.25)	150 (9.43)	0.98 (0.78; 1.23)
Hospitalizations	1 (0.14)	0 (0.00)	NA	5 (0.58)	10 (1.15)	0.50 (0.17; 1.47)	6 (0.38)	10 (0.63)	0.60 (0.22; 1.65)
ER Visits	0 (0.00)	2 (0.28)	NA	9 (1.04)	5 (0.57)	1.80 (0.60; 5.38)	9 (0.57)	7 (0.44)	1.29 (0.48; 3.46)
Non-routine medical office visits	16 (2.22)	14 (1.94)	1.14 (0.56; 2.34)	116 (13.36)	119 (13.67)	0.98 (0.76; 1.26)	132 (8.31)	133 (8.36)	0.99 (0.78; 1.26)
Medication use	26 (3.61)	33 (4.58)	0.79 (0.47; 1.32)	207 (23.84)	235 (27.00)	0.88 (0.73; 1.06)	233 (14.66)	268 (16.84)	0.87 (0.73; 1.04)
Antipyretics/analgesics/NSAIDs	10 (1.39)	20 (2.78)	0.50 (0.23; 1.07)	104 (11.98)	127 (14.59)	0.82 (0.63; 1.06)	114 (7.17)	147 (9.24)	0.78 (0.61; 0.99)
Antivirals	4 (0.55)	0 (0.00)	NA	18 (2.07)	24 (2.76)	0.75 (0.41; 1.38)	22 (1.38)	24 (1.51)	0.92 (0.51; 1.64)
Antibiotics	12 (1.66)	13 (1.80)	0.92 (0.42; 2.02)	85 (9.79)	84 (9.65)	1.01 (0.75; 1.37)	97 (6.10)	97 (6.10)	1.00 (0.76; 1.33)

* n = number of events, rate = events per 1,000 subject-seasons

8.2. Other efficacy studies

8.2.1. Study FIM01

8.2.1.1. *Study design, objectives, locations and dates*

Study FIM01 was a prospective randomised double blind study comparing the reactogenicity and immunogenicity of Fluzone High-Dose and Fluzone containing 60 µg and 15 µg of HA per strain respectively. The study enrolled 414 ambulatory and medical stable subjects > 65 years of age who were randomised 1:1 to the dosage arms.

Study FM01 was conducted at 5 centres in the USA between April and November 2005.

The main objective of the study was to compare the immunogenicity of a novel high-dose trivalent influenza vaccine containing 60 µg of HA per strain with a vaccine containing the standard dose of 15 µg HA per strain in patients over 65 years of age. It was proposed that a superior immunological response in this population could lead to greater protection from influenza infection.

8.2.1.2. *Inclusion and exclusion criteria*

The inclusion criteria for FM01 were that subjects were:

- 65 years of age or older
- Ambulatory; defined as not institutionalised, bedridden or homebound.
- Medically stable; chronic illnesses such as diabetes, hypothyroidism or heard disease assessed as controlled with medical therapy.
- Afebrile; patients with a fever were deferred from enrolment until 3 days after resolution of their illness

Significant exclusion criteria included:

- known allergy to eggs or components of the vaccine
- a history of Guillain-Barre syndrome
- immunosuppressive from underlying illness or treatment
- Use of oral steroids or high doses of inhaled steroids within 1 month prior to vaccination
- Active neoplastic disease or history of haematological malignancy within 5 years of the study.

Subjects were stratified according to whether they had received influenza vaccine for the 2004-2005 season (noting the study was conducted in the Northern summer) based on self-reporting.

8.2.1.3. *Study treatments*

Subjects received a single 0.5mL IM dose of a trivalent influenza vaccine containing either 15 µg or 60 µg HA per strain of A/New Caledonia/20/99 (H1N1), A/Fujian/411/2002 (H3N2) and B/Jiangsu/10/2003.

8.2.1.4. *Efficacy variables and outcomes*

The primary endpoint of FM01 was to proportion of subjects in each group who achieved a serum HAI titre of at least 1:32 for each of the three vaccine antigens assessed 1 month after vaccination.

Secondary endpoints included:

- The GMT of the serum of serum HAI antibody against each of the 3 vaccine antigens.
- The proportion of subjects in each group who achieved at least 4-fold increases in serum HAI antibody titres.
- The proportion of patients who achieved serum HAI titres of 1:64 and 1:128 for each of the 3 vaccine antigens.

The immunogenicity outcomes for this trial were obtained from both Baylor and Sanofi Pasteur laboratories; however, the results obtained from the Baylor laboratory were used for the primary analysis.

8.2.1.5. *Randomisation and blinding methods*

Investigators were blinded to the treatments being administered, which are identical in appearance. Subjects were randomised from a centrally administered randomisation table. Randomisation occurred within previously vaccinated/not previously vaccinated strata to produce equal representation of treatment arms among these two groups.

8.2.1.6. *Analysis populations*

ITT and Per-Protocol analyses were performed on all subjects who received a dose of vaccine and had at least 1 blood sample taken. The difference between the two analyses was the ITT population was analysed according to the treatment subjects were randomised to receive, while the Per-Protocol analysis was analysed according to the treatment the subject actually received. Only one subject received Fluzone High-Dose when they were randomised to receive Fluzone.

8.2.1.7. *Sample size*

206 and 208 subjects received Fluzone High-Dose and Fluzone respectively.

8.2.1.8. *Statistical methods*

95% confidence interval was calculated for the proportion of subjects achieving the specified HAI titres. A full description of the statistical tests applied was not provided.

8.2.1.9. *Participant flow*

A total of 415 subjects were enrolled, and 414 subjects were vaccinated (Table 16). One subject received the incorrect treatment for their randomisation.

Table 16: Participant flow in Study FIM01 Summary of subject disposition; All subjects

	High Dose n	Standard Dose n (%)	All n (%)
Enrolled[1]	207	208	415
Vaccinated[2]	206	208	414
Completed	205	208	413
Discontinued[3]	1	0	1
Death	1	0	1
ITT Population	207	207	414
PP Population	206	208	414

1) Subject [information redacted] was enrolled but not vaccinated; 2) Subject [information redacted] was randomised to receive the high dose but was given the standard dose. This subject was included in the standard group for all per protocol analyses but was included in the high dose group for ITT analyses;
3) Subject [information redacted] was classified as an early study discontinuation because the subject died during the study on Day 169 after vaccination.

8.2.1.10. *Major protocol violations/deviations*

Protocol violations were reported in 21 and 23 of the subjects in the 60 µg and 15 µg dose vaccine treatment arms respectively. None of these resulted in an adverse event or withdrawal of the subject from the study.

8.2.1.11. *Baseline data*

The demographic characteristics of the two treatment arms were well matched for gender, age and race. The average age of the treatment arms was 74 and 73 for the Fluzone High-Dose and Fluzone treatment arms respectively.

8.2.1.12. *Results for the primary efficacy outcome*

A HAI titre of 1:32 against the H1 antigen was observed in 62.3% and 48.3% of subjects ($p < 0.01$) in the Fluzone High-Dose and Fluzone dose vaccine respectively (Table 17). There

was no significant difference between treatment groups for the H3 or B antigens. The results were similar between previously vaccinated or unvaccinated groups.

Table 17: Comparative rate of subjects in Fluzone High-Dose and Fluzone treated arms achieving an HAI antibody titre > 1:32

			Fluzone High-Dose		Fluzone		
Population	Titre	Antigen	N	%	N	%	p-value
All	> 1:32	H1	129	62.3	100	48.3	<0.01
		H3	196	94.7	190	91.8	0.24
		B	129	62.3	118	57.0	0.27

8.2.1.13. ***Results for other efficacy outcomes***

Serum HAI antibody GMT

Overall the post-vaccination GMT was significantly higher for the Fluzone High-Dose (high dose) than the Fluzone (standard dose) vaccine for all three antigens at a 95% confidence level (Table 18).

