Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Quadrivalent Influenza Vaccine

Proprietary Product Name: Flucelvax Quad

Sponsor: Seqirus Pty Ltd

December 2020

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.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An 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.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia Specific Annex
AusPAR	Australian Public Assessment Report
AusVaxSafety	Australia vaccine safety system
CBER	Center for Biologics Evaluation and Research (United States Food and Drug Administration)
CCI	Cell culture derived influenza virus vaccine
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	Confidence interval
CPD	Certified Product Details
CSR	Clinical study report
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
GMT	Geometric mean titre
GVP	Good pharmacovigilance practices
HA	Haemagglutinin
HI	Hemagglutination inhibition
ILI	Influenza-like illness

Abbreviation	Meaning
IVV	Influenza virus vaccine
LBW	Low birth weight
LL	Lower limit
MCM	Major congenital malformation
NA	Not applicable
NE	Not evaluable
NA	Neuraminidase
NH	Northern Hemisphere
OMCL	Official medicines control laboratory
PI	Product Information
PP	Per protocol
QC	Quality control
QIVc	Cell culture derived quadrivalent influenza vaccine
RMP	Risk management plan
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SH	Southern Hemisphere
TGA	Therapeutic Goods Administration
TIVc	Cell culture derived trivalent influenza vaccine
TIVeA	Egg derived trivalent influenza vaccine
US(A)	United States (of America)
VE	Vaccine efficacy
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Flucelvax Quad
Active ingredient:	Influenza virus haemagglutinin
Decision:	Approved
Date of decision:	14 August 2020
Date of entry onto ARTG:	1 September 2020
ARTG numbers:	341450, 319093
▼ *Black Triangle Scheme*:[1]	No
Sponsor's name and address:	Seqirus Pty Limited 63 Poplar Road, Parkville, VIC, 3052
Dose form:	Suspension for injection
Strength:	60 µg (15 µg x 4) haemagglutinin/0.5 mL
Containers:	Syringe; and syringe with attached needle
Pack sizes:	1, 10
Approved therapeutic use:	*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.*
Route of administration:	Intramuscular
Dosage:	Adults and children from 9 year of age: a single 0.5 mL dose. For further information regarding dosage, refer to the Product Information (PI).

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Pregnancy 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.
	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 application by Seqirus Pty Ltd (the sponsor) to register Flucelvax Quad quadrivalent influenza vaccine (surface antigen, inactivated), suspension for injection for the following proposed 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*

Influenza, a respiratory orthomyxovirus, is a seasonal infectious disease that occurs in epidemics throughout the Northern Hemisphere (NH) and Southern Hemisphere (SH) winter months, and leads to considerable morbidity and mortality globally in all age groups. In general, influenza resolves within two to seven days, although symptoms of cough and malaise may be prolonged. However, for some population groups, notably the elderly and those with chronic diseases, influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia.[2,3] During influenza epidemics, there is an increased mortality risk among older adults (age > 65 years), people with chronic diseases, and very young children (age 0 to 12 months old), as well as an increase in morbidity and hospitalisation because of influenza-associated complications.[2]

Influenza A and B cause most human disease. Influenza A viruses are divided into subtypes based on two viral external proteins, haemagglutinin (HA) and neuraminidase (NA). Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are clinically the most important. Influenza type B viruses show extensive variation in antigenicity. Influenza B viruses are separated into two distinct genetic lineages, Yamagata and Victoria. In terms of infection, 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. Influenza epidemics have been associated with

[2] Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009 (58): 1-52.
[3] Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. *Am J Med* 2008 (121):258-64.

the circulation of type A/H3N2, type A/H1N1, and type B viruses, either individually or together.

Currently, based on viral surveillance data, an influenza B virus representing one of these two lineages is selected each year to be included in the annual vaccine. The cross protection against infection with one B lineage provided by immunisation with a vaccine derived from the other B lineage is uncertain, but expected to be low.[4] Predicting which lineage will predominate has been challenging, and in some seasons there has been a mismatch between the lineage chosen for the vaccine and the predominant circulating influenza B virus lineage. In Europe from 2003 to 2004 and through 2010, the predominant lineage of a given season differed from that contained in the vaccine in four out of eight seasons and overall an estimated 58% of laboratory confirmed influenza B samples were of the lineage not included in the vaccine.[5] Based on the demonstrated burden of influenza B, the limited cross-protection between the two influenza B lineages, and the inability to accurately predict which influenza B lineage will circulate, it may be expected that seasonal influenza vaccines will be improved by the inclusion of influenza B strains from both lineages. While a good antigenic match would still not be assured, this step would eliminate a mismatch in lineage between the vaccine strain and circulating strains.

Regulatory status

This product is considered to be a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in Canada (22 November 2019), European Union (EU) (12 December 2018), Switzerland (preliminary approval on 30 April 2020), Taiwan (23 March 2020) and the United States of America (USA) (23 May 2016).

Table 1: International regulatory history of Flucelvax Quad

Region	Submission date	Status	Approved indications
Brazil	6 December 2017	Approved on 26 February 2020	*For the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for persons 18 years of age and older*
Canada	3 October 2018	Approved on 22 November 2019	*For the active immunization of adults and children aged 9 years or older for the prevention of*

[4] Belshe, RB. The need for quadrivalent vaccine against seasonal influenza. *Vaccine* 2010 (28): D45-53.
[5] Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. *Hum Vaccin Immunother* 2012; (8):81-8.

Region	Submission date	Status	Approved indications
			influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.
EU (via centralised procedure) Rapporteur Spain; Co-rapporteur: France	31 October 2017	Approved on 12 December 2018	*Prophylaxis of influenza in adults and children from 9 years of age.*
Switzerland	15 March 2019	Preliminary approval on 30 April 2020	*Prophylaxis of influenza in adults and children from 9 years of age.*
Taiwan	2 September 2019	Approved on 23 March 2020	*For active immunization of children and adolescents 3 years of age and above for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine*
USA	20 November 2014	Approved on 23 May 2016	*For the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for persons 4 years of age and older.*

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-02591-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	14 January 2020
Sponsor provides responses on questions raised in first round evaluation	6 March 2020
Second round evaluation completed	6 May 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 May 2020
Sponsor's pre-Advisory Committee response	14 May 2020
Advisory Committee meeting	3 June 2020
Registration decision (Outcome)	14 August 2020
Completion of administrative activities and registration on the ARTG	1 September 2020
Number of working days from submission dossier acceptance to registration decision*	198

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There are no issues identified from the quality evaluation of the data, and information submitted in support of the registration of Flucelvax Quad (inactivated quadrivalent influenza vaccine surface antigen) that would indicate the product should not be registered on the basis of quality, or safety-related issues arising from the quality of the product.

All outstanding issues with regards to labels and PI are resolved prior to approval of Flucelvax Quad.

There are identified during the evaluation of the responses to the first round evaluation that the sponsor will need to address before the submission of the first annual strain update as a Category 3 submission.[6] The quality evaluator recommended a number of conditions of registration.

Proposed conditions of registration

- At least 45 working days before the submission of the first request under s.9D(3) of the Therapeutic Goods Act 1989 for a change to the strain composition of the vaccine, and not later than 31 October 2020, the additional requested quality data should be provided. The additional requested quality data should be provided prior to the lodgement of the annual strain update for the SH 2021 influenza season.
- Batch release testing**.** It is a condition of registration that all independent batches of Flucelvax Quad imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and the sponsor has received notification acknowledging release from the Laboratories Branch, TGA. For each independent batch of the product imported into Australia, the sponsor must supply the following:
  - A completed request for release form, available from vaccines@health.gov.au.
  - Complete summary protocols for manufacture and quality control (QC), including all steps in production.
  - At least 20 (twenty) doses of the first consignment of each batch of Flucelvax Quad with the Australian approved labels, PI and packaging.
  - At least 10 (ten) doses of any further consignment of each batch of Flucelvax Quad with the Australian approved labels, PI and packaging.
  - Certificate of Release from regulatory agency acting for the country of origin such as an official medicines control laboratory (OMCL) (if available).
  - Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

  Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.
- Certified Product Details: An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter.
- The sponsor must conduct an enhanced safety surveillance study in Australia, if requested by the TGA. A protocol for the proposed study will be required to be submitted with the annual strain update variation, if there is inadequate post-market safety data to demonstrate that the reactogenicity of that season's vaccine has been adequately characterised and the vaccine is not supplied on the National Immunisation Program in that season.

[6] A Category 3 application relates to changes to the quality data of medicines already included on the Australian Register of Therapeutic Goods (ARTG) which, in the opinion of the TGA, do not need to be supported by clinical, non-clinical or bioequivalence data.

Nonclinical

No nonclinical studies were conducted with the cell culture derived quadrivalent influenza vaccine (QIVc); previous studies with the cell culture derived trivalent vaccine (TIVc) Optaflu and some publications were submitted in nonclinical module. The trivalent vaccine was approved in Australia in 2015. New nonclinical studies with Flucelvax Quad are not warranted, consistent with the European Medicines Agency (EMA) guidance for a new influenza vaccine based on an existing manufacturing process provided comparative immunogenicity and efficacy is supported by clinical studies.[7]

The safety and immunogenicity of the QIVc were assessed mainly based on the previous evaluation of the already registered TIVc, Optaflu.

