Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Flucelvax Quad

Active ingredient: Influenza virus haemagglutinin

Sponsor: Seqirus Pty Ltd

November 2023

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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 the Australian public outweigh any risks associated with the use of therapeutic goods.
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- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
CI	Confidence interval
CMI	Consumer Medicines Information
Day 29 or 57	Day 29 data for previously vaccinated subjects and Day 57 data for subjects who have not been previously vaccinated with influenza vaccine
GMR	Geometric mean ratio
GMT	Geometric mean titre
HA	Haemagglutinin
HAI	Haemagglutination inhibition
MN	Microneutralisation
NIP	National Immunisation Program
PI	Product Information
PSUR	Periodic safety update report
QIV	Quadrivalent influenza vaccine
QIVc	Cell-based quadrivalent subunit influenza virus vaccine; Flucelvax Quad
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
TGA	Therapeutic Goods Administration
WHO	World Health Organization

Product submission

Submission details

Type of submission:	Extension of indication
Product name:	Flucelvax Quad
Active ingredient:	Influenza virus haemagglutinin
Decision:	Approved
Date of decision:	28 July 2023
Date of entry into ARTG:	31 July 2023
ARTG numbers:	319093 and 341450
▼Black Triangle Scheme	No
Sponsor's name and address:	Seqirus Pty Ltd 63 Poplar Road Parkville VIC 3052
Dose form:	Suspension for injection
Strength:	Each 0.5 mL dose contains a total of 60 µg influenza virus surface antigens (haemagglutinin and neuraminidase), comprised of 15 µg haemagglutinin for each of four strains as recommended by the Australian Influenza Vaccine Committee for the Southern Hemisphere Influenza season.
Containers:	Pre-filled syringe (needle free) and pre-filled syringe (with attached needle)
Pack sizes:	1 and 10 syringes
Approved therapeutic use for the current submission:	*For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 6 months of age and older.* *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*
Route of administration:	Intramuscular
Dosage:	Children from 6 months to less than 9 years of age should receive one or two 0.5 mL doses. Children less than 9 years of age who have not been previously vaccinated against influenza should receive a second dose. The 2 doses should be administered at least 4 weeks apart. Adults and children from 9 years of age should receive a single 0.5 mL dose. For further information regarding dosage, refer to the Product Information.

Pregnancy category:	A Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Seqirus Pty Ltd (the sponsor) to register Flucelvax Quad, a quadrivalent influenza vaccine (surface antigen, inactivated, prepared in cell cultures) suspension for injection in pre-filled syringes containing 60 µg influenza virus haemagglutinin as active ingredient for the following proposed extension of indication:[1]

> *For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 6 months of age and older.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*

Influenza, commonly known as 'the flu', is a highly infectious disease caused by the influenza virus, an orthomyxovirus. There are 4 types of influenza viruses: A, B, C, and D. Types A and B are responsible for most influenza infection in humans.[2] Influenza A viruses are divided into subtypes based on the surface glycoprotein antigens haemagglutinin (HA) and neuraminidase. Influenza B viruses are separated into 2 distinct genetic lineages: Yamagata and Victoria. Influenza type A viruses have been isolated from several non-human species, including birds, horses, and swine, whereas influenza type B viruses almost exclusively affect humans. The influenza A or B surface HA glycoprotein is the key antigen involved in attachment of the virus to receptors on respiratory epithelial cells, whereas the neuraminidase glycoprotein is involved in release of the virus from the cell surface.

Novel influenza strains arise from antigenic drift due to random accumulation of mutations, particularly in the HA gene.[3] These events result in emergence of new strains of the influenza virus capable of causing epidemics, as pre-existing antibodies resulting from previous virus exposure or vaccination are generally not cross-protective. For this reason, the World Health Organization (WHO) holds a strain consultation meeting annually to decide on influenza vaccine composition for the Southern Hemisphere. In Australia, the recommendation from WHO is further reviewed by the Australian Influenza Vaccine Committee (AIVC) to advise the TGA on the composition of the seasonal influenza vaccine.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.
[2] World Health Organization (WHO), Influenza (seasonal), last updated 12 January 2023. Available at https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal).
[3] World Health Organization (WHO) Regional office for Europe, How pandemic influenza emerges, last updated 4 March 2014. Available at How pandemic influenza emerges (who.int).

The public health impact of influenza is significant. In the reporting period for year 2022, of the 225,332 notifications of laboratory-confirmed influenza, 308 influenza-associated deaths (0.14%) across all age groups were notified to the National Notifiable Disease Surveillance System (NNDSS).[4] The median age of deaths notified to NNDSS was 82 years, with ages ranging from 1 year to 106 years of age. These data may underestimate the real impact of influenza on deaths in Australia, as people who died may not have been tested for influenza.

Current therapeutic options

Clinical management of influenza is based mostly on symptomatic treatment. There are registered antiviral medications such as the neuraminidase inhibitor oseltamivir,[5] which may reduce disease severity and duration. However, such therapy needs to commence within 48 hours from onset of symptoms and may induce drug-resistance. Corticosteroids are not routinely used, unless indicated for other respiratory conditions such as asthma.

Injected inactivated influenza vaccines are commonly used throughout the world for the prevention of influenza; however, these vaccines are susceptible to antigenic drift of the viral HA and NA. For this reason, vaccines against seasonal influenza may need to be updated annually.

The National Immunisation Program (NIP) provides free influenza vaccination for a range of groups including children from 6 months to less than 5 years of age, individuals who suffer specific medical risk conditions, and Aboriginal and Torres Strait Islander people from 6 months of age.[6] Further information on immunisation in Australia is available in the Australian Immunisation Handbook and online at influenza (flu) vaccine from the Department of Health and Aged Care.

The influenza vaccines supplied under the NIP in 2023 for individuals aged 6 month to 2 year are quadrivalent vaccines:[7] VaxiGrip Tetra (for individuals aged 6 months up to 64 years) [8] and Fluarix Tetra (for individuals aged from 6 months up to 64 years).[9] Additional vaccines available outside the NIP in 2023 for the 6 month to 2 year age group are FluQuadri (for individuals 6 months and older)[10] and Influvac Tetra (for individuals 6 months and older).[11]

Flucelvax Quad (also referred to as QIVc) is a quadrivalent, surface antigen, inactivated, influenza vaccine, prepared in Madin-Darby canine kidney (MDCK) cell cultures (that is, cell-based). The potential advantages and disadvantages of cell-based vaccines over egg-based vaccines have been discussed in earlier AusPARs for Flucelvax Quad.[12]

The 2023 version of Flucelvax Quad aligns with the AIVC recommendation for the composition of influenza vaccines for Australia for 2023,[13] and introduces one new strain when compared to the composition of the vaccine for Australia in 2022. The 2023 formulation of Flucelvax Quad is:

- an A/Sydney/5/2021 (H1N1) pdm09-like virus – new strain for 2023

[4] Australian Influenza Surveillance Report – 2022 national influenza season summary (health.gov.au).

[5] Oseltamivir oral suspension was first registered in the ARTG on 11 May 2012 (ARTG number 188016). The indication includes use for the treatment of infections due to influenza A and B viruses in adults and children including full-term neonates.

[6] National Immunisation Program Schedule | Australian Government Department of Health and Aged Care.

[7] ATAGI advice on seasonal influenza vaccines in 2023 (health.gov.au).

[8] Vaxigrip Tetra was first registered in the ARTG on 20 May 2019 (ARTG number 299922).

[9] Fluarix Tetra was first registered in the ARTG on 28 August 2013 (ARTG number: 200674).

[10] FluQuadri was first registered in the ARTG on 2 December 2014 (ARTG number 213963).

[11] Influvac Tetra was first registered in the ARTG on 2 November 2017 (ARTG number 281035).

[12] AusPAR for Flucelvax Quad as a new biological entity for immunisation of persons 9 years and older, published December 2020. Available at AusPAR: Influenza virus haemagglutinin | Therapeutic Goods Administration (TGA).

[13] AIVC Recommendations for the Composition of Influenza Vaccines for Australia in 2023 | Therapeutic Goods Administration (TGA).