Table 18: Comparison of GMT to HAI antibodies in Fluzone High-Dose and Fluzone treated subjects in Study FIM01

			High Dose		Standard Dose					
Population	Time	Antigen	n	GMT	n	GMT	GMT Ratio	LCI	UCI	*P* Value
All	Pre	H1	207	9.65	207	11.07	0.87	0.7	1.1	0.1835
		H3	207	50.29	207	58.86	0.85	0.7	1.1	0.1878
		B	207	12.91	207	15.58	0.83	0.7	1.0	0.0503
	Post	H1	207	35.50	207	21.34	1.66	1.3	2.1	<0.0001
		H3	207	137.79	207	96.94	1.42	1.1	1.8	0.0024
		B	207	31.26	207	25.40	1.23	1.0	1.5	0.0268

Serum HAI antibody 4-fold increases

There were a significantly higher proportion of subjects achieving a 4-fold increase in HAI antibody titres after vaccination for all 3 antigens in the Fluzone High-Dose than the Fluzone treatment arms (Table 19).

Table 19: Comparison of rates of subjects in Fluzone High-Dose and Fluzone treated arms achieving a 4 fold or greater increase in HAI antibody titre in Study FIM01

		High Dose			Standard Dose			*P* Value
Population	Antigen	N	n	%	N	n	%	CMH
All	H1	207	106	51.2	207	49	23.7	<0.0001
	H3	207	85	41.1	207	51	24.6	0.0004
	B	207	72	34.8	207	35	16.9	<0.0001

8.2.2. Study FIM07

8.2.2.1. *Study design, objectives, locations and dates*

Study FIM07 was a study with essentially the same design as Study FIM12 which was discontinued in its first year, 2009, after enrolling only 9,172 of an anticipated 33,000 patients. The study was ended prematurely because of the onset of the H1N1 'swine flu' pandemic which meant that > 95% of isolates occurring in the 2009-2010 northern winter were of the pandemic strain. The primary endpoint for Study FIM07 was the rate of influenza in subjects vaccinated with Fluzone or Fluzone High-Dose that was caused by virus considered antigenically similar to those in the vaccine. As the study vaccine contained the A/Brisbane/59/2007 strain this was not antigenically similar to the pandemic virus.

Limited efficacy data for secondary endpoints was examined and is available in Table 20. The study has been submitted as part of the safety analysis.

Table 20: Limited analysis of comparative rates of influenza in Fluzone HD and Fluzone treated arms in Study FIM07

	Fluzone HD	Fluzone	Relative Efficacy
	n/M (%)	n/M (%)	% (95% CI)
Cases of laboratory-confirmed influenza-like-illness caused by any viral types/subtypes [1] [2]	14/6013 (0.233)	8/3008 (0.266)	12.5 (-140.9; 65.7)
Cases of culture-confirmed influenza-like-illness caused by any viral types/subtypes [3] [4]	13/6013 (0.216)	7/3008 (0.233)	7.1 (-175.0; 65.6)
Cases of PCR-confirmed influenza-like-illness caused by any viral types/subtypes [1]	14/6013 (0.233)	8/3008 (0.266)	12.5 (-140.9; 65.7)

Source: Section 9, Table 9.27

Note: n is the number of subjects with laboratory (culture or PCR)-, culture-, or PCR-confirmed influenza illness caused by any viral types/subtypes.

Note: M is the number of subjects randomized with the respective vaccine in the year(s) shown.

Note: Influenza-like-illness refers to Protocol-defined ILI.

[1] All cases except one were caused by strains characterized as A/H1N1 California/07/2009-like

[2] This line corresponds to the first secondary objective

[3] All cases except 1 were caused by strains characterized as A/H1N1 California/07/2009-like

[4] This line corresponds to the third observational objective

The point estimate of the relative efficacy of Fluzone HD compared to Fluzone indicated higher efficacy for Fluzone HD. However the 95% confidence intervals around this estimate were wide indicating the relatively low power of Study FIM07 arising from the premature discontinuation of recruitment.

8.3. Evaluator's conclusions on clinical efficacy

The pivotal Studies FIM12 and FIM05 provide evidence of improved immune reactivity and clinical efficacy respectively of Fluzone High-Dose compared to Fluzone in the proposed target population. The number needed to treat to prevent a case of influenza with Fluzone High-Dose compared to using Fluzone is approximately 270 based on the primary endpoint for influenza A (rate of influenza of 1.56% and 1.19% in Fluzone and Fluzone High-Dose groups). This would potentially prevent a large number of cases of influenza if Fluzone High-Dose was used widely, but may limit acceptance by the individual given the slightly higher rate of injection site reactions.

Study FIM12 confirmed greater relative efficacy of Fluzone High-Dose compared to Fluzone in preventing Influenza A and influenza B in subjects > 65 years of age (Table 21). The subjects in

this study were comparatively well, and Study FIM12 provides little evidence of the comparative benefit of Fluzone High-Dose in settings such as aged care facilities where the population is very frail.

Table 21: Study FIM12 Relative vaccine efficacy of Fluzone High-Dose compared to Fluzone in the prevention of laboratory confirmed influenza associated with protocol defined influenza like illness, by age subgroups Per Protocol analysis

Efficacy Endpoint	Age (years)	Fluzone High-Dose N=10519 n (%)	Fluzone N=10518 n (%)	Relative Vaccine Efficacy of Fluzone High-Dose % (95% CI)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	< 75 years	166 (1.47)	193 (1.83)	19.7% (0.3; 35.4)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	75 to <85	64 (1.36)	96 (2.04)	33.1% (7.3; 52)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	>85 years	8 (1.19)	11 (1.63)	26.8% (-99.7; 74.5)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	< 75 years	47 (0.45)	72 (0.68)	34.73 (4.43; 55.79)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	75 to <85	25 (0.53)	37 (0.78)	32.20 (-15.68; 60.88)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	>85 years	1 (0.15)	4 (0.59)	74.85 (-154.1; 99.49)

An analysis of the effect by age was presented in the US FDA report of Fluzone High-Dose;[3] but was not included in the submitted dossier. It does not suggest a strong effect of age on the efficacy of Fluzone High-Dose within the limited power of the sub-analysis.

The evaluator notes that the modified-CDC-defined influenza like illness used as a secondary efficacy endpoint is closer to the WHO surveillance definition of an Influenza-like-Illness that is a fever ≥ 38°C and cough. While all cases in FIM12 were laboratory confirmed, the evaluator feels that the modified CDC definition is likely to better estimate the clinical syndrome which will be recognised as influenza and tested in the Australian clinical or public health setting than the protocol-defined case definition.

The evaluator notes that in the influenza seasons over which Study FIM12 was conducted H3N2 represented > 75% of the virus circulating in the US and Canada with comparatively little H1N1. This pattern was replicated in the adjacent Australian seasons. There were too few cases of H1N1 in Study FIM12 to effectively assess the clinical efficacy of the vaccine against this subtype. FIM07 does not provide supportive evidence because the vaccine was unmatched to the pandemic strain in that year. The evaluator therefore feels that the immunological response demonstrated against H1N1 in Study FIM05 is the best evidence of a protective response against the H1N1 subtype. This study observed a higher rate of seroprotection in subject vaccinated with Fluzone High-Dose than in those who received Fluzone.

[3] Evaluation of STN 103914/5726 by Roshan Ramanthan MD MPH, 29 October 2014

9. Clinical safety

9.1. Studies providing evaluable safety data

Safety data is available from the Studies FIM01, FIM05, FIM07, FIM12 submitted in this dossier as complete reports. Study NIH-01-574 was included in the dossier as a literature reference and so analysis of safety endpoints in this study was not possible. However, this dose-ranging study included only a low number of subjects who received the proposed dose of Fluzone High-Dose. No study assessed a safety as a primary endpoint.

A summary of safety data collected for this submission is shown in Table 22.

Table 22: Summary of safety data collected in studies providing safety information in this submission

Safety Parameter	Time window for capture	FIM05	FIM12	FIM01 (NIH Study 04-100)	FIM07
Immediate Reactions*	Day 0† + 30 minutes	X‡	NC	NC	NC
	Day 0† + 20 minutes	NC	NC	X‡	NC
Solicited Injection Site Reactions	Day 0 + 7 days	X	NC	X	NC
Solicited Systemic Reactions	Day 0 + 7 days	X	NC	X	NC
Non-Serious Unsolicited AEs	Day 0 to Day 28	X	NC	X	NC
SAEs	Day 0 to end of study participant's follow-up	X	X	X	X
AESIs	Day 0 to end of study participant's follow-up	NC	X	NC	X
Additional clinical information	Day 0 - Month 6	X§	NC	NC	NC

* In FIM05 these were unsolicited events reported during the period; In FIM01 these were solicited events reported during the period.