Immunogenicity was demonstrated for the TIVc in previously evaluated nonclinical studies. An immunogenicity study in mice with the TIVc compared the immunogenicity of in-process (monovalent bulk) egg-derived and cell culture-derived antigens, and showed no significant difference between the antigens produced by the two systems. Two published studies described various aspects of the administration of inactivated trivalent influenza vaccines in mice and are of limited relevance to this submission.

In previously evaluated toxicity studies with the TIVc, local injection site reactions were observed in repeat dose toxicity study in rabbits which are common in influenza vaccines administered intramuscularly. A repeat dose toxicity study and a reproductive toxicity study (investigating fertility, embryofetal development and postnatal development) in rabbits with the TIVc showed no evidence of significant local or systemic toxicity. There are no safety concerns over the QIVc based on the studies with the TIVc.

There are no studies in juvenile animals for the paediatric indication. The efficacy and safety in children are best addressed by clinical studies.

The nonclinical evaluator recommended PI changes in the nonclinical evaluation report [inclusion is beyond the scope of the AusPAR document].

The nonclinical safety specifications based on nonclinical studies with the trivalent vaccine detailed in the sponsor's draft risk management plan (RMP) are in general concordance with those of the nonclinical evaluator.

There are no nonclinical objections to registration of Flucelvax Quad vaccine based on previously evaluated nonclinical studies with the trivalent vaccine, Optaflu. However, evaluation of efficacy and safety of the QIVc in adults and children will largely rely on clinical data.

Clinical

The clinical dossier consisted of:

- 10 Phase III clinical studies;
- 6 Phase II clinical studies;
- 2 Phase I clinical studies; and
- 1 observational study.

[7] **EMA/CHMP/VWP/457259/2014**: European Medicine Agency Guideline on Influenza Vaccines, Non-clinical and Clinical Module.

Pharmacology

Pharmacokinetic studies are usually not required for vaccines.[8]

Efficacy

Efficacy study overview

Two efficacy (immunogenicity endpoint) studies that investigated the quadrivalent vaccine (Flucelvax Quad) were included:

- Study V130_01: A Phase III, stratified, randomised, double-blind, multicentre, non-inferiority study to evaluate the safety and immunogenicity of Flucelvax Quad compared to TIV1c/TIV2c in 2680 adults aged ≥ 18 years old.
- Study V130_03: A Phase III, stratified, randomised, double-blind, multicentre, non-inferiority study to evaluate the safety and immunogenicity of Flucelvax Quad compared to TIV1c/TIV2c in 2333 children (previously vaccinated or not previously vaccinated) aged 4 to < 18 years old.

One main efficacy (true vaccine efficacy endpoint) study investigated the cell based trivalent vaccine, and has been evaluated previously in submission of Optaflu. It forms the efficacy basis for the two immunogenicity endpoint studies shown above:

- Study V58P13: A Phase III, randomised, observer-blind, multicentre efficacy and immunogenicity study to compare TIVc (Optaflu) or egg derived trivalent vaccine (TIVeA) to placebo in 11,404 adults aged 18 to 49 years old.

The remaining efficacy/immunogenicity studies investigated the trivalent vaccine (Optaflu). Those studies are supportive to the current application, and most of those have been evaluated previously in submission of Optaflu, namely Studies V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58_23, V58P12, V58_31, and V58P16.

Study V130_01 and Study V130_03 are considered the pivotal trials with nearly identical study design (including the same strains used in in the 2013 to 2014 season, and the same comparator vaccines) with the major differences relating to the age group investigated.

In the pivotal clinical trials, a total of 2493 subjects were exposed to Flucelvax Quad. 1334 adults (≥ 18 years) were exposed in Study V130_01, and 1159 paediatric subjects (aged 4 to < 18 years) were exposed in Study V130_03.

An overview of vaccines used in the clinical studies (main studies only) is shown in Table 3.

Table 3: Overview of vaccines used in the clinical studies (main studies only)

Vaccine	Significance
QIVc (Flucelvax Quad)	Used in Studies V130_01 and V130_03: Quadrivalent cell-culture derived influenza vaccine under evaluation in this submission
TIVc (Flucelvax/Optaflu)	Used in Study V58P13: Trivalent cell-culture derived influenza vaccine under evaluation in the Optaflu submission; provides supportive data for this submission

[8] **CPMP/ICH/295/95,** EMEA, Committee for Proprietary Medicinal Products (CPMP), 2005. Guideline on clinical evaluation of vaccines.

Vaccine	Significance
	In parts of the dossier referred to as CCI (cell culture-derived influenza virus vaccine; not to be confused with culture-confirmed illness)
TIVeA (Agrippal)	Used in Study V58P13: Comparator trivalent egg-derived influenza virus vaccine (IVV) vaccine; provides supportive data for this submission In parts of the dossier referred to as IVV
TIV1c	Used in Studies V130_01 and V130_03: TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts)
TIV2c	Used in Studies V130_01 and V130_03: TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage

Study V130_01

This was a Phase III, stratified, randomised, double blind, multicentre (40 centres in the USA), non-inferiority study to evaluate the safety and immunogenicity of Flucelvax Quad compared to TIV1c/TIV2c in 2680 adults aged ≥ 18 years of age between November 2013 and July 2014.

The population was randomised 2:1:1 to receive QIVc, TIV1c, or TIV2c, and further analysed by age cohort (≥ 18 years to < 65 years, and ≥ 65 years).

The primary non-inferiority objective was assessed by the ratio of geometric mean titre (GMTs) and difference in seroconversion rates at Day 1 and 22, for each strain. Secondary objectives included superiority assessment using the same variables. Safety follow-up occurred until Day 181.

For the non-inferiority and superiority analyses, the criteria used are specified in Table 4.

Table 4: Study V130_01 Treatments and conditions (15 µg of haemagglutinin for each strain)

QIVc (Flucelvax Quad) (n = 1335)	TIV1c (Flucelvax) (n = 676)	TIV2c (n = 669)
A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Massachusetts/2/2012 (B1) B/Brisbane/60/2008 (B2)	A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Massachusetts/2/2012 (B1)	A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Brisbane/60/2008 (B2)

Magnitude of the treatment effect and its clinical significance

Demographic and other baseline characteristics were well balanced among the groups. Across all groups, the mean age was about 57 years. The majority were Caucasian (75.6% to 78.5% across groups), and female (54.8% to 58.6%). The total number of subjects > 75 years of age in the per protocol population was 315, of which 150, 83 and 82 were enrolled to receive QIVc, TIV1c and TIV2c, respectively.

Primary analysis: At Day 22, pre-specified non-inferiority criteria (as assessed by the ratio of GMTs and differences in seroconversion rates) were achieved for all 4 strains, indicating non-inferiority of QIVc vaccine over the TIV1c for the 3 influenza strains (A/H1N1, A/H3N2 and B1) and TIV2c vaccine for the B2 influenza strain (Table 5).

Table 5: Study V130_01 Primary analysis: non-inferiority of QIVc to TIVc in subjects ≥ 18 years of age using hemagglutination inhibition assay (geometric mean titre and seroconversion as per protocol set)

	Day 22	QIVc N = 1250	TIV1c/TIV2c[a] N = 635/N = 639	Vaccine Group Ratio[b] (95% CI)	Vaccine Group Difference[c] (95% CI)
A/H1N1	GMT (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-**1.1**)	NA
	Seroconversion Rate[d] (95% CI)	49.2% (46.4%-52.0%)	48.7% (44.7%-52.6%)	NA	-0.5% (-5.3%-**4.2%**)
A/H3N2	GMT (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-**1.1**)	NA
	Seroconversion Rate[d] (95% CI)	38.3% (35.6%-41.1%)	35.6% (31.9%-39.5%)	NA	-2.7% (-7.2%-**1.9%**)
B1	GMT (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-**1.0**)	NA
	Seroconversion Rate[d] (95% CI)	36.6% (33.9%-39.3%)	34.8% (31.1%-38.7%)	NA	-1.8% (-6.2%-**2.8%**)
B2	GMT (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-**1.0**)	NA
	Seroconversion Rate[d] (95% CI)	39.8% (37.0%-42.5%)	35.4% (31.7%-39.2%)	NA	-4.4% (-8.9%-**0.2%**)

[a] The comparator vaccine for non inferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, and for B2 is TIV2c.
[b] $GMT_{TIV1c/TIV2c}/GMT_{QIVc}$
[c] Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc
[d] Seroconversion rate = percentage of subject with either a pre-vaccination HI titre < 1:10 and post vaccination HI titre ≥ 1:40 or with a pre-vaccination HI titre ≥ 1:10 and a minimum 4-fold increase in post vaccination H1 antibody titre.
Bold = Non inferiority criterion met.
Abbreviations: NA = not applicable; GMT = geometric mean titre; CI = confidence interval

Age stratification: In subjects ≥ 18 to < 65 years of age, at Day 22, the QIVc and the TIV1c/TIV2c groups met both CBER immunogenicity criteria for seroconversion and HI titre ≥ 1:40 against all 4 influenza strains. In subjects ≥ 65 years of age, the HI titre criterion was met for all strains, but the seroconversion criterion was only met for H1N1, but not the others (for both QIVC, and TIV1c/TIV2c (see Table 6)).