- an A/Darwin/6/2021 (H3N2)-like virus
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Regulatory status

Flucelvax Quad received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 1 September 2020 for the following indication:

> *For the prevention of influenza caused by influenza virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 9 years of age and older.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*[12]

On 11 November 2021 the registration was extended to the following indication:

> *For the prevention of influenza caused by influenza virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 2 years of age and older.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*[14]

At the time the TGA considered this submission, a similar submission had been approved in the United States of America (USA) on 14 October 2021, Argentina on 12 November 2021, Canada on 8 March 2022, and in Taiwan on 24 June 2022. A similar submission was under consideration in New Zealand (submitted on 27 June 2022).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	14 December 2020	Approved on 14 October 2021	*Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for use in persons 6 months years of age and older.*
Argentina	10 June 2021	Approved on 12 November 2021	*Active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for persons 6 months of age and older.*

[14] AusPAR for Flucelvax Quad extending use to persons 2 years and older, published November 2022. Available at Australian public assessment report for Flucelvax Quad (tga.gov.au).

Region	Submission date	Status	Approved indications
Canada	26 March 2021	Approved on 8 March 2022	*Active immunization of adults and children aged 6 months or older for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.*
Taiwan	29 December 2021	Approved on 24 June 2022	*Active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in children above 6 months of age and adults.*
New Zealand	27 June 2022	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

This submission was evaluated under the standard prescription medicines registration process.

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2022-01977-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2022
First round evaluation completed	6 December 2022
Sponsor provides responses on questions raised in first round evaluation	16 January 2023
Second round evaluation completed	17 March 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice[15]	9 May 2023
Sponsor's pre-Advisory Committee response	19 May 2023

[15] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who approved the product under section 25 of the Act.

Description	Date
Advisory Committee meeting	7 June 2023
Registration decision (Outcome)	28 July 2023
Administrative activities and registration in the ARTG completed	31 July 2023
Number of working days from submission dossier acceptance to registration decision*	218

*Statutory timeframe for standard submissions is 255 working days

Submission overview and benefit-risk assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Influenza Vaccines - Non-clinical and Clinical Module, EMA/CHMP/VWP/457259/2014
- European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Evaluation of New Vaccines, EMEA/CHMP/VWP/164653/2005.

Quality

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration. [12]

Nonclinical

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- one Phase III study, V130_10, to evaluate safety and immunogenicity of Flucelvax Quad and a United States-licensed quadrivalent influenza virus vaccine (QIV) in healthy subjects aged 6 months through 47 months

- one Phase IV study V130_11OB, a prospective observational safety study of pregnancy outcomes in women immunised with seasonal Flucelvax Quad during pregnancy.[16]

Pharmacology

No clinical pharmacokinetics study was performed for the development of Flucelvax Quad. This is acceptable to the Delegate given that the pharmacokinetic properties would not provide useful information for establishing adequate dosing recommendations.[17] There is no dose adjustment proposed for the target paediatric population.

Immunogenicity

Study V130_10

Description

A Phase III, randomised, observer-blind, multicentre, noninferiority study to evaluate safety and immunogenicity of Flucelvax Quad (also referred to as QIVc) and a United States-licensed quadrivalent influenza virus vaccine (QIV; Afluria Quadrivalent) in healthy subjects aged 6 months through 47 months.[18]

Objectives

Primary objectives

Immunogenicity: To demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a QIV containing the recommended strains for the season, in subjects 6 to 47 months of age, as measured by haemagglutination inhibition (HAI) assay for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains and by microneutralisation (MN) assay for influenza A/H3N2 strain, using cell-derived target viruses.

Secondary objectives

Immunogenicity: To describe the immunogenicity of:

1. QIVc and QIV by HAI assay for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, and by MN assay for influenza A/H3N2 strain, using egg-derived target viruses
2. QIVc and QIV by HAI assay for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, and by MN assay for influenza A/H3N2 strain, using cell-derived target viruses
3. QIVc and QIV by MN assay for influenza A/H1N1, influenza B/Yamagata and influenza B/Victoria strains, in a subset.

Exploratory objectives

1. To evaluate the homologous cell-mediated immunity response, prior to and following vaccination, in a small population of subjects

[16] This study was designed to include cell-based trivalent and cell-based quadrivalent vaccines. The trivalent vaccine was no longer available on the US market at the time of active enrolment to the study.

[17] European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Evaluation of New Vaccines, EMEA/CHMP/VWP/164653/2005.

[18] Essink BJ, Heeringa M, Jeanfreau RJ, et al. Safety and Immunogenicity of Cell-Based Quadrivalent Influenza Vaccine: A Randomized Trial. *Pediatrics* 2022; 150(5):e2022057509. doi: 10.1542/peds.2022-057509.

2. To further describe the immune response to vaccination, additional immunogenicity analyses may be conducted such as HAI assay for influenza A/H3N2 using cell- and egg-derived target viruses.

End points

Analyses were performed on data for Day 29 for previously vaccinated subjects and Day 57 for subjects who have not been previously vaccinated with influenza vaccine.

Co-primary immunogenicity endpoints

- Serum HAI antibody titre against influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria vaccine strains at Day 29 or 57, using cell-derived target viruses: Geometric mean titre (GMT) by HAI assay; Seroconversion rate (SCR), the percentage of subjects with either a pre-vaccination HAI titre less than 1:10 and a post-vaccination HAI titre of 1:40 or higher, or a pre-vaccination HAI titre at least 1:10 and an at least 4-fold increase in post-vaccination HAI titre.
- Serum neutralising antibody titre against influenza A/H3N2 vaccine strain at Day 29 or 57, using cell-derived target viruses: GMT by MN assay; SCR, the percentage of subjects with either a pre-vaccination MN titre less than 1:10 and a post-vaccination MN titre of 1:40 or higher, or a pre vaccination MN titre at least 1:10 and an at least 4-fold increase in post-vaccination MN titre.
- Derived variables: The GMT ratio (QIV/QIVc) for each strain; the inter-group difference in the SCRs (QIV minus QIVc) for each strain.

Secondary immunogenicity endpoints

- Humoral immune response in terms of HAI antibodies against influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, using cell-derived and egg-derived target viruses
- Neutralizing antibody titres against influenza A/H3N2, using cell-derived and egg-derived target viruses
- Derived variables: The GMT ratio (QIV/QIVc) for each strain; the inter-group difference in the SCRs (QIV minus QIVc) for each strain.