† Day 0 = Immediately after vaccination.

‡ 'X' indicates that the parameter was documented in that particular study.

§ Study participant's Health Care Utilization was reviewed.

NC = Not collected

9.1.1. Pivotal efficacy studies

9.1.1.1. *Study FIM12*

Study FIM reported Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI). All adverse events which occurred from a subject's enrolment to the end of the respective study year in May were reported by investigators to the sponsor using an electronic data record. Investigators also reported Serious Adverse Events which occurred after the study year and were considered likely to be due to vaccination.

Serious adverse events were defined as those which:

- Result in death
- Were life threatening
- Required patient hospitalisation or prolongation of hospitalisation
- Resulted in significant disability/incapacity

- Were a congenital abnormality or birth defect
- Were judged to be an important medical event

The sponsor has noted the distinction between Serious Adverse Events and Severe Adverse Events. The latter implies a scale of severity such as used, for example, in the Common Terminological Criteria for Adverse Events (CTCAE) developed for reporting trials in cancer therapies.

Adverse Events of Special Interest (AESIs) were assessed in Studies FIM12 and FIM07 and included:

- Guillain-Barré syndrome (GBS)
- Bell's palsy
- Encephalitis/myelitis
- Optic neuritis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

9.1.1.2. ***Study FIM05***

Study FIM05 collected unsolicited non-serious and serious adverse events (SAE) as well as protocol-solicited safety endpoints for 28 days after vaccination. Subjects were monitored for 30 minute post-vaccination to assess 'Immediate Reactions' of any kind.

At vaccination subjects were given a 7 day memory aid, digital thermometer and ruler. They were instructed how to measure their temperature and assess the degree of redness/swelling at the injection site and contacted at Day 8 to review this information. This information was used to compare the rate of Solicited Injection Site Reactions and Solicited Systemic Reactions in the Fluzone High-Dose and Fluzone treatment arms. Solicited Injection Site Reactions included Pain, Swelling or Redness, while Solicited Systemic Reactions included Fever, Headache, Malaise and Myalgia. Each symptom was assessed on a scale of 0 (absence) to 3 (severe).

A description of how Solicited Injection Site Reactions and Solicited Systemic Reaction were scored were scored is provided in Table 23 of this report.

Table 23: Scoring scale for solicited injection site reactions in Study FIM05

	Injection Site Pain	Injection Site Erythema	Injection Site Swelling
Term used in the 7-day memory aid	Pain	Redness	Swelling
Definition	See intensity scale	Presence of redness including the approximate point of needle entry	Swelling at or near the injection site. Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling.
Intensity scale[1]	Mild = Easily tolerated Moderate = Sufficiently discomforting to interfere with normal behavior or activities Severe = Incapacitating, unable to perform usual activities	0 = None: absence of symptoms 1 = Mild: < 2.5 cm 2 = Moderate: ≥ 2.5 to < 5 cm 3 = Severe: ≥ 5 cm	0 = None: absence of symptoms 1 = Mild: < 2.5 cm 2 = Moderate: ≥ 2.5 to < 5 cm 3 = Severe: ≥ 5 cm

[1] Grading scale of 0, 1, 2, and 3 (in addition to none, mild, moderate, and severe) was used for FIM01 only. FIM05 used only none, mild, moderate, and severe.

Subjects were asked to record health-care utilisation; hospitalisation, visits to the emergency department or unscheduled physician visits on a card up to 28 days post vaccination as well as unsolicited adverse events. As prevention of health-care utilisation can be considered an efficacy outcome of vaccination, this data has been considered in the analysis of efficacy data for Study FIM05 in this report.

9.1.2. Supportive studies

9.1.2.1. *Study FIM01*

Study FIM01 collected the same protocol defined safety endpoints at day 8 and 28 regarding adverse events as Study FIM05. Study FIM01 did not analyse the time at which adverse events occurred to assess all immediate reactions as was done in Study FIM05. It is also smaller study than Study FIM05 and therefore is considered a supportive study for the safety analysis.

9.1.2.2. *Study FIM07*

Study FIM07 collected the same safety endpoints as Study FIM12 but over a shorter time period due to being interrupted. It is therefore considered supportive study for the safety analysis.

9.2. Patient exposure

The patient exposure in the studies submitted in support of this submission is shown in Table 24 below.

Table 24: Patient exposure in studies submitted in support of this submission

Study title	Fluzone High-Dose	Fluzone	First Visit of First Subject	Last Contact with Last Subject
FIM05	2588	1288	9 October 2006	9 July 2007
FIM12 (Year 1)	7254	7243	6 September 2011	31 May 2013
FIM12 (Year 2)	8738	8748		
FIM01	206	208	11 April 2005	28 November 2005
FIM07	6018	3050	22 September 2009	28 May 2010
NIH-01-597	50 at proposed dose/ 202 at all doses		18 June 2002	April 2003

9.3. Adverse events

9.3.1. All adverse events (irrespective of relationship to study treatment)

9.3.1.1. *Pivotal studies*

Study FIM05

Immediate reactions within 30 minutes of vaccination

Study FIM05 indicated that 0.3% of subjects in both the Fluzone High-Dose and Fluzone treatment arms had one or more immediate adverse events (Table 25). There were no significant differences in the type of reactions reported between treatment arms.

Table 25: Immediate reactions observed in Study FIM05 within 30 minutes of vaccination

	Pooled Fluzone HD (N=2573)			Fluzone (N=1260)		
Study participants with:	**n**	**(%)**	**95% CI**	**n**	**(%)**	**95% CI**
Any immediate reaction	8	0.3	(0.1; 0.6)	4	0.3	(0.1; 0.8)
Gastrointestinal disorders	1	0.0	(0.0; 0.2)	1	0.1	(0.0; 0.4)
Nausea	0	0.0	(0.0; 0.1)	1	0.1	(0.0; 0.4)
Stomach discomfort	1	0.0	(0.0; 0.2)	0	0.0	(0.0; 0.3)
General disorders and administration site conditions	2	0.1	(0.0; 0.3)	1	0.1	(0.0; 0.4)
Chills	2	0.1	(0.0; 0.3)	0	0.0	(0.0; 0.3)
Fatigue	0	0.0	(0.0; 0.1)	1	0.1	(0.0; 0.4)
Nervous system disorders	4	0.2	(0.0; 0.4)	2	0.2	(0.0; 0.6)
Dizziness	3	0.1	(0.0; 0.3)	2	0.2	(0.0; 0.6)
Dysgeusia	1	0.0	(0.0; 0.2)	0	0.0	(0.0; 0.3)
Hypoaesthesia	1	0.0	(0.0; 0.2)	0	0.0	(0.0; 0.3)
Respiratory, thoracic and mediastinal disorders	2	0.1	(0.0; 0.3)	0	0.0	(0.0; 0.3)
Cough	1	0.0	(0.0; 0.2)	0	0.0	(0.0; 0.3)
Pharyngolaryngeal pain	1	0.0	(0.0; 0.2)	0	0.0	(0.0; 0.3)

Note: The denominator (N) for percentages is the number of study participants in the Safety Analysis Set.

Note: Immediate reactions are unsolicited adverse events, and the denominator of percentage is the number of study participants in the Safety Analysis Set.

All adverse events to 28 days

A total of 559 (21.7%) of Fluzone High-Dose and 276 (21.9%) of Fluzone subjects reported unsolicited adverse events up to day 28. There were no significant differences in the rate of adverse event reported in each SOC between the two treatment arms.

9.3.1.2. ***Other studies***

Study FIM12

The Study Report for FIM12 has only analysed SAEs rather than all reported adverse events.

9.3.1.3. ***8.3.1.2.0 supportive studies***

Study FIM01

A total of 84 subjects in the Fluzone High-Dose (40.78%) and 60 in the Fluzone (28.85%) treatment arms reported at least one adverse event regardless of association over the duration of the study. The most notable difference was in the rate of cough and pharyngolaryngeal pain reported between the Fluzone High-Dose and Fluzone treatment arms; 5.3% versus 1.9% in each case.

Study FIM07

The Study Report for FIM07 has only analysed SAEs rather than all reported adverse events.