Table 6: Study V130_01 Immunogenicity analysis by age stratum using hemagglutination inhibition assay (geometric mean titre and seroconversion for full analysis set)

		18 to < 65 Years of Age		≥ 65 Years of Age	
	Day 22	QIVc N = 661	TIV1c/TIV2c[a] N = 328/N = 326	QIVc N = 650	TIV1c/TIV2c[a] N = 336/N = 332
A/H1N1	HI Titer ≥ 1:40	98.5% (**97.2%**-99.3%)	97.0% (**94.5%**-98.5%)	94.3% (**92.2%**-96.0%)	96.1% (**93.5%**-97.9%)
	Seroconversion Rate[b]	63.1% (**59.3%**-66.8%)	60.4% (**54.8%**-65.7%)	34.5% (**30.8%**-38.3%)	36.9% (**31.7%**-42.3%)
A/H3N2	HI Titer ≥ 1:40	98.6% (**97.4%**-99.4%)	99.1% (**97.4%**-99.8%)	98.3% (**97.0%**-99.2%)	98.2% (**96.2%**-99.3%)
	Seroconversion Rate[b]	49.2% (**45.3%**-53.1%)	47.3% (**41.7%**-52.8%)	27.2% (23.8%-30.8%)	24.7% (20.2%-29.7%)
B1	HI Titer ≥ 40	95.6% (**93.8%**-97.0%)	95.7% (**92.9%**-97.6%)	92.2% (**89.8%**-94.1%)	87.8% (**83.8%**-91.1%)
	Seroconversion Rate[b]	52.0% (**48.2%**-55.9%)	50.3% (**44.8%**-55.8%)	20.9% (17.9%-24.3%)	19.3% (15.3%-24.0%)
B2	HI Titer ≥ 40	99.1% (**98.0%**-99.7%)	98.8% (**96.9%**-99.7%)	96.2% (**94.4%**-97.5%)	95.2% (**92.3%**-97.2%)
	Seroconversion Rate[b]	52.8% (**48.9%**-56.7%)	50.3% (**44.7%**-55.9%)	26.3% (23.0%-29.9%)	20.8% (16.5%-25.6%)

Abbreviations: CBER = Center for Biologics Evaluation and Research; HI = hemagglutination inhibition; FAS = full analysis set; HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40; CI = confidence interval.
[a] The comparator vaccine for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 the comparator vaccine is TIV2c.
[b] Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.
Bold = CBER criterion for immunogenicity met CBER criteria for adults < 65 years of age and for the pediatric population: The lower bound of the 2-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%, and the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%. For adults ≥ 65 years of age: The lower bound of the 2-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30% and the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.
Figures in parentheses are 95% confidence intervals.

Results using Committee for Medicinal Products for Human Use (CHMP) criteria: These were generally similar to the results using the FDA's Center for Biologics Evaluation and Research (CBER) criteria.

Superiority analysis: Superiority was demonstrated for both influenza B strains in QIVc as compared to unmatched influenza B strain in TIV1c and TIV2c vaccines as assessed by the ratio of GMTs and differences in seroconversion rates.

Subgroup analysis: The majority of subjects were Caucasian (QIVc: 76.1%, TIV1c: 77.3%, TIV2c: 79.2%), followed by Black (QIVc: 13.0%, TIV1c: 11.5%, TIV2c: 11.4%) and Hispanic (QIVc: 9.0%, TIV1c: 8.5%, TIV2c: 7.8%). The results were similar between ethnic subgroups, but for all 4 strains in all vaccine groups. GMTs and seroconversion rates were generally lower in the Caucasian population when compared to Black and Hispanic subjects. However, there were large differences in sample size for Black (QIVc: 163, TIV1c and TIV2c: 73) and Hispanic subjects (QIVc: 113, TIV1c: 54, TIV2c: 50) when compared to Caucasian subjects (QIVc: 951, TIV1c: 491, TIV2c: 506), as well as differences in distribution within the different age subgroups (18 to < 65 and ≥ 65 years of age).

Post hoc analysis of subjects > 75 years of age (requested by EMA): The immune responses were less robust compared to the overall elderly group ≥ 65 years of age, but similar when compared to the TIVc results in the same age group.

Study V130_03

This was a Phase III, stratified, randomised, double-blind, multicentre (90 centres in the USA), non-inferiority study to evaluate the safety and immunogenicity of Flucelvax Quad compared to TIV1c/TIV2c in 2333 children (previously vaccinated or not previously vaccinated) aged 4 to < 18 years between November 2013 and August 2014.

The population was randomised 2:1:1 to receive QIVc, TIV1c, or TIV2c, and further analysed by vaccination status. Enrolled subjects were first split into age cohorts based on age at time of enrolment (≥ 4 to < 9 years of age and ≥9 to < 18 years of age). Subjects (≥ 4 to < 9 years of age) were further stratified as 'previously vaccinated' (would receive 1 vaccination) and "not previously vaccinated" (would receive 2 vaccinations approximately 4 weeks apart).

The primary non-inferiority objective was assessed by the ratio of GMTs and difference in seroconversion rates at Days 1 and 22 (for previously vaccinated subjects) or Day 1 and 50 (for not previously vaccinated subjects), for each strain. Secondary objectives included superiority assessment using the same variables (B strains only). Safety follow-up occurred until Day 181 (for previously vaccinated subjects) or Day 210 (for not previously vaccinated subjects).

For the non-inferiority and superiority analyses, the criteria used are specified in Table 7.

Table 7. Study V130_03 Assessment criteria

CBER Criteria for Immunogenicity	**< 18 years of age**
Lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥ 1:40	≥ 70%
Lower bound of the 2-sided 95% CI for seroconversion[a]	≥ 40%
CBER Criteria for Noninferiority	
Upper bound of the 2-sided 95% CI on the ratio[b] of the GMTs	≤ 1.5
Upper bound of the 2-sided 95% CI on the difference[c] between seroconversion[a] rates	≤ 10%
Criteria for Superiority	**All Ages**
Upper bound of the 2-sided 95% CI on the ratio[b] of the GMTs	≤ 1
Upper bound of the 2-sided 95% CI on the difference[c] between seroconversion[a] rates	≤ 0%

Source: criteria for noninferiority derived from CBER Guidance for Industry - Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, May 2007. Criteria for superiority were predefined in section 5.3.5.1, CSR V130_03 section 9.7.1.
Abbreviations: CBER = Center for Biologics Evaluation and Research; CI = confidence interval; HI = hemagglutination inhibition; GMT = geometric mean titer.
[a] Seroconversion = either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.
[b] Ratio of GMTs = $GMT_{TIV1c \text{ or } TIV2c}$ / GMT_{QIVc}.
[c] Difference between seroconversion rates = % seroconversion TIV1c or TIV2c - % seroconversion QIVc.

Table 8: Study V130_03 Treatment and conditions (15 µg of haemagglutinin per strain)

QIVc (Flucelvax Quad) (n = 1159)	TIV1c (Flucelvax) (n = 593)	TIV2c (n = 581)
A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Massachusetts/2/2012 (B1) B/Brisbane/60/2008 (B2)	A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Massachusetts/2/2012 (B1)	A/Brisbane/10/2010 (H1N1) A/Texas/50/2012 NYMC X-223A (H3N2) B/Brisbane/60/2008 (B2)

Magnitude of the treatment effect and its clinical significance

A total of 2333 subjects were enrolled. Of these, 1159 subjects were enrolled in QIVc group, 593 subjects in TIV1c group and 581 subjects in TIV2c group. Demographic and other baseline characteristics were well balanced. Across all groups, the mean age of subjects was about 9.5 years; weight was about 40 to 41 kg and height was about 139 cm. The majority of the enrolled subjects across the 3 groups were Caucasian 53% to 54% followed by Black 20% to 23% and Hispanic 19% to 21%. The proportion of male and female subjects were similar across the 3 groups.

Primary analysis: At Day 22 or Day 50, pre-specified non-inferiority criteria (as assessed by the ratio of GMTs and differences in seroconversion rates) were achieved for all 4 strains, indicating non-inferiority of QIVc vaccine over the TIV1c for the 3 influenza strains (A/H1N1, A/H3N2 and B1) and TIV2c vaccine for B2 influenza strain (Table 9).

Table 9. Study V130_03 Non-inferiority of QIVc to TIVc in subjects 4 to < 18 years of age using hemagglutination inhibition assay (geometric mean titre and seroconversion as per protocol set)

	Day 22/Day 50[a]	QIVc	TIV1c/TIV2c[b]	Vaccine Group Ratio[c]	Vaccine Group Difference[d]
A/H1N1		N = 1014	N = 510		
	GMT (95% CI)	1090 (1027-1157)	1125 (1034-1224)	1.03 (0.93-**1.14**)	NA
	Seroconversion Rate[e] (95% CI)	72% (69%-75%)	75% (70%-78%)	NA	2% (-2.5%-**6.9%**)
A/H3N2		N = 1013	N = 510		
	GMT (95% CI)	738 (703-774)	776 (725-831)	1.05 (0.97-**1.14**)	NA
	Seroconversion Rate[e] (95% CI)	47% (44%-50%)	51% (46%-55%)	NA	4% (-1.4%-**9.2%**)
B1		N = 1013	N = 510		
	GMT (95% CI)	155 (146-165)	154 (141-168)	0.99 (0.89-**1.1**)	NA
	Seroconversion Rate[e] (95% CI)	66% (63%-69%)	66% (62%-70%)	NA	0% (-5.5%-**4.5%**)
B2		N = 1009	N = 501		
	GMT (95% CI)	185 (171-200)	185 (166-207)	1 (0.87-**1.14**)	NA
	Seroconversion Rate[e] (95% CI)	73% (70%-76%)	71% (67%-75%)	NA	-2% (-6.5%-**3.2%**)

[a] Analyses are performed on data for Day 22 for previously vaccinated subjects and Day 50 for not previously vaccinated subjects.
[b] The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for the B2 strain the comparator vaccine is TIV2c.
[c] $GMT_{TIV1c/TIV2c}/GMT_{QIVc}$.
[d] Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc.
[e] Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.
Noninferiority criteria; The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV1c} or $_{TIV2c}$ $/GMT_{QIVc}$) for HI antibody should not exceed the noninferiority margin of 1.5. The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%.
Bold = Noninferiority criterion met.