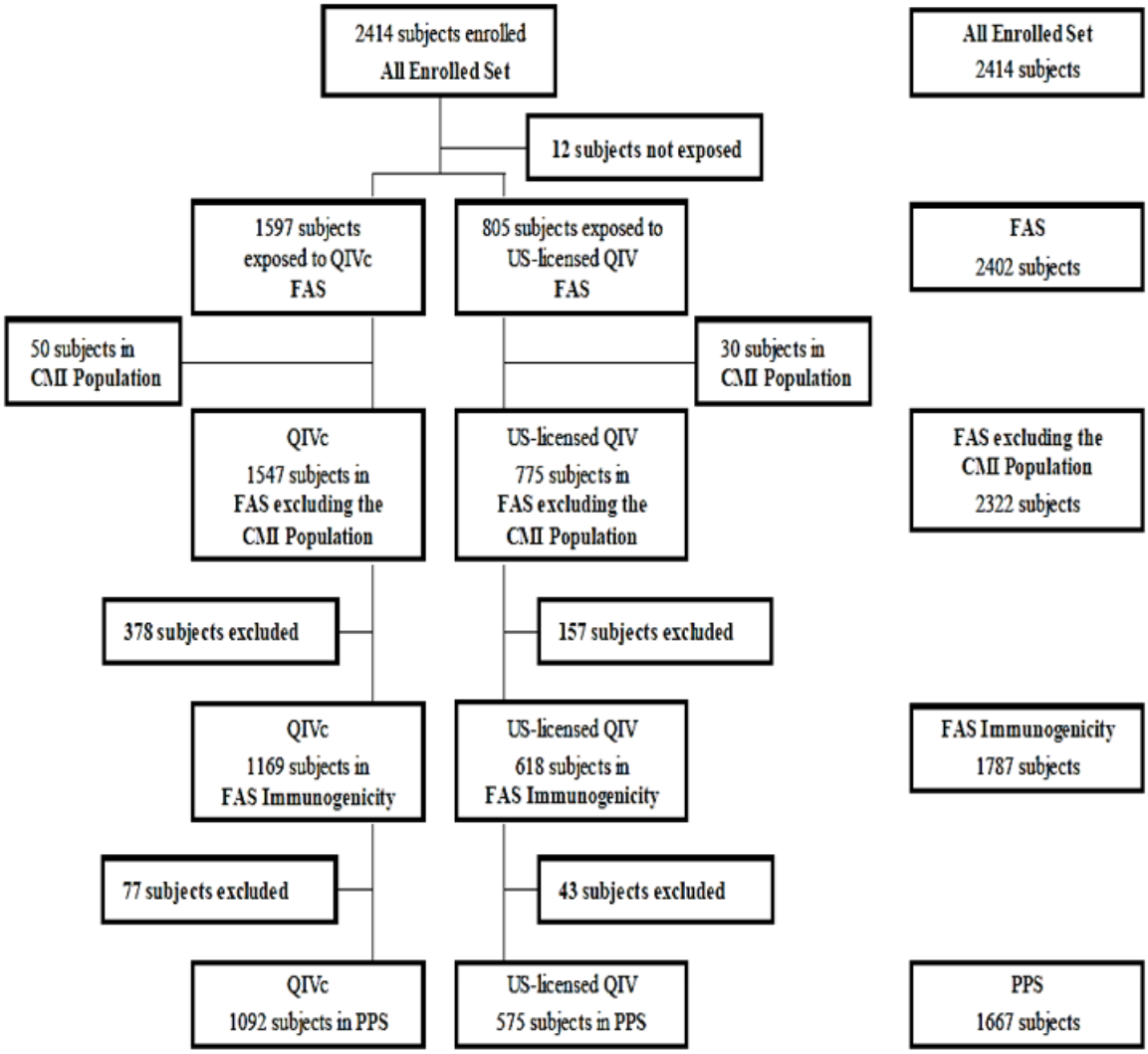
Exploratory immunogenicity endpoints

- Cell-mediated immunity response to vaccination: Measurement of antigen-stimulated CD4+ T-cell and CD8+ T-cell responses via expression of cytokines
- Humoral immune response in terms of HAI antibodies against influenza A/H3N2, using cell- and egg-derived target viruses: GMT by HAI assay at Days 1 and Day 29 or 57; GMR, defined as the fold increase in serum HAI GMT post-vaccination (Day 29 or 57) compared to pre-vaccination (Day 1)
- Seropositivity rates (percentages of subjects with HAI titre at least 1:10 at Days 1 and Day 29 or 57
- Percentages of subjects with HAI titre at least 1:40 at Days 1 and Day 29 or 57; seroconversion rate by HAI assay.
- Derived variables: GMT ratio (QIV/QIVc) for each strain; The inter-group difference in the seroconversion rates (QIV minus QIVc) for each strain.

Participant flow

Of 2,414 subjects aged 6 to 47 months who were randomised, 2080 (86.2%) completed the study and 334 (13.8%) discontinued from the study. At least 1 study vaccination was administered to 2402 subjects (1597 QIVc; 805 QIV). Of these 2402 subjects, 2322 subjects were enrolled for evaluation of immunogenicity (Immunogenicity Group) and 80 enrolled for exploratory evaluation of CMI response. Participant disposition is shown in Figure 1.

Figure 1: Study V130_10 Study disposition flowchart



Abbreviations: CMI = cell-mediated immunity; FAS = full analysis set; PPS = per protocol set; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; US = United States

Major protocol violations and deviations

Overall, 439 of 1,605 subjects (27.4%) in the QIVc group and 204 of 809 subjects (25.2%) in the QIV group had a major protocol deviation. The most common major protocol deviation in both vaccine groups was a serology sample not being taken, reported by 276 subjects (17.2%) in the QIVc group and 117 subjects (14.5%) in the QIV group.

Baseline data

The mean age was 28.1 months (standard deviation 11.57 months; range 6 to 47 months). Overall, 37.2% of subjects (894 of 2,402 subjects) were aged 6 to 23 months and 62.8% of subjects (1,508 of 2,402 subjects) were aged 24 to 47 months. The study population was balanced with respect to sex (1,209 of 2,402 (50.3%) subjects were males; 1,193 of 2,402 (49.7%) subjects were female). Most subjects were White (1,578 of 2,402 subjects (65.7%)) or

Black or African American (664 of 2,402 subjects(27.6%)), and predominantly 'Not Hispanic or Latino' origin (1,735 of 2,402 subjects (72.2%)). The study population consisted of 51.6% of subjects who had had influenza vaccine previously and 48.4% of subjects who had not received a previous influenza vaccine. Demographic characteristics were generally balanced between the groups. The Delegate noted that the study population was not representative of typical Australian demographic characteristics.

Results

Primary efficacy outcome

The primary immunogenicity objective was met. For all 4 strains, the upper bound of the 2-sided 95% confidence interval (CI) did not exceed the pre-specified non-inferiority margin of 1.5 for the Day 29 or 57 GMT ratio (influenza A/H1N1: 0.836; influenza A/H3N2: 1.160; influenza B/Yamagata: 0.809; influenza B/Victoria: 0.972) or the pre-specified non-inferiority margin of 10% for the seroconversion rate difference (influenza A/H1N1: -6.423%; influenza A/H3N2: 7.812%; influenza B/Yamagata: -9.983%; influenza B/Victoria: -1.440%). As all 8 co-primary immunogenicity endpoints were met, non-inferiority of QIVc versus QIV in subjects 6 to 47 months of age was concluded; see Table 3 and Table 4 for results of the per protocol set.[19]

Table 3: Study V130_10 Post-vaccination geometric mean titre (GMT), GMT ratio, and analysis of non-inferiority of QIVc relative to QIV, in subjects 6 to 47 months of age for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria (HAI assay data) and influenza A/H3N2 (MN assay data), using cell-derived target viruses (per protocol set)

	Day 29/57 GMT		GMT Ratio	
	QIVc N_{HAI}=1092 / N_{MN}=1078 (95% CI)	US-licensed QIV N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV over QIVc (95% CI)	Met predefined noninferiority criteria?
A/H1N1	78.0 (70.75, 86.03)	57.3 (50.76, 64.63)	0.73 (0.645, **0.836**)	Yes
A/H3N2	23.1 (21.21, 25.12)	23.9 (21.57, 26.57)	1.04 (0.927, **1.160**)	Yes
B/Yamagata	35.6 (32.93, 38.58)	26.0 (23.54, 28.63)	0.73 (0.656, **0.809**)	Yes
B/Victoria	22.4 (20.70, 24.19)	19.6 (17.81, 21.58)	0.88 (0.791, **0.972**)	Yes

Abbreviations: CI = confidence interval; GMT = geometric mean titre; HAI = haemagglutination inhibition; MN = microneutralisation; NHAI = number of subjects with valid HAI assay results; NMN = number of subjects with valid MN assay results; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; US = United States

Note 1: Immunogenicity measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain.

Note 2: Immunogenicity measured using cell-derived target viruses in both the HAI and MN assays. The cell-derived target viruses were A/Idaho/07/2018 (A/H1N1), A/Indiana/08/2018 (A/H3N2), B/Singapore/INFTT-16 0610/2016 (B/Yamagata), and B/Iowa/06/2017 (B/Victoria)

Note 3: Adjusted GMT and GMT ratio are presented

Note 4: Adjusted analysis GMT model: Log-transformed Post-vaccination HAI (or MN) Titre = Vaccine + Age Strata + Gender + Vaccination History (yes or no) + Log-transformed Pre-vaccination HAI (or MN) Titre + Site + Age Strata*Vaccine

Note 5: Non-inferiority criterion for the GMT ratio: upper bound of the 2-sided 95% CI on the GMT ratio of US-licensed QIV over QIVc does not exceed 1.5.