9.3.2. Treatment-related adverse events (adverse drug reactions)

9.3.2.1. ***Pivotal studies***

Study FIM05

Solicited injection site reactions

The majority of injection-site reactions reported in both the Fluzone High-Dose and Fluzone groups were of mild to moderate intensity (Table 26). Swelling, erythema and pain occurred

approximately 1.4 times more frequently in subjects treated with Fluzone High-Dose than Fluzone.

Severe swelling or erythema was uncommon in both groups but more frequent in Fluzone High-Dose (1.5% and 1.8% respectively) compared to Fluzone (0.6% and 0.6% respectively). Rates of severe pain at the injection site were similar between the two treatment arms.

Table 26: Solicited site reactions observed in subjects receiving Fluzone High-Dose or Fluzone in Study FIM05 within first week after vaccination

		Pooled Fluzone HD (N = 2573)			Fluzone (N = 1260)		
Study participants with:	**Intensity**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Swelling	Any	230/2572	8.9	(7.9; 10.1)	73/1260	5.8	(4.6; 7.2)
	Mild	150/2572	5.8	(5.0; 6.8)	49/1260	3.9	(2.9; 5.1)
	Moderate	41/2572	1.6	(1.1; 2.2)	16/1260	1.3	(0.7; 2.1)
	Severe	39/2572	1.5	(1.1; 2.1)	8/1260	0.6	(0.3; 1.2)
	Missing	1/2573	0.0	(0.0; 0.2)	0/1260	0.0	(0.0; 0.3)
Erythema	Any	384/2572	14.9	(13.6; 16.4)	136/1260	10.8	(9.1; 12.6)
	Mild	290/2572	11.3	(10.1; 12.6)	119/1260	9.4	(7.9; 11.2)
	Moderate	48/2572	1.9	(1.4; 2.5)	10/1260	0.8	(0.4; 1.5)
	Severe	46/2572	1.8	(1.3; 2.4)	7/1260	0.6	(0.2; 1.1)
	Missing	1/2573	0.0	(0.0; 0.2)	0/1260	0.0	(0.0; 0.3)
Pain	Any	915/2572	35.6	(33.7; 37.5)	306/1260	24.3	(21.9; 26.8)
	Mild	810/2572	31.5	(29.7; 33.3)	283/1260	22.5	(20.2; 24.9)
	Moderate	96/2572	3.7	(3.0; 4.5)	21/1260	1.7	(1.0; 2.5)
	Severe	9/2572	0.3	(0.2; 0.7)	2/1260	0.2	(0.0; 0.6)
	Missing	1/2573	0.0	(0.0; 0.2)	0/1260	0.0	(0.0; 0.3)

Note: For solicited reactions, the denominator (M) for percentages is the number of vaccinated study participants with at least one non-missing value for the reaction.

Note: For Missing values, the denominator is the number of vaccinated study participants.

Note: Each study participant is counted once and classified according to their highest intensity score for the solicited reaction

Solicited systemic reactions

The rates of solicited systemic reactions were similar between the two treatment arms, but generally more frequent in the Fluzone High-Dose than Fluzone treatment arms (Table 27). The 95% confidence interval for the relative risk for of these adverse events between the two treatment arms fell within the protocol specified margin on non-inferiority of RR < 3.

Table 27: Solicited Systemic Reactions observed in subjects receiving Fluzone High-Dose or Fluzone in Study FIM05 within first week after vaccination

		Pooled Fluzone HD (N = 2573)			Fluzone (N = 1260)		
Systemic reaction	Intensity	n/M	%	95% CI	n/M	%	95% CI
Fever	Any	93/2569	3.6	(2.9; 4.4)	29/1258	2.3	(1.5; 3.3)
	Mild	64/2569	2.5	(1.9; 3.2)	25/1258	2.0	(1.3; 2.9)
	Moderate	28/2569	1.1	(0.7; 1.6)	3/1258	0.2	(0.0; 0.7)
	Severe	1/2569	0.0	(0.0; 0.2)	1/1258	0.1	(0.0; 0.4)
	Missing	4/2573	0.2	(0.0; 0.4)	2/1260	0.2	(0.0; 0.6)
Headache	Any	431/2572	16.8	(15.3; 18.3)	182/1260	14.4	(12.5; 16.5)
	Mild	324/2572	12.6	(11.3; 13.9)	147/1260	11.7	(9.9; 13.6)
	Moderate	79/2572	3.1	(2.4; 3.8)	31/1260	2.5	(1.7; 3.5)
	Severe	28/2572	1.1	(0.7; 1.6)	4/1260	0.3	(0.1; 0.8)
	Missing	1/2573	0.0	(0.0; 0.2)	0/1260	0.0	(0.0; 0.3)
Malaise	Any	462/2570	18.0	(16.5; 19.5)	176/1259	14.0	(12.1; 16.0)
	Mild	301/2570	11.7	(10.5; 13.0)	123/1259	9.8	(8.2; 11.5)
	Moderate	120/2570	4.7	(3.9; 5.6)	46/1259	3.7	(2.7; 4.8)
	Severe	41/2570	1.6	(1.1; 2.2)	7/1259	0.6	(0.2; 1.1)
	Missing	3/2573	0.1	(0.0; 0.3)	1/1260	0.1	(0.0; 0.4)
Myalgia	Any	550/2572	21.4	(19.8; 23.0)	230/1260	18.3	(16.2; 20.5)

Study FIM12

The Study Report for FIM12 has only analysed SAEs rather than all reported adverse events.

9.3.2.2. *Other studies*

Study FIM01

Slightly higher rates of Fluzone High-Dose than Fluzone subjects reported solicited injection site and solicited systemic reactions. A total of 57% Fluzone High-Dose and 44% of Fluzone subjects reported at least one solicited injection site reaction. A total of 41% of Fluzone High-Dose and 29% of Fluzone subjects reported at least on solicited systemic reaction. These results to not differ from the trends identified in Study FIM05.

Other than the solicited adverse events, no SAE was considered related to study drug.

Study FIM07

The Study Report for FIM07 has only analysed SAEs rather than all reported adverse events.

9.3.3. Deaths and other serious adverse events

9.3.3.1. *Pivotal studies*

Study FIM05

The rate of SAE reported in Study FIM05 to Day 180 of follow-up was similar between the Fluzone High-Dose (6.47%) and Fluzone (7.4%) treatment arms. No trends in specific SAEs reported between the treatment arms were evident.

Other than the protocol solicited adverse events, two SAEs in Study FIM05 were considered by investigators to be due to study treatment with one occurring in each treatment arm.

No deaths were reported during the active phase of the study (to Day 28). There were 23 deaths in follow-up to Day 180; 16 (0.62%) in the Fluzone High-Dose and 7 (0.56%) in the Fluzone treatment arms. These were all considered unrelated to treatment.

Study FIM12

A total of 8.27% of Fluzone High-Dose and 9.02% of Fluzone subjects experienced at least one SAE, a relative risk of 0.92 (95% CI 0.85 to 0.99) (Table 28). The most frequently reported SOC for these SAEs was Cardiac Disorders, reported in 1.61% of Fluzone High-Dose and 1.79% of Fluzone subjects respectively. The most common cardiac disorders were atrial fibrillation, occurring in 0.32% of Fluzone High-Dose and 0.42% of Fluzone subjects, and cardiac failure, occurring in 0.03% of Fluzone High-Dose and 0.03 of Fluzone subjects.

Among the subjects reporting Infections and Infestations the most common causes were bronchitis in 0.09% and 0.06% of Fluzone High-Dose and Fluzone subjects, and pneumonia in 0.39% of Fluzone High-Dose and 0.55% of Fluzone subjects.

Three subjects in the Fluzone High-Dose group experience SAEs which were considered related to treatment.

There were 83 deaths in the Fluzone High-Dose and 84 deaths in the Fluzone treated groups respectively. Of these, 6 deaths occurred in the Fluzone High-Dose group within 30 days of vaccination compared to none in the Fluzone Group. None of these were considered related to treatment, however. Two of the deaths were accidental, and four were related to re-existing medical conditions.