Abbreviations: NA = not applicable; GMT = geometric mean titre; CI = confidence interval

Additional results using CBER or CHMP criteria: At Day 22 or Day 50, both CBER immunogenicity criteria and all 3 CHMP immunogenicity criteria for seroconversion and HI titre ≥ 1:40 were met for A/H1N1, A/H3N2, B1 and B2 influenza strains by the QIVc and the TIV1c/TIV2c vaccines.

Superiority analysis: Superiority was demonstrated for both influenza B strains in QIVc as compared to unmatched influenza B strain in TIV1c and TIV2c vaccines as assessed by the ratio of GMTs and differences in seroconversion rates.

Subgroup analyses:

- subjects with Baseline HI titre < 1:10 vs. titre ≥ 1:10: At Day 22 or Day 50, the proportion of subjects achieving seroconversion and HI titre ≥ 1:40 were comparable between groups for all strains.
- previously vaccinated and not previously vaccinated subjects: In previously vaccinated subjects, at Day 22, in both age strata, the proportion of subjects achieving seroconversion and HI titre ≥ 1:40 was comparable between groups, except: in

subjects ≥ 9 to < 18 years of age, for A/H3N2, the proportion of subjects achieving seroconversion was lower for QIVc vs. TIV1c/TIV2c. In not previously vaccinated subjects aged 4 to < 9 years, at Day 50, the proportion of subjects achieving seroconversion and HI titre ≥ 1:40 were comparable between groups for all strains.

Study V58P13

This was a Phase III, randomised, observer-blind, multicentre (17 centres in US, 15 centres in Finland, and 24 centres in Poland) efficacy and immunogenicity (in a subset) study conducted in 11404 healthy adults 18 to 49 years of age in the 2007 to 2008 influenza season (study dates: 9 October 2007 to 8 July 2008). The population was randomised 1:1:1 to receive TIVc, TIVeA, or placebo.

A total of 3818 subjects in the TIVc group, 3668 subjects in the TIVeA group and 3896 subjects in the placebo group were vaccinated. A subset of 978 subjects were included in the immunogenicity per protocol subset, 228 in the TIVc group, 695 in the TIVeA group and 55 in the placebo group.

Table 10: Study V58P13 Treatment and conditions (15 µg of haemagglutinin for each strain)

TIVc (Flucelvax/Optaflu)	TIVeA (IIV) (Agrippal)	Placebo
A/Solomon Islands/3/2006 (H1N1)-like A/Wisconsin/67/2005 (H3N2)-like B/Malaysia/2506/2004-like	A/Solomon Islands/3/2006 (H1N1)-like A/Wisconsin/67/2005 (H3N2)-like B/Malaysia/2506/2004-like	No active component

Magnitude of the treatment effect and its clinical significance

Primary efficacy objectives, primary analysis: Both TIVc and TIVeA met the pre-specified criteria for estimating absolute vaccine efficacy (VE) against placebo (TIVc: overall VE of 83.8% with 97.5% CI lower limit (LL) of 61%; TIVeA: overall VE of 78.4% with 97.5% CI LL of 52.1%) (Table 11). The H1N1 strain was matched for that season.

For the B strain, the VE was 100%, as no influenza cases were reported in the TIVc vaccine group, while one case was reported in the placebo group. For the A/H3N2 strain, the VE of the TIVc vaccine vs. placebo was considered not evaluable since no influenza case was observed in the placebo group.

Secondary efficacy objectives, VE against non-vaccine-like strains: Neither TIVc and TIVeA met the pre-specified CBER criteria for estimating VE against placebo for preventing virus-confirmed symptomatic influenza A or B illness caused by non-vaccine-like strains (TIVc: overall VE of 58.7% with 97.5% CI LL of 33.5%; TIVeA: overall VE of 58.6% with 97.5% CI LL of 32.9%).

Secondary efficacy objectives, VE against circulating strains: Both TIVc and TIVeA met the pre-specified CBER criteria for estimating vaccine efficacy (VE) against placebo for preventing virus-confirmed symptomatic influenza A or B illness caused by circulating (vaccine-matched, non-vaccine-matched and not further specified) strains (TIVc: overall VE of 69.5% with 97.5% CI LL of 55.0%; TIVeA: overall VE of 63.0% with 97.5% CI LL of 46.7%).

Among the subset of subjects in the per protocol (PP) efficacy population who had culture confirmed influenza and non-missing influenza-like illness (ILI) follow-up data, there was no significant difference between the influenza vaccine groups and placebo in the mean number of days in bed, mean number of inpatient/outpatient visits due to influenza, or the mean number of days of usual activity lost due to influenza. However, when considering

the whole PP efficacy population, there was a statistically significant difference between TIVc and placebo in the mean number of days in bed due to culture-confirmed influenza (TIVc: mean = 0.04 days (n = 3775); placebo: mean = 0.12 days (n = 3837); p< 0.0001) and TIVeA and placebo (TIVeA mean = 0.04 days (n = 3668); placebo mean = 0.12 days (n = 3837); p< 0.0001).

Table 11: Study V58P13 Vaccine efficacy against culture-confirmed influenza caused by vaccine-like strains, subjects 18 to < 50 years of age (per protocol set)

	Proportion of Subjects with Influenza (# Subjects)			VE (%) (LL of 1-Sided 97.5% Simultaneous CI of VE[a])		P-value[b]	
	TIVc N = 3776	TIVeA N = 3638	Placebo N = 3843	TIVc vs. Placebo	TIVeA vs. Placebo	TIVc vs. Placebo	TIVeA vs. Placebo
Overall	0.0019 (7/3776)	0.0025 (9/3638)	0.0114 (44/3843)	83.8 (61.0)	78.4 (52.1)	0.0005*	0.0035*
A/H3N2	0.0005 (2/3776)	0.0003 (1/3638)	0 (0/3843)	N/E	N/E	0.9989	0.9915
A/H1N1	0.0013 (5/3776)	0.0022 (8/3638)	0.0112 (43/3843)	88.2 (67.4)	80.3 (54.7)	0.0001*	0.0022*
B	0 (0/3776)	0 (0/3638)	0.0003 (1/3843)	100.0 (-410.0)	100.0 (-429.4)	0.3936	0.4002

Abbreviations: PPS = per protocol set; VE = vaccine efficacy = (1 - relative risk) x 100%; LL = lower limit; CI = confidence interval; N/E = Not evaluable; TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal).
[a] Simultaneous 1-sided 97.5% confidence intervals for the vaccine efficacy (VE) of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the 2 relative risks.
[b] Adjusted p-values are from the score statistic with Sidak correction testing the null hypothesis that the vaccine efficacy of each influenza vaccine relative to placebo ≤ 40% against the alternative hypothesis that the VE > 40% (or equivalently, the null hypothesis that the relative risk ≥ 0.60 vs. the alternative hypothesis that the relative risk < 0.60). If the adjusted p-value is < 0.025, then the comparison is statistically significant.
* p < 0.025.

Immunogenicity: Both the CBER criteria for seroconversion and for HI titre ≥ 40 were met for all 3 strains in both the TIVc and TIVeA groups at Day 22. Conversely, none of the criteria were met by the placebo group.

Other efficacy studies

Additional studies with an efficacy component (to evaluate TIVc, and mostly previously evaluated) were provided in the dossier: Studies V58P13, V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58_23, V58P12, and V58P16.

Overall, those studies with TIVc were generally supportive of the pivotal trials for QIVc. Additional evaluator comments are summarised below.

Adults and elderly: Overall, outcomes as evaluated by post-vaccination GMTs, geometric mean ratios and seroconversion rates across all the studies in adults 18 to < 65 years of age, elderly ≥ 65 years of age and elderly > 75 years of age, indicate robust and consistent immune responses to a given antigen, whether it is contained in a cell-based TIV, an egg-based TIV, or a quadrivalent cell-based vaccine formulation (QIVc).

Paediatric subjects: Results obtained with the QIVc vaccine were consistent with results obtained with the TIVc vaccines in this age group.

Safety

Exposure

The only studies that administered Flucelvax Quad (QIVc) were the pivotal studies, Studies V130_01 and V130_03 (monitoring periods are shown in Table 12).

- Adult (≥ 18 years of age) exposure: 2680 subjects were exposed in Study V130_01, 1334 of those received QIVc (see Table 13).
- Paediatric (4 to < 18 years of age) exposure: 2332 subjects were exposed in Study V130_03, 1159 of those received QIVc (see Table 14).