[19] The per-protocol (PP) analysis is restricted to the participants who strictly adhered to the protocol. Also known as 'on-treatment' analysis.

Table 4: Study V130_10 Seroconversion rate, seroconversion rate difference, and analysis of non-inferiority of QIVc relative to QIV, in subjects 6 to 47 months of age for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria (HAI assay data) and influenza A/H3N2 (MN assay data), using cell-derived target viruses (per protocol set)

	SCR		SCR Difference	
	QIVc N_{HAI}=1092 / N_{MN}=1078 % (95% CI)	US-licensed QIV N_{HAI}=575 / N_{MN}=572 % (95% CI)	US-licensed QIV minus QIVc % (95% CI)	Met predefined noninferiority criteria?
A/H1N1	58.24 (55.25, 61.19)	46.78 (42.64, 50.96)	-11.46 (-16.447, -**6.423**)	Yes
A/H3N2	27.64 (24.99, 30.42)	30.77 (27.01, 34.73)	3.13 (-1.443, **7.812**)	Yes
B/Yamagata	46.52 (43.53, 49.53)	31.65 (27.87, 35.63)	-14.87 (-19.610, -**9.983**)	Yes
B/Victoria	30.31 (27.60, 33.13)	24.35 (20.89, 28.07)	-5.96 (-10.327, -**1.440**)	Yes

Abbreviations: CI = confidence interval; HAI = haemagglutination inhibition; MN = microneutralisation; NHAI = number of subjects with valid HAI assay results; NMN = number of subjects with valid MN assay results; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate; US = United States

Note 1: Immunogenicity measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain.

Note 2: Immunogenicity measured using cell-derived target viruses in both the HAI and MN assays. The cell-derived target viruses were A/Idaho/07/2018 (A/H1N1), A/Indiana/08/2018 (A/H3N2), B/Singapore/INFTT-16-0610/2016 (B/Yamagata), and B/Iowa/06/2017 (B/Victoria).

Note 3: Non-inferiority criterion for the SCR difference: upper bound of the 2-sided 95% CI on the SCR difference for US-licensed QIV minus QIVc does not exceed 10%.

Secondary immunogenicity outcomes

Immunogenicity of QIVc and the QIV by HAI assay for the influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, and by MN assay for the influenza A/H3N2 strain, using egg-derived target viruses, showed no notable differences in the immunogenicity between the 2 vaccines for the GMT, geometric mean ratio (GMR), seropositivity rates, percentage with titre at least 1:40, and seroconversion rates for all 4 vaccine strains.

Immunogenicity of QIVc and the QIV by HAI assay for the influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains, and by MN assay for the influenza A/H3N2 strain, using cell-derived target viruses showed no notable differences in the immunogenicity between the 2 vaccines for the GMT, GMR, seropositivity rates, percentage of subjects with titre at least 1:40, and seroconversion rates for the influenza A/H3N2 and influenza B/Victoria strains. For the influenza A/H1N1 and influenza B/Yamagata strains, there were no notable differences in seropositivity rates between the 2 vaccines, while the Day 29 or 57 GMTs, GMRs, Day 29 or 57 percentage with titre at least 1:40, and SCRs were observed to be higher for QIVc than QIV.

Immunogenicity of QIVc and the QIV by MN assay for the influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria strains using cell-derived target viruses in a randomly selected subset showed no notable differences in immunogenicity between the 2 vaccines for the GMT, GMR, seropositivity rates, percentage of subjects with titre at least 1:40, and seroconversion rates for the 3 vaccine strains.

Table 5: Study V130_10 Pre-vaccination and post-vaccination geometric mean titre, geometric mean ratio, seropositivity rates, percentage of subjects with titre at least 1:40, and seroconversion rates, in subjects 6 months through 47 months of age for influenza A/H1N1, influenza B/Yamagata, and influenza B/Victoria (HAI assay data) and influenza A/H3N2 (MN assay data), using egg-derived target viruses (per protocol set)

	QIVc No./% (95% CI)		US-licensed QIV No./% (95% CI)
A/H1N1	**N=1092**		**N=575**
Day 1 HAI GMT	14.0 (12.54, 15.74)		13.9 (12.11, 16.04)
Day 29/57 HAI GMT	92.2 (83.62, 101.71)		82.9 (73.51, 93.58)
Day 29/57 HAI GMT Ratio		0.90 (0.790, 1.024)	
GMR HAI Titer	5.67 (5.117, 6.290)		5.11 (4.503, 5.809)
Day 1 % HAI Titer ≥1:10	52.47 (49.46, 55.47)		53.04 (48.87, 57.18)
Day 29/57 % HAI Titer ≥1:10	88.74 (86.71, 90.55)		92.35 (89.86, 94.39)
Day 1 % HAI Titer ≥1:40	30.86 (28.13, 33.70)		30.96 (27.20, 34.91)
Day 29/57 % HAI Titer ≥1:40	73.99 (71.28, 76.57)		74.78 (71.02, 78.28)
SCR (%) HAI Titer	58.52 (55.53, 61.46)		56.00 (51.83, 60.10)
SCR Difference		-2.52% (-7.526, 2.461)	
A/H3N2	**N=1079**		**N=572**
Day 1 MN GMT	12.9 (11.87, 13.96)		12.6 (11.42, 13.95)
Day 29/57 MN GMT	43.4 (39.58, 47.52)		44.7 (39.98, 50.08)
Day 29/57 MN GMT Ratio		1.03 (0.914, 1.165)	
GMR MN Titer	3.13 (2.856, 3.431)		3.22 (2.878, 3.608)
Day 1 % MN Titer ≥1:10	66.82 (63.92, 69.63)		66.78 (62.76, 70.64)
Day 29/57 % MN Titer ≥1:10	90.82 (88.94, 92.48)		87.94 (84.98, 90.49)
Day 1 % MN Titer ≥1:40	19.93 (17.58, 22.44)		19.06 (15.92, 22.52)
Day 29/57 % MN Titer ≥1:40	50.70 (47.67, 53.72)		46.68 (42.53, 50.86)
SCR (%) MN Titer	37.44 (34.55, 40.41)		39.34 (35.31, 43.47)
SCR Difference		1.89% (-3.006, 6.856)	
B/Yamagata	**N=1092**		**N=575**
Day 1 HAI GMT	6.7 (6.33, 7.16)		6.7 (6.23, 7.26)
Day 29/57 HAI GMT	23.0 (21.21, 24.89)		24.7 (22.39, 27.26)
Day 29/57 MN GMT Ratio		1.08 (0.968, 1.195)	
GMR HAI Titer	3.04 (2.808, 3.298)		3.27 (2.964, 3.615)
Day 1 % HAI Titer ≥1:10	28.75 (26.08, 31.54)		28.17 (24.53, 32.04)
Day 29/57 % HAI Titer ≥1:10	77.11 (74.50, 79.57)		79.13 (75.58, 82.38)
Day 1 % HAI Titer ≥1:40	9.62 (7.93, 11.52)		8.87 (6.68, 11.50)
Day 29/57 % HAI Titer ≥1:40	47.62 (44.62, 50.63)		45.57 (41.44, 49.74)
SCR (%) HAI Titer	38.64 (35.74, 41.61)		38.61 (34.61, 42.73)
SCR Difference		-0.04% (-4.912, 4.911)	
B/Victoria	**N=1092**		**N=575**
Day 1 HAI GMT	6.1 (5.77, 6.38)		6.0 (5.68, 6.43)
Day 29/57 HAI GMT	13.6 (12.58, 14.61)		14.8 (13.46, 16.19)
Day 29/57 HAI GMT Ratio		1.09 (0.986, 1.202)	
GMR HAI Titer	2.14 (1.987, 2.308)		2.33 (2.126, 2.558)
Day 1 % HAI Titer ≥1:10	17.03 (14.85, 19.40)		16.35 (13.42, 19.63)
Day 29/57 % HAI Titer ≥1:10	62.00 (59.04, 64.89)		68.17 (64.19, 71.97)
Day 1 % HAI Titer ≥1:40	4.58 (3.42, 5.99)		3.65 (2.27, 5.53)
Day 29/57 % HAI Titer ≥1:40	23.81 (21.31, 26.45)		25.04 (21.55, 28.79)
SCR (%) HAI Titer	19.69 (17.37, 22.17)		20.87 (17.62, 24.42)
SCR Difference		1.18% (-2.805, 5.353)	