Table 28: Serious Adverse Events reported in Study FIM12 reported by System Organ Class

System Organ Class (SOC)	Fluzone High-Dose (%) (n = 15992)	Fluzone (%) (n = 15991)
Blood and lymphatic system	0.16	0.14
Cardiac disorders	1.61	1.79
Congenital, familial and genetic disorders	0.00	0.01
Ear and labyrinth disorders	0.03	0.08
Endocrine disorders	0.02	0.03
Eye disorders	0.02	0.01
Gastrointestinal disorders	0.64	0.93
General disorders and administration site conditions	0.52	0.50
Hepatobiliary disorders	0.16	0.16
Immune system disorders	0.03	0.01

System Organ Class (SOC)	Fluzone High-Dose (%) (n = 15992)	Fluzone (%) (n = 15991)
Infections and infestations	1.26	1.66
Injury, poisonings and procedural complications	0.66	0.72
Investigations	0.00	0.02
Metabolism and nutrition disorders	0.14	0.21
Musculoskeletal and connective tissue disorders	1.18	0.87
Neoplasms	0.88	0.87
Psychiatric disorders	0.09	0.11
Renal and urinary disorders	0.29	0.29
Reproductive system and breast disorders	0.08	0.06
Skin and subcutaneous tissue disorders	0.04	0.03
Social circumstances	0.01	0.00
Surgery and medical procedures	0.01	0.03
Vascular disorders	0.43	0.42

9.3.3.2. ***Other studies***

Study FIM01

During Study FIM01 there were a total of 23 SAEs, 14 in the Fluzone High-Dose and 9 in the Fluzone treated groups. None of these was considered related to treatment. There was one death from myocardial infarction 169 days post-vaccination which was not considered due to treatment.

Study FIM07

A total of 8.1% of Fluzone High-Dose treated subjects and 7.7% of Fluzone treated subjects suffered SAEs in Study FIM07. Cardiac Disorders and Infections were the most frequently reported SOC, each occurring in 1.1% of Fluzone High-Dose treated subjects. Among these cardiac failure and pneumonia were the most common conditions, occurring in 0.3% and 0.2%

of Fluzone High-Dose subjects respectively. There were 3 SAEs considered related to treatment in the Fluzone High-Dose group.

There were 31 (0.5%) deaths in the Fluzone High-Dose treatment group and 12 (0.4%) deaths in the Fluzone treatment group. None of these were considered related to treatment.

9.3.4. Discontinuation due to adverse events

9.3.4.1. *Pivotal studies*

Study FIM05

Withdrawal from the study due to adverse events occurred in 0.6% of the Fluzone High-Dose treated arm and 0.9% of the Fluzone treated arm in Study FIM05. All of these adverse events were considered unrelated to treatment.

Study FIM12

Withdrawal from the study occurred in 0.62% of Fluzone High-Dose treated and 0.64% of Fluzone treated subjects in Study FIM12 due to SAEs. None of these SAEs were considered related to treatment.

Three subjects in the Fluzone High-Dose and 1 subject in the Fluzone group withdrew from the study due to non-SAE adverse events.

9.3.4.2. *Other studies*

Study FIM01

Other than one subject who died, no other subject discontinued Study FIM01 due to an adverse event.

Study FIM07

A total of 0.6% of Fluzone High-Dose and Fluzone treated subjects withdrew from Study FIM07 due to SAEs. None of these were considered related to treatment. No withdrawals due to non-SAE adverse events occurred in the Fluzone High-Dose group.

9.4. Laboratory tests

No laboratory assessment was performed.

9.5. Adverse events of special interest

9.5.1. Pivotal studies

9.5.1.1. *Study FIM12*

In Study FIM12 there was 1 case of Guillain-Barré syndrome in the Fluzone treatment arm 96 days post vaccination, which was reported as not related to treatment (Table 29). There were 5 cases of Bell's palsy in the Fluzone and 1 case in the Fluzone High-Dose treatment arms respectively, all of which were reported as unrelated to treatment. One case of encephalomyelitis was considered related to study treatment in the Fluzone High-Dose treatment group.

The single case of Stevens-Johnson syndrome in the Fluzone High-Dose arm was reported as unrelated to study treatment as the patient received a sulphamethoxazole/trimethoprim. The subject has a known allergy to sulphur containing medications.

Table 29: Comparative rate of adverse events of special interest (AESI) in Fluzone High-Dose and Fluzone treated subjects in Study FIM12

	Year 1						Year 2						Combined					
	Fluzone High-Dose (N=7254)			Fluzone (N=7243)			Fluzone High-Dose (N=8738)			Fluzone (N=8748)			Fluzone High-Dose (N=15992)			Fluzone (N=15991)		
Subjects experiencing at least one:	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)	n	%	(95% CI)
SAE	680	9.37	(8.71; 10.07)	704	9.72	(9.05; 10.43)	643	7.36	(6.82; 7.93)	738	8.44	(7.86; 9.04)	1323	8.27	(7.85; 8.71)	1442	9.02	(8.58; 9.47)
Death	48	0.66	(0.49; 0.88)	40	0.55	(0.39; 0.75)	35	0.40	(0.28; 0.56)	44	0.50	(0.37; 0.67)	83	0.52	(0.41; 0.64)	84	0.53	(0.42; 0.65)
AE of Special Interest	2	0.03	(0.00; 0.10)	2	0.03	(0.00; 0.10)	1	0.01	(0.00; 0.06)	4	0.05	(0.01; 0.12)	3	0.02	(0.00; 0.05)	6	0.04	(0.01; 0.08)
Guillain-Barré syndrome	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	1	0.01	(0.00; 0.06)	0	0.00	(0.00; 0.02)	1	0.01	(0.00; 0.03)
Bell's palsy	0	0.00	(0.00; 0.05)	2	0.03	(0.00; 0.10)	1	0.01	(0.00; 0.06)	3	0.03	(0.01; 0.10)	1	0.01	(0.00; 0.03)	5	0.03	(0.01; 0.07)
Encephalitis/myelitis	1	0.01	(0.00; 0.08)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.04)	1	0.01	(0.00; 0.03)	0	0.00	(0.00; 0.02)
Optic neuritis	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.02)	0	0.00	(0.00; 0.02)
Stevens-Johnson syndrome	1	0.01	(0.00; 0.08)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.04)	1	0.01	(0.00; 0.03)	0	0.00	(0.00; 0.02)
Toxic epidermal necrolysis	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.02)	0	0.00	(0.00; 0.02)
SAE leading to study discontinuation	52	0.72	(0.54; 0.94)	45	0.62	(0.45; 0.83)	47	0.54	(0.40; 0.71)	58	0.66	(0.50; 0.86)	99	0.62	(0.50; 0.75)	103	0.64	(0.53; 0.78)
Related SAE	1	0.01	(0.00; 0.08)	0	0.00	(0.00; 0.05)	2	0.02	(0.00; 0.08)	0	0.00	(0.00; 0.04)	3	0.02	(0.00; 0.05)	0	0.00	(0.00; 0.02)
Related SAE leading to study discontinuation	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.05)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.04)	0	0.00	(0.00; 0.02)	0	0.00	(0.00; 0.02)

9.5.1.2. *Study FIM07*

In Study FIM07 there were no cases of Guillain-Barré syndrome reported in either treatment arm (Table 30). Five cases of Bell's palsy were reported, 3 in the Fluzone High-Dose and 2 in the Fluzone treated arms. One case was considered related to treatment in the Fluzone treatment arm.

Table 30: Comparative rate of adverse events of special interest (AESI) in Fluzone High-Dose and Fluzone treated subjects in Study FIM07

	Fluzone HD (N=6108)			Fluzone (N=3050)		
Subjects experiencing at least one	n/M	%	(95% CI)	n/M	%	(95% CI)
SAE	493/6108	8.1	(7.4; 8.8)	236/3050	7.7	(6.8; 8.7)
Death	31/6108	0.5	(0.3; 0.7)	12/3050	0.4	(0.2; 0.7)
AE of Special Interest	4/6108	0.1	(0.0; 0.2)	2/3050	0.1	(0.0; 0.2)
Guillain-Barré syndrome	0/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)
Bell's palsy	3/6108	0.0	(0.0; 0.1)	2/3050	0.1	(0.0; 0.2)
Encephalitis/myelitis	1/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)
Optic neuritis	0/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)
Stevens-Johnson syndrome	0/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)
Toxic epidermal necrolysis	0/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)
SAE leading to study discontinuation*	36/6108	0.6	(0.4; 0.8)	17/3050	0.6	(0.3; 0.9)
Related SAE	2/6108	0.0	(0.0; 0.1)	2/3050	0.1	(0.0; 0.2)
Related SAE leading to study discontinuation*	0/6108	0.0	(0.0; 0.1)	0/3050	0.0	(0.0; 0.1)

9.5.2. Other studies

Studies FIM05 and FIM01 did not assess AESIs.