Solicited adverse event overview

Adults (≥ 18 years of age) (Study V130_01)

The percentage of subjects with solicited local adverse events (AE) was higher in the QIVc group compared to TIV1c and TIV2c (41.8%, 35.8% and 36.5%, respectively). Overall, the most common solicited local AE was injection site pain (33.6%, 27.8%, 29.4% respectively)

Similar proportions of subjects in the QIVc, TIV1c, and TIV2c groups reported solicited systemic AEs (28.5%, 28.7%, 29.3% respectively). Overall, the most common solicited systemic AEs were headache (14.0%, 13.4%, 13.4%), fatigue (13.5%, 16.3%, 12.2%) and myalgia (11.8%, 11.9%, 11.6%)).

Most subjects had a body temperature within normal range (< 38.0°C) after receiving a study vaccination, and < 1% of subjects in all groups had a body temperature ≥ 38°C. No subject reported a body temperature ≥ 40°C. The proportion who reported other solicited reactions (analgesic and antipyretic use) was similar between groups (5.0%, 3.0%, 4.5%).

Children (4 to < 18 years of age) (Study V130_03)

In general, solicited AE reporting rates were similar between groups. Solicited AEs were reported by 72%, 71%, and 67% of subjects in the QIVc, TIV1c, and TIV2c groups, respectively. Most subjects reported local AEs (66%, 65%, 60%), while fewer reported systemic AEs (38%, 39%, 34%).

Table 12: Study V130_03 Solicited local adverse events reported in subjects 9 to < 18 years of age

Vaccine Group		Number (%) of Subjects		
		QIVc N = 579	TIV1c N = 294	TIV2c N = 282
Injection site pain	Any	334 (58)	150 (51)	142 (50)
	Severe	4 (1)	1 (< 1)	0
Injection site induration	Any	88 (15)	43 (15)	36 (13)
	Severe (> 100 mm)	0	0	1 (< 1)
Injection site erythema	Any	110 (19)	51 (17)	43 (15)
	Severe (> 100 mm)	2 (< 1)	0	1 (< 1)
Injection site ecchymosis	Any	24 (4)	16 (5)	13 (5)[a]
	Severe (> 100 mm)	0	0	0

Solicited AEs were reported from Day 1including 30 min data through Day 7.
[a] N = 281.

Local AEs: The most common solicited local AEs were injection site pain (4 to < 18 years of age) (59%, 58%, and 57%) or injection site tenderness (4 to < 6 years of age) (55%, 51%,

and 48%). Severe injection site pain was reported by 1% in all 3 vaccine groups, while severe injection site tenderness was reported by 2%, 1%, and 2%. Other common solicited local AEs included injection site erythema (21%, 21%, and 19%) and injection site induration (16%, 18%, and 14%). Severe erythema and induration were reported by ≤ 1% in any group. Most of the solicited local AEs had their onset from 6 hours to 2 days after the vaccination.

Generally, smaller proportions of subjects 4 to < 6 years of age reported individual solicited local AEs with the second vaccination (except for: injection site tenderness in the QIVc group). Among the subjects who received a second vaccination, the most commonly reported solicited local AEs was injection site tenderness (50%, 38%, 32%) followed by erythema (17%, 8%, 15%), induration (11%, 5%, 9%) and ecchymosis (6%, 8%, 4%).

Generally, a smaller proportion of subjects 6 to < 9 years of age reported individual solicited local AEs with the second vaccination and the proportions were similar between groups (for example. injection site pain (46%, 54%, 53%)).

Table 13: Study V130_03 Solicited systemic adverse events reported in subjects 4 to < 18 years of age

	Number (%) of Subjects		
Vaccine Group	**QIVc**	**TIV1c**	**TIV2c**
Chills	**N = 1135**	**N = 570**	**N = 563**
Any	71 (6)	29 (5)	20 (4)
Severe	3 (< 1)	5 (1)	2 (< 1)
Nausea	**N = 952**	**N = 479**	**N = 469**
Any	90 (9)	37 (8)	34 (7)
Severe	6 (1)	2 (< 1)	3 (1)
Myalgia	**N = 952**	**N = 479**	**N = 469**
Any	150 (16)	83 (17)	66 (14)
Severe	5 (1)	2 (< 1)	8 (< 1)
Arthralgia	**N = 952**	**N = 479**	**N = 469**
Any	55 (6)	32 (7)	31 (7)
Severe	0	1 (< 1)	1 (< 1)
Headache	**N = 952**	**N = 479**	**N = 469**
Any	186 (20)	97 (20)	77 (16)
Severe	8 (1)	7 (1)	3 (1)
Fatigue	**N = 952**	**N = 479**	**N = 469**
Any	163 (17)	80 (17)	79 (17)
Severe	10 (1)	6 (1)	1 (< 1)
Vomiting	**N = 1135**	**N = 570**	**N = 563**
Any	39 (3)	14 (2)	14 (2)
Severe	2 (< 1)	0	0
Diarrhea	**N = 1135**	**N = 570**	**N = 563**
Any	47 (4)	29 (5)	23 (4)
Severe	1 (< 1)	1 (< 1)	1 (<1%)
Loss of appetite	**N = 952**	**N = 479**	**N = 469**
Any	90 (9)	42 (9)	44 (9)
Severe	1 (< 1)	1 (< 1)	1 (< 1)
Change in Eating Habits	**N = 183**	**N = 91**	**N = 94**
Any	25 (14)	7 (8)	7 (7)
Severe	1 (1)	4 (4)	0
Sleepiness	**N = 183**	**N = 91**	**N = 94**
Any	39 (21)	12 (13)	13 (14)
Severe	2 (1)	3 (3)	1 (1)
Irritability	**N = 183**	**N = 91**	**N = 94**
Any	35 (19)	13 (14)	14 (15)
Severe	3 (2)	2 (2)	1 (1)
Fever	**N = 1135**	**N = 570**	**N = 563**
≥ 38.0 °C	39 (3)	20 (4)	13 (2)

Solicited AEs were reported from Day 1including 30 min data through Day 7.

Systemic AEs: In the 4 to < 18 years of age group, the most common individual solicited systemic AEs were headache (20%, 20%, 16%), fatigue (17%, 17%, 17%), myalgia (16%, 17%, 14%) (Table 13).

In subjects 4 to < 6 years of age, the most common individual solicited systemic AEs were sleepiness (21%, 13%, 14%), irritability (19%, 14%, 15%), and change in eating habits (14%, 8%, 7%) (Table 13).

Individual solicited systemic AEs were mostly similar across the 3 groups, except that more subjects 4 to < 6 years of age in the QIVc group experienced a change in eating habits, sleepiness, and irritability compared to TIV1c/TIV2c.

Most of the solicited systemic AEs had their onset from 6 hours to 2 days after the vaccination.

Severe, solicited systemic AEs were infrequent. Those experienced by > 1% were change in eating habits in the TIV1c group (4%), sleepiness in the TIV1c group (3%), and irritability (2% in the QIVc and TIV1c groups). Fever (body temperature ≥ 38.0°C) was reported by similar proportion across groups (3%, 4%, 2%).

Unsolicited adverse event overview

Adults (≥ 18 years of age) (Study V130_01)

Similar proportions of subjects in the QIVc (16.1%), TIV1c (14.7%), and TIV2c (16.5%) groups reported unsolicited AEs from Day 1 through Day 22 after vaccination (see Table 14). The proportion of AEs judged by the investigator as possibly/probably related to the study vaccine were also similar across the groups (3.9%, 3.1%, 4.2%). Most unsolicited AEs were mild to moderate in severity. The majority were regarded as resolved or stabilised at the time of study end. There were 2 cases of confirmed influenza.

Table 14: Study V130_01 Unsolicited adverse events reported in subjects ≥ 18 years of age by medical dictionary for regulatory activities preferred term (> 1% after any vaccination), by age group and overall

	Number (%) of Subjects								
	18 to < 65 Years of Age			≥ 65 Years of Age			≥ 18 Years of Age		
Preferred Term	QIVc N = 665	TIV1c N = 330	TIV2c N = 328	QIVc N = 659	TIV1c N = 343	TIV2c N = 337	QIVc N = 1324	TIV1c N = 673	TIV2c N = 665
Upper resp. tract infection	23 (3.5)	9 (2.7)	15 (4.6)	22 (3.3)	12 (3.5)	11 (3.3)	45 (3.4)	21 (3.1)	26 (3.9)
Nasopharyngitis	20 (3.0)	8 (2.4)	9 (2.7)	29 (4.4)	14 (4.1)	11 (3.3)	49 (3.7)	22 (3.3)	20 (3.0)
Sinusitis	16 (2.4)	10 (3.0)	9 (2.7)	10 (1.5)	11 (3.2)	9 (2.7)	26 (2.0)	21 (3.1)	18 (2.7)
Cough	8 (1.2)	7 (2.1)	6 (1.8)	14 (2.1)	17 (5.0)	11 (3.3)	22 (1.7)	24 (3.6)	17 (2.6)
Bronchitis	12 (1.8)	5 (1.5)	2 (0.6)	19 (2.9)	5 (1.5)	4 (1.2)	31 (2.3)	10 (1.5)	6 (0.9)
Urinary tract infection	11 (1.7)	2 (0.6)	1 (0.3)	15 (2.3)	6 (1.7)	5 (1.5)	26 (2.0)	8 (1.2)	6 (0.9)
Arthralgia	6 (0.9)	3 (0.9)	6 (1.8)	9 (1.4)	12 (3.5)	5 (1.5)	14 (1.1)	15 (2.2)	10 (1.5)
Oropharyngeal pain	10 (1.5)	5 (1.5)	5 (1.5)	8 (1.2)	6 (1.7)	5 (1.5)	18 (1.4)	11 (1.6)	10 (1.5)
Diarrhoea	10 (1.5)	4 (1.2)	3 (0.9)	7 (1.1)	9 (2.6)	4 (1.2)	17 (1.3)	13 (1.9)	7 (1.1)
Rhinorrhea	6 (0.9)	3 (0.9)	2 (0.6)	7 (1.1)	9 (2.6)	7 (2.1)	13 (1.0)	12 (1.8)	9 (1.4)
Headache	12 (1.8)	1 (0.3)	5 (1.5)	4 (0.6)	6 (1.7)	5 (1.5)	16 (1.2)	7 (1.0)	10 (1.5)
Influenza-like illness	13 (2.0)	3 (0.9)	6 (1.8)	4 (0.6)	3 (0.9)	4 (1.2)	17 (1.3)	6 (0.9)	10 (1.5)
Nasal congestion	4 (0.6)	4 (1.2)	4 (1.2)	7 (1.1)	6 (1.7)	4 (1.2)	11 (0.8)	10 (1.5)	8 (1.2)
Hypertension	5 (0.8)	3 (0.9)	6 (1.8)	7 (1.1)	4 (1.2)	3 (0.9)	12 (0.9)	7 (1.0)	9 (1.4)
Fatigue	6 (0.9)	1 (0.3)	2 (0.6)	7 (1.1)	7 (2.0)	3 (0.9)	13 (1.0)	8 (1.2)	5 (0.8)
Back pain	3 (0.5)	3 (0.9)	1 (0.3)	9 (1.4)	6 (1.7)	3 (0.9)	12 (0.9)	9 (1.3)	4 (0.6)