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; HAI = haemagglutination inhibition; MN = microneutralisation; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate; US = United States

Note 1: Immunogenicity measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain; Note 2: Immunogenicity measured using egg-derived target viruses in both the HAI and MN assays. The egg-derived target viruses were A/Brisbane/02/2018 (IVR-190) (A/H1N1), A/Kansas/14/2017 (X-327) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata), and B/Maryland/15/2016 (B/Victoria); Note 3: Adjusted GMT, GMT ratio, and GMR are presented; Note 4: The Day 29 or 57 HAI GMT ratio is the Day 29 or 57 GMT for the US-licensed QIV over the Day 29 or 57 GMT for QIVc; the SCR difference is the SCR for the US-licensed QIV minus the SCR for QIV.

Exploratory immunogenicity objectives outcome

Cell-mediated immunity response in subjects 24 to 47 months of age showed CD4+ and CD8+ T-cells responsive to influenza antigen stimulation *in vitro*, as measured by antigen-induced expression of markers of T-cell activation, were detected at low frequencies for both QIVc and QIV.

Immunogenicity of QIVc and QIV by HAI assay for the influenza A/H3N2 strain using cell-derived target viruses showed no notable differences in the immunogenicity results between the 2 vaccines for the endpoints of GMR, seropositivity rates, and Day 29 or 57 percentage of subjects with titre of at least 1:40, while the Day 29 or 57 GMT and seroconversion rates were observed to be higher for QIVc than QIV. Evaluation of the immunogenicity of QIVc and the QIV by HAI assay for the influenza A/H3N2 strain using egg-derived target viruses showed no notable differences in the immunogenicity results between the 2 vaccines for any of the endpoints.

Clinical Safety

Study ID V130_10

Patient exposure

In Study V130_10, a total of 2,402 subjects received at least one study vaccination; 1,597 subjects received QIVc and 805 subjects received the QIV.

Overall, QIVc and the QIV were well tolerated in this paediatric population 6 to 47 months of age, with both vaccines associated with a clinically acceptable safety profile.

Solicited adverse events

Reactions were similar between the QIVc (n = 1,564) and QIV (n = 784) groups after any vaccination (63.7% versus 65.9%), at 30 minutes after any vaccination (12.3% versus 13.3%), and from Day 1 through Day 7 after any vaccination (60.1% versus 62.6%). At 30 minutes after any vaccination, the proportions reporting solicited local and systemic adverse events (AEs) were similar between the 2 vaccine groups.

Rates of solicited AEs were similar between the QIVc and QIV groups after Vaccination 1 (59.7% versus 62.5%). In both the QIVc and QIV groups, the rates of solicited AEs were lower after the second vaccination than after the first (QIVc: 47.0% versus 59.7%; QIV: 46.8% versus 62.5%).

Solicited local adverse events

Solicited local AEs (after any dose) after 30 minutes were reported by 171 of 1,564 subjects (10.9%) in the QIVc group and 95 of 784 subjects (12.1%) in the QIV group. Solicited systemic AEs were reported by 30 subjects (1.9%) in the QIVc group and 18 subjects (2.3%) in the QIV group. From Day 1 through Day 7 after any vaccination, the proportions of subjects reporting solicited local and systemic AEs were similar between the 2 vaccine groups. Solicited local AEs were reported by 656 subjects (41.9%) in the QIVc group and 350 subjects (44.6%) in the QIV group, and systemic AEs were reported in 681 (43.5%) and 358 (45.7%) subjects in QIVc and QIV group respectively; see Table 6.

The most reported solicited local AEs after any vaccination in the QIVc and QIV groups were tenderness (27.9% and 30.0%, respectively) and erythema (25.8% and 24.6%, respectively).

The rates of induration, erythema, ecchymosis, and tenderness occurring Day 1 through Day 7 after each vaccination and after any vaccination were similar between the QIVc and QIV groups (Table 7). The rates of each of the individual solicited local AEs were lower after the second vaccination than after the first vaccination in both vaccine groups. Induration, erythema, ecchymosis, and tenderness persisting beyond 7 days after vaccination were very low in both groups.

Table 6: Study V130_10 Number (%) of subjects 6 months through 47 months of age with at least one solicited adverse event 30 minutes post-vaccination and/or Day 1 through 7 days after vaccination (solicited safety set)

Solicited Adverse Event	QIVc n (%)	US-licensed QIV n (%)
After Any Vaccination	**N=1564**	**N=784**
Any solicited AE after any Vaccination	997 (63.7)	517 (65.9)
30 Minutes After Any Vaccination		
Any	192 (12.3)	104 (13.3)
Local	171 (10.9)	95 (12.1)
Systemic	30 (1.9)	18 (2.3)
Analgesic/Antipyretic Use	8 (0.5)	2 (0.3)
Day 1 Through Day 7 After Any Vaccination		
Any	940 (60.1)	491 (62.6)
Local	656 (41.9)	350 (44.6)
Systemic	681 (43.5)	358 (45.7)
Analgesic/Antipyretic Use	240 (15.3)	136 (17.3)
After Vaccination 1	**N=1564**	**N=784**
Any solicited AE after Vaccination 1	934 (59.7)	490 (62.5)
30 Minutes After Vaccination 1		
Any	163 (10.4)	90 (11.5)
Local	146 (9.3)	81 (10.3)
Systemic	25 (1.6)	15 (1.9)
Analgesic/Antipyretic Use	5 (0.3)	1 (0.1)
Day 1 Through Day 7 After Vaccination 1		
Any	882 (56.4)	465 (59.3)
Local	619 (39.6)	325 (41.5)
Systemic	625 (40.0)	328 (41.8)
Analgesic/Antipyretic Use	197 (12.6)	117 (14.9)
After Vaccination 2	**N=698**	**N=340**
Any solicited AE after Vaccination 2	328 (47.0)	159 (46.8)
30 Minutes After Vaccination 2		
Any	56 (8.0)	27 (7.9)
Local	48 (6.9)	26 (7.6)
Systemic	7 (1.0)	4 (1.2)
Analgesic/Antipyretic Use	4 (0.6)	1 (0.3)
Day 1 Through Day 7 After Vaccination 2		
Any	307 (44.0)	148 (43.5)
Local	173 (24.8)	89 (26.2)
Systemic	235 (33.7)	110 (32.4)
Analgesic/Antipyretic Use	70 (10.0)	38 (11.2)

Abbreviations: AE = adverse event; n = number of subjects; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; US = United States

Note 1: Analgesic or antipyretic use was for prevention or treatment of pain or fever

Note 2: Solicited AEs were reported through the first 30 minutes after vaccination (by clinical study staff) and from Day 1 through Day 7 after vaccination using Subject Diary Cards. On Day 1, it was recommended to assess solicited AEs preferably in the evening, at approximately 6 hours post-vaccination.