9.6. Post-marketing experience

The sponsor has not provided Post Market Safety Update Reports (PSURs) or post-marketing data. They have noted that between February 2009 and February 2014 a total of 20,702,980 doses of Fluzone High-Dose were distributed in the US. They have referenced the US Product Information (Package Insert) regarding adverse events reported on the basis of this experience. The summary of post-marketing data provided does not reference post-marketing experience from Canada.

9.7. Evaluator's overall conclusions on clinical safety

More injection site and systemic reactions were observed within one week of vaccination in subjected treated with Fluzone High-Dose than in those treated with Fluzone in Study FIM05. The majority of these occurred within 3 days of vaccination and lasted 1 to 3 days without sequelae.

The evaluator notes that equivalence for solicited systemic reactions between Fluzone and Fluzone High-Dose by defining equivalence to be a relative risk of < 3. While this might reflected the limitations of the power of this study, the evaluator does not feel that a relative risk of 3 is equivalent in a clinical sense and notes the higher point estimates for solicited systemic reactions in Fluzone High-Dose compared to Fluzone treated subjects

Study FIM12 provides a very large population exposed to Fluzone High-Dose, including 7,645 over two successive years. There is no indication of an imbalance in the incidence of adverse events reported after 30 days, the majority of which are consistent with the older population enrolled. There was no increase in AESIs observed among Fluzone High-Dose treated patients compared to those who received Fluzone.

The evaluator notes that the sponsor's decision to report only SAEs potentially lowers the sensitivity of Studies FIM12 and FIM07 to detect adverse events which did not result in hospitalisation. While these are likely to include the more medically serious adverse events, a full analysis of all AEs reported in the period immediately following vaccination would be preferable for a vaccine which is intended for use in a large population. This is partially mitigated by the extensive post-marketing experience with Fluzone High-Dose in the United States and influenza vaccination generally but a full analysis of the post-marketing data has not been provided in this submission.

The evaluator notes that sub-analyses of adverse events in immune-compromised subjects were included in the US FDA evaluation of Fluzone High-Dose.[4]

Table 31: Sub-analyses of adverse events in immune-compromised subjects

	Fluzone High-Dose (N=2892) n (%)	Fluzone (N=2835) n (%)
SAE[3]	51 (1.76)	52 (1.83)
Death	1 (0.03)	0 (0)
Adverse Event of Special Interest[2]	0 (0)	0 (0)
SAE leading to study discontinuation	4 (0.14)	0 (0)
Related SAE	1 (0.03)	0 (0)
Related SAE leading to study discontinuation	0 (0)	0 (0)

[1]Chronic Comorbid Immunodeficiency includes subjects with cancer, long-term systemic corticosteroid therapy, HIV/AIDS or potentially immunosuppressive therapy at baseline.
[2]Adverse Events of Special Interest (AESIs) include Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis
[3]SAE = serious adverse event

The evaluator concurs with the FDA evaluator's conclusion that this limited post-hoc analysis does not indicate any particular safety concerns in this group. The supplemental tables on which this analysis was based were not, however, included in this submission.

[4] Evaluation of STN 103914/5726 by Roshan Ramanthan MD MPH, 29 October 2014

10. First round benefit-risk assessment

10.1. First round assessment of benefits

The benefits of Fluzone High-Dose in the proposed usage are:

- Improved protection from influenza than offered by standard adult dose influenza vaccine, for example, Fluzone. The degree of benefit will differ as the match between circulating strains of influenza and the vaccine strains varies from year to year.
- It would be expected that decreased rates of influenza in the > 65 year old age group would produce lower rates of health care utilisation and secondary illness in this population.

10.2. First round assessment of risks

The risks of Fluzone High-Dose in the proposed usage are:

- Increase immune mediated reactions, for example, site injection reactions and systemic reactions in the first week post vaccination compared to standard adult dose influenza vaccine such as Fluzone.
- Post-marketing data may include information regarding adverse events which were not reported in the clinical trials either due to the lower number of patients exposed, or the reporting only of SAEs.

10.3. First round assessment of benefit-risk balance

The benefit-risk balance of Fluzone High-Dose, given the proposed usage, is favourable based on the currently available trial data. However, given the large population of generally well people for which Fluzone is indicated in a preventative role, it is necessary to examine the largest body of safety information available to be certain of the incidence of potentially rare adverse events. This data is comprised of the significant post-marketing exposure to Fluzone High-Dose in the USA and an analysis of post-marketing adverse events reported to the Sponsor should be evaluated before Fluzone High-Dose is registered in Australia.

11. First round recommendation regarding authorisation

The evaluator recommends that Fluzone High-Dose be registered for the proposed indication provided:

1. Amendments to the Australian Product Information are made as in this report [not included here as beyond the scope of this AusPAR].
2. Evaluation of post-marketing safety data as detailed in this report does not provide additional information which would lead to a materially different assessment of the safety of Fluzone High-Dose from that which the evaluator has formed on the basis of clinical trial data evaluated in this report.

12. Clinical questions

12.1. Efficacy

1. The sponsor should submit the full set of supplementary data tables from Study FIM12.

12.2. Safety

1. The sponsor should submit any Postmarket Surveillance Update Reports (PSUR) documents and/or an analysis of the incidence of any adverse events reported in the post market period in subjects treated with Fluzone High-Dose including but not limited to:
    a. Safety analyses available from any trials using Fluzone High-Dose not included in the submission
    b. Regulatory reviews or analyses performed by regulatory agencies regarding Fluzone High-Dose.
2. An analysis of the incidence of AESIs based on the post-marketing exposure for Fluzone High-Dose.

13. Second round evaluation of clinical data submitted in response to questions

13.1. Overview of data provided for second round evaluation

The sponsor has provided data in response to the clinical questions raised in the first round evaluation.

These include:

1. Supplementary data tables for Study FIM12
2. The most recent Global Pharmacovigilance Periodic Benefit-Risk Evaluation Report for September 2015-September 2016 (PBRER).
3. The most recent Data Safety Update Report (DSUR) for April 2016- April2017

The sponsor has noted in its response that the DSUR provides safety analyses from clinical trials, while the PBRER provides data on AESIs and other post-market safety signals. The evaluator notes that these reports contain information from a range of vaccine formulations such as quadrivalent influenza vaccine, of which only data relevant to Fluzone High-Dose are presented in this report.

The first round evaluator requested the supplementary data tables for Study FIM12 to ensure complete data were available for assessment. These 55 supplementary data tables for Study FIM12 provide subpopulation efficacy and safety analyses for example sub-analyses by ethnicity, sex and so on. The evaluator has concluded that these tables do not materially alter the analysis of safety or efficacy in Study FIM12 in the first-round assessment and therefore these data are not discussed further in the second-round evaluation.

The evaluator notes that while the DSUR is more contemporaneous than the PBRER, the latter contains significantly more detailed information on post-marketing surveillance. Overall the evaluator considers that the sponsor has provided adequate additional information about the post-marketing experience of Fluzone in its response to supplement the clinical data assessed in the first round evaluation.

13.2. Global Pharmacovigilance Periodic Benefit-Risk Evaluation Report for September 2015-September 2016 (PBRER)

The PBRER provides a report of safety issues identified by the sponsor as part of ongoing surveillance of marketed vaccines for the year leading up to September 2016. This is based on

a range of data sources including individual case notifications of adverse events, clinical trials or post-marketing safety trials, and regulatory reports. The sponsor has identified a range of safety issues (signals) for ongoing monitoring which include AESIs such as anaphylaxis, Guillain-Barré syndrome etc. These are presented in the PBRER as separate analyses for each signal.

The PBRER notes that during the reporting period no significant actions were taken by the Marketing Authorisation Holder, regulatory authorities, data monitoring committees, or ethics committees in relation to the safety of Fluzone vaccines, including Fluzone High-Dose. The Company Core Data Sheet (CCDS) was not changed during the reporting period reviewed by the PBRER. No new safety information was received between the locking of the data in the PBRER and its finalisation.