Children (4 to < 18 years of age) (Study V130_03)

From Day 1 through Day 22 (Day 1 to Day 50 for not previously vaccinated subjects), similar percentages of subjects in the QIVc, TIV1c, and TIV2c groups reported unsolicited AEs (24.3%, 24.0%, 26.7%) (see Table 15). The proportion of AEs judged by the investigator as possibly or probably related to the study vaccine were also similar across the groups (4.9%, 5.9%, 5.4%). Throughout the study, the most commonly reported unsolicited AEs were upper respiratory infection (5.1%, 3.1%, 6.7%), cough (3.9%, 6.0%, 4.2%), influenza-like illness (4.3%, 4.0%, 3.2%), headache (3.6%, 2.1%, 3.2%), and pharyngitis streptococcal (2.6%, 3.1%, 3.5%). There were 13 cases of confirmed influenza.

Table 15: Study V130_03 Unsolicited adverse events reported in subjects 4 to < 18 years of age by medical dictionary for regulatory activities preferred term (> 1% after any vaccination)

	Number (%) of Subjects		
MedDRA Preferred Term	QIVc N = 1149	TIV1c N = 579	TIV2c N = 570
Upper respiratory tract infection	59 (5.1)	18 (3.1)	38 (6.7)
Cough	45 (3.9)	35 (6.0)	24 (4.2)
Influenza-like illness	49 (4.3)	23 (4.0)	18 (3.2)
Headache	41 (3.6)	12 (2.1)	18 (3.2)
Pharyngitis streptococcal	30 (2.6)	18 (3.1)	20 (3.5)
Oropharyngeal pain	37 (3.2)	14 (2.4)	16 (2.8)
Nasopharyngitis	27 (2.3)	12 (2.1)	18 (3.2)
Otitis media	15 (1.3)	14 (2.4)	18 (3.2)
Vomiting	29 (2.5)	8 (1.4)	17 (3.0)
Pyrexia	20 (1.7)	10 (1.7)	14 (2.5)
Nasal congestion	14 (1.2)	13 (2.2)	2 (0.4)
Rhinorrhoea	17 (1.5)	13 (2.2)	8 (1.4)
Pharyngitis	15 (1.3)	12 (2.1)	9 (1.6)
Diarrhoea	23 (2.0)	8 (1.4)	6 (1.1)
Nausea	10 (0.9)	3 (0.5)	11 (1.9)
Gastroenteritis viral	13 (1.1)	9 (1.6)	10 (1.8)
Gastroenteritis	12 (1.0)	10 (1.7)	7 (1.2)
Rhinitis allergic	3 (0.3)	2 (0.3)	9 (1.6)
Viral infection	16 (1.4)	6 (1.0)	9 (1.6)
Attention deficit/hyperactivity disorder	11 (1.0)	9 (1.6)	7 (1.2)
Conjunctivitis	12 (1.0)	9 (1.6)	7 (1.2)
Injection site haemorrhage	6 (0.5)	9 (1.6)	4 (0.7)
Sinusitis	16 (1.4)	7 (1.2)	5 (0.9)
Laceration	6 (0.5)	8 (1.4)	5 (0.9)
Abdominal pain upper	12 (1.0)	7 (1.2)	3 (0.5)
Fatigue	7 (0.6)	3 (0.5)	6 (1.1)
Ear pain	12 (1.0)	3 (0.5)	2 (0.4)

Deaths

Adults (≥ 18 years of age)

There were 12 deaths in QIVc Study V130_01. None of the deaths were deemed to be possibly/probably related to a study vaccine. 11/12 were in patients ≥ 65 years of age. 17 deaths (TIVc 9, TIVe, 7, placebo 1) were reported in the TIVc safety set, all of which were considered unrelated to vaccination.

Children (4 to < 18 years of age)

No deaths were reported in paediatric Study V130_03, or in the pooled TIVc paediatric safety set.

Serious adverse events

Adults (≥ 18 years of age)

A similar proportion of subjects in the QIVc (3.9%), TIV1c (3.3%), and TIV2c (3.2%) groups reported serious adverse event (SAE). No SAE was judged by the investigator as possibly or probably related to a study vaccine. In the TIVc studies, all reported SAEs were judged as unrelated to the vaccinations by the investigators, except for an SAE of

spontaneous abortion in Study V58_23 (occurring on Day 13 in an egg derived trivalent influenza vaccine (Fluvirin);[9] recipient) which was considered possibly related.

Children (4 to < 18 years of age)

In Study V130_03, 0.5%, 1.2% and 0.4% (QIVc, TIV1c and TIV2c, respectively), reported SAEs, none of which were considered as possibly/probably related to the study vaccines. In the TIVc studies, none of the SAEs were considered vaccine related.

Discontinuations

Adults (≥ 18 years of age)

Across all the TIVc and QIVc adult and elderly studies, no subject withdrew due to an AE possibly related to vaccination.

Children (4 to < 18 years of age)

3 paediatric subjects in Study V130_03 withdrew from the study or the study vaccine because of AEs probably related to vaccination (prolonged erythema and induration at injection site; pain in extremity; and pruritus). No paediatric subject withdrew due to an AE possibly related to vaccination.

Safety in special populations

Sex

Overall, slightly more female subjects were included in the studies, but evenly spread between treatment groups. Solicited AEs, both local and systemic, were generally more frequently reported in female subjects. Unsolicited AEs were generally more frequently in female subjects in the adult and elderly population, but occurred at similar rates in the paediatric studies.

Age

There were no consistent trends in solicited AE reporting across all age groups. Unsolicited AEs were reported in higher percentages in the youngest age group (4 to < 6 years, 50.5% to 52.7% subjects in each group; 6 to < 9 years, 46.1% to 49.2% subjects in each group) and oldest subjects (≥ 65 years of age, 42.8% to 45.2% subjects in each group).

The highest percentages of subjects with possibly/probably related unsolicited AEs occurred in subjects 4 to < 6 years of age (6.5% to 7.5% subjects in each group) and subjects 6 to < 9 years of age (6.3% to 9.0% subjects in each group). No possibly/probably related unsolicited AE was reported in > 1% of subjects in each adult group.

SAEs were most commonly reported in subjects aged ≥ 65 years of age. However, in no age group was any SAE judged as possibly/probably related to study vaccine.

Ethnicity

In general, solicited and unsolicited AEs were more frequently reported in Caucasian than in non-Caucasian subjects. However, there appeared to be similar with regard to AEs that were considered to be possibly/probably related to a study vaccine. However, given the small number of non-Caucasian subjects, meaningful comparisons are difficult.

Pregnancy

The clinical dossier only contains limited information on pregnancy shown in the summary of clinical safety. Information from the provided periodic safety update reports (PSUR) indicate no causal relationship between QIVc and poor pregnancy outcomes.

[9] Fluvirin inactivated influenza vaccine (surface antigen) registered in Australia on 28 January 2003, ARTG 92695.

Although the overall experience of the use of QIVc and TIVc in pregnant women in clinical studies is very limited (most studies excluded pregnant women), there appear to be no safety signals.

A pregnancy registry was initiated in the Northern Hemisphere 2017 season in the US and is designed as a prospective observational safety study. The objective is to evaluate pregnancy outcomes as well as major congenital malformations, preterm birth and low birth weight among women immunised as part of routine care with TIVc or QIVc during pregnancy.

TIVc studies

Additionally, the following studies provided supportive safety data in the TIVc: V58P13, V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58_23, V58P12, V58P15, V58_31, V58P16, and V58_30OB. The immunogenicity and safety in those who are at risk of complication of influenza was studied in V58P15 using the TIVc, and revealed no safety concerns.