Table 7: Study V130_10 Number (%) of subjects 6 months through 47 months of age with solicited local adverse events from Day 1 through Day 7 after vaccination (solicited safety set)

Solicited Local Adverse Event	QIVc n (%)	US-licensed QIV n (%)
After Any Vaccination	**N=1564**	**N=784**
Induration (mm)	n=647	n=344
Any	270 (17.3)	125 (15.9)
Severe	6 (0.4)	0
Erythema (mm)	n=648	n=346
Any	403 (25.8)	193 (24.6)
Severe	7 (0.4)	0
Ecchymosis (mm)	n=647	n=345
Any	168 (10.7)	85 (10.8)
Severe	2 (0.1)	0
Tenderness	n=655	n=349
Any	436 (27.9)	235 (30.0)
Severe	34 (2.2)	11 (1.4)
After Vaccination 1	**N=1564**	**N=784**
Induration (mm)	n=604	n=319
Any	236 (15.1)	109 (13.9)
Severe	6 (0.4)	0
Erythema (mm)	n=605	n=320
Any	374 (23.9)	177 (22.6)
Severe	7 (0.4)	0
Ecchymosis (mm)	n=603	n=319
Any	150 (9.6)	74 (9.4)
Severe	1 (0.1)	0
Tenderness	n=618	n=324
Any	397 (25.4)	216 (27.6)
Severe	29 (1.9)	10 (1.3)
After Vaccination 2	**N=698**	**N=340**
Induration (mm)	n=171	n=86
Any	64 (9.2)	36 (10.6)
Severe	0	0
Erythema (mm)	n=171	n=86
Any	99 (14.2)	46 (13.5)
Severe	0	0
Ecchymosis (mm)	n=171	n=86
Any	36 (5.2)	18 (5.3)
Severe	1 (0.1)	0
Tenderness	n=173	n=89
Any	108 (15.5)	56 (16.5)
Severe	8 (1.1)	2 (0.6)

Abbreviations: AE = adverse event; N = number of participants; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; US = United States

Note 1: For induration, ecchymosis, and erythema, severe was defined as over 50 mm. For tenderness, severe was defined as 'Cried when limb was moved or spontaneously painful' in subjects under 24 months of age at time of first dose of vaccine and 'Prevents daily activity' in subjects 24 months of age and older at time of first dose of vaccine.

Note 2: Solicited AEs were reported from Day 1 through Day 7 after vaccination.

Note 3: 'n' shown for each specific event represents the sum of subjects reporting 'any' or 'none' for that particular solicited local AE. The individual solicited AE counts are based on the number of subjects in each vaccine group with at least one occurrence of a solicited local AE after any vaccination during the Day 1 through Day 7 assessment interval only.

Note 4: Percentages are based on the number of subjects in each vaccine group in the solicited safety set.

Solicited systemic adverse events

There were no notable differences in rates of solicited systemic AEs after each vaccination and after any vaccination between the QIVc and QIV groups, reported by 681 of 1,564 subjects (43.5%) in the QIVc group and 358 of 784 subjects (45.7%) in the QIV group.

The most frequently reported solicited systemic AEs occurring from Day 1 through Day 7 after any vaccination reported in both the QIVc and QIV groups were irritability (27.9% and 29.6%, respectively) and sleepiness (26.9% and 25.5%, respectively). The majority of solicited systemic AEs after any vaccination in both vaccine groups were mild or moderate in severity. The percentage reporting severe solicited systemic AEs was less than 2.0% in both vaccine groups, apart from severe sleepiness in the QIVc group (2.1%) and severe irritability in the QIVc (3.1%) and QIV (2.7%) groups. The mean time of onset of the individual solicited systemic AEs after any vaccination ranged from 1.6 to 3.1 days in the QIVc group and from 1.5 to 3.1 days in the QIV group. Proportions in the QIVc and QIV groups reporting solicited systemic AEs progressively decreased over the 7 day period following any vaccination. Proportions of subjects with individual solicited systemic AEs persisting beyond 7 days after any vaccination were low in both QIVc (0.3% to 2.3%) and QIV (0.1% to 1.5%) groups.

Fever (38.0°C and higher) was reported after any vaccination by 6.8% and 6.9% of subjects in the QIVc and QIV groups, respectively. Fever (40.0°C and higher) was reported by 0.6% and 0.1% of subjects in the QIVc and QIV groups, respectively. Proportions of subjects experiencing fever of at least 38.0°C was similar between the vaccine groups. In QIVc and QIV groups, 4.6% and 5.1%, respectively reported a fever between 38.0°C and 38.9°C; fever of 39.0°C to 39.4°C was reported in 1.2% and 1.3 %, in QIVc and QIV groups, respectively. Reports of fever 39.5°C to 39.9°C and fever 40°C and higher were low and similar in QIVc (0.5% and 0.6%) and QIV (0.4% and 0.1%) groups. The use of analgesics or antipyretics from Day 1 to Day 7 after any vaccination for prevention and treatment of pain and/or fever were similar in both groups.

Unsolicited adverse events

Similar proportions of subjects in the QIVc and QIV groups reported unsolicited AEs: 26.2% (418 of 1,597 subjects) and 25.7% (207 of 805 subjects) respectively in the QIVc and QIV groups). The most frequently reported unsolicited AEs by System Organ Class (SOC)[20] in the QIVc and QIV groups were: 'Infections and Infestations' (14.1% and 13.8%, respectively) and 'General Disorders and Administration Site Conditions' (5.1% and 5.3%, respectively). On a SOC level, proportions reporting any unsolicited AEs was similar. The proportion reporting all-causality unsolicited AEs during the treatment period was similar, with 418 of 1,597 subjects (26.2%) in the QIVc group and 207 of 805 subjects (25.7%) in the QIV group reporting unsolicited AEs. The most frequently reported AEs by preferred term (PT)[21] in the QIVc and QIV groups were upper respiratory tract infection (3.7% and 5.5%, respectively) and pyrexia (2.9% and 3.1%, respectively).

[20] System Organ Class (SOC) is the highest level of the MedDRA terminology for classification of adverse events. There are 27 classes. The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical conditions, medicines and medical devices. It was created to assist regulators with sharing information. It is also used by industry, academics, health professionals and other organisations that communicate medical information.

[21] In MedDRA, preferred terms (PT) are single concepts for symptoms, signs, disease diagnosis, therapeutic indications, investigations, procedures, and characteristics. There are over 20,000 preferred terms.

Treatment related adverse events (adverse drug reactions)

Similar proportions of subjects in the QIVc and QIV groups reported related unsolicited AEs (4.4% and 4.5%, respectively). The most frequently reported related unsolicited AEs by PT in the QIVc and QIV groups were injection-site bruising (0.8% and 1.0%, respectively) and irritability (0.8% and 0.7%, respectively).

No serious AEs (SAE) were assessed as related to the study vaccine during Study V130_10.

Deaths and other serious adverse events

Two deaths not considered related to the study vaccine were reported.

There were 15 (0.9%) subjects in the QIVc group and 7 (0.9%) subjects in the QIV group with reported SAEs during the study. None of the SAEs were assessed as related to study vaccine. The majority of SAEs were reported in the SOC of 'Infections and Infestations' (10 of 1,597 subjects (0.6%) in the QIVc group and 3 of 805 subjects (0.4%) in the QIV group). Pneumonia was reported for 3 subjects (QIVc group) and bronchiolitis was reported for 3 subjects (QIV group); all other conditions reported for this SOC were of nil or 1 subject in each vaccine group. The SAEs in the other listed SOC categories were reported by nil or 1 subject in each group except in the QIVc group where 2 subjects reported asthma in the SOC 'Respiratory, thoracic and mediastinal disorders' and 2 subjects reported seizures in the SOC 'Nervous system disorders'.

Discontinuations due to adverse events

Three out of 1,597 subjects (0.2%) in the QIVc group reported AEs leading to withdrawal from the study including the 2 deaths described above. No subjects in the QIV group withdrew from the study because of an AE.

Safety in special populations

There were no meaningful differences in frequency of solicited local or systemic or unsolicited AEs reported according to age, gender, or race.

In the QIV group, the proportion reporting solicited local AEs was higher in the 24 to 47 months age subgroup than in the 6 to 23 months age subgroup. In both QIVc and QIV groups, the proportion reporting solicited systemic AEs was higher in the 6 to 23 months age subgroup than in the 24 to 47 months age subgroup.

In both QIVc and QIV groups, the proportion reporting all-causality unsolicited AEs was higher in the 6 to 23 months age subgroup than the 24 to 47 months age subgroup.