The PBRER presents data for all Fluzone preparations but the evaluator has chosen to only present information regarding Fluzone High-Dose as this is the most relevant to this evaluation report. It is noted that the DSUR is slightly more contemporaneous than the PBRER but the evaluator has considered the PBRER to be pivotal as it contains a more complete analysis of safety information.

13.2.1. Estimated population exposure to Fluzone High-Dose

Since 2006-2007 a total of 25,463 patients have received at least one dose of Fluzone High-Dose in all clinical trials, including those not included in the current dossier. The majority of these have been patients > 65 years of age (n = 24,976).

The sponsor has estimated the non-trial post-marketing exposure of people to Fluzone High-Dose from sales to wholesalers and distributers. It is estimated that nearly 60 million doses of Fluzone High-Dose have been distributed since 2010, when Fluzone High-Dose became available in the United States.

As sales data do not capture demographic characteristics of individual vaccine recipients and a more detailed analysis of Fluzone High-Dose distribution cannot be provided.

13.2.2. Safety findings from clinical trials involving Fluzone High-Dose

No new safety related issues were discovered in trials using Fluzone High-Dose during the reporting period.

13.2.2.1. *Interventional studies*

Two MAH sponsored interventional studies (Studies GRC 71 and GRC 57) involving Fluzone High-Dose and with the primary objective of post-authorisation safety monitoring were reported in the PBRER. The protocols of these studies are summarised in Table 32.

Table 32: Status of sponsor initiated studies reported in PBRER

Study ID	Phase	Country	Study Title	Study Design	Dosing regimen	Study Population	FPFV*	Planned enrollment	Subject exposure;
GRC57	IV	United States	Safety and Immunogenicity Among Adults of Fluzone Quadrivalent, Fluzone Intradermal Quadrivalent, and Fluzone High-Dose, Influenza Vaccines, 2015–2016 Formulations	Multi-center, randomized, open-label	Fluzone Quadrivalent Influenza vaccine, No Preservative (0.5-mL dose), 2015–2016 formulation: each dose contains 15 µg HA of each antigen Fluzone Intradermal Quadrivalent Influenza vaccine, (0.1-mL dose), 2015–2016 formulation: each dose contains 9 µg HA of each antigen Fluzone High-Dose Influenza vaccine (0.5 mL-dose), 2015–2016 formulation: each dose contains 60 µg HA of each antigen	Adults 18 to < 65 years of age and ≥ 65 years of age	28 Sep 2015	Planned Total: 208 Group 1: (Adults 18 to < 65 years, 0.5 mL dose of Fluzone Quadrivalent Influenza vaccine): 52 Group 2: (Adults 18 to < 65 years, 0.1 mL dose of Fluzone Intradermal Quadrivalent Influenza vaccine): 52 Group 3: (Adults ≥ 65 years, 0.5 mL dose of Fluzone Quadrivalent Influenza vaccine): 52 Group 4: (Adults ≥ 65 years, 0.5 mL dose of Fluzone High-Dose Influenza vaccine): 52	Total: 208 Group 1: (Adults 18 to < 65 years, 0.5 mL dose of Fluzone Quadrivalent Influenza vaccine): 53 Group 2: (Adults 18 to < 65 years, 0.1 mL dose of Fluzone Intradermal Quadrivalent Influenza vaccine): 51 Group 3: (Adults ≥ 65 years, 0.5 mL dose of Fluzone Quadrivalent Influenza vaccine): 53 Group 4: (Adults ≥ 65 years, 0.5 mL dose of Fluzone High-Dose Influenza vaccine): 51

Study ID	Phase	Country	Study Title	Study Design	Dosing regimen	Study Population	FPFV*	Planned enrollment†	Subject exposure‡
GRC71	IV	United States	Safety and Immunogenicity of Fluzone Quadrivalent and Fluzone High-Dose, Influenza Vaccines, 2016–2017 Formulations	Multicenter, open-label trial	Fluzone Quadrivalent Influenza vaccine, No Preservative (0.5-mL dose), 2016–2017 formulation: each dose contains 15 µg HA of each antigen (children 3 years to < 9 years and adults 18 to < 65 years of age) Children: 1 or 2 doses of (Fluzone Quadrivalent Influenza vaccine) 4 weeks apart) per ACIP guidance for the 2016-2017 influenza season Fluzone High-Dose Influenza vaccine (0.5 mL-dose), 2016–2017 formulation: each dose contains 60 µg HA of each antigen (adults ≥ 65 years of age)	Children 3 years to < 9 years of age Adults 18 to < 65 years of age and ≥ 65 years of age	15 Sep 2016	Planned total: 180 Children 3 years to < 9 years of age: 60 Adults 18 to < 65 years of age: 60 Adults ≥ 65 years of age: 60	Total: 29 Children 3 years to < 9 years of age: 4 Adults 18 to < 65 years of age: 24 Adults ≥ 65 years of age: 1

One patient in Study GRC 57 suffered three adverse events (atrial fibrillation, cardiac failure and transient ischemic attack) that were considered unrelated to vaccine. There were no adverse events leading to discontinuation or deaths during the study. Study GRC 71 is ongoing but thus far has reported no SAEs, deaths or adverse events leading to discontinuation.

13.2.2.2. *Non-interventional studies*

Three non-interventional studies were reported in the PBRER but these did not include Fluzone High-Dose treatment.

13.2.2.3. *Investigator initiated studies*

The PBRER noted 13 investigator-initiated trials of which the sponsor was aware, 11 of which were ongoing, 1 of which was completed and 1 cancelled. No safety issues referencing these studies were reported to the sponsor during the PBRER reporting period. Six of the studies

appear from their titles to involve Fluzone High-Dose, and as protocols were not reported all have been included for completeness.

13.2.3. Literature reports of safety issues

During the reporting period 2 original studies were published which included analysis of the safety of Fluzone High-Dose. These reports did not identify any new safety issues related to Fluzone High-Dose.

13.2.4. Cumulative SAEs from post-marketing data

The cumulative incidence of SAEs reported between 1993 and September 2016 was line listed in the PBRER. This provides a long-term baseline of adverse events beyond the reporting period of the PBRER submitted. These data include both medically confirmed reports from health care providers, reports in the scientific literature and reports from consumers.

While rates of adverse events cannot be calculated from these data, the general trends in case and reaction numbers are consistent with those observed in Study FIM12 and do not suggest a different pattern of adverse events in the post-marketing environment from those in the pivotal trial.

Table 33: Summary of cumulative incidence of serious cases and serious reactions by System Organ Class over the marketing history of Fluzone High-Dose

System Organ Class (SOC)	Cumulative Number of cases (SAEs)	Cumulative Number of reactions (SAEs)
Blood and lymphatic system	3	6
Cardiac disorders	14	19
Ear and labyrinth disorders	6	7
Eye disorders	12	16
Gastrointestinal disorders	33	49
General disorders and administration site conditions	77	120
Hepatobiliary disorders	19	19
Immune system disorders	19	19
Infections and infestations	52	59
Injury, poisonings and procedural complications	19	25
Investigations	18	19
Metabolism and nutrition disorders	8	9
Musculoskeletal and connective tissue disorders	39	77

System Organ Class (SOC)	Cumulative Number of cases (SAEs)	Cumulative Number of reactions (SAEs)
Neoplasms	4	5
Nervous system disorders	57	92
Psychiatric disorders	11	14
Renal and urinary disorders	6	7
Reproductive system and breast disorders	0	0
Pregnancy, puerperium and perinatal conditions	0	0
Respiratory, thoracic and mediastinal disorders	58	75
Skin and subcutaneous tissue disorders	26	36
Social circumstances	5	5
Surgery and medical procedures	1	1
Vascular disorders	0.43	

13.2.5. Deaths

Three deaths after Fluzone High-Dose administration were assessed during the reporting period of the PBRER. In two of these cases there was insufficient documentation to assess relationship to the vaccine. The third death was a 75 year old patient with a myelodysplastic disorder who died 34 days after co-administration of Fluzone High-Dose and a pneumococcal vaccine. The sponsor has not reported a level of association between with vaccination and this case.