Post-market data

Flucelvax Quad is currently approved in the USA and the EU with post-market data available in periodic safety update reports (PSUR) (US data). The latest PSUR covered a period between 16 March 2018 and 15 March 2019. The total number of doses of QIVc supplied worldwide during the reporting period was 23,480,620. All doses were sold in the US. The post-marketing exposure data were not stratified by sex and age. The safety data of QIVc remained consistent with known information. However, rare adverse events will likely only be revealed from ongoing post-market surveillance.

The TIVc vaccine was given to more than 40 million individuals, and summary safety data for 12568 subjects (7978 adults, 997 elderly, and 3593 children) vaccinated with TIVc and 9186 subjects (6205 adults, 1016 elderly, and 1965 children) vaccinated with TIVe indicate that the safety profile of TIVc is comparable to that of a licensed egg-based comparator.

No new safety events were identified in post-marketing observational safety Study V58_30OB with > 4500 persons > 18 years of age received the seasonal TIVc (Optaflu) between 2012 and 2015 in a general primary care setting in the UK.

Additional AEs were reported from post-marketing surveillance. The frequency and causal relationship could not be established. They included: allergic or immediate hypersensitivity reactions, including anaphylactic shock; generalised skin reactions including pruritus, urticaria or nonspecific rash; extensive swelling of injected limb and paraesthesia. In addition, syncope and pre-syncope have been observed as a vasovagal reaction to injections, as for other vaccines and not specific to QIVc.

Clinical evaluator's recommendation

The safety data from 2493 subjects (674 adults, 660 elderly, and 1159 children) vaccinated with QIVc in Studies V130_01 and V130_03 indicate that the safety profile for QIVc is comparable to the licensed TIVc vaccine. In these studies, 2519 subjects (666 adults, 680 elderly, and 1173 children) were vaccinated with TIVc.

The evaluator concludes that QIVc appears safe with a comparable safety profile in children, adolescents and adults, including elderly patients to TIVc. There are some minor gender differences, more in females, for solicited local and systemic AEs, but these were rarely severe, and were short-lived.

Risk management plan

Seqirus Pty Limited has submitted EU-RMP version 2.0 (draft dated 25 September 2018 and approved 20 December 2018; data lock point (DLP) 30 May 2017) and Australia Specific Annex (ASA) version 1.0 (dated 11 June 2019) in support of this application. An updated ASA was submitted at round 2 evaluation (version 1.1; dated 12 March 2020). An updated ASA was submitted at round 3 evaluation (version 1.1; dated 7 April 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 16.[10]

Table 16:Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Nil				
Important potential risks	Neuritis	✓ †		✓	
	Convulsion	✓ †		✓	
	Encephalitis	✓ †		✓	
	Vasculitis	✓ †			
	Guillain-Barre Syndrome	✓ †		✓	
	Demyelination	✓ †			
	Bell's Palsy	✓ †			
	Immune Thrombocytopenia	✓ †			
Missing information	Safety in immunocompromised patients	✓		✓	
	Safety in subjects with underlying diseases	✓		✓	
	Use in pregnant and breastfeeding women	✓ †	✓ *	✓	

* Pregnancy registry (multinational, including Australian patients)
† Specific follow-up forms for adverse events

The summary of safety concerns is acceptable. The EU is evaluating EU-RMP version 2.1; when approved it is expected that EU-RMP version 2.1 and companion updated ASA will be submitted to the TGA, in accord with usual regulatory requirements.

[10] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine and additional pharmacovigilance activities (pregnancy registry) will be undertaken. A commitment relating to undertaking enhanced passive surveillance has been provided, if Australia vaccine safety system (AusVaxSafety) does not provide this service in any particular influenza season. Follow-up questionnaires have been provided for each of the important potential risks and use in pregnancy, as part of enhanced routine pharmacovigilance.

Routine risk minimisation will be undertaken and appears to be adequate.

There is no outstanding recommendation.

Recommended conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The Flucelvax Quad EU-Risk Management Plan (RMP) (version 2.0, dated 25 September 2018, data lock point 30 May 2017), with Australian Specific Annex (version 1.1, dated 7 April 2020), included with submission PM-2019-02591-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

> 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 EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this 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 (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Risk-benefit analysis

Delegate's considerations

The study design of the two pivotal clinical trials was acceptable overall and generally complied with TGA adopted guidance documents.[11],[12]

The results of the two pivotal QIVc immunogenicity trials (Studies 130_01 and 130_03) and the supportive TIVc efficacy trial (Study V58P13) were generally supportive of the proposed indication (except for the age range).

[11] **CPMP/BWP/214/96**. Note for guidance on harmonisation of requirements for influenza vaccines. Committee for Proprietary Medicinal Products (CPMP), March 1997 CPMP/EWP/463/97. Guideline On Clinical Evaluation Of New Vaccines. Committee for Medicinal Products for Human Use (CHMP), May 1999.

[12] **EMA/CHMP/VWP/457259/2014**. Guideline on influenza vaccines: non-clinical and clinical module, 21 July 2016

Efficacy and safety: Flucelvax Quad appears safe and immunogenic in the population tested (despite no true efficacy endpoint available). QIVc provides evidence of its benefits over those of the TIVC by inducing immune responses to two B lineages simultaneously, and the addition of the second B strain did not appear to negatively impact immune responses to the other 3 strains in the QIVc.

Post-market experience: Given the vaccine is registered in large jurisdictions (US and EU), there are a large amount of post-market safety data available (predominantly US data) with only a few reports of vaccine failure in the post-market reports 2016 to 2019.

The sponsor has not provided true efficacy studies for the QIVc, but only immunogenicity efficacy studies in the age group from 4 years and above (across two trials) combined with the TIVc true efficacy trial in subjects 18 years and above.

Generally, this approach is acceptable for a new quadrivalent vaccine, where there are available efficacy data for the corresponding trivalent vaccine. In this case, true efficacy data for the trivalent vaccine is only available for subjects 18 years and above. The relevant TGA-adopted EMA guideline would potentially allow extrapolation of that efficacy data to subjects 9 years of age and above, but not subjects younger than 9 years. Consequently, the approved age range for the QIVc in the EU using the same studies is for 9 years of age and above.

It is noted that there is a true efficacy trial in subjects aged 2 years and over (Study V130_12: A Phase III/IV, stratified, randomised, observer blind, multicentre clinical study to evaluate the efficacy, safety and immunogenicity of a cell-based quadrivalent subunit influenza virus vaccine compared to non-influenza comparator vaccine in subjects ≥2 years to < 18 years of age). This study appeared not to have been completed at the time of submission of this application (and consequently no data was provided), but it is complete now.

At this stage, with the data available, the indication proposed by the sponsor should be amended. A more appropriate indication may be:

> *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.*

Advice from the Advisory Committee on Vaccines (ACV) is sought.

Deficiencies of the data

No QIVc efficacy data in children: As stated above, the sponsor has not conducted true efficacy studies for the QIVc, but only immunogenicity efficacy studies in the age group from 4 years and above (across two trials) combined with the TIVc efficacy endpoint trial (Study V58P13) in subjects 18 years and above. Study V58P13 was not a double-blind, but only single-blind. However, Study V130_12 (not part of sponsor submitted dossier) may address this in future applications.

Generalisability: The populations studied were relevant for the claimed indication. However, the exclusion criteria were more restrictive compared to other clinical trials of influenza vaccine. Thus, the results are generalisable to the general Australian population with the exception of Asian and Indigenous Australian populations. It is unlikely that there are significant efficacy differences in immunocompetent adults, including the elderly population.

Relative paucity of QIVc immunogenicity and safety data in the elderly population aged ≥ 75: The total number of subjects > 75 years of age in the PP population of Study V130_01 was 315. The immune responses were less robust compared to the overall elderly group ≥ 65 years of age, but similar when compared to the TIVc results in the same age group.

No direct comparison of QIVc to other quadrivalent influenza vaccines: Both pivotal studies used a trivalent vaccine comparator.

Size of QIVc safety database for children and elderly (< 18 years and ≥ 75 years): The clinical trial exposure of QIVc in children could have been expanded. Relevant post-market data reports did not specifically analyse data by age stratum. TIVc data can be extrapolated to some extent to the QIVc. However, the additionally conducted study in children (Study V130_12; not part of sponsor submitted dossier) should add to the knowledge base of Flucelvax Quad.

No data for immunocompromised individuals: The Phase III QIVc studies all specifically excluded immunocompromised (congenital or acquired) subjects, and hence there are no data in any age group.

Co-administration with other vaccines: No actual studies of QIVc co-administered with other vaccines have been performed, but instead the data on co-administered vaccine has been extrapolated from the TIVc vaccines (only a small amount of data for the safety and immunogenicity of TIVc with pneumococcal vaccines in adults).

Limited or no data in subpopulations relevant to Australia: Given that the studies were mainly conducted in the US/Europe, there are limited data for the Asian population, and limited or no data for the Indigenous Australian population.

Longitudinal data: There appears to be no or limited longitudinal safety and immunogenicity data for QIVc over several influenza seasons. However, there are some data from TIVc in adults arising from the Study V58P4 extensions.

Pregnancy/breastfeeding safety data: There appears to be a paucity of safety data for QIVc in pregnancy or breastfeeding, noting that there appears to be no safety signal of concern for the TIVc.