Use in pregnancy category

This application also sought to change the Australian category for prescribing medicines in pregnancy from Category B1 to Category A.[22]

[22] **Category A:** Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Study V130_11OB

Description

Study V130_11OB was a prospective observational cohort study in the US with the safety objective to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birthweight among women immunised as part of routine care with the trivalent or quadrivalent cell-based influenza vaccine during pregnancy.[23]

Data collection for each participant began at enrolment (during pregnancy), with follow-up at the end of the second trimester (approximately 24 weeks' gestation) and/or at pregnancy outcome (delivery or early termination).

Participants

There were 693 women enrolled with 1 woman confirmed as ineligible after enrolment. Of the 692 eligible women, 27 (3.9%) were lost to follow-up. Hence, there were 665 evaluable women who had received QIVc as part of routine care, enrolled over 3 consecutive northern hemisphere influenza seasons commencing 2017.

Mean maternal age at conception was 28 years; 399 (60%) were White, 194 (29.2%) were Black and 29 (4.4%) were of Asian race. Non-Hispanic ethnicity was reported by 437 (65.7%) women. The majority of women in the primary analysis population (n = 527; 79.2%) reported at least one concurrent condition. Most (n = 651; 97.9%) reported use of concomitant medications (including prenatal vitamins). Tobacco use was reported by 84 (12.6%) women and one woman reported alcohol use. No illicit drug use was reported. No major differences were evident in the demographic and baseline characteristics between women enrolled by different dedicated reporters. All women were exposed to QIVc. Of prospectively enrolled women, 196 (28.3%) were exposed during their first trimester, 286 (41.3%) during the second trimester and 211 (30.4%) during the third trimester. Of the 665 women, 211 (31.7%) enrolled prior to 20 weeks gestation.

Results

A total of 99.1% of the women had a pregnancy outcome of a live birth. No stillbirth was reported. Among the 211 subjects with an enrolment prior to 20 weeks gestation, 4 spontaneous abortions (1.9%) and 1 elective termination (0.5%) were reported. One ectopic pregnancy was reported. For the 665 reported pregnancy outcomes, data were reported for 673 infants. There were 656 singleton pregnancies and 9 multiple gestation pregnancies enrolled (all twins), however, for 1 multiple gestation pregnancy one of the twins died *in utero* prior to vaccination and enrolment.

For the infant events of interest, preterm birth was reported for 52 infants (9.2%; upper 95% CI:11.5%) and low birthweight reported for 37 infants (5.8%, upper 95% CI: 7.6%). For 17 fetuses and infants at least one major congenital malformation was reported by a healthcare provider. For 3 cases with a reported major congenital malformation, the event of interest was adjudicated as not being an MACDP-listed defect.[24] Of the 14 cases with a confirmed MACDP defect, one was observed in an elective termination prior to 20 weeks gestation. Using the primary method to calculate the prevalence (that is, excluding major congenital malformations reported in non-live births prior to 20 weeks gestation), 13 of 667 live births with an MACDP defect account for 1.9% (upper 95% CI: 3.1%). For 2 of the 14 fetuses and infants, their mother

[23] All women enrolled in this study were exposed to Flucelvax Quad as the trivalent cell-based influenza vaccine was no longer available on the US market at the time of active enrolment to the study.

[24] The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based tracking system for birth defects. MACDP was established in 1967. See Metropolitan Atlanta Congenital Defects Program (MACDP) | CDC.

had a first trimester exposure, and for both the reported defect had a known cause other than exposure to the study vaccine.

Risk management plan

In support of the extended indications, the sponsor submitted draft European Union (EU) risk management plan (RMP) version 3.1 (dated 27 August 2021; data lock point 30 June 2021) in association with Australia-specific annex (ASA) version 3.1 (dated 9 May 2022). At the second round of evaluation, the sponsor submitted ASA version 3.2 (dated 6 January 2023).

As the TGA has previously evaluated RMPs for this product, the focus of this evaluation is on the differences between the RMP versions that could have an impact on the safety profile, and any new safety related information relevant to this submission.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 8: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	None	–	–	–	–
Missing information	Safety in immunocompromised patients	✓	–	✓	–
	Safety in subjects with underlying diseases	✓	–	✓	–

Missing information 'Use in pregnant and breastfeeding women' has been removed as a safety concern. This is a result of data from the completed pregnancy registry Study V130_11OB. The summary of safety concerns for Flucelvax Quad is acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance for all safety concerns and no additional pharmacovigilance activities are to be implemented in Australia. The status of the pregnancy registry Study V130_11OB has been updated to 'complete' and the pregnancy outcome follow-up questionnaire has been removed from the pharmacovigilance plan as 'Use in pregnant and breastfeeding women' is no longer considered missing information. The pharmacovigilance plan is acceptable form an RMP perspective.

Routine risk minimisation is proposed for the safety concerns. The risk minimisation plan for Flucelvax Quad is acceptable from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

Immunogenicity

Flucelvax Quad (also referred to as QIVc) is a quadrivalent surface antigen, inactivated, influenza vaccine, prepared in Madin-Darby canine kidney (MDCK) cell cultures (that is, cell-based).

No dose-finding studies were conducted since the vaccine composition and dosing are based on the EMA's *Guideline on Influenza Vaccines* and is also consistent with other influenza vaccine products approved for children in this age group. This is considered acceptable.

The immunogenicity data for this submission were provided by Study V130_10, a Phase III study conducted in healthy subjects 6 months through 47 months of age.

In Study V130_10, immunogenicity endpoints were assessed by the haemagglutination inhibition (HAI) and microneutralisation (MN) assay. The HAI assay used for immunogenicity evaluation of influenza vaccines is considered adequate for study V130_10, as it is in line with the *Guideline on Influenza Vaccines*. Due to the technical challenges with the HAI assay, particularly with the influenza A/Singapore/GP2050/2015 strain , quantification of neutralising antibody titres using the MN assay against influenza A/H3N2 has been used as an alternative. This is considered acceptable.

Haemagglutination inhibition and microneutralisation titres are not true surrogate markers as there is no defined cut-off titre correlating with clinical protection. However, it has been demonstrated that higher titres tend to correlate with better protection. Although the immunogenicity data are descriptive and without predetermined criteria for success, the QIVc group showed increase in the HAI titres.

In general, the design of Study V130_10, conducted to evaluate safety and immunogenicity of the QIVc in children 6 months to 47 months of age, is considered adequate. The study was carried out as observer blind. Although the optimal design would have been a double-blinded trial, it is considered that the observer blind strategy used here is sufficient as it is very unlikely that this design would have affected the study outcomes.

The sample size, and the stratification by age, inclusion and exclusion criteria, and statistical methods are considered satisfactory. However, only one-third of subjects were from the target age group of 6 months to 2 years.

There was no notable difference in the distribution of demographic and baseline characteristics between the 2 vaccine groups. The percentages and reason for discontinuation were similar in the 2 treatment groups.

The predefined success criteria of non-inferiority for the primary immunogenicity objectives were met, demonstrating that QIVc was non-inferior to QIV in children 6 to 47 months of age. For each of the 4 vaccine strains, the upper bound of the 2-sided 95% CI for the GMT ratio did not exceed 1.5, and the upper bound of the 2-sided 95% CI of the difference in the seroconversion rates between the vaccines did not exceed 10%.

Regarding the secondary immunogenicity endpoints, for the assays using egg-derived target viruses, no notable differences in immune responses were observed for QIVc compared with QIV across all endpoints, including GMT, GMR, seropositivity rates (percentage of subjects with titre above 1:10), percentage of subjects with titre above1:40, and SCR. Using cell-derived target viruses, immune responses to influenza A/H3N2 and influenza B/Victoria were not different for the 2 vaccines, whereas for influenza A/H1N1 and influenza B/Yamagata, higher

post-vaccination GMTs, GMRs, percentage of subjects with titre above 1:40, and SCRs were observed for QIVc compared with QIV.

Overall, QIVc was as immunogenic as a comparator QIV in infants and children aged 6 to 47 months of age against all 4 strains. Cell-mediated responses were equally low to both vaccines, which is acceptable for an inactivated, non-adjuvanted vaccine.