13.2.6. Safety signals under assessment

The status of a number of known safety risks, or 'signals' under ongoing surveillance by the sponsor was reported. No new safety signals were added during the reporting period of the PBRER. The evaluator notes that these safety signals include several of the adverse events of special interest (AESIs) examined in Study FIM12.

Risk 1: Anaphylaxis/hypersensitivity

A total of 10 cases of anaphylactic reaction were reported during the review period of the PBRER, 8 of which were serious. In six cases (4 serious, 2 non-serious) the adverse event was considered related to vaccination.

The sponsor has estimated the rate of anaphylaxis in Fluzone High-Dose as 0.158/100,000 doses distributed.

The sponsor has noted that the potential for anaphylaxis was already noted in Product Information, and that these cases (and those reported for other formulations of Fluzone) indicate no new safety concerns.

Risk 2: Syncope

No cases were reported for Fluzone High-Dose. Syncope is a known adverse event and the sponsor has noted that cases in other formulations of Fluzone did not reveal any new safety concerns.

Risk 3: Guillain-Barré Syndrome (GBS)

Two cases of GBS occurred during the review period of the PBRER. In one case latency after vaccination was not recorded and relationship to the vaccine has not been reported. In the second case the diagnosis of GBS was not confirmed and there was insufficient documentation to assess relationship to vaccination.

The sponsor has estimated the incidence of GBS as 0.0226/100,000 doses of Fluzone High-Dose distributed.

GBS is listed as a potential adverse event for all Fluzone formulations. The sponsor has noted that these cases (and those in other formulations of Fluzone) raised no new safety concerns with respect to the frequency or severity of GBS observed.

Risk 4: Neuritis

No new cases of neuritis were reported with Fluzone High-Dose administration during the reporting period of the PBRER.

The sponsor has estimated the rate of neuritis as 0.0226/100,000 doses of Fluzone High-Dose distributed.

The sponsor has noted that no new safety concerns regarding the frequency or severity of neuritis were raised with regard to adverse events occurring in all other Fluzone preparations.

Risk 5: Convulsion

Two cases of convulsion were reported following vaccination with Fluzone High-Dose. In one case the cause was considered to be concomitant gastroenteritis and dehydration. In a second case an alternative aetiology of Guillain-Barre syndrome was considered a possible alternative aetiology.

The sponsor has estimated the incidence of convulsion as 0.0113/100,000 doses of Fluzone High-Dose distributed.

Convulsions are already listed in the company core data sheet, and the sponsor noted that these cases (and those reported in other formulations of Fluzone) revealed no new safety concerns with respect to the severity or frequency of convulsions.

Risk 6: Encephalomyelitis and transverse myelitis

One new case of encephalomyelitis was reported during the review period of the PBRER. Latency after vaccination was not reported with the case and so relationship to vaccination has not been assigned. Encephalomyelitis is listed as a known adverse event and the sponsor has noted that review of this case (and those in other Fluzone formulations) indicated no new safety concerns with respect to its frequency or severity.

Risk 7: Thrombocytopenia

One new case of thrombocytopenia was recorded in a patient taking Fluzone High-Dose. An elderly patient received vaccine concomitantly with pneumococcal vaccination and was diagnosed 3 months later with thrombocytopenia. The patient had metastatic disease and bleeding and given this past medical history, a relationship between vaccination and thrombocytopenia was considered unlikely by the sponsor.

The sponsor has not estimated the incidence of thrombocytopenia for Fluzone High-Dose in the PBRER.

Thrombocytopenia is listed as a potential adverse event of Fluzone High-Dose vaccination. The sponsor has noted that this case (and those reported in other Fluzone formulations) indicates no new safety concerns with respect to its frequency or severity.

Risk 8: Vasculitis

Two cases of vasculitis were reported in association with Fluzone High-Dose vaccination. In the first case the onset 2 days after vaccination was considered to indicate a possible role for the vaccine, but no information on alternative causes was available. In the second case there was insufficient information to assess an association with vaccination.

The sponsor has not estimated the incidence of vasculitis for Fluzone High-Dose in the PBRER.

Vasculitis is listed as a potential adverse event of Fluzone High-Dose. The sponsor has noted that these cases (and those reported for other formulations of Fluzone) do not indicate any new safety concerns with respect to the severity or frequency of vasculitis associated with vaccination.

Risk 9: Nausea, vomiting and diarrhoea (NVD)

This adverse event was being monitored for Fluzone High-Dose only.

A total of 15 new cases of NVD were reported during the review period of the PBRER. In all of these cases the sponsor has noted that either insufficient information was available to establish an association between the patient's symptoms and vaccination, or alternative causes to vaccination could not be excluded.

The sponsor has estimated the incidence of gastrointestinal disorders (nausea, vomiting and diarrhoea) to be 0.218/100,000 doses of Fluzone High-Dose distributed.

Gastrointestinal disorders (nausea, vomiting and diarrhoea) are listed in the adverse events section of the current core data sheet for Fluzone High-Dose.

13.3. Development Safety Update Report (DSUR)

The DSUR reports on the period between April 2016 and April 2017, and therefore overlaps the scope and reporting period of the PBRER significantly. The DSUR summarises safety data for three presentations, including Fluzone High-Dose.

The DSUR notes that no actions were taken in relation to the safety of Fluzone High-Dose during the reporting period, nor were any changes made to the core data sheets or US prescribing information.

13.3.1. Estimated population exposure to Fluzone High-Dose

The DSUR reports the cumulative exposure of patients in trials to Fluzone High-Dose as 25,504.

The sponsor has estimated that cumulative post-market exposure to Fluzone High-Dose to be 69,220,066 doses based on wholesale distribution information.

13.3.2. Safety findings from clinical trials involving Fluzone High-Dose

The DSUR has reported on safety data in ongoing clinical trials, all of which except one have been reviewed in the PBRER. This investigator initiated trial GRC00096 reported no new safety information. No new safety information was identified in the sponsor-initiated Trials GRC57 and GRC71, which were also reviewed in the PBRER.

No deaths associated with Fluzone High-Dose or other formulations were reported in clinical trials during the reporting period of the DSUR.

13.3.3. Literature reports of safety issues

The DSUR identified 6 publications. These have not identified significant new safety issues.

13.3.4. Cumulative SAES and non-serious AEs from post-marketing data

Line listings of SAEs reported to the sponsor since 1993 was reported. The evaluator has not re-extracted the data for organ classes presented as Table 33 in the evaluation of the PBRER.

However, the System Organ Class totals of SAEs are similar to those in the PBRER and do not indicate to the evaluator any additional safety issues.

13.3.5. Deaths

Deaths in post-marketing experience were not reported in the DSUR.

14.3.6 Post-marketing experience

The DSUR provides a list of adverse events included in the USPI for Fluzone High-Dose. These are not new safety signals from the reporting period of the DSUR. The important safety risks such as hypersensitivity, GBS and so on are noted but no additional information to that in the PBRER has been provided.

14. Second round benefit-risk assessment

14.1. Second round assessment of benefits

A noted in the first round evaluation, the benefits of Fluzone High-Dose in the proposed usage is protection from influenza that is greater than that offered by standard adult dose trivalent influenza vaccine (such as Fluzone). The extent of benefit will fluctuate as the match between circulating strains of influenza and the included vaccine strains varies from year to year.

14.2. Second round assessment of risks

The risks of Fluzone High-Dose in the proposed usage as previously noted are:

- Increased immune-mediated reactions such as higher rates of injection site and systemic reactions in the first week post vaccination compared with the standard adult dose influenza vaccine (for example Fluzone).

14.3. Second round assessment of benefit-risk balance

The evaluator notes that a quadrivalent inactivated influenza vaccine (Afluria Quad) is now included in the Australian National Immunisation Program (NIP) for adults aged 18 years and over (although it is not the recommended product for those aged 65 and over). As Fluzone has not been compared to any quadrivalent IIV in clinical studies, the benefits of Fluzone High-Dose against the three included strains have to balance against the lack of coverage of one of the B strain lineages.

Overall, however, the evaluator considers that benefit-risk balance of Fluzone High-Dose for the proposed indication is favourable.

15. Second round recommendation regarding authorisation

In the view of the evaluator that the benefit-risk balance of Fluzone High-Dose for the proposed indication remains favourable and recommends that it be registered for the proposed indication.

16. References

Nil.

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