The RMP evaluator stated that '*Use in pregnancy*' appears as missing information in the RMP. This is consistent with there being an ongoing additional pharmacovigilance activity (pregnancy register) assessing safety in pregnant women. It is incongruous for a medicine where use in pregnancy is considered missing information to also be assessed as pregnancy category A.[13]

The sponsor provided the following response to the RMP evaluator:

> 'Influenza vaccination is recommended for pregnant women during any stage of pregnancy. This recommendation in Australia is based on the known adverse consequences of influenza infection during pregnancy and the large body of data showing that large numbers of women have been vaccinated during pregnancy with inactivated influenza vaccines with no increased risk of adverse foetal or maternal outcomes attributable to the vaccine.
>
> Whilst the Flucelvax pregnancy registry is still ongoing, it is anticipated that the safety of Flucelvax in pregnant women is similar to that of inactivated influenza vaccines. Maintaining use of Flucelvax in pregnancy – Pregnancy Category A is also consistent with the recommendation made in the Australian Immunisation Handbook September 2019 in relation to vaccinating pregnant women with influenza vaccine.
>
> Many influenza vaccines had their Pregnancy Category reclassified to Category A, but none of those are a cell-based influenza vaccine.'

[13] 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.

Proposed action

The Delegate had no reason to say, at the time, that the application for Flucelvax Quad should not be approved for registration for the following indication (in lieu of the sponsor proposed 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.*

Questions for sponsor

1. The sponsor should provide a current summary of pregnancy data for QIVc

Seqirus Pty Ltd (the sponsor) acknowledges that limited data exists for use of QIVc in pregnant women given its first approval for marketing in the US was 2016. However, as mentioned above, inactivated influenza vaccines can be used in all stages of pregnancy. This is in line with the recommendation in the Australian Immunisation Handbook April 2020.[14]

A summary of the data from the ongoing pregnancy registry is provided below.

The pregnancy registry commenced in the US NH 2017/2018 season; enrolment commenced 01 September 2017 (target enrolment 600). The safety objective of the study was to evaluate pregnancy outcomes as well as events of interest (major congenital malformations (MCM), preterm birth and low birth weight (LBW)) among women immunised as part of routine care with QIVc during pregnancy. The last data collection timepoint is scheduled in September 2020 and the clinical study report (CSR) will be finalised in April 2021.

Cumulatively up to 1 May 2020, 643 pregnant women have enrolled in the study for QIVc, of which 542 reported pregnancy outcomes. Of these,540 were live births; 1 was elective termination and 1 was spontaneous abortion. Of the 540 cases with the outcome of live birth, 54 were reported as preterm, 39 as 1 LBW, 23 were both preterm and LBW, and 15 as MCM cases. A MCM is defined as any major structural or chromosomal defect or combination of two or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or birth weight < 500 g). In 13 of the MCM cases, exposure to QIVc was after origin of defect and for 2 the exposure to QIVc was within origin of defect. This is a temporary assessment and not necessary cause of effect.

In accordance with the US FDA post-approval pregnancy safety studies guidance for industry,[15] Seqirus established a scientific advisory committee (SAC) to ensure scientific integrity and ongoing safety monitoring for the study. The SAC comprises recognised independent external experts including but not limited to experts in the fields of obstetrics, teratology, and epidemiology.

The SAC meet regularly to review the accumulated body of data from the study, including review and classification of reported MCMs and other events of interest, and to carry out any actions required, including review and interpretation of interim data analyses. Interim review of the registry data by the SAC on 31 August 2019 concludes that the incidence of the outcomes monitored are in accordance with expected background rates. Importantly, to date, no safety concerns have been raised by the SAC.

An interim analysis of pregnancy registry data (as of May 2020) is presented in Table 17.

[14] Australian Immunisation Handbook April 2020. Access via immunisationhandbook.health.gov.au
[15] FDA post-approval pregnancy safety studies guidance for industry Access via.fda.gov

Table 17: Interim results overview of pregnancy registry data (data lock point: May 2020)

QIVc pregnancy outcomes (n = 542)	Subjects with MCMs	Subjects with preterm birth (prior to 37 weeks) - 10,02%*	Subjects with LBW (under 2500 grams) - 8,28%*	Subjects with twins	Subjects with non-live births
Total:	15	46**	33**	5	2
Denominator:	540	520	520	542	542
incidence/prevalence:	2.77%	8.84%	6.34%	0.96%	0.36%

* Reference: national vital statistics reports, volume 68, number 13, 2018
** For preterm labor and low birth weight subjects with a multiple gestation pregnancy, a non-livebirth pregnancy outcome or a livebirth with MCM(s) were excluded

Request for Advisory Committee on Vaccines advice

The committee is requested to provide advice on the following specific issues:

1. The age group for which Flucelvax Quad should be indicated; and
2. The appropriate pregnancy category for Flucelvax Quad.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee considerations[16]

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:

The ACV considered the vaccine 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 9 years of age and older.*

In providing this advice the ACV:

- was of the view that vaccine efficacy was acceptable with appropriate immunobridging studies for persons 9 years and over
- considered the safety profile was adequate, although limited.

[16] The **Advisory Committee on Vaccines (ACV)** provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market assessment, post-market monitoring and safe use in national immunisation programs.

The Committee is established under Regulation 39F of the Therapeutic Goods Regulations 1990 and the members are appointed by the Minister for Health.

The ACV was established in January 2017, following consolidation of previous functions of the Advisory Committee on the Safety of Vaccines (ACSOV) and the pre-market functions for vaccines of the Advisory Committee on Prescription Medicines (ACPM).

Membership comprises professionals with expertise in specific scientific, medical or clinical fields, or consumer health issues.

The ACV advised the following in response to the Delegate's specific questions.

1. Can the ACV comment on the age group in the proposed indication?

The ACV advised that the vaccine should be indicated for use in adults and children 9 years of age and older. The committee considered:

- the relevant TGA-adopted EMA guideline allows extrapolation of efficacy data from an adult population to persons 9 years and older, but not the extrapolation to efficacy in children younger than 9 years.
- while an efficacy study in children 2 years and over (Study V130_12) has recently concluded, the study has not been evaluated by the TGA and is under evaluation by other regulators.

2. Can the ACV comment on the proposed pregnancy category based on the data available?

The ACV advised that Pregnancy Category B1;[17] is appropriate for the vaccine. The committee advised that Pregnancy Category A;[13] is not appropriate, as:

- The formal definition of Pregnancy Category A;[13] includes 'taken by a large number of pregnant women and women of childbearing age'. The extent of use of QIVc by pregnant women is unclear in the absence of detailed post-market data from the US and EU on use during pregnancy.
- The change from Pregnancy Category B1;[17] to Category A;[13] for egg-grown influenza vaccines reflects real world experience and analysis of the available evidence for each of these vaccines.
- The sponsor relies on the same nonclinical data for the TIVc as for the QIVc. The Pregnancy Category for the TIVc was B1;[17] reflecting the state of knowledge at that time.
- The US pregnancy registry closes in 2020. The Pregnancy category can be reviewed once the pregnancy registry results become available and the '*taken by a large number of pregnant women and women of childbearing age*' criterion is confirmed.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Flucelvax Quad quadrivalent influenza vaccine (surface antigen inactivated), 60 µg haemagglutinin suspension for injection, indicated for:

> *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.*

Specific conditions of registration applying to these goods

- At least 45 working days before the submission of the first request under s.9D(3) of the Therapeutic Goods Act 1989 for a change to the strain composition of the vaccine, and not later than 31 October 2020, the following be provided to the TGA for approval

[17] Pregnancy 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.

under s9D(3) of the Therapeutic Goods Act 1989 The additional requested quality data should be provided prior to the lodgement of the Annual strain Update for the SH 2021 influenza season.

- Batch Release Testing and Compliance with the Certified Product Details Conditions of Registration for Flucelvax Quad quadrivalent influenza vaccine

  It is a condition of registration that all independent batches of Flucelvax Quad imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the laboratories branch, TGA.

  For each independent batch of the product imported into Australia, the sponsor must supply the following:

  - A completed Request for Release Form, available from vaccines@health.gov.au.
  - Complete summary protocols for manufacture and QC, including all steps in production.
  - At least 20 (twenty) doses of the first consignment of each batch of Flucelvax Quad with the Australian approved labels, PI and packaging.
  - At least 10 (ten) doses of any further consignment of each batch of Flucelvax Quad with the Australian approved labels, PI and packaging and at least 20 (twenty) doses of any further consignment of each batch of Flucelvax Quad with the Australian approved labels, PI and packaging.
  - Certificate of Release from a regulatory agency acting for the country of origin such as an OMCL (if available).
  - Any reagents, reference material and standards required to undertake testing, as requested by laboratories branch, TGA.

  Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the laboratories branch acknowledging release.

  Samples and data should be forwarded to the biomedicines and influenza vaccines section, laboratories branch before release of each batch and with sufficient lead time to allow for laboratories branch testing. All shipments (including reagents) must be sent to TGA from the Australian sponsor/agent who will be required to facilitate the import and customs clearance process.

- Certified Product Details: An electronic copy of the CPD as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) https://www.tga.gov.au/guidance-7-certified-product-details should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website https://www.tga.gov.au/form/certifiedproduct-details-cpd-biological-prescription-medicines]. The CPD should be sent as a single bookmarked PDF document to vaccines@health.gov.au as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

- The Flucelvax Quad EU-RMP (version 2.0, dated 25 September 2018, data lock point 30 May 2017), with ASA (version 1.1, dated 7 April 2020), included with submission PM-2019-02591-1-2, 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 PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this 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 (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Flucelvax Quad approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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