Safety: use in infants and children 6 months to 2 years of age

The current indication for Flucelvax Quad is established for children aged 2 years and older, adolescents and adults. Study Phase 3 (V130_10) provides safety data to support the extension of indication to children aged 6 months to 2 years.

The safety database in study V130_10 was of 2,402 subjects from 6 months to 47 months of age. Of this group, 1,597 subjects received QIVc.

Rates of solicited and unsolicited AEs were similar between the 2 vaccine groups; any solicited AE after any vaccination was reported in 63.7% and 65.9% of subjects receiving QIVc and QIV, respectively, and any unsolicited AE was reported during the treatment period in 26.2% and 25.7%, respectively.

The majority of solicited AEs were of mild to moderate severity in both groups. The most common solicited local AEs were tenderness and erythema at the injection site, and most common solicited systemic AEs were irritability and sleepiness. Fever (at least 38°C) was reported for 6.8% and 6.9% of subjects in the QIVc and QIV groups, respectively with temperatures of 40°C or higher reported in less than 1% of subjects in either group.

The most frequently reported unsolicited AEs during the treatment period for both vaccine groups were upper respiratory tract infection and pyrexia. Subjects reporting unsolicited AEs assessed as at least possibly related to study vaccine were similar for QIVc (4.4%) and QIV (4.5%), with injection site bruising and irritability being the most common events. At least 1 medically attended AE were reported by 10.8% of QIVc and 9.3% of QIV recipients. Adverse events leading to new onset chronic disease were reported by 1.4% of QIVc and 1.6% of QIV recipients with more than 1 subject reporting asthma (0.2%), seasonal allergy (0.1%), ear infection (0.1%), and atopic dermatitis (0.1%) in the QIVc group and cardiac murmur (0.2%) in the QIV group. Serious AEs were reported in less than 1% of subjects in each vaccine group and none were assessed as related to the vaccine. One subject in the QIVc group had a SAE of new onset seizures 17 days after study vaccination and withdrew from the study. Two subjects in the QIVc group had SAEs with a fatal outcome: one subject was diagnosed with adenoviral encephalopathy 27 days after receipt of second dose of QIVc, and one subject died of injuries sustained in a traffic accident.

Data limitations

- Only around a third of enrolled participants were aged 6 to 23 months of age, the proposed age group for this extension of indication.
- No clinical efficacy data were available.
- No data on subjects with co-morbidities and immune deficiency were available.
- No immunogenicity and safety data on co-administration with other vaccines in this age group were available, including for those recommended in the childhood immunisation programs.

Safety: pregnancy category change

Study V130_11OB provided data to support the change of the Australian category for prescribing medicines in pregnancy from Category B1 to Category A. The study was a prospective observational cohort study with safety objective to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birthweight among women immunised as part of routine care with Flucelvax Quad during pregnancy.

Of the 665 evaluable participants, 659 (99.1%) had a live birth. No stillbirth (0%; 95% CI: 0.0–0.6), 4 spontaneous abortions (1.9%; 95% CI: 0.5–4.8), and 1 elective termination (0.5%; 95% CI: 0.0–2.6) were reported. Among 673 infants, 9.2% (upper 95% CI: 11.5%) were born prematurely, 5.8% (upper 95% CI: 7.6%) had low birth weight, and 1.9% (upper 95% CI: 3.1%) were reported to have a major congenital malformation. No maternal deaths were reported. Of the 2 infants who died shortly after birth, one death was adjudicated as not related to the vaccine; the cause of death of the other infant could not be determined due to maternal loss to follow-up. The prevalence of adverse pregnancy outcomes or preterm birth, low birth weight, or major congenital malformations in newborns was similar in persons vaccinated with Flucelvax Quad compared to the rates observed in US surveillance systems.

For all outcomes, the point estimate of the prevalence observed in the study population was below the background prevalence for the general population. These data suggest no evidence of a safety concern for QIVc received during any stage of pregnancy. These findings are consistent with published data from various databases and surveillance systems that monitor the safety of influenza vaccines in pregnant women. Based on these outcomes, the pregnancy category for Flucelvax Quad can be changed to Category A.

Proposed action

There is existing public health need for cell based quadrivalent influenza vaccine, particularly for use in infants and younger children. Based on the acceptable immunogenicity and safety demonstrated by the submitted data, the Delegate's preliminary view is that the extension of indication for Flucelvax Quad in the proposed age group of 6 months to 2 years is appropriate.

Advisory Committee considerations

The Advisory Committee on Vaccines (ACV), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Does ACV consider that there is a favourable benefit risk balance for the use of this vaccine in the proposed population, and the submitted data has satisfied the regulatory requirement for the extension of registration to individuals 6 months to 2 years of age? Especially in view of that, immunogenicity data having only one-third population from the target age group and also the absence of clinical efficacy data.***

The ACV advised that there is a favourable benefit risk balance for the use of Flucelvax Quad in individuals 6 months to 2 years of age.

The ACV noted that the sample size and diversity of the trial population allowed for a meaningful comparison of safety as well as immunogenicity outcomes.

Immunogenicity assessment was extensive with antibody responses evaluated in 2 types of assays (haemagglutination inhibition and microneutralisation) with both cell and egg-derived

target viruses. Pre-defined success criteria of non-inferiority for the primary immunogenicity objectives were met, demonstrating that Flucelvax Quad was non-inferior to approved comparator vaccine in children 6 to 47 months of age for all 4 influenza strains, which has demonstrated efficacy or effectiveness.

2. Does ACV consider safety data as adequate in the proposed age group?

The ACV advised that the safety data appeared to be sufficient and comparable to other inactivated influenza vaccine administered to the age group 6 months to 2 years.

Ongoing post-market monitoring should consider co-administration of Flucelvax Quad with vaccines that are included in childhood immunisation programs. Of note, AusVaxSafety surveillance in Australia provides analysis of adverse events following immunisation by age and brand and should be useful in this regard.[25] No immunogenicity and safety data had been provided on co-administration of Flucelvax Quad with other vaccines in this age group.

3. Does ACV agree with the proposed indication?

The ACV advised that the proposed indication was appropriate.

No dose adjustment is required for the proposed age group, and rates of adverse events were similar between the Flucelvax Quad and comparator vaccine with no serious adverse events related to vaccination.

While reiterating that people with egg allergy, including a history of anaphylaxis, can be safely vaccinated with any inactivated influenza vaccine (including egg-based vaccines) unless they have reported a serious adverse reaction to influenza vaccines,[26] the ACV noted that the availability of a cell-based vaccine for individuals 6 months to 2 years of age provided choice for parents and prescribers.

Conclusion

The ACV considered this product to have an overall positive benefit-risk profile for the indication:

> *For the prevention of influenza caused by influenza virus, types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 6 months of age and older.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Flucelvax Quad, a quadrivalent influenza vaccine (surface antigen, inactivated, prepared in cell cultures) suspension for injection in pre-filled syringes containing 60 µg influenza virus haemagglutinin as active ingredient, for the following extension of indication:

> *For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use in children 6 months to 2 years of age.*

[25] AusVaxSafety is Australia's national collaborative vaccine safety surveillance system led by the National Centre for Immunisation Research and Surveillance and funded by the Australian Government Department of Health and Aged Care.
[26] Influenza (flu) | The Australian Immunisation Handbook (health.gov.au).

As such, the full indications at this time were:

> *For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use in adults and children 6 months of age and older.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*

Specific conditions of registration applying to these goods

The influenza virus haemagglutinin European Union Risk management plan (RMP) version 3.1 (dated 27 August 2021, data lock point 30 June 2021), with Australia-specific annex (version 3.2, dated 6 January 2023), included with Submission PM-2022-01977-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Reports are to be provided in line with the current published list of European Union reference dates and frequency of submission of PSURs until the period covered by such reports is not less than 3 years from the date of the approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Revision 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within 90 calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Flucelvax Quad approved with the submission which is described in this AusPAR is at Attachment 1. It may have been superseded. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #